The Evolving Epidemiology of HIV Exposed Uninfected Children

Kate Powis
Harvard University; kpowis@mgh.harvard.edu

Amy Slogrove
Stellenbosch University; amy@sun.ac.za; @amyslogrove
Overview

1. HEU children in global context
2. HEU child risk factors
3. HEU child outcomes – Current evidence
4. The long-term view
Terminology

Mother to Child Transmission
Peri- and post-natal HIV transmission

HIV exposed uninfected (HEU) = HIV affected
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Africa in the Global HIV Epidemic

In 2017 14.8 million HEU children (age 0-14 years) - 90% in sub-Saharan Africa
Contributions by Country to Global HEU Child Burden in 2017

- South Africa: 21%
- Nigeria: 10%
- Mozambique: 7%
- Tanzania: 7%
- Uganda: 6%
- Kenya: 6%
- Zimbabwe: 5%
- Malawi: 4%
- Zambia: 4%
- Ethiopia: 2%
- Cameroon: 2%
- DR Congo: 2%
- Other: 24%
Number and prevalence of HEU Children (0-14 years) in sub-Saharan African Focus Countries: 2017

UNAIDS Estimates 2018; aidsinfo.unaids.org
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Universal Risk Factors

Unique HEU Infant Risk Factors
Variations in HIV and ARV Exposure Status

- **HIV Exposure**: Varied timing and intensity
- **Antiretroviral Exposure**: Varied timing and type
7% of all children in Malawi are exposed *in utero* to

<table>
<thead>
<tr>
<th>A chronic <strong>viral infection</strong></th>
<th>At least 3 highly <strong>active drugs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Antiretroviral Therapy</td>
</tr>
</tbody>
</table>
At least 1 in 5 children in Botswana, Eswatini, South Africa are exposed *in utero* to

**A chronic viral infection**

HIV

**At least 3 highly active drugs**

Antiretroviral Therapy
Impact on HEU Child Survival and ECD

**Universal infant factors**
- Preterm / Small for gestation
- Suboptimal infant feeding
- Infectious pathogen exposure
- Maternal morbidity and mortality
- Poverty

**HEU-unique factors**
- HIV product exposure
- Maternal immune compromise
- Altered infant immunity
- Antiretroviral drug exposure

Slogrove, Frigati, Gray, 2016
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Elevated mortality in HEU children

Le Roux, TMIH 2016

Overall: RR 1.93 (1.17; 3.17)

No change in this mortality trend with expanding maternal ART, improved maternal health and safer breastfeeding

Brennan, AIDS 2016

Overall: RR 1.70 (1.30; 2.22)
2013 in Botswana and South Africa – 15% of all HIV-uninfected infant mortality associated with excess mortality in HEU infants.

In South Africa, mortality in children with HIV accounted for ±7% of all childhood mortality, whereas excess mortality in HEU infants accounts for ±14% of all infant mortality.

Slogrove, Johnson, Powis, JTP 2018

From Thembisa Demographic Model
Tsepamo – an observational study in Botswana that captures birth outcomes of all births at 8 government health facilities - ±45% of all births in Botswana; ongoing since 2014

Increased risk in women with HIV on EFV-based ART compared to women without HIV of:

- Preterm birth (aRR 1.18; 95% CI 1.12,1.25)
- Small for gestational age (aRR 1.30; 95% CI 1.23,1.38)
## HIV and Adverse Birth Outcomes

Women living with HIV in LMIC: 40% increased risk of preterm birth when conceiving on ART compared to initiating ART during pregnancy (RR 1.41; 95% CI 1.22-1.63)

![Infant image](image)

### Figure 2: Forest plot of risk of preterm birth before 37 weeks (prematurity) in women with HIV who initiated ART before conception versus women who initiated ART after conception

<table>
<thead>
<tr>
<th></th>
<th>Pre-conception ART</th>
<th>Post-conception ART</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Event</td>
<td>Total (%)</td>
</tr>
<tr>
<td>Low-income and middle-income economies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anijii et al (2013)</td>
<td>16</td>
<td>76</td>
</tr>
<tr>
<td>Li et al (2016)</td>
<td>222</td>
<td>582</td>
</tr>
<tr>
<td><strong>Random-effects model</strong></td>
<td>5009</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk ratio (95% CI)</td>
<td>Weight (%)</td>
</tr>
<tr>
<td>Low-income and middle-income economies</td>
<td>0.87 (0.52-1.45)</td>
<td>7.4</td>
</tr>
<tr>
<td>High-income economies</td>
<td>1.33 (1.15-1.55)</td>
<td>16.4</td>
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<tr>
<td></td>
<td>1.48 (1.24-1.77)</td>
<td>15.6</td>
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<tr>
<td></td>
<td>1.23 (0.76-2.00)</td>
<td>7.8</td>
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<tr>
<td></td>
<td>1.65 (1.41-1.93)</td>
<td>16.3</td>
</tr>
<tr>
<td></td>
<td>1.41 (1.22-1.63)</td>
<td>63.5</td>
</tr>
</tbody>
</table>

### Table 1: Prevalence of preterm birth before 37 weeks (prematurity) in women with HIV who initiated ART before conception versus women who initiated ART after conception

Uthman, Lancet HIV 2016
In utero HIV and ARV exposure – a fetal origin of disease

Length-for-age Z-scores from 6 weeks to 12 months of age

Approximate age at study visit

- HU-AGA (n=347)
- HU-SGA (n=38)
- HEU-AGA (n=361)
- HEU-SGA (n=48)

*Adjusted mixed effects model; time-interaction p=0.08

Stanzi Le Roux – Lancet Child & Adolescent Health 2019
SHINE: Sanitation Hygiene Infant Nutrition Efficacy

- HEU versus HUU at 18-months
  - Mortality RR 1.39 (95% CI 1.02, 1.89)
  - Stunting RR 1.48 (95% CI 1.34, 1.64)

- Significant differences in gross and fine motor, and language but not social or behavioral performance at 24-months
  - Combined nutrition + WASH interventions normalized HEU child neurodevelopment
Initiation of ART before pregnancy may reduce infectious morbidity risk in HEU infants

In Belgium, conception on ART was protective against immune abnormalities and infectious morbidity in HEU infants

What about in Southern Africa?

Goetghebuer et al, CID 2018
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Maternal and Child Health

Maternal and Grandchild Health...
Diethylstilbesterol (DES)

• 6 million in utero exposures 1940-1971
• Young adult women exposed in utero
  • 40 fold ↑ risk of rare cervical/vaginal cancers
  • 2 x ↑ risk of breast cancer
• Birth defects in offspring of DES
  Daughters - Epigenetic changes in primordial germ cells resulting in 2nd generation effects
• Also effects in sons and grandsons
• Effects of DES exposure not recognized for decades (*record of exposure)

Advertisement for DES from a 1957 medical journal
Long Term View
Surviving and Thriving throughout the Life Course
Additive Exposures

HIV & ART

Tuberculosis & Treatment

Smoking

Alcohol

Obesity
Finding the balance

Maternal Health  
Child Health
Finding the balance

Safety

Confidentiality
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Mechanisms for Driving the HEU Child Outcomes Agenda

- **Expert Panels**
- **Technical Working Groups**
- **Data Centre**

**INFORM – AIDS FREE**

- **Study Teams**
- **CIPHER Fellows**
- **DECIPHER Fellow**

**CIPHER-DECIPHER**

**HEU Data Sharing and Dissemination**
- **HEU Child & Adolescent Workshop**
- **Western Cape HEU Child and Adolescent Forum**

**Research Cohorts**
- **Infant/Child Health Systems and Social Programs**
- **Civil Society**