HIV-Affected but not Infected –
*The Dilemma of HIV-Exposed Uninfected Infants and Children*
Disclosures

No financial conflicts or disclosures
Objectives

• HIV-exposed uninfected (HEU) child population

• HEU selected infant/child outcomes
  • Mortality
  • Morbidity

• Review HEU child health surveillance challenges
GLOBAL PLAN TOWARDS THE ELIMINATION OF NEW HIV INFECTIONS AMONG CHILDREN BY 2015 AND KEEPING THEIR MOTHERS ALIVE

2011-2015

2015 PROGRESS REPORT ON THE GLOBAL PLAN

towards the elimination of new HIV infections among children and keeping their mothers alive

170,000
THE NUMBER OF NEW INFECTIONS AMONG CHILDREN IN 2014

48%
DECREASE IN THE NUMBER OF NEW HIV INFECTIONS AMONG CHILDREN, 2009-2014

8 OUT OF 10
PREGNANT WOMEN LIVING WITH HIV RECEIVED ANTIRETROVIRAL MEDICATIONS TO PREVENT MOTHER-TO-CHILD TRANSMISSION OF HIV

14%
MOTHER-TO-CHILD HIV TRANSMISSION RATE, INCLUDING DURING BREASTFEEDING
GLOBAL PLAN TOWARDS THE ELIMINATION OF NEW HIV INFECTIONS AMONG CHILDREN BY 2015 AND KEEPING THEIR MOTHERS ALIVE

2011-2015

START FREE

STAY FREE

AIDS FREE

2015 PROGRESS REPORT ON THE GLOBAL PLAN
towards the elimination of new HIV infections among children and keeping their mothers alive

48% DECREASE IN THE NUMBER OF NEW HIV INFECTIONS AMONG CHILDREN, 2009–2014

14% MOTHER-TO-CHILD HIV TRANSMISSION RATE, INCLUDING DURING BREASTFEEDING
Objectives

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HIV+ Women by ARV Access in Pregnancy

Pregnant Women Living with HIV Women without ARV Use in Pregnancy

Pregnant Women Living with HIV with ARV Use in Pregnancy
HIV+ Women by ARV Access in Pregnancy & New HIV Infections among Children

- Pregnant Women Living with HIV Women *without* ARV Use in Pregnancy
- Pregnant Women Living with HIV with ARV Use in Pregnancy
- Newly HIV-Infected Children

UNAIDS-SPECTRUM 2016
After climbing a great hill, one only finds that there are many more great hills to climb – *Nelson Mandela*
Infants Born to Women Living with HIV by Infant HIV Status

HIV-Exposed Uninfected Infants

HIV-Infected Infants

- New Child HIV+
- HIV-Exposed Uninfected Children

UNAIDS-SPECTRUM 2016
Infant born to Women Living with HIV by HIV and ARV status

- **HIV-Infected Infants**
- **HIV Exposed – ARV Unexposed Uninfected Infants**
- **HIV & ARV Exposed Uninfected Infants**

UNAIDS-SPECTRUM 2016
Prevalence of Infant HIV & ARV *In Utero* Exposure

2015: 7.1 million HEU under 5 year olds
~ 5.6 million also ARV-exposed
Objectives

• HIV-exposed uninfected (HEU) child population

• HEU selected infant/child outcomes
  • Mortality
  • Morbidity

• Review HEU child health surveillance challenges
Elevated HEU Mortality

Source: le Roux et al TMIH 2016;21:829-845

Source: Brennan et al AIDS 2016;30:2351-2360
Elevated HEU Mortality

Source: le Roux et al TMIH 2016;21:829-845

Overall Risk Ratio: 1.93 (1.17, 3.17)

Source: Brennan et al AIDS 2016;30:2351-2360

Overall Risk Ratio: 1.70 (1.30, 2.22)
Elevated HEU Mortality

Source: le Roux et al TMIH 2016;21:829-845

Overall Risk Ratio: 1.93 (1.17, 3.17)

RR birth – 12 months: 1.8 (1.1, 2.8)
RR 12 – 24 months: 1.6 (1.1, 2.3)
RR > 24 months: 1.7 (1.1, 2.6)

Source: Brennan et al AIDS 2016;30:2351-2360
Botswana Child Mortality – Bending the Curve

Botswana Child Mortality – Bending the Curve

Zash et al., BMC Pediatrics 2016;16:103
Botswana Child Mortality – Bending the Curve

Maikaelelo Study
HEU Mortality 47.3

Mpepu Study
HEU Mortality 22.5

Maikaelelo Study
HU Mortality 16.0

Zash et al., BMC Pediatrics 2016;16:103
Complexity of HEU Child Health Outcomes Disparities

HEU Risk Areas
- Morbidity
- Mortality
- Growth
- Cognition
- Behavioral
- NCDs

Adapted from Slogrove et al. Pediatr Infect Dis J 2017;36:e38-e44
The Tsepamo Study – Preterm Delivery by ARV Regimen

*Models adjusted for maternal age, educational attainment and gravida

<table>
<thead>
<tr>
<th>HIV-unexposed (N=34,616)</th>
<th>TDF/FTC/EFV (N=2,503)</th>
<th>TDF/FTC/NVP (N=775)</th>
<th>ZDV/3TC/NVP (1,403)</th>
<th>TDF/FTC/LPV-r (N=237)</th>
<th>ZDV/3TC/LPV-r (N=169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm Birth aRR* (95% CI)</td>
<td>ref</td>
<td>0.9 (0.8,1.1)</td>
<td>1.2 (1.0,1.3)</td>
<td>1.1 (0.9,1.4)</td>
<td>1.4 (1.1,1.8)</td>
</tr>
<tr>
<td>Very Preterm Birth aRR* (95% CI)</td>
<td>ref</td>
<td>1.2 (0.8,1.8)</td>
<td>1.4 (1.1,2.0)</td>
<td>1.4 (0.8,2.5)</td>
<td>2.2 (1.3,3.8)</td>
</tr>
</tbody>
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*Models adjusted for maternal age, educational attainment and gravida

Zash  CROI 2017 – Oral Presentation
The Tsepamo Study – Small-for-Gestational-Age

<table>
<thead>
<tr>
<th>HIV-Unexposed (N=34,616)</th>
<th>TDF/FTC/EFV (N=2,503)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>SGA aRR* (95% CI)</td>
<td>ref</td>
<td>1.4 (1.2,1.7)</td>
<td>1.7 (1.5,1.9)</td>
<td>1.6 (1.3,2.0)</td>
<td>1.1 (0.8,1.6)</td>
</tr>
<tr>
<td>Very SGA aRR* (95% CI)</td>
<td>ref</td>
<td>1.5 (1.2,1.9)</td>
<td>1.8 (1.4,2.2)</td>
<td>1.8 (1.3,2.6)</td>
<td>1.7 (1.1,2.6)</td>
</tr>
</tbody>
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*Models adjusted for maternal age, educational attainment and gravida.

Zash CROI 2017 – Oral Presentation
### Geometric mean (95% CI) antibody concentration (EU/ml) against Respiratory Viruses and Pneumococcus at Birth

<table>
<thead>
<tr>
<th>Respiratory Infection Type</th>
<th>HIV Exposed Uninfected Infants</th>
<th>HIV-Unexposed Infants</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Concentration (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Influenza A</td>
<td>198</td>
<td>52 (44, 63)</td>
<td>88</td>
</tr>
<tr>
<td>Respiratory Syncytial Virus</td>
<td>200</td>
<td>77 (67, 90)</td>
<td>88</td>
</tr>
<tr>
<td>Parainfluenza Virus 1</td>
<td>202</td>
<td>4 (3, 6)</td>
<td>88</td>
</tr>
<tr>
<td>Parainfluenza Virus 2</td>
<td>200</td>
<td>8 (6, 11)</td>
<td>88</td>
</tr>
<tr>
<td>Parainfluenza Virus 3</td>
<td>195</td>
<td>11 (9, 15)</td>
<td>88</td>
</tr>
<tr>
<td>Pneumococcus 5</td>
<td>188</td>
<td>0.8 (0.8, 0.9)</td>
<td>88</td>
</tr>
<tr>
<td>Pneumococcus 6B</td>
<td>188</td>
<td>0.7 (0.6, 0.7)</td>
<td>88</td>
</tr>
<tr>
<td>Pneumococcus 14</td>
<td>199</td>
<td>2.9 (2.6, 3.1)</td>
<td>88</td>
</tr>
</tbody>
</table>
## HEU Children and Immune Abnormalities

<table>
<thead>
<tr>
<th>Feature</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced transfer of maternal antibody including IgG</td>
<td>de Moraes-Pinto <em>et al.</em> [40]; Farquhar <em>et al.</em> [46]; Cumberland <em>et al.</em> [42]; Scott <em>et al.</em> [45]; Bunders <em>et al.</em> [44]; Jones <em>et al.</em> [93]</td>
</tr>
<tr>
<td>Altered CD4⁺ and CD8⁺ T cell counts</td>
<td>Clerici <em>et al.</em> [33]; Miles <em>et al.</em> [98]; Slogrove <em>et al.</em> [11]; Borges-Almeida, <em>et al.</em> [126]</td>
</tr>
<tr>
<td>Increased proinflammatory responses in cord blood to polyclonal stimulation</td>
<td>Hygino <em>et al.</em> [47]; Hygino <em>et al.</em> [48]</td>
</tr>
<tr>
<td>Increased T cell immune activation</td>
<td>Rich <em>et al.</em> [36]; Clerici <em>et al.</em> [33]; Romano <em>et al.</em> [59]; Vigano <em>et al.</em> [54]</td>
</tr>
<tr>
<td>Skewed T cell memory and differentiation subset distributions</td>
<td>Rich <em>et al.</em> [36]; Clerici <em>et al.</em> [33]; Nielson <em>et al.</em> [128]; Vigano <em>et al.</em> [54]; Miles <em>et al.</em> [98]</td>
</tr>
<tr>
<td>Increased susceptibility to T cell apoptosis</td>
<td>Economides <em>et al.</em> [49]</td>
</tr>
<tr>
<td>Increased plasma IL-7 levels</td>
<td>Clerici <em>et al.</em> [33]</td>
</tr>
<tr>
<td>Altered DC phenotype and <em>in-vitro</em> IL-12 production</td>
<td>Chougnet <em>et al.</em> [51]; Velilla <em>et al.</em> [53]</td>
</tr>
<tr>
<td>Reduced thymic size</td>
<td>Kolte <em>et al.</em> [56]</td>
</tr>
<tr>
<td>Reduced TREC levels in periphery</td>
<td>Nielson <em>et al.</em> [128]</td>
</tr>
<tr>
<td>Skewed maturation of B cell subsets and susceptibility to apoptosis</td>
<td>Bunders <em>et al.</em> [44]; Miyamoto <em>et al.</em> [129]; Borges-Almeida <em>et al.</em> [126]</td>
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## Infant Viral Respiratory Infections and Outcomes – South Africa

<table>
<thead>
<tr>
<th>Viral Infection Type</th>
<th>HIV Exposed Uninfected Infants Incident Rates (95% CI)</th>
<th>HIV-Unexposed Infants Incident Rates (95% CI)</th>
<th>Incidence RR</th>
</tr>
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<tbody>
<tr>
<td>All LRTIs</td>
<td>14,097 (13,252-14,982)</td>
<td>10,313 (9,858-10,784)</td>
<td>1.4 (1.3-1.5)</td>
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<tr>
<td>RSV</td>
<td>5003 (4,505-5,541)</td>
<td>3,507 (3,244-3,787)</td>
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</tr>
<tr>
<td>Rhinovirus</td>
<td>4,581 (4,105-5,097)</td>
<td>3,074 (2,827-3,357)</td>
<td>1.5 (1.3-1.7)</td>
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<tr>
<td>Adenovirus</td>
<td>1,563 (1,291-1,8770)</td>
<td>1,253 (1,097-1,424)</td>
<td>1.2 (1.0-1.6)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>1,196 (959-1,474)</td>
<td>680 (567-809)</td>
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</tr>
<tr>
<td>hMPV</td>
<td>816 (622-1,050)</td>
<td>573 (470-692)</td>
<td>1.4 (1.1-2.0)</td>
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<td>Influenza</td>
<td>503 (354-693)</td>
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## Infant Viral Respiratory Infections and Outcomes – South Africa

### Incidents Rates of Viral Lower Respiratory Tract Infections per 100,000 Population of Hospitalized Infants > 2 Days of Life but ≤ 6 Months of Life

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</table>

### Mortality from Viral Respiratory Infections in the First Six Months of Life by Infant HIV-Exposure Status

<table>
<thead>
<tr>
<th>Infection Type</th>
<th>HEU Case Fatality Ratio</th>
<th>HUU Case Fatality Ratio</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RSV</td>
<td>5/592 (2%)</td>
<td>0/523 (0%)</td>
<td>12.2 (1.7-∞)</td>
</tr>
<tr>
<td>Influenza</td>
<td>2/28 (7%)</td>
<td>1/54 (2%)</td>
<td>4.1 (0.4-17.1)</td>
</tr>
<tr>
<td>Rhinovirus</td>
<td>7/288 (2%)</td>
<td>9/477 (2%)</td>
<td>1.3 (0.5-3.5)</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>3/119 (3%)</td>
<td>2/228 (1%)</td>
<td>2.9 (0.5-17.7)</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>0/9 (0%)</td>
<td>1/86 (1%)</td>
<td>1.7 (0-64.5)</td>
</tr>
<tr>
<td>hMPV</td>
<td>0/59 (0%)</td>
<td>2/76 (3%)</td>
<td>0.5 (0.6.9)</td>
</tr>
</tbody>
</table>
Pneumonia Treatment Failure/Mortality among HEUs Infants/Children in Botswana

- Botswana hospital based prospective cohort study of infants/children 1-23 months admitted for pneumonia
  - 153 (64%) HIV-unexposed
  - 64 (27%) HIV-exposed uninfected
  - 8 (20%) HIV-infected
Pneumonia Treatment Failure/Mortality among HEUs Infants/Children in Botswana

- **HEU children experienced higher risk of treatment failure at 48 hours**
  - ALL [RR 1.83; 95% CI 1.27-2.64; p=0.001]
  - < 6 mos [RR 2.10; 95% CI 1.42-3.08; p=0.001]

- **HEU children experienced higher risk of in-hospital mortality**
  - ALL [RR 4.31; 95% CI 1.44-12.87; p=0.01]
  - < 6 mos [RR 6.05; 95% CI 2.08-17.58; p=0.0009]
HEU Children and Growth – Botswana Studies

- Breastfed HEU Infants in the Mashi (n=303) and Mma Bana (n=516) studies

- *In utero* exposure to triple ARVs compared with AZT monotherapy associated with lower mean length-for-age z-score at 24 months \([-0.34; 95\%\ CI -0.53 to -0.15; p=0.0004]\)

### In utero AZT Exposure

<table>
<thead>
<tr>
<th></th>
<th>Stunting Prevalence</th>
<th>Multivariate Relative Risk of Stunting</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEU Children (n=100)</td>
<td>20.0%</td>
<td>1.91 (1.17 – 3.09) REF</td>
<td>0.01</td>
</tr>
<tr>
<td>HUU Children (n=283)</td>
<td>11.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 year to &lt; 2 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEU Children (n=109)</td>
<td>22.9%</td>
<td>0.64 (0.43 – 0.95) REF</td>
<td>0.03</td>
</tr>
<tr>
<td>HUU Children (n=282)</td>
<td>29.8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years to &lt; 5 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEU Children (n=187)</td>
<td>31.0%</td>
<td>1.42 (1.07 – 1.87) REF</td>
<td>0.01</td>
</tr>
<tr>
<td>HUU Children (n=544)</td>
<td>20.8%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In utero Triple ARV Exposure

- Cross-sectional survey conducted in 5 health districts in Botswana enrolling caregiver-child pairs attending monthly under 5 well child clinics

- 67% of the excess risks of stunting in children ≥ 2 years of age attributable to birth weight < 2500 grams

Sudfeld et al. JAIDS 2016;73:182-189

Powis et al AIDS 2016;30:211-220
HEU Children and Neurodevelopment

Neurodevelopmental outcomes in HIV-exposed-uninfected children versus those not exposed to HIV

Stephen J. Kerr\textsuperscript{a,b}, Thanyawee Puthanakit\textsuperscript{a,c,e}, Ung Vibol\textsuperscript{d}, Linda Aurnpibul\textsuperscript{e}, Sophan Vonthanak\textsuperscript{f}, Pope Kosalaraks\textsuperscript{a,g}, Suparat Kanjanavani\textsuperscript{h}, Rawiwan Hansudewechakul\textsuperscript{i}, Jurai Wongsawan\textsuperscript{j}, Wicharn Luesomboon\textsuperscript{k}, Kattiya Ratanadilok\textsuperscript{l}, Wasana Prasitsuebsai\textsuperscript{a}, Kanchana Pruksakaew\textsuperscript{a}, Jasper van der Lugt\textsuperscript{a,m}, Robert Paul\textsuperscript{n}, Jintanat Ananworanich\textsuperscript{a,o} and Victor Valcour\textsuperscript{p} on Behalf of the SEARCH 012 Study Team

- 160 HEU and 167 HU children age and gender matched controls in the PREDICT Trial in Thailand and Cambodia age 2-15 years.

- HEU children with statistically lower scores in verbal IQ, full scale IQ, and Binet Bead Memory

Conclusions:
Small differences in some but not all neurodevelopmental outcomes among HEU children

Unclear as to the immediate and long-term clinical significance

Kerr et al AIDS Care 2014;26;1327-1335
Objectives

- HIV-exposed uninfected (HEU) child population
- HIV-exposed uninfected infant/child outcomes
  - Mortality
  - Morbidity
- Review HEU child health surveillance challenges
Maternal ARV Use in Pregnancy over Time – Canadian Perinatal HIV Surveillance Program

Courtesy of Dr. Jason Brophy
Maternal ARV Use in Pregnancy over Time – Botswana Research Data

% of Women on ART from Conception

Before 2012
PMTCT: WHO Option A
- ZDV if CD4 >250
- ZDV/3TC/NVP if CD4 <250

2012-2016
PMTCT: WHO Option B
- TDF/FTC/EFV (life-long if CD4 <350)
HEU Health Disparities – *Etiology Matters*

- HIV
- Maternal Health
- Low Birth Weight
- More Household Pathogens
- Food Insecurity
- Poor Access to Healthcare
- Preterm Delivery
- Altered Gut Microbiome
- Poor Passive Immunity
- Maternal co-Infections
- Pro-inflammatory in utero Environment
- Infant Feeding Practices
- Poor Sanitation
HEU Health Disparities – *Etiology Matters*

- Poor Passive Immunity
- Poor Sanitation
- Preterm Delivery
- Food Insecurity
- Maternal Health
- ARVs HIV
- Infant Feeding Practices
- More Household Pathogens
- Low Birth Weight
- Poor Access to Healthcare
- Pro-inflammatory in utero Environment
No thanks!

We are too busy
Establishing an HEU Child Outcomes Agenda

Maternal-Child Health Care Infrastructure

Community Advocacy

Ministry of Health & Public Health Policy

Bench Research

Clinical Research
AIDS is clearly a disaster, effectively wiping out the development gains of the past decades and sabotaging the future.

- President Nelson Mandela, South Africa
It always seems impossible until it is done – Nelson Mandela
We invite you to join us to continue the collaborative conversation around HIV-exposed uninfected (HEU) child health outcomes at the 3rd HEU Child Workshop.

CIPHER is excited to be co-sponsoring the Workshop with WHO and PHACS. This International AIDS Society (IAS) Conference satellite symposium will be held on Sunday, 23 July 2017 from 10:15am until 2:30pm at the Palais des Congrès, 2 Place de la Porte, Maillot, Paris.
Acknowledgements

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