Surviving and thriving?
Outcomes of children exposed to HIV in rural Zimbabwe

Ceri Evans
Wellcome Trust Clinical PhD Fellow

@Ceri_Evans
No conflicts to disclose
Children who are exclusively breastfed for the first 6 months of life are 14 times more likely to survive than non-breastfed children.

It's a baby's first immunization.

#BREASTFEEDING
Modern era
Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial

- Two rural districts in Zimbabwe
- Interventions started in pregnancy
- **Primary outcomes**: Linear growth and haemoglobin at 18 mo
- **Substudy at 24 mo of age**: early child development
Delivery of the trial

- In partnership with Ministry of Health and Child Care (MoHCC)
  - Village health workers

- Key messages
  - Exclusive breastfeeding

- MoHCC services
  - Antenatal care, immunisations, family planning, PMTCT

- Trial did not deliver ART
  - Coverage 80%
5270 pregnant women
5270 pregnant women

-139 exits/LTFU
-365 miscarriages/stillbirths
-4 maternal deaths
-114 HIV-unknown
+82 multiple pregnancies
5270 pregnant women

738 Live births exposed to HIV

3989 Live births not exposed to HIV
## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>HIV-positive (N=726)</th>
<th>HIV-negative (N=3937)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; mean (SD)</td>
<td>29.2 (6.3)</td>
<td>25.6 (6.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MUAC, cm; mean (SD)</td>
<td>26.2 (2.9)</td>
<td>26.4 (3.1)</td>
<td>0.17</td>
</tr>
<tr>
<td>Completed schooling, years; mean (SD)</td>
<td>9.1 (2.1)</td>
<td>9.6 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lowest wealth quintile</td>
<td>27%</td>
<td>19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Highest wealth quintile</td>
<td>16%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>50%</td>
<td>49%</td>
<td>0.73</td>
</tr>
<tr>
<td>Birth weight, kg; mean (SD)</td>
<td>2.99 (0.5)</td>
<td>3.08 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Breastfeeding duration, mo; mean (SD)</td>
<td>15 (4)</td>
<td>16 (3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## HIV disease severity and treatment

<table>
<thead>
<tr>
<th>CD4 count in pregnancy, cells/uL; mean (SD)</th>
<th>474 (221)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 count &lt;200 cells/uL</td>
<td>8%</td>
</tr>
<tr>
<td>Co-trimoxazole prophylaxis during pregnancy</td>
<td>55%</td>
</tr>
<tr>
<td>Antiretroviral therapy during pregnancy</td>
<td>81%</td>
</tr>
<tr>
<td>Tenofovir-based</td>
<td>67%</td>
</tr>
<tr>
<td>Zidovudine-based</td>
<td>20%</td>
</tr>
<tr>
<td>Other/unknown regimen</td>
<td>14%</td>
</tr>
</tbody>
</table>
Children who are HEU – SURVIVING AND THRIVING?

HIV-exposed uninfected children through 18mo
Survival
5270 pregnant women

738 Live births exposed to HIV
51/738 died 7%

3989 Live births not exposed to HIV
198/3989 died 5%
aHR 1.41 (95% CI 1.02-1.93)

*Adjusted for trial arm
### Number at risk

<table>
<thead>
<tr>
<th>Analysis time (days)</th>
<th>HIV-exposed</th>
<th>HIV-unexposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>738</td>
<td>3989</td>
</tr>
<tr>
<td>50</td>
<td>687</td>
<td>3783</td>
</tr>
<tr>
<td>100</td>
<td>678</td>
<td>3747</td>
</tr>
<tr>
<td>150</td>
<td>674</td>
<td>3721</td>
</tr>
<tr>
<td>200</td>
<td>673</td>
<td>3695</td>
</tr>
<tr>
<td>250</td>
<td>671</td>
<td>3685</td>
</tr>
<tr>
<td>300</td>
<td></td>
<td>1751</td>
</tr>
<tr>
<td>350</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>450</td>
<td></td>
<td></td>
</tr>
<tr>
<td>500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>550</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*aHR 1.41 (95%CI 1.02-1.93)\* Adjusted for trial arm

*P = 0.04*
5270 pregnant women

738
Live births exposed to HIV

51/738 died
7%

3989
Live births not exposed to HIV

198/3989 died
5%
Children who are HEU – SURVIVING AND THRIVING?

HIV-exposed uninfected children through 18mo
Children who are HEU – SURVIVING AND THRIVING?
HIV transmission
5270 pregnant women

- 738 Live births exposed to HIV
  - 51/738 died (7%)

- 3989 Live births not exposed to HIV
  - 198/3989 died (5%)

594 HIV-negative (89%)
52 unknown (8%)
22 HIV-positive (3%)
## Sensitivity analysis

<table>
<thead>
<tr>
<th>Assumption about HIV-unknown infants</th>
<th>Assumed transmission of unknown</th>
<th>Overall transmission rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same transmission as known</td>
<td>4%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Exposed to ART 2.7% Not exposed ART 11%</td>
<td>6%</td>
<td>4.3%</td>
</tr>
<tr>
<td>2x higher than known group</td>
<td>8%</td>
<td>4.6%</td>
</tr>
<tr>
<td>3x higher</td>
<td>12%</td>
<td>5.3%</td>
</tr>
<tr>
<td>5x higher</td>
<td>20%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Pre-ART ZVITAMBO trial</td>
<td>27%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>
5270 pregnant women

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Live births exposed to HIV

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Children who are HEU – SURVIVING AND THRIVING?
Children who are HEU – SURVIVING AND THRIVING?

ALIVE, HIV-FREE

ALIVE, HIV-POSITIVE/UNKNOWN

DIED
5270 pregnant women

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Live births exposed to HIV

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5270 pregnant women

738
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594 assessed at 18 months

3686 assessed at 18 months
Growth and development
Stunting

The Global Crisis You’ve Never Heard Of: Stunting

Chronic malnutrition affects children’s bodies and brains and has received far too little attention for too long.
Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial

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Sanitation Hygiene Infant Nutrition Efficacy (SHINE) trial

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Prevalence of stunting (non-IYCF arms)

- HEU: 51%
- HIV-unexposed: 34%
Absolute difference 16% (95% CI 10, 22)

RR 1.46 (95% CI 1.28, 1.67), $P < 0.001$
Children who are HEU – SURVIVING AND THRIVING?
Children who are HEU – SURVIVING AND THRIVING?

ALIVE, HIV-FREE

ALIVE, HIV-POSITIVE/UNKNOWN

DIED
Children who are HEU – SURVIVING AND THRIVING?

- Alive, HIV-free, non-stunted
- Alive, HIV-free, stunted
- Alive, HIV-positive/unknown
- Died
Severe stunting
RR 1.60 (1.15, 2.21)

Underweight
RR 1.51 (1.12, 2.04)

Wasting
RR 1.52 (0.78, 2.97)

Microcephaly
RR 1.74 (1.18, 2.56)
5270 pregnant women

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Live births exposed to HIV

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Live births not exposed to HIV

205 evaluated at 24 months

1175 evaluated at 24 months
Malawi Developmental Assessment Tool (MDAT)
## Malawi Developmental Assessment Tool (MDAT)

<table>
<thead>
<tr>
<th>HEU Mean (SD)</th>
<th>HIV-unexposed Mean (SD)</th>
<th>Difference (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>90.6 (8.7)</td>
<td>92.4 (9.1)</td>
<td>-1.6 (-2.7, -0.5)</td>
<td>0.005</td>
</tr>
</tbody>
</table>
Malawi Developmental Assessment Tool (MDAT)

<table>
<thead>
<tr>
<th>MDAT outcome</th>
<th>HEU</th>
<th>HIV-unexposed</th>
<th>Mean difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean score (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gross motor</td>
<td>23.0 (2.9)</td>
<td>23.7 (3.1)</td>
<td>-0.6 (-0.9, -0.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fine motor</td>
<td>22.8 (2.9)</td>
<td>23.2 (2.5)</td>
<td>-0.4 (-0.8, 0.0)</td>
<td>0.06</td>
</tr>
<tr>
<td>Language</td>
<td>20.5 (3.9)</td>
<td>21.4 (4.2)</td>
<td>-0.7 (-1.3, -0.2)</td>
<td>0.006</td>
</tr>
<tr>
<td>Social</td>
<td>24.3 (2.3)</td>
<td>24.2 (2.3)</td>
<td>0.1 (-0.2, 0.4)</td>
<td>0.65</td>
</tr>
</tbody>
</table>
MacArthur Bates Communicative Development Inventories

Mrpliskin/Getty Images
(http://discovermagazine.com/2017/nov/my-forgotten-language)
<table>
<thead>
<tr>
<th>HEU Mean (SD)</th>
<th>HIV-unexposed Mean (SD)</th>
<th>Difference (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>57.9 (19.2)</td>
<td>61.3 (18.8)</td>
<td>-3.3 (-6.1, -0.5)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Children who are EXCLUSIVELY BREASTFED for the first 6 months of life are 14 times more likely to survive than NON-BREASTFED CHILDREN. #BREASTFEEDING

HIV
- HIV Envelope
- HIV Capsid
- HIV Enzymes
- HIV RNA
- HIV Glycoproteins
Maternal HIV +/- ART exposure

- HIV
- Immune activation / inflammation
- ART toxicity

Common risk factors
- Infections
- Toxins
- Birth outcomes
- Breastfeeding
- Maternal morbidity and mortality
- Maternal mental health

Mechanisms
- Infections
- Microbiome
- Anaemia
- Malnutrition
- Inflammation
- Growth hormone axis
- Mother-child interaction
- Brain development

Outcome
Poor childhood growth & development

Adapted from Wedderburn CJ, Evans C et al.
Collaborators and donors

Zimbabwe Ministry of Health and Child Care
Goldberg Mangwadu, Ancikaria Chigumira, Cynthia Chasokela

Zvitambo Institute for Maternal and Child Health Research
Mduduzi Mbuya (currently GAIN), Robert Ntozini, Naume Tavengwa, Kuda Mutasa, Florence Majo, Bernard Chasekwa, Virginia Sauramba, Phillipa Rambanepasi

Johns Hopkins Bloomberg School of Public Health Jean Humphrey, Lawrence Moulton
Queen Mary University of London Andrew Prendergast, Ceri Evans
Cornell University Rebecca Stoltzfus
University of Liverpool Melissa Gladstone, Jaya Chandna
University of British Columbia Amee Manges
George Washington University James Tielsch
Middlebury College John Maluccio
University of Michigan Andrew Jones