Background

• Children born to HIV-infected mothers, who remain HIV-uninfected have a higher risk of morbidity and mortality than children born to HIV-uninfected mothers.

• The mechanisms underlying this relationship are multifactorial, including: (1) HIV-exposed uninfected (HEU) children have impaired immune responses compared to HIV-uninfected uninfected children (HUU) and (2) indirect effects, such as increased poverty, parental mortality, and exposure to infectious pathogens.

• The impact of age and breastfeeding on the relationship between HIV exposure and morbidity remains unclear.

Methods (cont’d)

Primary outcomes of interest:

• (1) Death
• (2) Hospitalizations: all-cause and non-malarial
• (3) Severe febrile illness/pneumonia: composite of sepsis syndromes (septic shock and/ or septic appearance) or severe pneumonia (pneumonia with severe respiratory distress or ill appearance)
• (4) Malaria: positive blood smear and fever
• (5) Severe malnutrition: weight-for-height z-score<-3 SD and/or kwashiorkor and/or marasmus

Methods

• Stratified analysis of 186 HEU (257 person years) and 389 HUU (542 person years) children in Tororo, Uganda, who were participating in a trial examining the effect of antimarial chemoprevention.

• Children were randomized to trimethoprim-sulfamethoxazole, dihydroartemisinin-piperaquine, sulfadoxine-pyrimethamine, or no chemoprevention.

• Children were seen in a dedicated study clinic for children who were HIV-exposed uninfected children (HEU) and HIV-uninfected have a markedly higher risk of all non-malarial morbidity compared to breastfeeding HEU. Whereas, there is no difference between non-malarial morbidity outcomes among breastfeeding HEU and HUU.

• These data suggest that early cessation of breastfeeding may at least partially account for the excess risk of non-malarial morbidity among HEU.

• Age: The higher risk of non-malarial morbidity outcomes declined with increasing age. This may be due to maturation of the immune system of HIV-exposed uninfected children.

• Mortality and Breastfeeding in HIV-Exposed Uninfected Children in Uganda

• At enrollment 85% of HIV-infected mothers reported taking trimethoprim-sulfamethoxazole and 38% taking combination anti-retroviral therapy.

• At 6 months, HIV-exposed uninfected children were initially counseled to stop breastfeeding at 6 months. Midway through the trial the Uganda Ministry of Health guidelines changed and HIV-exposed-infected mothers were counseled to breastfeed their Children for 2 years. HIV-uninfected uninfected children were counseled to breastfeed for up to two years or beyond.

• The higher risk of non-malarial morbidity among HEU compared to HUU had a higher risk of death (RR 13.5, 95% CI: 1.12-167.3, p=0.04), adjusting for age, months, weight, breastfeeding, and chemoprevention.

• The proportion of children breastfeeding differed between HEU and HUU children: at 6 months 82.5% vs. 99.5%, (p<0.001), at 12 months 29.4% vs. 98.6%, (p<0.001), and at 24 months 0 % vs. 24.7% (p<0.001), respectively.

• There was a difference in gender and wealth level household between HIV-exposure groups.

• At enrollment 88% of HIV-infected children reported taking trimethoprim-sulfamethoxazole and 38% taking combination anti-retroviral therapy.

• The mechanisms underlying this relationship are multifactorial, including: (1) HIV-exposed uninfected (HEU) children have impaired immune responses compared to HIV-uninfected uninfected children (HUU) and (2) indirect effects, such as increased poverty, parental mortality, and exposure to infectious pathogens.

• The impact of age and breastfeeding on the relationship between HIV exposure and morbidity remains unclear.

Hypothesis

• Early weaning among HIV-exposed uninfected children may account for the excess risk of mortality and morbidity associated with HIV-exposure.

Effects of Breastfeeding on Mortality and Morbidity in HIV-Exposed Uninfected Children in Uganda

Results

• Methods (cont’d)

Baseline Characteristics

• Age-stratified analysis was performed with three HIV-exposure and breastfeeding risk categories. Due to lack of person-time, HUU non-breastfeeding children were excluded from the analysis for the 12-24 month age-group.

• The incidence of malaria from 6-24 months of age in both HEU and HUU children was 4.5 per person year and 2.8 per person years respectively, p<0.001.

• HEU children had a 37% decreased risk of malaria compared to HUU children (RR 0.63, 95% CI: 0.53-0.73, p<0.001).

• Mortality and Non-Malarial Morbidity

• 7 deaths among HEU and 1 death among HUU. HEU compared to HUU had a higher risk of death (RR 13.5, 95% CI: 1.12-167.3, p=0.04), adjusting for age, months, weight, breastfeeding, and chemoprevention

• Results (cont’d)

Table 1: Associations between HIV exposure and breastfeeding status with morbidity outcomes among infants 6-11 months of age

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events</th>
<th>Incidenceb</th>
<th>RR (95% CI) c</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEU not breastfeeding</td>
<td>(289 PY of follow-up)</td>
<td>(43 PY of follow-up)</td>
<td>(48 PY of follow-up)</td>
<td></td>
</tr>
<tr>
<td>All hospitalizations</td>
<td>6</td>
<td>0.031</td>
<td>0.047 (0.003-0.997)</td>
<td>0.046</td>
</tr>
<tr>
<td>Non-malarial hospitaliza</td>
<td>2</td>
<td>0.011</td>
<td>0.023 (0.000-0.997)</td>
<td>0.021</td>
</tr>
<tr>
<td>Severe febrile illnesses</td>
<td>17</td>
<td>0.09</td>
<td>0.134 (0.044-0.407)</td>
<td>0.65</td>
</tr>
<tr>
<td>Severe diarrhea</td>
<td>11</td>
<td>0.056</td>
<td>0.078 (0.017-0.38)</td>
<td>0.22</td>
</tr>
<tr>
<td>Severe malnutrition</td>
<td>3</td>
<td>0.016</td>
<td>0.023 (0.000-0.997)</td>
<td>0.048</td>
</tr>
</tbody>
</table>

Table 2: Associations between HIV exposure and breastfeeding status with morbidity outcomes among children 12-24 months of age

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events</th>
<th>Incidenceb</th>
<th>RR (95% CI) c</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEU not breastfeeding</td>
<td>(285 PY of follow-up)</td>
<td>(42 PY of follow-up)</td>
<td>(48 PY of follow-up)</td>
<td></td>
</tr>
<tr>
<td>All hospitalizations</td>
<td>24</td>
<td>0.062</td>
<td>0.129 (0.04-0.37)</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-malarial hospitaliza</td>
<td>14</td>
<td>0.053</td>
<td>0.032 (0.013-0.206)</td>
<td>0.6</td>
</tr>
<tr>
<td>Severe febrile illnesses</td>
<td>13</td>
<td>0.05</td>
<td>0.127 (0.02-0.64)</td>
<td>0.07</td>
</tr>
<tr>
<td>Severe diarrhea</td>
<td>9</td>
<td>0.011</td>
<td>0.023 (0.000-0.997)</td>
<td>0.05</td>
</tr>
<tr>
<td>Severe malnutrition</td>
<td>14</td>
<td>0.054</td>
<td>0.181 (0.020-1.30)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Results (cont’d)

Morbidity Due to Malaria

• The incidence of malaria from 6-24 months of age in both HEU and HUU children was 4.5 per person year and 2.8 per person years respectively, p<0.001.

• HEU children had a 37% decreased risk of malaria compared to HUU children (RR 0.63, 95% CI: 0.53-0.73, p<0.001).

Conclusions

• In this cohort, HEU have a higher risk of non-malarial morbidity and mortality compared to HUU children, and this association is moderated by breastfeeding status and age.

• Among children 6-11 months, non-breastfeeding HEU have a markedly higher risk of all non-malarial morbidity compared to breastfeeding HEU. Whereas, there is no difference between non-malarial morbidity outcomes among breastfeeding HEU and HUU.

• These data suggest that early cessation of breastfeeding may at least partially account for the excess risk of non-malarial morbidity among HEU.

• Age: The higher risk of non-malarial morbidity outcomes declined with increasing age. This may be due to maturation of the immune system of HIV-exposed uninfected children.

• Among breastfeeding children 12-24 months of age, only the risk of severe malnutrition was higher in HEU compared to HUU.

• Mortality: The lower risk of malaria among HEU compared to HUU may be due to differences in chemoprophylaxis adherence, as HIV-infected women may receive their child’s risk of infection to be higher and are more accustomed to taking medications.