Mortality among HIV-positive postpartum women with high CD4 cell counts in Zimbabwe

John W. Hargrovea, Jean H. Humphreymb,c, for the ZVITAMBO Study Group

AIDS 2010, 24:000–000

Keywords: antiretroviral therapy, CD4, women

There is increasing evidence that starting HAART at higher CD4 cell counts reduces mortality and delays development of AIDS [1]. In a recent analysis [2], mortality was compared according to CD4 cell count at HAART initiation among adult patients in 18 cohorts in the United States and Europe. In this analysis, deferring HAART until CD4 cell count reached 251–350 cells/\(\mu\)l was associated with a 28% [95% confidence interval (CI) 4–57] higher rate of AIDS and death compared with starting when CD4 cell count was 351–450 cells/\(\mu\)l, but initiating HAART at CD4 cell counts higher than 351–450 cells/\(\mu\)l conferred no significant benefit. The authors concluded that 350 cells/\(\mu\)l should be the minimum threshold for HAART initiation.

We enrolled a cohort of 14,110 postpartum women within 96 h of delivery in Zimbabwe between 1997 and 2000 and followed them for up to 24 months as part of a vitamin A supplementation trial [3]. HAART was not available in the public sector during the time of the trial. At baseline, 4,595, 9,562, and 53 women tested HIV-positive, negative and indeterminate, respectively, and CD4 cells were counted for HIV-positive women and a representative subsample of 721 HIV-negative women. At baseline, CD4 cell count was 436 cells/\(\mu\)l [95% confidence interval (CI) 428–444] and 782 cells/\(\mu\)l [95% CI 759–805] among the HIV-positive and HIV-negative women, respectively. Cause of death was determined from medical records, if available, or by review of verbal autopsy by the study gynecologist, who was masked to treatment group and HIV status; multiple causes were recorded and not ranked. Deaths due to injuries following accidents were excluded from this analysis. As expected, mortality was strongly associated with HIV status (HIV-positive women were 14.2 (8.9–22.6) and 54.1 (13.3–220) times more likely to die in the first and second year postpartum, respectively, compared with HIV-negative women, and among infected women, mortality risk steadily increased with decreasing baseline CD4 cell count [4]. Cause-specific mortality was higher among HIV-positive compared with HIV-negative women for all causes except hypertensive disorders and injuries; risk ratios were highest for HIV-associated causes (e.g., tuberculosis, pneumonia, meningitis), but HIV-positive women were also significantly more likely to die of obstetric causes (e.g., puerperal sepsis, uterine hemorrhage, pelvic inflammatory disease).

In a new analysis, we stratified HIV-positive women into six CD4 cell count groups (<200, 200 < 400, 400 < 600, 600 < 800, 800 < 1000, and >1000 cells/\(\mu\)l). In Cox models adjusting for maternal age, education and marital status, delivery method (caesarean vs. other), survival of a previous child, upper arm circumference, and vitamin A treatment, we compared the 2-year mortality risk of HIV-positive women in each CD4 cell count range with that of all the HIV-negative women enrolled in the trial. Expectedly, the hazard ratio was extremely high for

---

aDST/NRF Centre of Excellence in Epidemiological Modelling and Analysis (SACEMA), Stellenbosch, South Africa, bThe Johns Hopkins Bloomberg School of Public Health, Department of International Health, Baltimore, MD, USA, and cZVITAMBO Project, Harare, Zimbabwe.

Correspondence to Jean H. Humphrey, ZVITAMBO Project, #1 Borrowdale Rd, Borrowdale, Harare, Zimbabwe.

Tel: +263 4 850 732; fax: +263 4 850 734; e-mail: jhumphrey@zvitambo.co.zw

Received: 22 October 2009; revised: 17 November 2009; accepted: 17 November 2009.

DOI:10.1097/QAD.0b013e328335749d

ISSN 0269-9370 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins
HIV-positive women in the lowest CD4 cell strata and sharply declined for each higher CD4 cell count stratum between less than 200 and 400–600 cells/µl (Fig. 1). Unexpectedly, the risk of death remained significantly higher for HIV-positive women across the entire CD4 cell distribution up to 1000 cells/µl, compared with HIV-negative women. Among all HIV-positive women with CD4 counts higher than 600 cells/µl [mean 803 cells/µl (95% CI 790–817), slightly higher than the mean concentration of negative women], mortality between delivery and 24 months postpartum was 6.2 (95% CI: 3.2–11.9) times higher than that in HIV-negative women. Over the first 6 months postpartum, the corresponding hazard ratio was similar at 5.8 (95% CI: 2.0–17.1) (Table 1).

Among the HIV-positive women who died, we examined cause of death among those whose baseline CD4 cell count was more than 280 cells/µl. This cut-off was chosen because the mean increase in CD4 cell count between baseline and 6 weeks due to normalizing hydration postpartum among study women was 70 cells/µl (unpublished data), so 280 cells/µl at delivery approximated those women whose ‘true’ CD4 cell count was more than 350 cells/µl and would, therefore, not be HAART-eligible by current guidelines. Among this group of women, there were 71 deaths: seven died of unknown causes and two died of injuries. Of the remaining 62 deaths, 31 (50%) were associated with tuberculosis, 15 (24%) with nonobstetric infectious conditions (e.g., acute respiratory infection, meningitis), three (5%) with direct obstetric infectious causes (e.g., puerperal sepsis), three (5%) with malaria, and 10 (16%) with a chronic medical condition (e.g., heart or kidney disease).

These data suggest that (unlike nonpostpartum adults in developed countries) for postpartum women in developing country settings, HIV infection is associated with substantial mortality even in its very early stages. This might be due to the additional morbidity associated with pregnancy [5], the additional metabolic demands of breastfeeding [6,7] (90% of HIV-positive women in ZVITAMBO breastfed to ≥6 months), the physiologic immune suppression of pregnancy and the early postpartum period [8], or the confluence of all these factors. We have no formal evidence that the observed excess mortality would have been amenable to prevention by early antiretroviral treatment. However, given the beneficial effect of HAART on tuberculosis [9] and assuming HAART may also prevent or reduce case fatality of other infectious diseases, an estimated 50–90% of the deaths observed among these HIV-positive women with high CD4 cell counts in this study may have been averted by early HAART initiation.

![Fig. 1. Hazard ratios for mortality between delivery and 24 months postpartum among HIV-positive compared with HIV-negative mothers according to CD4 cell count soon after delivery.](image)

Hazard ratios are taken from Cox models adjusting for maternal age, education and marital status, delivery method (caesarean vs. other), survival of a previous child, upper arm circumference and vitamin A treatment.

Table 1. Deaths among HIV-positive and negative mothers in the first 24 months postpartum as a function of CD4 cell count shortly after delivery.

<table>
<thead>
<tr>
<th>Group</th>
<th>Deaths</th>
<th>Person-years</th>
<th>Mortality rate per 1000 person-years</th>
<th>Hazard Ratio (95% CI) from Cox model adjusting for age</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HIV-negative</td>
<td>22</td>
<td>11681</td>
<td>1.9</td>
<td>Reference</td>
</tr>
<tr>
<td>HIV-positive women by CD4 cells/µl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;200</td>
<td>109</td>
<td>756</td>
<td>144.2</td>
<td>54.0 (33.4–87.5)</td>
</tr>
<tr>
<td>200 &lt; 400</td>
<td>53</td>
<td>1808</td>
<td>29.3</td>
<td>13.2 (8.0–21.8)</td>
</tr>
<tr>
<td>400 &lt; 600</td>
<td>20</td>
<td>1598</td>
<td>12.5</td>
<td>5.4 (3.4–10.1)</td>
</tr>
<tr>
<td>600 &lt; 800</td>
<td>11</td>
<td>751</td>
<td>14.6</td>
<td>7.3 (3.6–15.1)</td>
</tr>
<tr>
<td>800 &lt; 1000</td>
<td>3</td>
<td>299</td>
<td>10.0</td>
<td>8.1 (1.6–17.1)</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>1</td>
<td>171</td>
<td>5.8</td>
<td>3.0 (0.4–22.2)</td>
</tr>
</tbody>
</table>

CI, confidence interval.
This intervention would also benefit their infants. Recent studies have demonstrated that provision of HAART to women with CD4 cell count 350–500 cells/µl from pregnancy up to 6 months postpartum substantially reduces vertical transmission without adverse effects [10–13]. However, because breastfeeding cessation at 6 months (at the time when ARV treatment is stopped) results in high rates of infant gastroenteritis and mortality [14], continuing maternal HAART and breastfeeding would likely improve infant HIV-free survival.

Early HAART for pregnant women in developing countries may even benefit their societies. Recent mathematical modeling has suggested that early HAART significantly reduces HIV transmission and, if started soon enough after sero-conversion, may hasten the end of the HIV epidemic [15].

Acknowledgements

The ZVITAMBO project was supported by the Canadian International Development Agency (CIDA) (R/C Project 690/M3688); United States Agency for International Development (USAID) (cooperative agreement number HRN-A-00-97-00015-00 between Johns Hopkins University and the Office of Health and Nutrition—USAID); a grant from the Bill and Melinda Gates Foundation, Seattle Washington, USA; the SARA Project operated by the Academy for Educational Development, Washington, District of Columbia, USA; and the Department for International Development (DFID), United Kingdom: ‘Saving Maternal and Newborn Lives in the Context of HIV and AIDS in Zimbabwe’ grant #AG 4996 (MIS code 073-555-013 CA 007).

The authors thank Brian Williams for statistical and conceptual advice. The donors of ZVITAMBO had no involvement in the collection, analysis or interpretation of the data.

The Medical Research Council of Zimbabwe, the Medicines Control Authority of Zimbabwe, the Johns Hopkins Bloomberg School of Public Health Committee on Human Research, and the Research Institute of the McGill University Health Centres Research Ethics Committee approved the study protocol. Clinical trials.gov identifier is NCT00198718.

Members of the ZVITAMBO Study Group, in addition to the named authors are Henry Chidawanyika, Peter J. Iliff, Agnes Mahonva, Florence Majo, Lucie Malaba, Edmore Marinda, Michael Mbizvo, Lawrence H. Moulton, Kuda Mutasa, Faith Mzengeza, Kusum J. Nathoo, Mary Ndlovu, Robert Ntozini, Ellen G. Piwoz, Lidia Propper, Phillipa Rambanepasi, Andrea Ruff, Naume Tavengwa, Brian J. Ward, Lynn S. Zijenah, and Clare Zunguza.

There are no conflicts of interest.

References

11. Chasela C. Giving ART to mothers or ARV prophylaxis to infants during breastfeeding equally effective at reducing HIV transmission: Nutrition (BAN) Study. 5th IAS Conference; 2009; Lilongwe, Malawi.
Dear Author,

During the preparation of your manuscript for typesetting, some queries have arisen. These are listed below. Please check your typeset proof carefully and mark any corrections in the margin as neatly as possible or compile them as a separate list. This form should then be returned with your marked proof/list of corrections to the Production Editor.

### QUERY:  to be answered by AUTHOR/EDITOR

<table>
<thead>
<tr>
<th>QUERY NO.</th>
<th>QUERY DETAILS</th>
<th>RESPONSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;AQ1&gt;</td>
<td>Please update Refs [10,14].</td>
<td></td>
</tr>
</tbody>
</table>