



# Impact of Highly Active Antiretroviral Therapy versus Short Course Zidovudine on Longitudinal Growth of HIV-Exposed Uninfected Breast Fed Infants, Botswana

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## Abstract

**Background:** HAART is a highly effective strategy for preventing mother-to child HIV transmission (PMTCT), but may lead to lower birth weight infants. Longitudinal effects of *in utero* HAART exposure on infant growth have not been reported.

**Methods:** The Mashi and Mma Bana PMTCT intervention trials enrolled HIV-infected pregnant women (regardless of CD4) at 4 sites in southern Botswana. Infant weight and length were evaluated at birth and monthly for six months. Only breastfed (BF), HIV-uninfected infants born  $\geq 37$  weeks and exposed *in utero* to at least 2 weeks of either HAART or ZDV were included in the current analysis. Infants in the HAART-exposed group received ZDV for 1 month. Infants in the ZDV-exposed group received 6 months of ZDV-prophylaxis during BF. Gender-based weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length (WLZ) z-scores were calculated using 2006gWHO Child Growth Standards. Mean z-scores were compared using the student's t-test and analysis of response profiles.

**Results:** 437 ZDV-exposed infants from Mashi and 592 HAART-exposed infants from Mma Bana were included. Median maternal baseline CD4 counts were 393 cells/mm<sup>3</sup> and 337 cells/mm<sup>3</sup> respectively, and demographics were generally similar between cohorts. Median *in utero* ZDV exposure was 5.7 weeks (range 2.0, 10.9 weeks), and median *in utero* HAART exposure was 12.1 weeks (range 2.6, 22.3 weeks). Median birth weights were 3.1 kg in ZDV-exposed and 3.0 kg in HAART-exposed ( $p < .001$ ), with significantly lower mean WAZ, LAZ, and WLZ among HAART-exposed infants ( $p = .001$ ,  $p = .02$ , and  $p = .007$ , respectively). By 3 months, median weight no longer differed by exposure group, and weight remained similar through 6 months. Mean WAZ differed over time by exposure group ( $p < .001$ ) (Figure 1). LAZ remained lower in the HAART-exposed group through 6 months, but WLZ improved significantly over time compared with ZDV-exposed infants ( $p < .001$ ) (Figures 2,3). The proportions of infants with z-scores more than 2 standard deviations below the mean were not different between exposure groups.

**Conclusions:** *In utero* exposure to HAART was associated with lower birth weight compared with ZDV exposure alone, but this difference resolved by 3 months. LAZ remained lower over time in the HAART-exposed group. Longer-term developmental comparisons are planned, but these results demonstrate a reassuring early correction of the birth weight reduction presumed to be associated with *in utero* HAART exposure.

## Background

The World Health Organization (WHO) 2009 revised recommendations for prevention of mother-to-child transmission of HIV (PMTCT) recommend maternal HAART as a potential PMTCT strategy for all HIV-infected women, regardless of HIV disease stage. Some (but not all) previous studies have demonstrated significantly lower birth weights among HAART-exposed infants, and the impact of HAART on the longitudinal growth of infants is unknown. We therefore evaluated the longitudinal growth impact of *in utero* HAART exposure compared to short course ARV's among full-term HIV-exposed uninfected infants.

## Methods

- Mother-infant pairs were included in this analysis if:
  - The mother was enrolled in the Mashi Study and received ZDV during pregnancy +/- single dose nevirapine during labor or
  - The mother was enrolled in the Mma Bana Study
    - all women received HAART (abacavir/ZDV/3TC or lopinavir/ritonavir/ZDV/3TC or nevirapine/ZDV/3TC)
  - The mother received either ZDV or HAART for a minimum of 14 days prior to delivery.
  - The infant was the product of a live, singleton birth occurring at 37-weeks gestational age or greater.
  - The infant remained HIV-negative through 6 months of age based on a qualitative HIV DNA-PCR assay
- Infants were evaluated at birth and monthly through the first six months of life with weight and recumbent length measured at each visit.
- Using WHO 2006 growth standards derived from The Multicentre Growth Reference Study, infant weight and length data was used to calculate gender based weight-for age (WAZ), length-for-age (LAZ) and weight-for-length (WLZ) z-scores at birth and monthly through 6 months of life.
  - A student's t-test was used to compare mean WAZ, LAZ and WLZ between the HAART-exposed infants and the ZDV exposed infants.
  - Analysis of response profile was employed to statistically compare the sequence of mean WAZ, LAZ and WLZ over the first six months of life between the two exposure groups.

## Findings

**Baseline Characteristics by exposure:** Maternal age and parity similar between groups. Baseline median HIV-1 log<sub>10</sub> copies was 4.34 for Mashi women and 4.19 for Mma Bana women ( $p = 0.04$ ) and median CD4 was 393 cells/ $\mu$ L for Mashi women and 337 cells/ $\mu$ L for Mma Bana women ( $p = < 0.001$ ).

### Growth patterns by exposure:

1. At delivery, HAART-exposed infants had significantly lower WAZ than infants exposed to short-course ZDV ( $p = < 0.001$ ).
  - By 3 months, mean WAZ were similar (Figure 1).
2. Mean LAZ increased in a similar manner between the two exposure groups over time. However, HAART-exposed infants had an overall lower mean LAZ throughout the first six months of life compared with ZDV-exposed infants ( $p = < 0.001$ ) (Figure 2).
3. Mean WLZ between exposure groups was not parallel over time ( $p = < 0.001$ ), with HAART exposed infants having a steeper mean WLZ trajectory in the first two months of life (Figure 3).

## Conclusions

• ***In utero* HAART exposure resulted in modest birth weight reduction compared with short-course ZDV, but this difference was no longer present by 3 months of life**

→ slightly lower median CD4 cell count may have also contributed to birth weight differences

• ***In utero* HAART exposure was associated with lower length-for-age z-scores throughout the first 6 months of life, but greater weight-for-length z-scores starting at one month of age than *in utero* ZDV exposure**

• **The early correction of birth weight differences among HAART-exposed infants is reassuring for programs utilizing maternal HAART for treatment and PMTCT**

Figure 1 Mean Infant WAZ From Birth by HAART-exposure vs ZDV-exposure

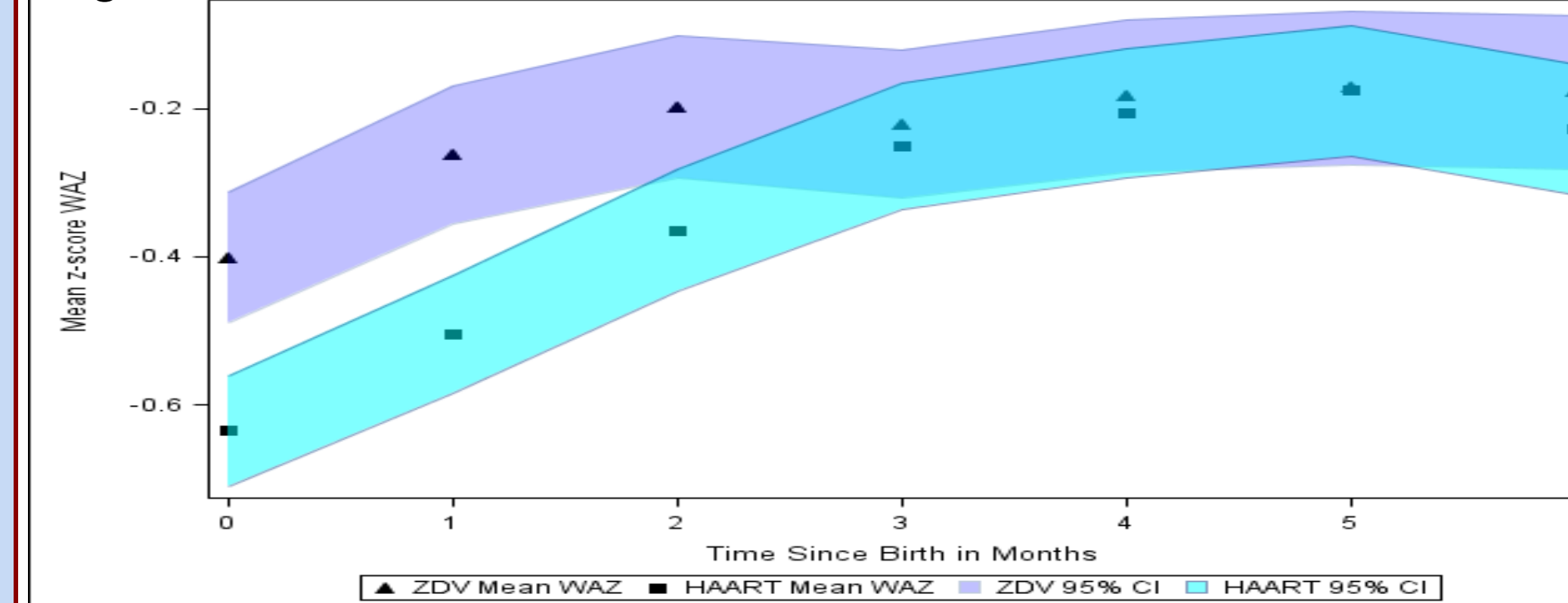


Figure 2 Mean Infant LAZ From Birth by HAART-exposure vs ZDV-exposure

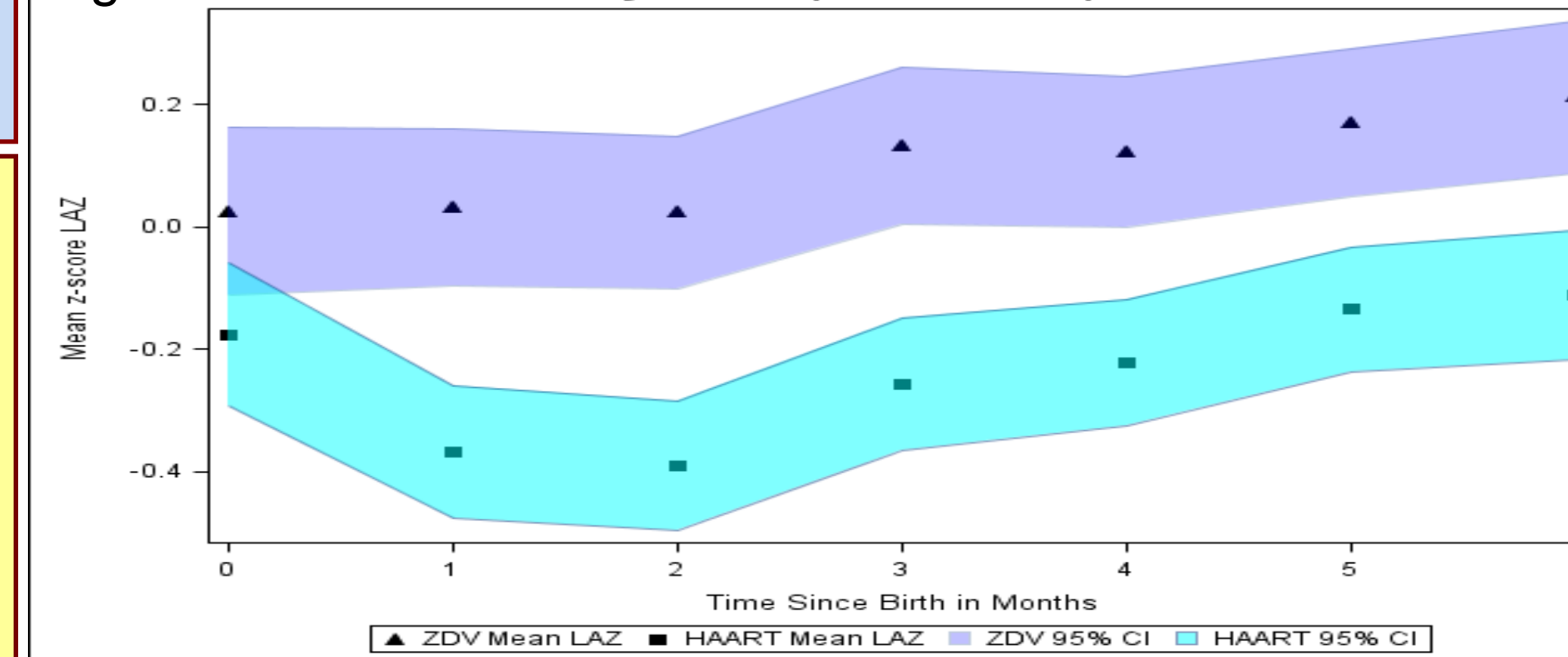


Figure 3 Mean Infant WLZ From Birth by HAART-exposure vs ZDV-exposure

