Outcomes in infants born to HIV-infected mothers receiving long-term ART in the DART trial 2004-2009

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ABSTRACT

Background: Five times more women were initiated on stavudine-based ART (ABT) mainly with zidovudine/tenofovir during the DART trial in Uganda compared to women followed up 2004-9.

Methods: Data on pregnancy outcome, congenital abnormalities and maternal ART were collected during ART; information on infant feeding, clinical status, growth, HIV status, adverse events and biochemistry/hematology results were collected in a separate infant follow-up study retrospectively 2004-6, then prospectively 2008-9. Effect of maternal stavudine ART exposure and feeding practices on growth and development were analyzed using random effects and time-dependent Cox models.

Results: Of 2238 mothers, 6 infants died ≥2 weeks from perinatal causes (trauma/accident), prematurity, pre-eclampsia, hemorrhage, diabetes; 772 (34.9%) congenital abnormalities (spina bifida 2.2%, cardiac, hydrocephalus 0.4%, skin tag, undescended testis, 4.0% with TDF exposure in utero). In 2017 surviving infants, 162 (4%) were enrolled in the follow-up study; median age at last visit was 24 months (IQR 18-39); 48% were TDF-user. 162/162 (100%) received prophylaxis (d4T, 44%, ZDV, 18%, 3TC, 23%). In 189/189 (100%) had no/20-89%/≥90% in utero TDF exposure during gestation; only 16/189 mothers interrupted ART for ≥4 days during pregnancy. 72/189 infants were ever breastfed for median duration (25-75) 5.0 (4.0-10.0) months; ≤30% (101) in ≥18 months and 70≤18 months respectively). 3 infants were born to follow-up in 3 and died before being tested. In total, 14 children died after median age 9 months at 32, giving 6.13 (1.1-32) infant mortality (6.13); 6 infants were lost to follow-up (spina bifida, infection, abnormality, burn, measles, untraceable). The adjusted HR for mortality for breastfed versus non-breastfed babies was 0.53 (95% 0.17-1.73). There was evidence of an effect of infant TDF exposure on growth after 48 weeks (p<0.01) and there were no bone fractures. Only 34 creatinine and 7.50 phosphates measurements were abnormal (all grade 1, 1<7 children).

CONCLUSIONS: No increase in congenital, renal or growth abnormalities was observed in in-utero TDF exposure. Although some children died untreated, overall infant mortality was similar to that of the general population and absence of recorded HIV infection is encouraging. Given the trend to higher mortality in non-breastfed infants, mothers taking ART:

INTRODUCTION

METHODS

• During DART, data were collected on: Pregnancy incidence and outcome (pregnancy tests every 24 weeks) and congenital abnormalities (spina bifida, cardiac, hydrocephalus, skin tag, undescended testis, 4.0% with TDF exposure in utero).

• ART-exposure and feeding practices at birth and in follow-up were assessed.

• Infant feeding: Results on breastmilk/stool pH and feeding practice and growth on mortality were analyzed using random effects and time-dependent Cox models.

CONCLUSION:

No increase in congenital, renal or growth abnormalities was observed in in-utero TDF exposure. Although some children died untreated, overall infant mortality was similar to that of the general population and absence of recorded HIV infection is encouraging. Given the trend to higher mortality in non-breastfed infants, mothers taking ART:

INFANT OUTCOMES

• 275 infants were alive 2 weeks after birth

• 417/465 (90%) had in vitro TDF exposure during gestation

• Congenital abnormalities occurred in 7/73 (10%) infants (of the 129 with in vitro TDF exposure, 33.3% without, exact p=0.14)

• Infants with surgical TDF exposure had higher testes size (p=0.01)

• No increase in congenital, renal or growth abnormalities was associated with TDF-exposure.

INFANT ART PROPHYLAXIS

• 152/162 (94%) of infants in follow-up received ARV prophylaxis at birth:

BREASTFEEDING

TENOFIVIR EXPOSURE IN-UTERO

CONCLUSIONS

We thank all the patients and staff from all the centres participating in the DART trial. We acknowledge the ARV Unit who helped with the DART Infant Follow-up study.

We declare that we have no competing interests.

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Declaration ofEthical Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the MRC/UVRI Uganda Research Unit on AIDS, Entebbe, Uganda, and the University of Zimbabwe Human Subjects Committee.

CLINICAL EVENTS AND BIOCHEMISTRY

- 14 children died at median age 9 months (IQR 2-32), giving 6.13 (1.1-32) infant mortality (6.13); 6 infants were lost to follow-up (spina bifida, infection, abnormality, burn, measles, untraceable). The adjusted HR for mortality for breastfed versus non-breastfed babies was 0.53 (95% 0.17-1.73). There was evidence of an effect of infant TDF exposure on growth after 48 weeks (p<0.01) and there were no bone fractures. Only 34 creatinine and 7.50 phosphates measurements were abnormal (all grade 1, 1<7 children).

- No increase in congenital, renal or growth abnormalities was observed in in-utero TDF exposure.

- Although some children died untreated, overall infant mortality was similar to that of the general population and absence of recorded HIV infection is encouraging.

- Given the trend to higher mortality in non-breastfed infants, mothers taking ART during pregnancy and postnatally should be encouraged to breastfeed.