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

DART Infant FU

Poster 924

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ABSTRACT

Background:

Infants born to women taking predominantly tenofovir-based ART (mostly with zidovudine/lamivudine) during the DART Trial in Uganda/Zimbabwe were followed 2004-9.

Methods:

Data on pregnancy outcome, congenital abnormalities and maternal/infant ART were collected during DART; information on infant feeding, clinical status, growth, development, HIV status, adverse events and biochemistry/haematology results were collected in a separate infant study (retrospectively 2004-6, then prospectively 3-monthly). Effect of intrauterine ART exposure and feeding practice on growth and mortality were analysed using random effects and time-dependent Cox models.

Results:

Of 223 livebirths, 6 infants died <2 weeks from perinatal causes (foetal distress(3), prematurity(2), haemorrhagic disease). There were 7(3%) congenital abnormalities (talipes (2*,1), cardiac, hydrocephalus*, skin tag*, undescended testes); 4(3%) of 129 with TDF exposure (* in above). Of 217 surviving infants, 182 (84%) were enrolled in the follow-up study; median age at last visit was 26 months (IQR 13-39); 69% were >12months. 152/182 (84%) received prophylaxis (sdNVP 44%, ZDV 18%, sdNVP+ZDV 23%, other 15%); 62/9/111 infants had no/20-89%/≥90% in utero TDF exposure during gestation; only 16(10%) mothers interrupted ART for >4 days during pregnancy. 73/182 infants were ever breastfed for median 3.6 months(IQR 2.5-10.8). All 171 children tested were HIV negative (latest HIV antibody and DNA PCR negative in 101≥18months and 70≤18 months respectively); 3 children were lost to follow-up and 8 died before being tested. In total, 14 children died at median age 9.4 months(IQR 3-23), giving 6% 12 month mortality: 6 were HIV uninfected; 8 untested died of respiratory infection(3), sepsis(2), burns, measles, unknown. The adjusted HR for mortality for breastfed versus non-breastfed babies was 0.53 [95% CI 0.17-1.63]. There was no evidence of an effect of in utero TDF on growth after 48 weeks (p=0.31) and there were no bone fractures. Only 4/386 creatinine and 7/310 phosphate measurements were abnormal (all grade 1, in 7 children).

Conclusion:

No increase in congenital, renal or growth abnormalities was observed with in-utero TDF exposure. Although some children died untested, 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

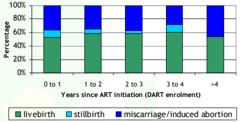
2156 women were enrolled into the DART trial in Uganda/Zimbabwe, of whom 1867 (87%) were of child bearing age (<45 years old). Infants born to women during DART were followed between 2004 to 2009. Their mothers took predominantly tenofovir (TDF)-based ART (mostly with zidovudine/lamivudine) throughout pregnancy.

METHODS

- During DART, data were collected on:
  - Pregancy incidence and outcome (pregnancy tests every 24 weeks)
  - Congenital abnormalities
  - ART received by mothers, and infants at birth
- In a separate Infant study (retrospectively 2004-6, then prospectively 3-monthly) data were collected on:
  - HIV status
  - Biochemistry/haematology results
  - Infant feeding
  - Growth and development
  - Clinical status and adverse events
- The effect of intrauterine ART exposure and feeding practice on growth and mortality were analysed using random effects and time-dependent Cox models.

RESULTS

- By the end of DART (median 4.9 years follow-up) a total of 384 pregnancy outcomes had been reported:



- During DART there were 223 live births: 6 infant deaths occurred at age <2 weeks from perinatal causes:
  - Foetal distress 3
  - Prematurity 2
  - Haemorrhagic disease 1

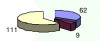
INFANT OUTCOMES

- **217 infants were alive 2 weeks after birth**
- 129/217 (59%) had in utero TDF exposure during gestation
- Congenital abnormalities occurred in 7/217 (3%) infants (4(3%) of the 129 with in utero TDF exposure, 3/88 (3%) without, exact p=1.00):
  - Talipes 3 (2 with intrauterine TDF exposure)
  - Cardiac 1
  - Hydrocephalus 1 (with intrauterine TDF exposure)
  - Skin tag 1 (with intrauterine TDF exposure)
  - Undescended testes 1
- **182/217 (84%) were enrolled in the infant follow up study**
  - At their last visit, median age was 26 months (IQR 13-39) and 69% were >12 months old
  - Children not enrolled were more likely to have been born earlier in the course of the DART trial

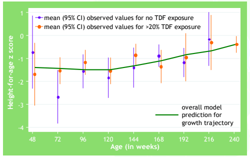
TENOFOVIR EXPOSURE IN-UTERO

120 (66%) of the 182 infants in the follow up study spent ≥20% of their time *in utero* exposed to TDF

Number of Infants with TDF exposure *in utero*



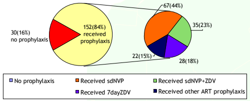
- There was no evidence of an effect of *in utero* TDF on infant growth after 48 weeks (no TDF vs ≥20%, p=0.1)



- Only 16(10%) mothers interrupted ART for >4days during pregnancy

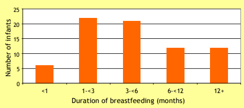
INFANT ART PROPHYLAXIS

- 152/182 (84%) of infants in follow-up received ARV prophylaxis at birth:

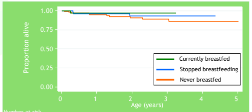


BREASTFEEDING

- 73/182 infants in follow up were ever breastfed for median 92 days (IQR 61-205), range 5-1186 days



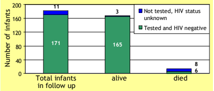
- The unadjusted HR for mortality for currently breastfed vs never-breastfed babies was 0.45 [95% CI 0.05-3.62] (p=0.45) and for those who had stopped breastfeeding vs never-breastfed babies was 0.70 [95% CI 0.19-2.57] (p=0.59).



Number at risk						
Never breastfed	109	78	57	31	12	1
Stopped breastfeeding	0	50	32	18	5	0
Currently breastfed	73	5	1	1	0	0

HIV STATUS

- 171/182 infants in follow up were tested for HIV infection by DNA PCR and HIV antibody (if>18 months):
  - All 171 (94%) children tested were HIV negative (latest HIV antibody and DNA PCR negative in 101≥18months and 70≤18 months resp.)
  - 3 children were lost to follow-up
  - 8 died before being tested



CLINICAL EVENTS AND BIOCHEMISTRY

- 14 children died at median age 9.4 months (IQR 3-23), giving 6% 12 month mortality
  - 8 had intrauterine TDF exposure* (all >75%)
  - 6 were HIV uninfected and 8 were untested, causes of deaths were:

6 HIV uninfected died of:	8 untested died of:
Acute diarrhoea (1*,1)	Respiratory infection (2*,1)
Malaria (1)	Sepsis (1*,1)
Airway obstruction (1*)	Burns (1)
Fever - no diagnosis (1*)	Measles (1*)
Severe anaemia (1*)	Unknown (1)

- Only 4/386 creatinine and 7/310 phosphate measurements were abnormal: all were grade 1 and in a total of 7 children
- 4/7 with grade 1 abnormalities had *in utero* TDF exposure:
  - 3/7 had 100% exposure (ie throughout time in-utero)
  - 1/7 had exposure for 61% of the time
- There were no bone fractures

CONCLUSIONS

- No increase in congenital, renal or growth abnormalities was observed with in-utero TDF exposure.
- Although some children died untested, 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

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