Poster # 637

Risk Factors for Mother-to-Child Transmission of HIV-1 from Breastfeeding in a Randomized Clinical Trial in Botswana (the Mashi Study)

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Abstract

Background: Early breastfeeding and potential late risk factors for mother-to-child HIV transmission (MTCT) were evaluated in a randomized infant feeding trial.
Methods: HIV-infected women were randomized to breastfeed (BF) or formula feed (FF) for 6 months. Mothers received antenatal and intrapartum zidovudine (ZDV), and single-dose nevirapine (NVP) or placebo. Infants received single-dose NVP or placebo, and ZDV prophylaxis for 1 month (FF arm) or 6 months (BF arm). Infant HIV DNA PCR was performed at birth, 1, 4, 7, and 12 months. Monthly visits occurred through 7 months. Exclusive breastfeeding (EBF) (no liquids or solids, 1 allowed liquid lapse) was defined at 5 months. Maternal highly active antiretroviral therapy (HAART) became available mid-study (CD4 cell count < 200 cells/mm3 or AIDS). Estimates were by Kaplan-Meier methods and Cox proportional hazards modeling.
Results: Of 1116 infants at risk, 6 (1.1%) FF and 7 (1.2%) BF were defined as infected between birth and 1 month (P=1.0). Maternal single-dose NVP receipt did not predict MTCT in the first month or thereafter in the BF arm. Of 549 BF infants alive and HIV-uninfected at 1 month, 24 (4.4%) late HIV transmissions occurred; 15 by 4 months, 6 from 4-7 months, and 3 thereafter. Univariate associations with late MTCT were higher maternal plasma or breast milk HIV-1 RNA (P=0.0002 and P=0.02, respectively), lower maternal CD4 cell count (P=0.005), infant diarrhea (P=0.03), and infant anemia (P=0.001); 3 (2.8%) of 109 EBF infants became infected compared with 20 (4.8%) of 400 mixed-fed infants (P=0.14). Infant feeding patterns were similar from months 1-4 regardless of eventual HIV status. In multivariable analysis (excluding breast milk HIV-1 RNA), maternal HIV-1 RNA (P=0.01), maternal CD4 cell count (P=0.06), no electricity in the home (P=0.05), infant diarrhea (P=0.04), and infant anemia (P=0.004) predicted late MTCT. No MTCT occurred in 34 BF infants whose mothers started HAART by delivery. Median baseline maternal CD4 cell count for late transmitters was 225 cells/mm3. No late MTCT occurred when baseline maternal plasma HIV-1 RNA was < 3,500 copies/ml.
Conclusions: With maternal and infant antiretroviral prophylaxis and partial HAART availability, breastfeeding was not a risk for MTCT in the first month of life. Late MTCT was rare at higher maternal CD4 cell count or lower HIV-1 RNA. Reverse causality may explain associations between infant illness and late MTCT when HIV testing is infrequent.

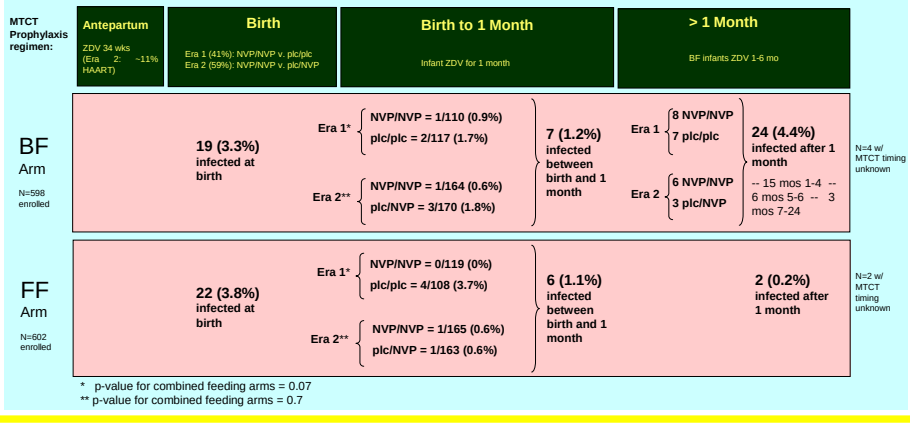
Background

- Breastfeeding (BF) is associated with 4-12% absolute risk of mother-to-child HIV transmission (MTCT) through 6 months
- Randomized feeding design allows Mashi Study to provide information about BF MTCT risk in first month of life
  - Most studies unable to distinguish peripartum MTCT from early BF MTCT
  - Previous study with similar design by Nduati et. al in Kenya (JAMA 2000) found substantial early BF transmission in absence of ARV prophylaxis
- Randomization to single-dose (SD) NVP vs. placebo (added to maternal and infant ZDV) allows Mashi Study to determine if maternal NVP has extended effect on BF MTCT
  - SD NVP hypothesized to reduce BF MTCT by lowering breast milk HIV-1 RNA
- Exclusive breast feeding (EBF) reduced late MTCT in previous studies

Methods

- ZDV to women from 34 weeks to delivery, to infants for 1 month
- HIV-infected women randomized to BF vs. FF for 6 months
- Women randomized to single-dose NVP vs. placebo, infants randomized to NVP vs. placebo in 1st study era only (all received NVP in 2nd study era)
- Infant HIV DNA PCR: birth, 1, 4, 7, and 12 months
- Monthly visits evaluated feeding, adverse events
- MTCT timing windows: Birth (first pos test <16d), Birth-1 month (first pos test 16-45d), > 1 mo (first pos test >45d).
- EBF (no liquids or solids, 1 allowed liquid lapse) defined through 5 months
- Estimates by Kaplan-Meier methods, Cox proportional hazards modeling, or Fisher's exact testing

MTCT at birth, between birth and 1 month, and after 1 month, by feeding arm and NVP receipt



* p-value for combined feeding arms = 0.07
** p-value for combined feeding arms = 0.7

Risk factors for late MTCT in the BF arm

	Univariate p-value*	Adjusted p-value	Adjusted HR (95% CI)
Baseline plasma VL (per 1 log increase)	0.0002	0.005	2.7 (1.4, 5.5)
Breast milk VL	0.02	--**	--
Baseline CD4 count (per 50 cell increase)	0.002	0.06	0.8 (0.76, 1.0)
Recent Infant Diarrhea	0.03	0.02	3.0 (1.2, 7.9)
Recent Infant Anemia	0.001	0.008	4.1 (1.5, 11.9)
Electricity in household	0.13	0.05	0.1 (0.02, 1.0)
Mixed BF before 5 mo	0.53	--	--

* p-values by Cox proportional hazards, ** co-linear with plasma VL

- 3 (2.8%) of 109 EBF infants became infected compared with 20 (4.8%) of 400 mixed-fed infants (Fisher's exact p=0.14)
  - Low power: only 21% maintained EBF through 5 months, and only 24 transmissions
  - No evidence for reverse causality
- No late MTCT when baseline maternal plasma VL < 3,500 copies/ml
- Median CD4 cell count among late transmitters = 225 cells/mm^3 (IQR 122, 399)

Conclusions

- **Extensive maternal/infant prophylaxis, and HAART availability, limit risk of BF MTCT in first month of life**
  - **Similar MTCT rates by feeding arm suggests that peripartum transmission may be more common than early BF transmission in this setting**
  - **Full month of ZDV to BF infants may add protection**
  - **Should 1 mo BF be considered if FF chosen (w/ prophylaxis)?**
    - **Mortality < 45d = 4.3% FF / 1.5% BF (but weaning would increase risk)**
- **Maternal SD NVP did not reduce early or late BF MTCT**
  - **Early MTCT: When transmissions during the first month isolated, non-significant trend for NVP efficacy during 1st study era, but no trend when all infants received NVP (and HAART availability) in 2nd study era**
  - **Late MTCT: No effect of maternal NVP**
- **Plasma and breast milk VL were the most modifiable risk factors for late MTCT (via maternal HAART)**
  - **Late MTCT rare with high CD4 / low VL**
  - **EBF not significantly protective, but low power**
  - **? reverse causality for associations w/ infant illness**