Triple-antiretroviral prophylaxis during pregnancy and breastfeeding compared to short-ARV prophylaxis to prevent mother-to-child transmission of HIV-1: the Kesho Bora randomized controlled clinical trial in five sites in Burkina Faso, Kenya and South Africa

Trial registration number ISRCTN71468401

Kesho Bora Study Group

Background

- ARV interventions to reduce MTCT during late pregnancy and delivery are well established, but no randomized trial has assessed safety and efficacy of continued maternal ARVs during breastfeeding (BF)
- Women with CD4 < 200 cells/mm^3 need ART for their own health and cannot be randomized, while MTCT risk for children born to mothers with CD4 > 500 cells/mm^3 is low and well controlled by recommended interventions (CROI 2008, Abstract 638)
- Balance of risks and benefits of continued ARVs during BF among women with CD4 200 - 500 cells/mm^3 is not known

Study endpoints

- HIV-free infant survival at 6 weeks (wks) and 12 months (mths), irrespective of mode of infant feeding, and among infants who received any breast milk
- AIDS-free survival among mothers 18 mths postpartum
- Incidence of serious adverse events in mothers and infants

Methods

Mother CD4 200-500 cells/mm^3 **- Randomisation**

TRIPLE ZDV+3TC+LPV/r *(28-36 weeks pregnancy to maximum until 6 months post partum)*

SHORT ZDV *(from 28-36 weeks until labour)*
+ ZDV+3TC+sd-NVP *(at onset of labour)*
+ ZDV+3TC *(one week after delivery)**

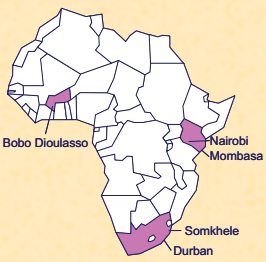
Child

Sd-NVP within 72h plus one week ZDV*

WHO/UNICEF infant feeding counselling:
- Replacement feeding - Free formula
- Breastfeeding – Exclusive BF for 5½ months, followed by weaning over a-2 week period

HIV status determined by real-time PCR (Biocentric)

** Amendment introduced in December 2007*



Current status

- Recruitment from Jun05 to Aug08
- By May09 all infants had been born > 6 months and 87% > 12 months previously
- Final 12 months results available in Dec09
- 18 months results available in Jun10

Results

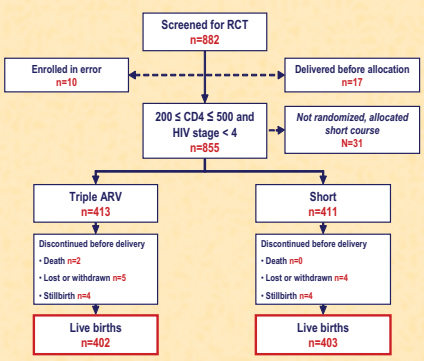


Table 1: Maternal and child's characteristics

Maternal characteristics	Triple n=413	Short n=411
Age (mean yrs)	27.4	27.4
Primigravida (%)	18.1	17.8
At least primary education (%)	85.7	84.4
Working (%)	32.7	27.7
Married/regular partner (%)	95.2	97.1
Enrolment CD4 (median cells/mm^3)	335	335
ARV ≥ 6 wks before delivery (%)	57.4	62.3
Cesarean Section (CS) (%)	11.3	12.3
CS < labour & membrane rupture (%)	3.9	3.2
Stillbirth (%)	0.99	0.98
Infant characteristics	n=402	n=403
Male (%)	50.5	47.4
Birth weight < 2500 g (%)	11.2	7.7
Delivery < 37 wk (%)	13.4	10.9
Ever breastfed (%)	76.4	78.2
Duration BF (median wks)	21.4	21.4
Exclusive BF to 3 mths (%)	47.5	45.6
Cumulative 12 mths follow-up (%)	92.2	90.5

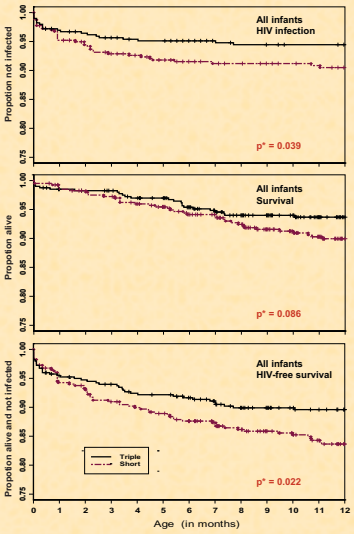
Table 2: Incidence of Serious Adverse Events (SAE)

	Mother (%)		Child (%)	
	Triple n=413	Short n=411	Triple n=402	Short n=403
Anaemia				
- Delivery/Birth	2.7	1.8	14.6	12.0
- 3 months	0.8	0.5	0.6	0.6
Neutropenia				
- Delivery/Birth	0.3	0.0	7.8	8.4
- 3 months	2.1	0.8	0.6	0.9
Elevated ALT				
- Delivery/Birth	0.8	0.0	0.3	0.3
- 3 months	0.0	0.0	0.0	0.0
≥ 1 clinical SAE	14.3	13.1	30.8	32.5
Fatal SAE	1.2	1.2	6.7	10.2

Table 3: Cumulative HIV infections and/or deaths - All infants

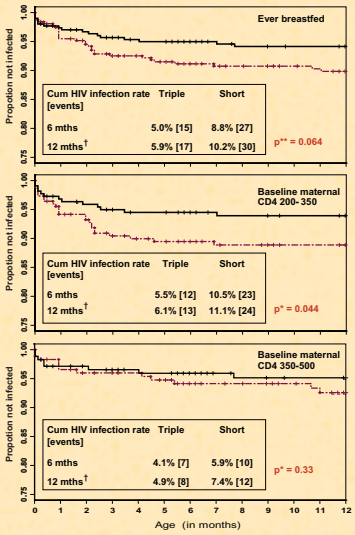
	Triple Events (cum)	Triple Rate (95% CI)	Short Events (cum)	Short Rate (95% CI)
HIV infections				
Birth	7	**1.8** (0.8, 3.7)	9	**2.2** (1.2, 4.3)
6 wks	13	**3.3** (1.9, 5.6)	19	**4.8** (3.1, 7.4)
6 mths	19	**4.9** (3.1, 7.5)	33	**8.5** (6.1, 11.8)
12 mths†	21	**5.5** (3.6, 8.4)	36	**9.5** (6.9, 13.0)
Risk reduction at 12 mths:		42%		
Deaths				
Birth	4	**1.0** (0.4, 2.6)	2	**0.5** (0.1, 2.0)
6 wks	6	**1.5** (0.7, 3.3)	7	**1.7** (0.8, 3.6)
6 mths	18	**4.6** (2.9, 7.2)	23	**5.9** (3.9, 8.7)
12 mths†	24	**6.3** (4.3, 9.3)	37	**10.0** (7.3, 13.6)
Risk reduction at 12 mths:		37%		
HIV infections or deaths				
Birth	11	**2.7** (1.5, 4.9)	11	**2.7** (1.5, 4.9)
6 wks	19	**4.8** (3.1, 7.4)	24	**6.0** (4.1, 8.8)
6 mths	33	**8.3** (6.0, 11.5)	50	**12.6** (9.7, 16.3)
12 mths†	40	**10.4** (7.7, 13.9)	62	**16.3** (12.9, 20.5)
Risk reduction at 12 mths:		36%		

† *Provisional*



** Log rank test at 12 mths (stratified on centre and intention to BF)*

Subgroup analysis – HIV infection



*** Log rank test at 12 mths (stratified on centre)*

Conclusions

- In HIV-positive mothers with CD4 200-500 cells/mm^3, triple-ARV prophylaxis given during pregnancy and continued during BF significantly reduces risk of HIV transmission to infants and improves HIV-free survival compared with standard recommended short course regimen
- Largest effects:
  - between 6 wks and 6 mths
  - when baseline maternal CD4 200-350 cells/mm^3
- Some reduction in HIV transmission when baseline maternal CD4 350-500 cells/mm^3
- Some postnatal HIV transmissions occurred despite 6 months postpartum maternal triple-ARV MTCT prophylaxis. Possible reasons:
  - Mothers not able to stop BF by 6 mths - underlines importance of continuing ARVs until complete BF cessation
  - Inadequate adherence to ARVs in this population
- Triple-ARV MTCT prophylaxis given to the mother and prolonged during BF period had low toxicity among mothers and children
- Impact of drug adherence and infant feeding patterns on MTCT rates not yet analysed
- Impact on longer-term maternal health (resistance, HIV disease progression) not yet analysed

Kesho Bora Study Group

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