

Kesho Bora: End of Project Report

Project number:

Organisation name: University of KwaZulu-Natal

Project Name: Kesho Bora

Project period covered by this report: October 2006 to December 2008

Project Summary:

Kesho Bora is a randomized controlled trial that aims to determine the impact of HAART on Prevention of Mother to Child Transmission and breastfeeding in HIV-infected women with CD4 count >200 and <500 cells/ml. The study is coordinated by the World Health Organization and has 5 implementing sites in Africa. The study has been implemented at Kwadabeka Community Health Centre located on the outskirts of Durban by a team from the Department of Paediatrics and Child Health at the Nelson R Mandela School of Medicine, University of KwaZulu-Natal. Antenatal HIV prevalence in this community is between 42-47%.

The **overall aim** of the study is to optimize the use of ARV drugs during the antepartum, intrapartum and postpartum periods to prevent MTCT of HIV and preserve the health of the mother in settings where the majority of HIV-infected women breastfeed.

Primary objectives

To compare the efficacy and safety of the triple-ARV MTCT-prophylaxis regimen with that of the short-course MTCT-prophylaxis regimen with regard to:

- 1) HIV-free infant survival at 6 weeks (in utero/intrapartum/early postpartum) and 12 months among all infants, irrespective of mode of infant feeding (intent-to-treat analysis);
- 2) HIV-free infant survival at 12 months among infants who receive any breast milk;
- 3) AIDS-free survival of mothers at 12 months following delivery; and
- 4) Incidence of serious adverse events in mothers.

Secondary objectives

- 1) Determine AIDS-free survival at 12 months among all enrolled women;
- 2) Assess HIV-free survival at birth, 2 weeks, 6 weeks, 6 months, 9 months (a point when all breast feeding is likely to have ceased) and 12 months of age among all enrolled children;
- 3) Estimate the rates of early and late postpartum transmission in ever breastfed infants, according to maternal HIV status and treatment received;
- 4) Describe the correlates of infant HIV-free survival including stage of maternal HIV disease (clinical, immunological and virological factors), ARV prophylaxis and/or

therapy given to the mother, and mode of infant feeding;

- 5) Describe the correlates of mother's HIV disease progression and survival including socio-demographic characteristics, disease and nutritional status at enrolment, ARV prophylaxis and/or therapy given to the mother, and mode of infant feeding;
- 6) Identify immunological and virological determinants of residual HIV-1 transmission during breastfeeding;
- 7) Describe and compare the feasibility, acceptability, safety, tolerability of and adherence to the maternal ARV prophylaxis and therapy regimens;
- 8) Describe changes in viral load and emergence of viral resistance in blood and breast milk according to the maternal ARV prophylaxis and therapy regimens and immunological and virological status at enrolment;
- 9) Assess the cost-effectiveness of the ARV prophylaxis and therapy regimens in preventing MTCT.

Hypothesis to be tested.

Triple drug HAART during the period of pregnancy and lactation is more effective than short course standard MTCT prophylaxis in reducing in utero, intrapartum and postnatal transmission of HIV from HIV-infected mothers with intermediate immune suppression (CD4 counts between 200-500) and protects against the emergence of viral resistance in mothers.

In brief, a randomised controlled trial (multi-country/site) in which asymptomatic pregnant women with intermediate stage HIV disease (CD4 count between 200 and 500 cells/mm³) will be allocated to receive either a triple-ARV regimen (ZDV, 3TC and Kaletra [Lopinavir/ritonavir combination LPV/r]) from 34-36 weeks gestation, through delivery and continued up to 6 months post-partum while breastfeeding or to a short-course ARV regimen (ZDV twice daily during the last month of pregnancy plus single-dose NVP at onset of labour).

Study end points:

- 1) HIV-free infant survival at 6 weeks and 12 months;
- 2) AIDS-free survival among mothers 12 months postpartum;
- 3) incidence of severe adverse events in mothers (including resistance).

The Durban site started about 18 months after the other three sites in Kenya and Burkina Faso because funds had not been secured.

Additional funding has been obtained from UNICEF and EDCTP to support implementation.

Recruitment began in February 2007 and was completed on 13 August 2008 with 191 participants enrolled.

Project Outcomes:

Objective	Outputs against objective
1. Establish a randomised cohort study (200 pregnant women) to fulfil the scientific objectives as detailed in the	Cohort established as per protocol. 191 women finally recruited (about 22% of entire cohort across all sites).

study protocol	
2. Follow study protocols and operating procedures to ensure accurate data collection and the highest level of care for mothers enrolled to the study	The Data Safety and Monitoring Committee has indicated that the Kesho Bora site at Kwadabeka has provided the best quality data between the 5 sites. Losses to follow-up of less than 10% testify to the high level of care provided by the team that is appreciated by enrolled mothers.
3. Conduct the study according to all ethical principles as required by the Biomedical Research Ethics Committee of UKZN	Reports of all Serious Adverse Events have been submitted to the BREC in accordance with their requirements and also the national Medicines Control Council. The study site has been recertified each year since its first approval.
4. To inform national and international policy and recommendations with respect to the benefits of ARVs to prevent MTCT through high quality data and analyses	The study will provide the first set of interim unblended results in July 2009 which will be presented to the SA National Department of Health and also to the international scientific community at the International Aids Society conference that will be convened in Cape Town at the same time.
5.	
<p>Provide below a written overview as to how this project has performed against it's original targets, providing explanations as to any opportunities or constraints that have affected project performance:</p> <p>The study has been implemented according to the study protocol. Originally the study adopted protocol version 9. However this was revised to version 10 in late 2007.</p> <p>Study implementation started following detailed discussion with the KwaZulu-Natal Department of Health to gain permission and buy-in for the concept. Following this, applications were made to the UKZN Biomedical Research Ethics Committee for approval of the study concept and procedures. An application was made in parallel to the Medicines Control Council, Trial Review Committee. Approvals were duly granted after external review of the protocols.</p> <p>The Kwadabeka Community Health Centre was chosen as the site for implementation as it had previously been the site for another PMTCT study and the research team were experienced in such work. Three park homes were available from this previous study as study offices and were sufficient to house the team and activities needed to support the study. The core team was recruited in October 2006. Following initial orientation and training from the WHO coordinating team study procedure were piloted in December 2006 and January 2007. Study forms were printed in Jan 2007 and the first patient enrolled in Feb 2007.</p> <p>The Kesho Bora team consists now of 2 doctors, two midwives, one nurse, three counsellors, two admin/ co-ordinators, a domestic assistant/ tracer, one pharmacist, an internal quality assurance monitor and a driver. The study team works in close partnership with the antenatal clinics of Kwadabeka, Clermont, New Germany and Wyebank, assisting in monitoring CD4 counts, providing information on PMTCT and living with HIV, and infant feeding options for all infected women. This partnership has facilitated referral of women with a CD4 < 200 for treatment and strengthened the existing service delivery infrastructure.</p> <p>All samples were processed at a private laboratory in Durban. Quality control measures were implemented to ensure consistency of standards between sites.</p>	

Drugs were purchased through local pharmaceutical suppliers and stored at the main pharmacy at Kwadabeka CHC.

Overall the study has progressed as well as could have been hoped for. There have been many local challenges such as coordinating with the ANC services, ensuring transport of samples and data management as well as responding to the national change in protocol. The relationships within the team remain excellent and this is seen in the relationships between the team and mothers who have been recruited into the study. As detailed below the small loss to follow up reflects the appreciation mothers have had for the team.

Some specific aspects of the study are highlighted below:

New National PMTCT Protocol

In April 2008, the National Department of Health implemented a new PMTCT protocol, which introduced the use of dual ARV therapy i.e. AZT any time from 28 weeks onwards + single dose nevirapine at delivery and nevirapine to the infant within 48 hours of birth, for all HIV-infected mothers and their exposed infants as a minimum standard of HIV care. The implications are that no participants can be enrolled once she is 28 weeks gestation since she would already be receiving AZT from her local clinic.

This had several logistical implications to study recruitment, which were tackled by a system of early screening methods – this particular period required great diligence and innovation from the Kesho Bora team. As reflected by the final number of 191 participants, the difficulties were well negotiated by the team and at the same time supported the implementation of the national protocol

Infant Feeding

We still provide feeding cups to mothers who intend to replacement feed; these have been very well received by the mothers. We continue to support these mothers with monthly food parcels to ensure adequate maternal nutrition. Although fewer women proportionally in the Durban site have opted to breastfeed the overall number of women breastfeeding across the study sites is higher than expected. This means that the sample size finally enrolled should be adequate to address the primary objectives.

Deaths

To date, we have had 1 maternal death; AIDS related illness implicated (?PCP, ?PTB) as recorded in case notes; and have had 8 infant deaths as follows:

1. One foetus was a fresh stillbirth at 31 wks gestation due to pregnancy induced hypertension
2. One infant died at 4 weeks from pneumonia – confirmed HIV negative
3. One died at 8 weeks from gastroenteritis - confirmed HIV negative
4. one died of gastroenteritis at 3 months - HIV positive – negative at birth, Mixed feeding implicated.
5. . 4 month old HIV positive from birth died from Gastroenteritis
6. 5 month old HIV positive from 6 weeks died of LRTI
7. 7 month old child HIV negative dying of Lower Respiratory Tract Infection
8. a 10 month old HIV negative child of acute gastroenteritis

Infected Children

Of the 168 infants tested at 6 weeks, 6 infants have been found to be PCR positive. 4 have

poor CD4 % and have been referred to local ARV Clinic for initiation of HAART because of their immunological status. Of these 4, 2 have already commenced HAART, 1 has died from gastroenteritis and the other 1 one is lost to follow up. From the remaining 2, one died from gastroenteritis(mixed feeding implicated) – no CD4 done, and the other is being followed up with 6 monthly CD4 counts.

Mothers on HAART

13 mothers had CD4 counts less than 200, six months postnatally or longer. They have been referred to commence HAART at the local ARV Clinic. 6 have already initiated HAART, 4 have completed literacy training and have been given dates to initiate HAART, 2 have subsequently had CD4 > 200 on repeat specimens and have not been started on HAART by ARV clinics, and the last one will give us an update of her progress on her next clinical visit.

Loss to Follow Up

There are 4 patients that are currently difficult to trace of which 1 has been discontinued from the study (relocated post delivery). 11 others mothers have missed several visits but are still in contact to make important visits where blood draws are required. We have a early identification tool to assist us in rapidly tracing patients that have missed visits, proceed to text messages and home visits as the next step – and keep a loss to follow-up register

Data quality

At a DSMB review in May, the Durban site had the lowest error and correction rate amongst all study sites. This is very gratifying and reflects the commitment of staff to conduct the study to the highest possible level. See accompanying DSMB report and tables.

Kesho Bora and Kwadabeka Clinic

The clinic management has been very supportive of the progress of the study and appreciate the importance and local value of the study objectives. There has be a continued and developing relationship with the Centre manager, Mrs Mdlalose the medical manager, Dr Hoque and the pharmacy manager, Mrs Essa.

WHO central coordinating team

Philippe Gaillard visited the site on 30 September till 1 October 2008 for a routine review of study implementation. No significant problems were identified.

External monitor for the study, Joyce Katuu most recently visited site in Oct 2008 and gave positive feedback on data quality and efficiency of the study team.

We have regular Serious Adverse Event conference calls with Isabel de Vincenzi in Geneva to ensure that reporting is up to date and congruent with other sites.

Other visits

We had a visit from a delegation from the House of Lords which they found very informative and helpful in understanding the issues of HIV and children in a country such as South Africa.

We have had visits from senior members of the SA National Department of Health (Lynne Moeng, Director for Nutrition) and also from the KZN Department of Health (Lenore Spies, Director of Maternal, Womens' and Child Health / Nutrition with responsibility for PMTCT). UNICEF have also visited the site and intend using some (anonymised) case studies in the international reports to illustrate the difficulties for HIV infected women in preventing transmission of the virus to their children.

Timelines

Recruitment to the study was completed in August 2008. The sample size from all sites is thus 846. Follow up will continue until Mid 2010. First major results will be available in the first or second quarter of next year and will be presented at the IAS meeting in Cape Town in

July 2009. It is expected that a confidential report will be presented to the National and Provincial Departments of Health prior to that in order to brief them of the results and likely policy implications. In addition, WHO is planning to host a PMTCT technical work group that will review the current PMTCT recommendations and how recent data and future study results, including from Kesho Bora, will likely impact on guidelines. Although there have been recent reports based on observational studies that HAART may be a strategy to make breastfeeding safer for HIV exposed infants, Kesho Bora and the BAN Study (Malawi) remain the only two randomized clinical controlled trial testing the utility of HAART in preventing postnatal HIV transmission.

Funding

The funding from DFID for the period October 2006 to November 2008 has enabled the necessary staff to be recruited, processes established, drugs provided, lab assays performed and data collected to be of the highest quality. Although funding from DFID concluded at the end of 2008, additional funds have been secured from UNICEF and EDCTP to complete follow up and the various lab assays. The study continues to offer the prospect of providing important data with respect to the use of HAART in preventing postnatal transmission.

Recruitment

01 February 2007 to 13 August 2008

Referred from ANC- 1018;

Enrolled – 191; ENROLMENT COMPLETED

Last delivery due mid-December 2008

Lessons Learned:

The main lessons of the study will come out when the data relating to HIV transmissions and infant and maternal survival are analysed.

However, additional lessons relate to how to integrate maternal and child care within the context of a community health care centre. Careful planning and communication with the health centre has resulted in a change of service delivery to all pregnant women attending the centre and not just to those who eventually enrolled to the study. Two examples:

Prior to the study, very few women who tested HIV positive at the antenatal clinic then received a CD4 test to determine their eligibility for lifelong antiretroviral therapy. The joint planning to implement Kesho Bora resulted in a simple system to ensure that all women received this service and that results were efficiently disseminated and that eligible women were referred to the ART service within the centre. This system has been disseminated to the other feeder clinics that also refer to the ART service at Kwadabeka.

The referral of HIV infected women from Kwadabeka for PAP smears was infrequent and results were rarely returned or acted upon in the centre. This was a quality of care issue within the Kesho Bora protocol. A system was designed with the local staff and referral hospital at which the PAP smears were processed. The system has been implemented with great effect so that all women (HIV-infected or not) are now appropriately referred and results are traced for action.

Good News Stories:

Kesho Bora Baby Party

We held a Party / Health Education event on the 21st November 2008 in order to celebrate

the birth of the final Kesho Bora baby, thank the study participants for their commitment to the study and strengthen health behaviour. The babies received T-shirts and refreshments were provided for all. The educational component consisted of role plays, a newsletter covering all major health issues facing study participants, a health quiz and an address from a guest speaker, nutritional specialist Joan Matji from UNICEF.

Dr Kevi Naidoo, project leader for the team at Kwadabeka is pursuing a Masters in Epidemiology through a distance learning course with the London School of Hygiene and Tropical Medicine.

In your opinion how has this project improved South Africa's response to HIV and AIDS:

The study has provided a mechanism for the SA National Department of Health to remain in close touch with the generation of high quality data that will inform their recommendation making process.

In time, the study will provide data that will significantly contribute to the development of international recommendations.

At a recent expert consultation convened by WHO in November 2008, Kesho Bora was acknowledged as one of two studies that will provide key evidence in these guideline-revising processes. See accompanying Meeting Conclusions.

	