Contemporary Clinical Trials 32 (2011) 74–85

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

# Safety and effectiveness of antiretroviral drugs during pregnancy, delivery and breastfeeding for prevention of mother-to-child transmission of HIV-1: The Kesho Bora Multicentre Collaborative Study rationale, design, and implementation challenges

The Kesho Bora Study Group *,[1]

ARTICLE INFO

*Article history:*
Received 23 April 2010
Accepted 14 September 2010

*Keywords:*
HIV/AIDS
Mother-to-child transmission
Randomized controlled trial
Cohort study
Design

ABSTRACT

To evaluate strategies to reduce HIV-1 transmission through breastfeeding, a multicentre study including a nested randomized controlled trial was implemented in five research sites in West, East and South Africa (The Kesho Bora Study). The aim was to optimize the use of antiretroviral (ARV) drugs during pregnancy, delivery and breastfeeding to prevent mother-to-child transmission of HIV-1 (PMTCT) and to preserve the health of the HIV-1-infected mother. The study included long-term ARV treatment for women with advanced disease, and short-course ARV prophylaxis stopped at delivery for women with early disease. Women with intermediate disease participated in a randomized controlled trial to compare safety and efficacy of triple-ARV prophylaxis prolonged during breastfeeding with short-course ARV prophylaxis stopped at delivery. Between January 2005 and August 2008 a total of 1140 women were enrolled. This paper describes the study design, interventions and protocol amendments introduced to adapt to evolving scientific knowledge, international guidelines and availability of ARV treatment. The paper highlights the successes and challenges during the conduct of the trial. The Kesho Bora Study included one of the few randomized controlled trials to assess safety and efficacy of ARV prophylaxis continued during breastfeeding and the only randomized trial to assess maternal prophylaxis started during pregnancy. The findings have been important for informing international and national guidelines on MTCT prevention in developing countries where, due to poverty, lack of reliable and affordable supply of replacement feed and stigma associated with HIV/AIDS, HIV-infected women have little or no option other than to breastfeed their infants. (ISRCTN71468401).



## 1. Introduction

Without intervention the rate of mother-to-child transmission (MTCT) of HIV-1 is approximately 35% in populations where prolonged breastfeeding is common. Approximately 5% of transmissions occur in utero, 15% during delivery and 15% during breastfeeding [1]. Maternal short-course antiretroviral (ARV) prophylaxis is associated with significantly lower HIV-1 transmission in utero and delivery, but the MTCT rate reaches 20% without interventions to prevent transmission during breastfeeding [2–6]. This rate is four to ten times higher than in developed countries [7–9] where multiple interventions are combined (ARV prophylaxis or treatment [9], caesarean section before labour and membrane rupture [10,11], and complete avoidance of breastfeeding). In developing countries, breastfeeding substantially increases MTCT risk [12,13].

In many developing countries, HIV-infected mothers continue to breastfeed despite the MTCT risk because of the lack of financial resources to provide formula, poor water sanitation to

* Corresponding author. Timothy MM Farley, World Health Organization, Department of Reproductive Health and Research, 20, Avenue Appia, CH-1211 Geneva 27, Switzerland. Tel.: +41 22 791 33 10; fax: +41 22 791 41 71.
*E-mail address:* forleyt@who.int.
[1] See full composition of Study Group in Appendix A.

1551-7144/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.cct.2010.09.008

prepare formula and stigma associated with not breastfeeding. In recent years, clinical trials have been implemented to assess the efficacy and safety of providing ARVs during breastfeeding to either the child (infant prophylaxis) [14–17] and/or to mother (maternal prophylaxis) [16].

The Kesho Bora study was conceived before the recent rapid expansion of antiretroviral treatment (ART) programmes, when antenatal care services often were unable to identify women requiring ART and even less able to provide access to ART. Moreover, mother's health appeared of lesser concern than preventing transmission and became an important motivation for the study. The Kesho Bora team chose to assess maternal prophylaxis adapted to HIV infection stage rather than infant prophylaxis, with the expectation that this strategy would facilitate identification of mothers during pregnancy in need of ART for their own health, accelerate their access to treatment and directly benefit maternal health and survival, with consequent benefits for the health and survival of their infants. However, the safety and efficacy of this approach in pregnant women not yet requiring treatment for their own health were not known.

Because MTCT risk [3,13] and risk of maternal AIDS or death [18,19] are strongly associated with maternal immunologic status, different ARV regimens were prescribed based on the mother's status (Table 1). HIV-1 infected pregnant women with advanced HIV disease (CD4+ cell count <200 cells/mm$^3$ or WHO Clinical Stage 4) were enrolled in a prospective cohort (Part IA) and offered long-term ART started in pregnancy and continued thereafter. Women with early HIV disease (CD4+ cell count >500 cells/mm$^3$ and WHO Clinical Stage 1, 2 or 3) were enrolled in another cohort (Part IB) and offered short-course ARV prophylaxis stopping around delivery. Prophylaxis was stopped at this stage because their transmission risk during breastfeeding is low (around 1%) [3] and risks associated with more than 6 months ARV prophylaxis were unknown. Women with intermediate stage HIV disease were offered enrolment into a randomized controlled trial to assess safety and efficacy of ARV prophylaxis continued during breastfeeding compared to prophylaxis stopping around delivery. In this paper, we present the design of the Kesho Bora study and some of the challenges faced during implementation. Study outcomes will be presented elsewhere.

## 2. Study design

### 2.1. Main objectives and end points

The first version of the protocol was developed in 2002. At that time, the two main questions concerning MTCT prevention were (1) how to reduce MTCT rates, not only during the antepartum and intrapartum periods but also during breastfeeding; and (2) how best to combine the use of ARVs for preventing transmission (MTCT prophylaxis) and preserving maternal health (by facilitating access to ART when required for the mother's health while minimizing adverse effects of MTCT prophylaxis when ART was not yet needed). Therefore, the main goal of the Kesho Bora study was to optimize the use of ARVs during the antepartum, intrapartum, and postpartum periods for prevention of MTCT and for preserving maternal health.

The main objectives of the prospective observational cohort components were to describe the rates and correlates of HIV-1 transmission, infant survival, infant HIV-1-free survival and maternal AIDS-free survival during the 18–24 month period following delivery among women with advanced HIV disease (Part IA) and those with early HIV disease (Part IB) who were receiving ARVs as per relevant national or international recommendations or best available evidence.

In the randomized controlled trial (RCT) (Part II) involving women with intermediate stage HIV disease, the main objectives were to compare rates of HIV-1 transmission, infant survival, infant HIV-1-free survival and maternal AIDS-free survival between two randomized groups of women receiving either the WHO recommended short-course ARV prophylaxis regimen stopping at delivery or a triple-ARV prophylaxis regimen continued during the breastfeeding period.

The study main endpoints for both the observational and the RCT components of Kesho Bora were:

1. HIV-1 transmission rates, survival, and HIV-1-free survival (defined as being alive and without HIV-1 infection) at six weeks and at 12 months among all infants, irrespective of the mode of infant feeding;
2. HIV-1 transmission rates, survival and HIV-1-free survival at 12 months among infants who received any breast milk;

**Table 1**
Rationale for the Kesho Bora study design.

| Maternal HIV stage | Subgroup specificity | Study design and ARV intervention |
|---|---|---|
| Advanced: CD4 <200 cells/mm$^3$ or WHO clinical stage 4 | – High risk of rapid maternal AIDS and death<br>– High risk of MTCT | Observational cohort (Part IA)<br>Maternal ART started during pregnancy and continued lifelong |
| Intermediate: 200≤CD4≤500 cells/mm$^3$ and WHO clinical stage 1, 2 or 3 | – Intermediate risk of maternal HIV disease progression<br>– Intermediate risk of MTCT | Randomized Controlled Trial (Part II) comparing<br>– "short-course" ARV prophylaxis during late pregnancy and delivery<br>– Triple-ARV prophylaxis during pregnancy, delivery and breastfeeding |
| Early: CD4 >500 cells/mm$^3$ and WHO clinical stage 1, 2 or 3 | – Low risk of maternal HIV disease progression<br>– Peripartum MTCT well controlled by ARV prophylaxis during late pregnancy and delivery<br>– Very low risk of transmission during breastfeeding | Observational cohort (Part IB)<br>ARV prophylaxis during late pregnancy and delivery |