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Modifications of a large HIV prevention clinical trial to fit changing realities: A case study of the Breastfeeding, Antiretroviral, and Nutrition (BAN) protocol in Lilongwe, Malawi ☆

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ABSTRACT

In order to evaluate strategies to reduce HIV transmission through breast milk and optimize both maternal and infant health among HIV-infected women and their infants, we designed and implemented a large, randomized clinical trial in Lilongwe, Malawi. The development of protocols for large, randomized clinical trials is a complicated and lengthy process often

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requiring alterations to the original research design. Many factors lead to delays and changes, including study site-specific priorities, new scientific information becoming available, the involvement of national and international human subject committees and monitoring boards, and alterations in medical practice and guidance at local, national, and international levels. When planning and implementing a clinical study in a resource-limited setting, additional factors must be taken into account, including local customs and program needs, language and socio-cultural barriers, high background rates of malnutrition and endemic diseases, extreme poverty, lack of personnel, and limited infrastructure. Investigators must be prepared to modify the protocol as necessary in order to ensure participant safety and successful implementation of study procedures. This paper describes the process of designing, implementing, and subsequently modifying the Breastfeeding, Antiretrovirals, and Nutrition, (BAN) Study, a large, on-going, randomized breastfeeding intervention trial of HIV-infected women and their infants conducted at a single-site in Lilongwe, Malawi. We highlight some of the successes, challenges, and lessons learned at different stages during the conduct of the trial.

1. Background

Among the estimated 700,000 children infected with HIV in 2003 worldwide, 315,000 were infected through breastfeeding [1]. Although some studies suggest that the risk of HIV transmission is higher in the first months of life, others indicate a relatively constant risk of transmission throughout breastfeeding beyond the first month [2–5]. Various factors have been associated with increased HIV transmission through breast milk including mastitis, cracked nipples, elevated maternal plasma and breast milk (BM) viral load, low maternal CD4 count and advanced stage of HIV disease, and mixed feeding (giving infants solid foods or other liquids in addition to breastmilk) [5–15].

Despite the risks of HIV transmission, the many advantages of breastfeeding have been well documented. The practice is known to confer nutritional, immunologic, developmental, psychologic, social, and economic benefits including overall lower infant morbidity and mortality. Compared with formula-fed infants, breastfed infants have fewer gastrointestinal and lower respiratory tract infections and are less likely to develop otitis media, necrotizing enterocolitis and other diseases, particularly in the first six months of life [16–24]. The greatest benefits accrue to exclusively breastfed infants (infants who only receive breast milk), who are less likely to have diarrheal or respiratory illness, to develop atopic disease, and to become infected with HIV than infants who receive both breast milk and other liquids or solids[15,18,25–27].

Breastfeeding also provides benefits to the mother including a delay in resumption of ovulation, resulting in increased child spacing [16]. In addition to individual health benefits, there are economic and social benefits due to savings from formula purchases [16,28]. Producing breast milk of adequate quantity and quality is, however, nutritionally demanding for mothers, particularly for those who have chronic infections. Unless diet during pregnancy and lactation is adequate, prolonged breastfeeding is likely to lead to maternal nutritional depletion (inadequate nutritional intake compared to metabolic needs) [29–32]. Depletion leading to rapid weight loss may place HIV-infected mothers at greater risk of succumbing to opportunistic infections, indirectly increasing their disease progression and risk of death [32,33].

Thus, HIV-infected women in resource-limited settings are faced with a tragic dilemma — breastfeeding their infants with its associated risk of HIV transmission or protecting their children from HIV by replacement feeding (anything other than breast milk), which may also be nutritionally less demanding for themselves, but increases the infant's risk of malnutrition and death if replacement feeding is not affordable, feasible, and safe [34,35].

Current WHO recommendations emphasize that [1] breastfeeding should be supported and promoted in the general population, irrespective of HIV infection rates; [2] there should be improved access to HIV counseling and testing; and, [3] HIV-infected women should be fully counseled about the benefits of breastfeeding, the risk of HIV transmission through breastfeeding, and the risks and possible advantages associated with other methods of infant feeding. Exclusive breastfeeding for the first 6 months is recommended in the general population and for HIV positive mothers who breastfeed. Recently revised recommendations state that early breastfeeding cessation should only be considered if criteria for replacement feeding are met [36].

In Malawi, liquid formula is impractical due to the weight and shipping costs. The cost of dry formula is $13.60 month for an infant age 7–12 months, which far exceeds the per capita health budget in most sub-Saharan countries [28]. Powdered formula must be mixed with water, which is often contaminated and can lead to severe and sometimes fatal diarrheal disease [17,18,34]. In addition Malawi guidelines follow the WHO guidelines.

In light of the complex risk–benefit ratio of breastfeeding for HIV-infected mothers and their infants, there is an urgent need to identify ways to make breastfeeding safer for both mothers and infants in resource-limited settings. In Lilongwe, Malawi, despite broad coverage of prevention of mother-to-child transmission (PMTCT) programs that offer short-course perinatal antiretroviral regimens to HIV-infected women [37], the risks of HIV transmission during the postnatal period are still substantial due to nearly 100% breastfeeding, almost no weaning before 12 months, and negligible exclusive breastfeeding, thus minimizing the effect of the PMTCT program.

In April 2001 the Centers for Disease Control and Prevention and the University of North Carolina began designing the Breastfeeding, Antiretrovirals and Nutrition Study, hereafter referred to as BAN, a randomized clinical trial to address these issues. The purpose of the study was to evaluate the following: 1) the benefit and safety of antiretroviral prophylaxis given either to infants or to their mothers to prevent HIV transmission during breastfeeding, 2) the benefit of nutritional supplementation