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Abstract

Purpose of the review. Mother-to-child transmission of HIV is responsible for most paediatric HIV infections. Short-course peri-partum antiretroviral therapy, available in resource-constrained settings, can reduce the risk of transmission around the time of delivery, but acceptable, efficient and safe interventions aimed at preventing the risk of postnatal HIV transmission through breastmilk remain elusive.

Recent findings. This review summarises the current state of knowledge on interventions to reduce the risk of postnatal transmission. New information from studies conducted in Africa, where breastfeeding is the norm, suggest that modified infant feeding practices are associated with reduced transmission risk, but women need support as well as appropriate care and nutritional counselling to safely practise these feeding modes. In addition, antiretroviral therapy for HIV-infected breastfeeding mothers is a promising strategy to prevent HIV transmission through breastmilk in Africa. The safety and efficacy of this strategy now needs to be assessed within large African longitudinal studies using a variety of antiretroviral regimens.

Summary. Promising interventions do exist to prevent the risk of HIV transmission through breastmilk, but their implementation at a population level remains insufficient. The development of a safe and effective paediatric preventive HIV vaccine would be an extremely important advance and have a major effect on control of the HIV/AIDS pandemic.

Introduction

Mother-to-child transmission of HIV, which can occur in utero, during delivery, or through breastfeeding, is responsible for most paediatric HIV infections. Each day, an estimated 2,200 children become infected with HIV worldwide, 90% of them in sub-Saharan Africa, where vertically acquired HIV remains a public health problem of large proportions. [1]. Short-course peri-partum antiretroviral therapy reduces the risk of mother-to-child transmission of HIV around delivery [2], but the subsequent risk of postnatal HIV transmission results in a great number of paediatric HIV infections in settings, where prolonged breastfeeding is widely practiced [3]. Acceptable, efficient and safe interventions aimed at preventing this risk of HIV transmission through breastmilk in resource constrained settings, especially in Sub-Saharan Africa, are urgently needed. The purpose of this review is to summarise the current state of knowledge on these interventions.

Modifying infant feeding practices: promising interventions

In Africa, HIV-infected pregnant women face a dilemma regarding the feeding practices of their infant [4]: the overall risk of HIV transmission through breastmilk is an estimated 8.9 new cases per 100 child-years of breast-feeding [3], while, in the absence of specific nutritional counselling and adapted clinical management, non-breastfed children have a greater risk of dying from infectious diseases than breastfed children, especially early in infancy [5].

Modifications of the breastfeeding practices in terms of duration (complete avoidance of breastfeeding or early cessation) and pattern (promotion of exclusive breastfeeding) aim to reduce the postnatal risk of HIV transmission [6]. In the past few years, the efficacy of these interventions as well as the repercussions on mothers and infants health have been evaluated in research studies conducted in rural and urban Africa.

Limited observational evidence suggests that exclusive breastfeeding may be less likely to result in postnatal HIV transmission than breastfeeding given with other fluids, solids or non-human milks (infant feeding definitions are detailed in Table 1) [7-9]. Contaminants or bacteria in complementary feeds introduced early may indeed damage the infant's immature gut, impair mucosal integrity, and thus facilitate postnatal transmission of HIV [10,11]. In Harare, Zimbabwe, the 18-month postnatal risk of acquisition of HIV was evaluated by infant feeding practices in the first 3 months of life, recorded through two recall histories at 6 weeks

and 3 months of age [9]. The cumulative 18-month percentage with HIV infection was significantly more elevated among the 1,414 mixed fed children (13.9; 95%CI, 11.6-16.3) than in the 156 exclusively breastfed children (6.9; 95%CI, 2.0-12.9). This risk was 8.6 (95%CI, 5.5-11.6) among the 490 predominantly breastfed children. There was a protective effect of exclusive breastfeeding, but very few women initiated and maintained this practice. Moreover, the proportion of exclusively breastfed children might have been overestimated because of maternal recall bias [12]. More recently, a large cohort study was conducted in rural South Africa supporting the practice of exclusive breastfeeding from birth until 6 months of age [7]. HIV-infected women were individually and regularly counselled at home. Infant feeding practices were recorded on a weekly basis, using 7-day recall histories. With the most stringent definition of exclusive breastfeeding based on all available information on infant feeding practices, 67% and 54% of the 1,372 children were exclusively breastfed from birth to 3 and 5 months of age, respectively. The rate of transmission between 6 weeks and 6 months in exclusively breastfed children was 4%. Infants who were breastfed but also received solids any time after birth, were 11 times more likely to acquire infection by 6 months of age than were exclusively breastfed children (p=0.02). Similarly, children who received both breastmilk and infant formula by 3-month were 2 times more likely to acquire HIV infection (p=0.06). Both these studies underline the risk of early introduction of solids, semi solids or non-human milk in breastfed children in terms of HIV postnatal transmission.

However, duration of breastfeeding is also a strong determinant of this risk. The longer the breastfeeding duration, the higher the resulting risk of postnatal transmission of HIV [3]. For instance, in the above mentioned Zimbabwean study, more than two thirds of postnatal HIV infections occurred after 6 months of age [9]. Therefore, emphasis has also been placed on reducing breastfeeding duration, with the promotion of interventions including complete avoidance of breastfeeding from birth or early cessation of breastfeeding. To fully evaluate these interventions, postnatal HIV transmission risk needs to be balanced with possible adverse outcomes for mother and child health [13].

In the absence of specific interventions to prevent mother-to-child transmission of HIV, the historical Kenyan clinical trial randomised on infant feeding practices showed that the overall (in utero, peripartum and postpartum) probability of HIV infection at age two-year was 37% in breastfed and 21% in formula fed children (p=0.001) [14]. In line with the finding on overall transmission risk, a study from Uganda recently showed six-month HIV transmission

rates of 17% in breastfed and 5% among formula fed children [15]. In a study in Abidjan, Côte d'Ivoire, the provision of peri-partum antiretroviral prophylaxis combined with promotion of alternatives to prolonged breastfeeding (exclusive formula feeding from birth or breastfeeding with early cessation from 4 months of age) considerably reduced overall mother-to-child transmission rates at age 18-month [16]. 18-month HIV transmission rates as low as 6.8% and 5.6% were obtained in short-term breastfed and formula fed children respectively, whose mothers had received peri-partum zidovudine and single-dose nevirapine. The 18-month probability of postnatal HIV infection in infants who were negative at or after 6 weeks of age, was 5% (95%CI, 3-8) in breastfed and 1% (95%CI, 0-3) in formula-fed infants ($p<0.001$). Postnatal transmission risk was associated with breastfeeding beyond 6 months (AOR 7.5, $p=0.003$) and mixed feeding in the first month of life (AOR 6.3, $p=0.04$).

Compared to unrestricted breastfeeding, complete avoidance of breastfeeding was shown to be safe in the urban Kenyan trial: morbidity and mortality were similar over two years in breastfed and formula fed children [17]. More recently, in a trial in Botswana, infants were randomly allocated to six months' breastfeeding and six months' zidovudine, or formula feeding and one month zidovudine [18]. The risk of infant death by 7 months of age was significantly higher in the formula-fed than in the breastfed group (9.3% vs. 4.9%; $p=0.003$), but the difference reduced thereafter, and by 18 months of age mortality risk did not significantly differ between the groups (10.7% vs. 8.5%; $p=0.21$).

In the study conducted in Côte d'Ivoire, the risk of severe events (hospitalization or death) before 2 years of age was similar among early-weaned breastfed and formula fed children (15% and 14%, respectively) [19]. To also assess whether these modified infant feeding practices were safe compared to the standard more prolonged breastfeeding, the 18-month mortality among these early weaned breastfed and formula-fed children was compared with that observed in long-term breastfed children in a previous cohort study in the same setting. There was no excess mortality in children with short or no breastfeeding: overall survival at 18 months was 96% among HIV-uninfected, early weaned and formula-fed children, similar to the 95% in the prolonged breastfed children.

In a study in Lusaka, Zambia, women were randomly assigned to either breastfeeding with abrupt cessation at 4 months, or to continued breastfeeding until the mothers chose to wean [20]. Preliminary results suggest that at two-year of age, there was no difference in HIV-free

survival between these two groups. In this study, stopping breastfeeding at 4 months resulted in less than anticipated reduction of HIV transmission, the benefit of which was offset by increased mortality among uninfected infants. In the context of a nutritional intervention aimed at preventing HIV acquisition through breastmilk, adequate feeding practices around the period of breastfeeding cessation are crucial for achievement of optimal child growth [21]. HIV-infected women therefore should cease breastfeeding early only when adequate complementary feeding for their infant can be guaranteed [22,23].

Given appropriate nutritional counselling and care, access to clean water, and a supply of breastmilk substitutes, alternatives to prolonged breast-feeding can be safe interventions to prevent mother-to-child transmission of HIV in urban African settings. However formula feeding is associated with higher mortality, morbidity, and stigma in less supported field settings [24-26]. Similarly, preliminary results from studies conducted in Malawi and Kenya suggest increased rates of diarrhoea during and following the weaning period among children breastfed for six months [27,28]. It is therefore crucial to provide adequate support to HIV-infected pregnant women so that they can choose the feeding practice adapted to their individual situation; they also need to be supported in their feeding choice after delivery [29]. International recommendations stress that [23] "exclusive breastfeeding is recommended for HIV-infected women for the first 6 months of life. When replacement feeding is acceptable, feasible, affordable, sustainable and safe, avoidance of all breastfeeding by HIV-infected women is recommended. At six months, if replacement feeding is still not acceptable, feasible, affordable, sustainable and safe, continuation of breastfeeding with additional complementary foods is recommended, while the mother and baby continue to be regularly assessed. All breastfeeding should stop once a nutritionally adequate and safe diet without breast milk can be provided".

Antiretroviral therapy among breastfeeding mothers: hopes and questions

HIV-infected pregnant women face a dilemma regarding the feeding practices of their forthcoming infant: alternatives to prolonged breastfeeding significantly reduce the risk of HIV transmission through breastmilk, but they may also endanger infant's health. Modified infant feeding practices are not universally appropriate [4]. There is therefore also a need for interventions that could allow safe breastfeeding, especially when water safety and provision of breastmilk substitutes is not assured.

Maternal highly active antiretroviral therapy (HAART) starting during the late prenatal period and continued during lactation constitutes such an intervention [30]. The presence of detectable HIV viral load in breastmilk is associated with an increased risk of postnatal HIV transmission [31,32]. By lowering viral load in breastmilk, maternal HAART could therefore substantially reduce the risk of HIV transmission, in a similar manner to that seen with peripartum HAART [33]. To date, this question has been investigated in two small studies only. A study in Mozambique recently showed lower cell-free HIV RNA load in breastmilk, and a reduced likelihood of detectable viral load in HIV-infected women (n=40) treated with HAART compared to untreated women (n=40) [34]. HAART was initiated in the third trimester of pregnancy and continued for a median of three months, irrespective of maternal CD4 cell counts at delivery. Similar results were previously reported from a smaller study in Botswana among 23 women with CD4 cell counts below 200 cells/ml, treated with HAART before and/or after delivery, with breastmilk samples collected a median 3 months after HAART initiation [35]. In this latter study, HAART had no apparent effect on cell-associated HIV DNA load in breastmilk, while in the Mozambique study, although non-significant statistically, cell-associated DNA viral load tended to be less often detected in breastmilk of women treated with HAART than in untreated women. The lack of effect on DNA viral load in the Botswana study could be explained by the fact that the duration of HAART treatment may have been too short [36]. Although the effect of HAART on reducing cell-free HIV RNA viral load in breastmilk provides encouraging results, neither study presented findings on HIV transmission risk through breastfeeding. More than half of the HAART- treated women had detectable cell-free (RNA) viral load in breastmilk, which implies the risk of postnatal mother-to-child transmission of HIV remains. That the effect of HAART was less apparent on HIV DNA load is also of concern, since this cell-associated viral load has been reported to be more often associated with HIV transmission through breastmilk than cell-free viral load [32,37].

The efficacy of maternal HAART in preventing HIV transmission through breastmilk now needs to be formally assessed within African cohort studies using a variety of antiretroviral regimens. The issue of the safety of maternal treatment for the breastfed infants is also crucial and needs to be thoroughly studied [38-40]. First, the quantity of antiretroviral drugs in breastmilk and subsequently in the plasma of breastfed infants, whose mothers receive HAART, needs to be assessed. Preliminary results suggest a possible lag in elimination of drugs in breastmilk [34,41]. Although the issue of the drug toxicity in infants exposed to

antiretrovirals through breastfeeding remains unresolved, as does the impact of this exposure on infant growth, morbidity and mortality [42,43], by ingesting breastmilk containing substantial antiretroviral concentrations, infants could be protected against the risk of HIV postnatal transmission (post-exposure prophylaxis principle), but which could be detrimental to subsequent therapy options for infected children. Indeed, development of resistance to antiretroviral drugs is possible since these infants will be receiving suboptimal levels of drugs for relatively long periods [44].

Despite these concerns, antiretroviral therapy among HIV-infected breastfeeding mothers is a promising strategy to prevent HIV transmission through breastmilk in Africa. Moreover, this strategy could provide a link between prevention and care, since maternal HAART offered in pregnancy and during the breastfeeding period to prevent HIV mother-to-child transmission can thereafter be continued among eligible women for their own health [30].

Translating research into practice: operational implementation of these interventions

Implementation of interventions to prevent postnatal HIV transmission require that African pregnant women have access to prenatal HIV counselling and testing. However, global coverage of HIV testing and counselling remains unsatisfactorily low, especially in sub-Saharan Africa. Among the 100 low- and middle-income countries having established programmes of prevention of mother-to-child transmission of HIV, only seven reached 40% or more of HIV-infected pregnant women in 2005 [45]. In sub-Saharan Africa, where 85% of HIV-infected pregnant women live, coverage ranged from less than 1% to 54% [45].

The lack of trained staff and the deteriorating quality of health systems in developing countries explain many of the organisational constraints of integrating strategies to prevent mother-to-child transmission of HIV within maternity and child care services. Many women who actually use prenatal HIV counselling and testing services never come back for their test results, and among those who are informed of their HIV infection, too few are offered effective interventions to prevent both peri-partum and postnatal HIV transmission [46,47]. Health care workers also have a key role in the successful implementation of these interventions [48]. Their training is essential and should at least include specific practice sessions on mother and child health issues in the context of HIV, correct knowledge of the risk of mother-to-child transmission of HIV, the advantages and disadvantages of each conceivable alternative to prolonged breastfeeding or antiretroviral based interventions, and

appropriate infant feeding counselling and support methods for HIV-infected women [29]. Above all, implementation of safe interventions to prevent risk of HIV transmission through breastmilk depends on a high level of political commitment.

Conclusion: towards the development of a paediatric preventive HIV vaccine

HIV transmission through breastmilk is a major mode of paediatric acquisition in African breastfeeding populations. Promising interventions do exist to prevent this risk, but their implementation at a population level remains insufficient. The development of a safe and effective paediatric preventive HIV vaccine would be an extremely important advance and would have a major effect on control of the HIV/AIDS pandemic [49,50]. Such a vaccine could prevent transmission of the virus via breastmilk, allow more prolonged breastfeeding with associated infant health benefits and provide the basis for lifetime immunity [51].

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A literature review discussing the rationale for the development of HIV vaccines for infants.

Table 1. World Health Organization infant feeding definitions.

Infant feeding practice	Definition
Exclusive breastfeeding	Giving a child no other food or drink, including no water, in addition to breastfeeding with the exception of medicines, vitamin drops or syrups, and mineral supplements
Predominant breastfeeding	Breastfeeding a child but also giving small amounts of water or water based drinks. Neither food-based fluid nor solid food are allowed under this definition
Artificial feeding	Feeding a child on artificial feeds (including infant formula and powdered animal milk), and not breastfeeding at all
Mixed feeding	Breastfeeding a child while giving non-human milk such as infant formula or food-based fluid or solid food

Source: Indicators for assessing breast-feeding practices (WHO, 1991); Breastfeeding counselling, a training course (WHO, 1993); HIV transmission through breastfeeding: a review of available evidence (WHO, 2004).