

Prevention of postnatal HIV infection: infant feeding and antiretroviral interventions

Renaud Becquet, Marie-Louise Newell

► **To cite this version:**

Renaud Becquet, Marie-Louise Newell. Prevention of postnatal HIV infection: infant feeding and antiretroviral interventions. *Current Opinion in HIV and AIDS*, Lippincott, Williams & Wilkins, 2007, 2 (5), pp.361-366. inserm-00168585

HAL Id: inserm-00168585

<https://www.hal.inserm.fr/inserm-00168585>

Submitted on 1 Sep 2008

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

**Prevention of postnatal HIV infection:
infant feeding and antiretroviral interventions**

Renaud BECQUET, PhD ^{1,2,3}, Marie-Louise NEWELL, MB, MSc, PhD ^{1,4}

¹ Africa Centre for Health and Population Studies, University of KwaZulu-Natal, Somkhele, South Africa

² INSERM, Unité 593, Bordeaux, France

³ Institut de Santé Publique Epidémiologie Développement, Université Victor Segalen Bordeaux 2, Bordeaux, France

⁴ Centre for Paediatric Epidemiology and Biostatistics, Institute of Child Health, University College London, London, United Kingdom

Funding sources

Renaud Becquet was funded by the French charity SIDACTION as a visiting epidemiologist at the Africa Centre for Health and Population Studies (University of KwaZulu Natal, South Africa).

Acknowledgment

The authors thank Dr. Ruth Bland (Africa Centre for Health and Population studies, South Africa) for her helpful suggestions and comments.

Word count

Abstract: 208 words; Manuscript: 2,528 words; 51 references.

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].

References

Papers of particular interest, published within the annual period of review, have been highlighted as of special (*) and outstanding (***) interest.

1. UNAIDS: **AIDS epidemic update**. Edited by. Geneva, Switzerland: United Nations program on HIV/AIDS; 2006.
2. Leroy V, Sakarovich C, Cortina-Borja M, McIntyre J, Coovadia H, Dabis F, Newell ML: **Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa?** *AIDS* 2005, **19**:1865-1875.
3. Breastfeeding and HIV International Transmission Study Group (BHITS): **Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis.** *J Infect Dis* 2004, **189**:2154-2166.
- *4. John-Stewart GC: **When is replacement feeding safe for infants of HIV-infected women?** *PLoS Med* 2007, **4**:e30.
This paper emphasizes the complexity of the HIV and infant feeding topic, underlying the gap between results from research studies and less supported operational programs.
5. WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality: **Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis.** *Lancet* 2000, **355**:451-455.
6. Rollins N, Meda N, Becquet R, Coutoudis A, Humphrey J, Jeffrey B, Kanshana S, Kuhn L, Leroy V, Mbori-Ngacha D, et al.: **Preventing postnatal transmission of HIV-1 through breast-feeding: modifying infant feeding practices.** *J Acquir Immune Defic Syndr* 2004, **35**:188-195.
- ***7. Coovadia HM, Rollins NC, Bland RM, Little K, Coutoudis A, Bennish ML, Newell ML: **Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding: the first six months of life.** *Lancet* 2007, **369**:1107-1116.
A large rural African cohort with very precise infant feeding data underlying the association between mixed breastfeeding and increased HIV transmission risk.
8. Coutoudis A, Pillay K, Kuhn L, Spooner E, Tsai WY, Coovadia HM: **Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa.** *AIDS* 2001, **15**:379-387.
9. Iliff P, Piwoz E, Tavengwa N, Zunguza C, Marinda E, Nathoo K, Moulton L, Ward B, Humphrey J: **Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival.** *AIDS* 2005, **19**:699-708.
10. Kourtis AP, Butera S, Ibegbu C, Beled L, Duerr A, Wu Z, Viisainen K, Wang Y, Hemminki E: **Breast milk and HIV-1: vector of transmission or vehicle of protection?** *Lancet Infect Dis* 2003, **3**:786-793.
11. Willumsen J, Darling JC, Kitundu JA: **Dietary management of acute diarrhoea in children: effect of fermented and amylase-digested weaning foods on intestinal permeability.** *J Pediatr Gastroenterol Nutr* 1997, **24**:235-241.
12. Bland RM, Rollins NC, Solarsh G, Van den Broeck J, Coovadia HM: **Maternal recall of exclusive breast feeding duration.** *Arch Dis Child* 2003, **88**:778-783.
13. Becquet R, Leroy V: **HIV and infant feeding: a complex issue in resource-limited settings.** *AIDS* 2005, **19**:1717-1718.
14. Nduati R, John G, Mbori-Ngacha D, Richardson B, Overbaugh J, Mwatha A, Ndinya-Achola J, Bwayo J, Onyango FE, Hughes J, et al.: **Effect of breastfeeding and**

- formula feeding on transmission of HIV-1: a randomized clinical trial.** *JAMA* 2000, **283**:1167-1174.
15. Magoni M, Bassani L, Okong P, Kituuka P, Germinario EP, Giuliano M, Vella S: **Mode of infant feeding and HIV infection in children in a program for prevention of mother-to-child transmission in Uganda.** *AIDS* 2005, **19**:433-437.
 16. Leroy V, Ekouevi DK, Becquet R, Viho I, Dequae-Merchadou L, Tonwe-Gold B, Rouet F, Sakarovitch C, Horo A, Timite-Konan M, et al.: **18-month effectiveness of short-course antiretroviral regimens combined to breastfeeding alternatives to prevent mother-to-child transmission of HIV-1: ANRS 049a DITRAME & ANRS 1201/1202 DITRAME-PLUS, Abidjan, Côte d'Ivoire.** Oral communication N°THAC0101. In *The XVI International AIDS Conference; Toronto, Canada: 2006.*
 17. Mbori-Ngacha D, Nduati R, John G, Reilly M, Richardson B, Mwatha A, Ndinya-Achola J, Bwayo J, Kreiss J: **Morbidity and mortality in breastfed and formula-fed infants of HIV-1-infected women: A randomized clinical trial.** *Jama* 2001, **286**:2413-2420.
 - **18. Thior I, Lockman S, Smeaton LM, Shapiro RL, Wester C, Heymann SJ, Gilbert PB, Stevens L, Peter T, Kim S, et al.: **Breastfeeding plus infant zidovudine prophylaxis for 6 months vs formula feeding plus infant zidovudine for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi Study.** *Jama* 2006, **296**:794-805.
- A randomized clinical trial concluding that breastfeeding with zidovudine prophylaxis was not as effective as formula feeding in preventing postnatal HIV transmission, but that both strategies had comparable HIV-free survival at 18 months.*
- **19. Becquet R, Bequet L, Ekouevi DK, Viho I, Sakarovitch C, Fassinou P, Bedikou G, Timite-Konan M, Dabis F, Leroy V: **Two-year morbidity–mortality and alternatives to prolonged breast-feeding among children born to HIV-infected mothers in Côte d'Ivoire.** *PLoS Medicine* 2007, **4**:e17-e31.
- A cohort study showing that when appropriate support is provided and clean water is available, replacement feeding can be safe in an urban African setting.*
20. Sinkala M, Kuhn L, Kankasa C, Kasonde P, Vwalika C, Mwiya M, Scott N, Semrau K, Aldrovandi G, Thea D: **No benefit of early cessation of breastfeeding at 4 months on HIV-free survival of infants born to HIV-infected mothers in Zambia: The Zambia Exclusive Breastfeeding Study.** In *The 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, USA: 2007.*
 21. Becquet R, Leroy V, Ekouevi DK, Viho I, Castetbon K, Fassinou P, Dabis F, Timite-Konan M: **Complementary feeding adequacy in relation to nutritional status among early weaned breastfed children who are born to HIV-infected mothers: ANRS 1201/1202 Ditrime Plus, Abidjan, Côte d'Ivoire.** *Pediatrics* 2006, **117**:e701-710.
 22. WHO: **Guiding principles for feeding non-breastfed children 6-24 months of age.** Edited by. Geneva, Switzerland: World Health Organisation; 2005.
 - *23. Consensus statement of the WHO HIV and infant feeding technical consultation held on behalf of the Inter-agency Task Team (IATT) on prevention of HIV infections in pregnant women, mothers and their Infants, Geneva, October 25-27, 2006. URL: http://www.who.int/child-adolescent-health/New_Publications/NUTRITION/consensus_statement.pdf
- The most up to date WHO guidelines on HIV and infant feeding.*
24. Bahl R, Frost C, Kirkwood BR, Edmond K, Martines J, Bhandari N, Arthur P: **Infant feeding patterns and risks of death and hospitalization in the first half of infancy: multicentre cohort study.** *Bull World Health Organ* 2005, **83**:418-426.

25. Creek T, Arvelo W, Kim A, Lu L, Bowen A, Mach O, Finkbeiner T, Zaks L, Masunge J, Davis M: **A Large Outbreak of Diarrhea among Non-breastfed Children in Botswana, 2006--Implications for HIV Prevention Strategies and Child Health.** In *The 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, USA: 2007.*
26. Doherty T, Chopra M, Nkonki L, Jackson D, Greiner T: **Effect of the HIV epidemic on infant feeding in South Africa: "When they see me coming with the tins they laugh at me".** *Bulletin of the World Health Organization* 2006, **84**:90-96.
27. Kourtis AP, Fitzgerald D, Hyde L, Tien HC, Chavula C, Mumba N, Magawa M, Knight R, Chasela C, van der Horst C: **Diarrhea in uninfected infants of HIV-infected mothers who stop breastfeeding at 6 months: the BAN study experience.** In *The 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, USA: 2007.*
28. Thomas T, Masaba R, van Eijk A, Ndivo R, Nasokho P, Thigpen M, Fowler MG: **Rates of diarrhea associated with early weaning among infants in Kisumu, Kenya.** In *The 14th Conference on Retroviruses and Opportunistic Infections; Los Angeles, USA: 2007.*
29. Bland RM, Rollins NC, Coovadia HM, Coutsooudis A, Newell ML: **Infant feeding counselling for HIV-infected and uninfected women: appropriateness of choice and practice.** *Bull WHO* 2007, **85**:289-296.
30. Gaillard P, Fowler M, Dabis F, Coovadia H, van der Horst C, van Rompay K, Ruff A, Taha T, Thomas T, de Vincenzi I, et al.: **Use of antiretroviral drugs to prevent HIV-1 transmission through breast-feeding: from animal studies to randomized clinical trials.** *J Acquir Immune Defic Syndr* 2004, **35**:178-187.
31. Chung MH, Kiarie JN, Richardson BA, Lehman DA, Overbaugh J, John Stewart GC: **Breast milk HIV-1 suppression and decreased transmission: a randomized trial comparing HIVNET 012 nevirapine versus short-course zidovudine.** *AIDS* 2005, **19**:1415-1422.
32. Rousseau CM, Nduati RW, Richardson BA, John Stewart GC, Mbori Ngacha DA, Kreiss JK, Overbaugh J: **Association of levels of HIV-1-infected breast milk cells and risk of mother-to-child transmission.** *J Infect Dis* 2004, **190**:1880-1888.
33. European collaborative study: **Mother-to-child transmission of HIV infection in the era of highly active antiretroviral therapy.** *Clin Infect Dis* 2005, **40**:458-465.
- *34. Giuliano M, Guidotti G, Andreotti M, Pirillo MF, Villani P, Liotta G, Marazzi MC, Mancini MG, Cusato M, Germano P, et al.: **Triple antiretroviral prophylaxis administered during pregnancy and after delivery significantly reduces breast milk viral load: a study within the drug resource enhancement against AIDS and malnutrition program.** *J Acquir Immune Defic Syndr* 2007, **44**:286-291.
An important study showing that HIV-infected women treated with HAART from before delivery were less likely to have a detectable viral load in breastmilk one week after delivery, when compared to untreated women.
35. Shapiro RL, Ndung'u T, Lockman S, Smeaton LM, Thior I, Wester C, Stevens L, Sebetso G, Gaseitsiwe S, Peter T, et al.: **Highly Active Antiretroviral Therapy Started during Pregnancy or Postpartum Suppresses HIV-1 RNA, but Not DNA, in Breast Milk.** *J Infect Dis* 2005, **192**:713-719.
36. Bulterys M, Weidle PJ, Abrams EJ, Fowler MG: **Combination antiretroviral therapy in african nursing mothers and drug exposure in their infants: new pharmacokinetic and virologic findings.** *J Infect Dis* 2005, **192**:709-712.

37. Koulinska IN, Villamor E, Chaplin B, Msamanga G, Fawzi W, Renjifo B, Essex M: **Transmission of cell-free and cell-associated HIV-1 through breast-feeding.** *J Acquir Immune Defic Syndr* 2006, **41**:93-99.
38. Briand N, Lallemand M, Jourdain G, Techapalokul S, Tunthanathip P, Suphanich S, Chanpoo T, Traisathit P, McIntosh K, Le Coeur S: **Haematological safety of perinatal zidovudine in pregnant HIV-1 infected women in Thailand: secondary analysis of a randomized trial.** *PLoS Clinical Trials* 2007, **2**:e11.
39. European collaborative study: **Levels and patterns of neutrophil cell counts over the first 8 years of life in children of HIV-1-infected mothers.** *AIDS* 2004, **18**:2009-2017.
40. Le Chenadec J, Mayaux MJ, Guihenneuc-Jouyaux C, Blanche S: **Perinatal antiretroviral treatment and hematopoiesis in HIV-uninfected infants.** *AIDS* 2003, **17**:2053-2061.
41. Shapiro RL, Holland DT, Capparelli E, Lockman S, Thior I, Wester C, Stevens L, Peter T, Essex M, Connor JD, et al.: **Antiretroviral concentrations in breast-feeding infants of women in botswana receiving antiretroviral treatment.** *J Infect Dis* 2005, **192**:720-727.
42. European collaborative study: **Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women.** *J Acquir Immune Defic Syndr* 2003, **32**:380-387.
43. European collaborative study: **Does exposure to antiretroviral therapy affect growth in the first 18 months of life in uninfected children born to HIV-infected women?** *J Acquir Immune Defic Syndr* 2005, **40**:364-370.
44. John-Stewart G, Mbori-Ngacha D, Ekpini R, Janoff E, Nkengasong J, Read J, Van de Perre P, Newell ML, Ghent IAS Working Group on HIV in Women and Children: **Breast-feeding and Transmission of HIV-1.** *J Acquir Immune Defic Syndr* 2004, **35**:196-202.
45. UNAIDS, WHO, UNICEF: **Access to HIV therapy grew significantly in 2006, but significant obstacles remain to approaching universal access to HIV services.** Edited by: United Nations Programme on HIV/AIDS; 2007:3.
46. Ekouevi DK, Leroy V, Viho A, Bequet L, Horo A, Rouet F, Sakarovitch C, Welfens-Ekra C, Dabis F: **Acceptability and uptake of a package to prevent mother-to-child transmission using rapid HIV testing in Abidjan, Cote d'Ivoire.** *AIDS* 2004, **18**:697-700.
47. Temmerman M, Quaghebeur A, Mwanyumba F, Mandaliya K: **Mother-to-child HIV transmission in resource poor settings: how to improve coverage?** *AIDS* 2003, **17**:1239-1242.
48. Becquet R, Ekouevi DK, Sakarovitch C, Bequet L, Viho I, Tonwe-Gold B, Dabis F, Leroy V: **Knowledge, attitudes, and beliefs of health care workers regarding alternatives to prolonged breast-feeding (ANRS 1201/1202, Ditrane Plus, Abidjan, Cote d'Ivoire).** *J Acquir Immune Defic Syndr* 2005, **40**:102-105.
49. Jaspan HB, Lawn SD, Safrit JT, Bekker LG: **The maturing immune system: implications for development and testing HIV-1 vaccines for children and adolescents.** *AIDS* 2006, **20**:483-494.
50. Safrit JT: **HIV vaccines in infants and children: past trials, present plans and future perspectives.** *Curr Mol Med* 2003, **3**:303-312.
- *51. Luzuriaga K, Newell ML, Dabis F, Excler JL, Sullivan JL: **Vaccines to prevent transmission of HIV-1 via breastmilk: scientific and logistical priorities.** *Lancet* 2006, **368**:511-521.

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).