

# **Universal antiretroviral therapy for pregnant and breastfeeding HIV-infected women: Towards the elimination of mother-to-child transmission of HIV-1 in resource-limited settings**

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## Abstract

Prevention of mother-to-child transmission of HIV-1 (MTCT) remains a challenge in most resource-limited settings, particularly in Africa. Single-dose and short-course antiretroviral (ARV) regimens are only partially effective and have failed to achieve wide coverage despite their apparent simplicity. More potent ARV combinations are restricted to pregnant women who need treatment for themselves but are also infrequently used. Furthermore, postnatal transmission via breastfeeding is a serious additional threat. Modifications of infant feeding practices aim to reduce breast-milk HIV transmission: replacement feeding is neither affordable nor safe for the majority of African women, and early breastfeeding cessation (e.g. prior to 6 months of life) requires substantial care and nutritional counselling to be practised safely. The recent roll out of ARV treatment has changed the paradigm of prevention of MTCT. To date, postnatal ARV interventions that have been evaluated target either maternal ARV treatment to selected breastfeeding women, with good efficacy, or single-drug post-exposure prophylaxis for short periods of time to their neonates, with a partial efficacy and at the expense of acquisition of drug-related viral resistance. We hypothesize that a viable solution to eliminate paediatric AIDS lies in the universal provision of fully suppressive ARV regimens to all HIV-infected women through pregnancy, delivery, and covering the entire breastfeeding period. Based on the available evidence, we suggest translating into practice the recently available evidence on this matter without any further delay.

The purpose of this viewpoint is to review the current challenges in the science of prevention of mother-to-child transmission of HIV-1 (MTCT) in breastfeeding populations. First, we describe the unmet scientific needs that account for the partial failure of MTCT prevention efforts in resource-constrained settings (managerial and operational obstacles to successful programme scale-up, while important, are not reviewed here). Second, we argue that expanding access to highly active antiretroviral therapy (HAART) therapy presents an unprecedented opportunity to radically reduce the burden of paediatric AIDS worldwide, through the universal use of antiretroviral (ARV) regimens in pregnant and breastfeeding women.

### **Prevention of MTCT in Africa: Past successes and current programmatic challenges**

MTCT can occur in utero, during delivery, or through breastfeeding, and is responsible for the majority of paediatric HIV infections. Each day, an estimated 1,600 children become infected with HIV worldwide, 90% of whom live in sub-Saharan Africa, where vertically-acquired HIV disease remains a major contributor to child mortality [1]. Scientific successes have been achieved over the past decade to prevent MTCT with the development of effective ARV interventions. However, this prevention is to date challenging in Africa [2-5]. This relative failure of MTCT prevention at the public health level is mostly explained by three reasons [3]: (1) global coverage of HIV testing and counselling remains unsatisfactorily low and too few women are offered effective interventions to prevent MTCT; (2) the mainstay intervention of single-dose nevirapine (NVP) prophylaxis is moderately effective and induces viral drug resistance in HIV-infected mothers and infants; and (3) prevention of breastfeeding transmission has remained largely elusive.

#### ***The need for effective interventions to prevent HIV transmission through breastmilk***

As detailed in Table 1, short-course peripartum prophylaxis with one or more ARV drugs reduces the MTCT risk around delivery [6], but the subsequent risk of postnatal transmission remains high in settings where prolonged breastfeeding is practised [7]. Various infant feeding interventions, such as early breastfeeding cessation or replacement feeding from birth, can reduce or eliminate, respectively the postnatal transmission risk without increasing infant mortality in well-supported research settings [8-10]. However, when introduced under routine circumstances, such interventions are often associated with higher mortality, morbidity, and stigma, often to the extent that their MTCT prevention benefit is completely eliminated [11-13]. As a result, the implementation of these interventions remains

largely untenable at a population level and is not recommended as a public health approach by the World Health Organization (WHO).

Maternal HAART with three ARV drugs initiated in pregnancy and continued during lactation might represent an alternative intervention that allows safe breastfeeding, especially when water availability and uninterrupted supplies of breastmilk substitutes are not assured [14]. Indeed, HAART reduces the infectivity of all body secretions and thus lowers HIV transmission [15, 16]. The safety and efficacy of this strategy is currently being assessed among women in Africa within intervention trials using a variety of ARV regimens.

Acceptable, efficient, and safe ARV interventions aimed at preventing HIV transmission for the majority of women, i.e. with very few restrictions, are needed in resource-limited settings.

### ***The need for alternatives to ARV regimens with a single dose of nevirapine***

Short-course peripartum ARV regimens administered to HIV-infected pregnant mothers and their infants in resource-constrained settings typically involve intrapartum and neonatal single-dose NVP and may be supplemented with antenatal zidovudine (ZDV) and/or lamivudine (3TC). These regimens produce MTCT risk reductions ranging from 37 to 77% compared to no intervention [17-23]. But one-tenth to two-thirds of women who take a single-dose of NVP will develop viral resistance to the non-nucleoside reverse transcriptase inhibitors (NNRTIs) [24]. This problem can be substantially reduced by combining the use of single-dose NVP with short-courses of 3TC ( $\pm$  ZDV) for 7 days after delivery [25, 26]. A single intrapartum dose of tenofovir and emtricitabine will also reduce this NNRTI resistance by half [27]. None of these approaches fully eliminates the selection of drug-resistant virus. The main drawback is that these NNRTI resistance mutations will reduce the effectiveness of a subsequent NNRTI-based HAART (the WHO recommended first-line treatment) initiated within six months of exposure to single-dose NVP [28, 29]. Previous single dose of nevirapine did not compromise the efficacy of subsequent NNRTI-based HAART started 6 months or more after delivery [28-30]. Anyhow, there is an unmet need for optimal ARV regimens aimed at reducing MTCT, while not compromising the therapeutic response to HAART in women requiring it later for their own health.

### ***The need for interventions tailored for women presenting at delivery with unknown HIV status***

HIV testing for pregnant women in antenatal clinics is usually not routinely performed: an estimated 18% of pregnant women in sub-Saharan Africa received an HIV test in 2007

[31]. In this context, most women present late in pregnancy or even in the labour ward unaware of their HIV status. These women may be offered ARV regimens partially effective, such as single dose NVP, and usually no intervention for preventing postnatal transmission [32]. Such interventions induce viral resistance to NNRTIs, thus depriving these women of attaining the full benefits of ARV therapy once it needs to be initiated. As a result, interventions taking into these women and strategies to increase the proportion of pregnant women knowing their HIV results [33] are needed to improve the coverage and quality of prevention of MTCT in Africa.

### ***The challenge of enhancing the roll-out of MTCT prevention***

Global PMTCT service coverage remains unacceptably low in sub-Saharan Africa (34%), and is especially poor in western and central Africa (11%) [4, 31]. From a programmatic perspective, it is now crucial to speed up the transition from research to wide-scale practice with innovative, easy to implement interventions that address the overall MTCT risk from pregnancy through breastfeeding cessation [3]. All these prevention strategies must be ARV-based, safe in pregnancy, labour and lactation, well tolerated, durable, and not inducing viral drug resistance. Moreover, the ideal drug combinations would also be appropriate in women presenting late for delivery [5, 34].

### **The scientific challenges of the prevention of MTCT through breastfeeding**

#### ***Efficacious PMTCT interventions exist for women eligible for ARV treatment***

The risk of HIV transmission through breastfeeding is 3 to 10 times higher among women with CD4 count <200 cells/ml than above this threshold [35, 36]. According to WHO guidelines, pregnant women with a low CD4 count are eligible for ARV therapy for their own health. Once initiated, HAART will rapidly and constantly reduce the maternal viral load in plasma and breastmilk, likely reducing the MTCT risk through breastfeeding [37, 38]. However, at least two-thirds of HIV-infected pregnant and breastfeeding women are not ill enough to require ARV therapy for their own health according to the rather restrictive WHO guidelines (CD4 <200 cells/ml, WHO clinical stage IV or CD4 <350 cells/ml and clinical stage III) [39]. Thus, in settings where breastfeeding women with low CD4 counts receive HAART, while women with higher CD4 counts do not, the majority of postnatal transmission would be expected to occur among the healthier women. As shown in Table 2, 80% of the postnatal cases of HIV transmission occurred in women with CD4 count >200 cells/ml [35]. In this pooled analysis, the breastfeeding duration was 6.4 months in median (inter-quartile range

(IQR): 4.4-12.4), which is shorter than durations commonly observed in Africa. Similarly, in the ongoing Kesho Bora trial, the 12-month cumulative risk of MTCT was 7.5% (95% CI 2.2-12.8) among children born to mothers with baseline CD4 count >500 cells/ml who received a short-course of ZDV antenatally, a single-dose of intrapartum NVP and no post-partum ARV intervention. The median breastfeeding duration was 18 months in this group (IQR: 9-25) [40, 41]. Thus, the universal use of maternal HAART regimens throughout the entire breastfeeding period might represent an attractive solution to the MTCT problem in women with moderate to high CD4 counts.

### ***Whether to stop maternal HAART after cessation of breastfeeding***

In a context where all HIV-infected pregnant women would be offered HAART, the question of whether and when to stop this intervention in women who do not meet WHO criteria for treatment is of interest.

In developed countries, all pregnant women are generally advised to receive a fully suppressive HAART regimen until delivery. In such settings, ARV therapy should be initiated in adults when the CD4 count reach 350 cells/ml, and international guidelines are currently in revision to adjust to this new evidence [42, 43]. In Africa, bacterial infections are among the leading causes of early severe morbidity, even among women whose CD4 counts are well above 200 cells/ml [44].

According to the current WHO recommendations, only pregnant and breastfeeding women who are eligible for ARV therapy because of their own health should continue HAART during the breastfeeding period and beyond in resource-limited settings. Starting then stopping HAART for the remaining mothers who do not meet this criteria after delivery may be risky. Studies in non-pregnant adults have suggested that intermittent, CD4-guided HAART (i.e. stopping therapy when the CD4 count fell below 350 cells/ml) was associated with an increased risk of opportunistic diseases or death [45, 46]. Similarly, a fixed 2-month off intermittent therapy lead to a higher proportion of patients with <350 cells/ml [47].

We therefore suggest that HAART be initiated for all pregnant and delivering women, irrespective of the clinical stage or CD4 count, and continued throughout the breastfeeding period. Rules for stopping HAART in the fraction of women who are symptom-free and have reached high CD4 counts at the time of breastfeeding cessation (say, 500 cells/ml and above) will need to be tailored to the evolving knowledge in this field. We strongly advocate for this universal maternal HAART approach that may allow narrowing the gap with the rapidly evolving treatment guidelines for adults.

### ***Supporting women to make breastfeeding cessation at six months of age conceivable, feasible and safe***

The provision of maternal HAART to all women, including those who are not eligible for treatment, would allow the benefits of breastfeeding in the first months of life whilst minimising the HIV transmission risk. This needs to be coupled with breastfeeding cessation around six months of age, so that infants are no longer exposed to the MTCT risk beyond that age.

Results from the above-mentioned pooled analysis from Côte d'Ivoire and South Africa showed that the overall risk of MTCT was twice as high among children breastfed for >6 months than among children breastfed ≤6 months [35]. Breastfeeding beyond six months should therefore be avoided when replacement feeding after breastfeeding cessation can be safely and sustainably provided, as recommended by WHO [48]. Women need to be counselled properly to provide adequate complementary feeding with locally available foods to take over breastmilk from six months onwards. Adequate feeding practices around the weaning period are indeed crucial for achieving optimal child growth. A study from Côte d'Ivoire showed that inadequate complementary feeding at age six months was associated with impaired child growth during the following 12 months [49]. In this cohort, the risk of stunting was 50% higher in children for whom the dietary diversity was inappropriate in the months following the breastfeeding cessation process, than among those adequately fed during this crucial period.

Further research will be required to provide HIV-infected women with innovative strategies to reduce the risk of postnatal transmission beyond six months of age while ensuring postnatal nutritional support for adequate complementary feeding practices [50]. This should be done in addition to, and not as an alternative to, maternal HAART.

### ***The maternal versus infant approach to prevent the postnatal MTCT risk***

ARV drugs can be administered to infants as prophylaxis against HIV exposure. In Malawi, a very short course of NVP was administered to newborns of HIV-infected women presenting late for delivery and who had insufficient time to receive a maternal ARV intervention: peripartum MTCT risk was reduced by one third [51].

More recently, three studies have documented the efficacy of a more extended ARV prophylaxis in breastfed infants [52-55] and provide provocative but not entirely satisfactory results (Table 3, detailed interpretation of these results in Online Appendix 1).

Thus, the administration of ARV drugs to breastfed infants is another possible strategy to reduce postnatal HIV transmission, especially for children born to women who



present late in pregnancy. However, it appears that to be maximally effective this ARV-based intervention would need to be maintained throughout the breastfeeding exposure [56] and should involve drugs that are not as likely as NVP to select resistant virus and compromise the future treatment needs of HIV-infected children. The BAN study, currently underway in Malawi, is expected to yield more results on this issue [57]. A new clinical trial (PROMISE-PEP) is also in preparation in Burkina Faso, Uganda, Zambia and South Africa to evaluate infant prophylaxis with lamivudine for a maximum of 38 weeks (<http://www.clinicaltrials.gov/ct2/show/NCT00640263?term=promise-pep&rank=1>).

### ***Universal maternal HAART could largely eliminate the overall MTCT risk***

The effect of maternal HAART on HIV load in breastmilk has been reported in three African studies so far. In Mozambique, ARV treatment had been initiated in the third trimester of pregnancy and continued for a median duration of three months [37]. In this study, all HIV-infected women treated with HAART had lower cell-free HIV RNA load in breast milk and were less likely to have a detectable breastmilk viral load when compared to untreated women. These results are in line with those previously reported in a smaller study conducted in Botswana among women with baseline CD4 count <200 cells/ml and treated with HAART before and/or after delivery, with breastmilk samples collected three months in median after HAART initiation [38]. In this study, HAART had no apparent effect on cell-associated HIV DNA load in breastmilk [38]. Similarly, a third study recently conducted in Kenya among HAART-treated breastfeeding women showed the suppression of cell-free HIV-1 RNA in breastmilk without suppression of HIV-1 DNA in this compartment [58].

As shown in Table 4, HAART in breastfeeding women results in transmission rates generally below 5% in breastfeeding populations (the detailed interpretation of these results is provided in Online Appendix 2) [59-65].

Not negligible in this new perspective is the fact that infants will be exposed to the ARV drugs through breastfeeding [38, 66]. These infants' plasmatic concentrations of the transferred drugs vary according to the ARV used. A study in Kenya showed that lamivudine and nevirapine, but not zidovudine, were transmitted through breastfeeding to infants in biologically significant concentrations when their mothers received these drugs [66]. In Mozambique, detectable concentrations of ARV drugs in breastmilk were found one week after delivery in women treated with HAART since 28 weeks of gestational age, despite some of them having undetectable plasma levels at the same time [37]. This result suggests a possible lag in elimination of ARV drugs in breastmilk. Based on current knowledge, the diffusion in breastmilk of Lopinavar/ritonavir and Tenofovir is unknown. Three questions can be raised from this growing body of evidence: 1- are these concentrations of ARV drugs safe

for infants?; 2- are they effective by themselves against postnatal MTCT?; 3- is there a risk of selection of drug-resistant virus in HIV-infected children who will received sub-optimal concentrations of ARVs?

The issue of infant toxicities associated with exposure to maternal HAART is of crucial interest. A study in Botswana among breastfed infants born to HAART-treated women suggest that hematologic and hepatic toxicities associated with antenatal and postnatal exposure to maternal HAART were minimal, with the exception of increased early neutropenia that did not persist beyond one month of age [67]. This study also showed that excess infant anemia related to either in utero or breastfeeding HAART exposure were not detected [67]. Thorne and Newell synthesized recently in an extensive literature review the evidence for short to medium-term potential adverse effects and toxicities of exposure to antiretroviral drugs in utero and neonatal life (including haematological, mitochondrial, teratogenic and carcinogenic effects) [68]. They concluded that "the immense benefits of antiretroviral prophylaxis in prevention of mother-to-child transmission far outweigh the potential for adverse effects". These adverse effects require further and longer term monitoring because they are likely to occur later in childhood [68]. Moreover, the extent and effect of infant drug exposure through breastmilk should now be well understood to evaluate the benefits and risks of maternal HAART during breastfeeding [66].

## Conclusions

We suggest the active promotion of the universal maternal HAART approach as a way towards elimination of MTCT in resource-limited settings. Such an approach is already well established in industrialized countries. We argue that HAART should be made available to all HIV-infected pregnant women in resource-limited settings, irrespective of their CD4 count or clinical stage, and even to those who present late in pregnancy. This universal ARV-based strategy should be accompanied by proper pharmacovigilance systems. It should consider the breastfeeding cessation around six months of age, which implies the need for a proper nutritional support. Continuing investigations will compare the safety, acceptability, feasibility and efficiency of various maternal HAART regimens for preventing the peripartum and postnatal risks of MTCT in order to rank them according to the best risk-benefit balance.

The gap between the current level of knowledge and the public health implementation is still considerable [4, 5]. Expanding the indication of use of potent ARV drug combinations to all pregnant, delivering and breastfeeding women aware of their HIV status should be the immediate future of MTCT in resource-limited settings. This advanced biomedical approach should be closely linked to the development and evaluation of interventions at the community level to improve the coverage of HIV testing and counselling among pregnant women,

reduce stigma and favour the overall family care approach. Finally, our suggested approach is also in line with the recently advocated universal HIV voluntary HIV testing with immediate potent ARV treatment [3].

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## References

1. UNAIDS. AIDS epidemic update. Geneva, Switzerland: United Nations program on HIV/AIDS, **2008**.
2. Becquet R, Newell ML. Prevention of postnatal HIV infection: infant feeding and antiretroviral interventions. *Current Opinion in HIV and AIDS* **2007**;2(5):361-6.
3. Médecins sans frontières. Responding to the failure of prevention of mother-to-child transmission (PMTCT) programmes: What needs to change? Expert roundtable 23-24 June 2008. [Accessed: 2009 July 16]; Available from: <http://www.msfaaccess.org/main/hiv-aids/pmtct-experts-roundtable/>
4. Orne-Gliemann J, Becquet R, Ekouevi DK, Leroy V, Perez F, Dabis F. Children and HIV/AIDS. From research to policy and action in resource-limited settings. *AIDS* **2008**;22(7):797-805.
5. UNICEF. Children and AIDS. Second Stocktaking Report. 2008 [Accessed: 2009 July 16]; Available from: [http://www.unicef.org/publications/files/ChildrenAIDS\\_SecondStocktakingReport.pdf](http://www.unicef.org/publications/files/ChildrenAIDS_SecondStocktakingReport.pdf)
6. Leroy V, Sakarovich C, Cortina-Borja M, et al. Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa? *AIDS* **2005**;19(16):1865-75.
7. 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(12):2154-66.
8. Becquet R, Bequet L, Ekouevi DK, et al. 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(1):e17.
9. Mbori-Ngacha D, Nduati R, John G, et al. Morbidity and mortality in breastfed and formula-fed infants of HIV-1-infected women: A randomized clinical trial. *Jama* **2001** Nov 21;286(19):2413-20.
10. Thior I, Lockman S, Smeaton LM, 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** Aug 16;296(7):794-805.
11. Bahl R, Frost C, Kirkwood BR, et al. Infant feeding patterns and risks of death and hospitalization in the first half of infancy: multicentre cohort study. *Bull World Health Organ* **2005** Jun;83(6):418-26.
12. 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** Feb;84(2):90-6.
13. Mach O, Lu L, Creek T, et al. Population-based study of a widespread outbreak of diarrhea associated with increased mortality and malnutrition in Botswana, January-March, 2006. *Am J Trop Med Hyg* **2009** May;80(5):812-8.
14. Becquet R. Antiretroviral therapy among HIV-infected breastfeeding mothers: a promising strategy to prevent HIV transmission through breastmilk in Africa. *Future HIV Therapy* **2007**;1(1):17-21.
15. Granich RM, Gilks CF, Dye C, De Cock KM, Williams BG. Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model. *Lancet* **2009** Jan 3;373(9657):48-57.
16. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakai Project Study Group. *N Engl J Med* **2000** Mar 30;342(13):921-9.
17. Dabis F, Msellati P, Meda N, et al. 6-month efficacy, tolerance, and acceptability of a short regimen of oral zidovudine to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME Study Group. *Diminution de la Transmission Mere-Enfant. Lancet* **1999**;353(9155):786-92.
18. Dabis F, Bequet L, Ekouevi DK, et al. Field efficacy of Zidovudine, Lamivudine and single-dose Nevirapine to prevent peripartum transmission of HIV. The ANRS 1201/1202 Ditrane Plus study, Abidjan, Cote d'Ivoire. *AIDS* **2005**;19(3):309-18.
19. Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet* **1999** Sep 4;354(9181):795-802.
20. Lallemand M, Jourdain G, Le Coeur S, et al. Single-Dose Perinatal Nevirapine plus Standard Zidovudine to Prevent Mother-to-Child Transmission of HIV-1 in Thailand. *N Engl J Med* **2004** July 9, 2004;351(3):217-28.
21. Petra study team. Efficacy of three short-course regimens of zidovudine and lamivudine in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra study): a randomised, double-blind, placebo-controlled trial. *Lancet* **2002** Apr 6;359(9313):1178-86.
22. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. *The Lancet* **1999** 1999/3/6;353(9155):773-80.
23. Wiktor SZ, Ekpini E, Karon JM, et al. Short-course oral zidovudine for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet* **1999**;353(9155):781-5.
24. Arrive E, Newell ML, Ekouevi DK, et al. Prevalence of resistance to nevirapine in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *International Journal of Epidemiology* **2007** Oct;36(5):1009-21.
25. Chaix ML, Ekouevi DK, Rouet F, et al. Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrane Plus, Abidjan, Cote d'Ivoire. *J Infect Dis* **2006** Feb 15;193(4):482-7.

26. McIntyre JA, Martinson NA, Gray G. Addition of short course Combivir (CBV) to single dose Viramune (sdNVP) for the prevention of mother to child transmission (pMTCT) of HIV-1 can significantly decrease the subsequent development of maternal and paediatric NNRTI-resistant virus. Abstract TuFo0204. In: The Third Conference on HIV Pathogenesis and Treatment. Rio De Janeiro, Brasil, **2005**.
27. Chi BH, Sinkala M, Mbewe F, et al. Single-dose tenofovir and emtricitabine for reduction of viral resistance to non-nucleoside reverse transcriptase inhibitor drugs in women given intrapartum nevirapine for perinatal HIV prevention: an open-label randomised trial. *Lancet* **2007** Nov 17;370(9600):1698-705.
28. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med* **2004** July 9, 2004;351(3):229-40.
29. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. *N Engl J Med* **2007**;356(2):135-47.
30. Coffie PA, Ekouevi DK, Chaix ML, et al. Maternal 12-month response to antiretroviral therapy following prevention of mother-to-child transmission of HIV type 1, Ivory Coast, 2003-2006. *Clin Infect Dis* **2008** Feb 15;46(4):611-21.
31. WHO, UNICEF, UNAIDS. Towards universal access. Scaling up priority HIV/AIDS interventions in the health sector. Geneva, Switzerland, **2008**.
32. Cohen MH, Olszewski Y, Webber MP, et al. Women identified with HIV at labor and delivery: testing, disclosing and linking to care challenges. *Matern Child Health J* **2008** Sep;12(5):568-76.
33. Mkwanazi NB, Patel D, Newell M-L, et al. Rapid Testing May Not Improve Uptake of HIV Testing and Same Day Results in a Rural South African Community: A Cohort Study of 12,000 Women. *PLoS ONE* **2008** 10/23;3(10):e3501.
34. Dabis F, Ekpini ER. HIV-1/AIDS and maternal and child health in Africa. *Lancet* **2002** Jun 15;359(9323):2097-104.
35. Becquet R, Bland RM, Leroy V, et al. Duration and pattern of breastfeeding and postnatal transmission of HIV: pooled analysis of individual data from a West and South African cohort study. Oral communication, abstract 45. In: The 15th Conference on Retroviruses and Opportunistic Infections. Boston, USA, **2008**.
36. Leroy V, Karon JM, Alioum A, et al. Postnatal transmission of HIV-1 after a maternal short-course zidovudine peripartum regimen in West Africa. *AIDS* **2003**;17(10):1493-501.
37. Giuliano M, Guidotti G, Andreotti M, 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(3):286-91.
38. Shapiro RL, Ndung'u T, Lockman S, 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** Sep 1;192(5):713-9.
39. Ekouevi DK, Inwoley A, Tonwe-Gold B, et al. Variation of CD4 count and percentage among women receiving antiretroviral prophylaxis for the prevention of mother-to-child transmission of HIV: Implication for HAART initiation in resource-limited settings. *AIDS Research and Human Retroviruses* **2007**;23(12):1469-74.
40. De Vincenzi I, Kesho Bora Study Group. HIV-free Survival at 12 Months among Children Born to HIV-infected Women Receiving Antiretrovirals from 34 to 36 Weeks of Pregnancy. Abstract 638. In: The 15th Conference on Retroviruses and Opportunistic Infections. Boston, USA, **2008**.
41. De Vincenzi I, Kesho Bora Study Group. Triple-antiretroviral (ARV) Prophylaxis during Pregnancy and Breastfeeding Compared to Short-ARV Prophylaxis to Prevent Mother-to-Child Transmission of HIV-1 (MTCT): The Kesho Bora Randomized Controlled Clinical Trial in Five Sites in Burkina Faso, Kenya and South Africa (Trial registration number ISRCTN71468401). Abstract LBPEC01. In: The 5th IAS Conference on HIV Pathogenesis and Treatment. Cape Town, South Africa, **2009**.
42. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med* **2009** Apr 30;360(18):1815-26.
43. Phillips A. Morbidity and Mortality in the HAART Era. Abstract 8. In: The 15th Conference on Retroviruses and Opportunistic Infections. Boston, USA, **2008**.
44. Anglaret X, Chene G, Attia A, et al. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Cote d'Ivoire: a randomised trial. *Cotrimo-CI Study Group. Lancet* **1999** May 1;353(9163):1463-8.
45. Danel C, Moh R, Minga A, et al. CD4-guided structured antiretroviral treatment interruption strategy in HIV-infected adults in west Africa (Trivacan ANRS 1269 trial): a randomised trial. *Lancet* **2006** Jun 17;367(9527):1981-9.
46. El-Sadr W, SMART study group. Re-initiation of ART in the CD4-guided ART Interruption Group in the SMART Study Lowers Risk of Opportunistic Disease or Death. Abstract 38. In: The 15th Conference on Retroviruses and Opportunistic Infections. Boston, USA, **2008**.
47. Danel C, Moh R, Chaix ML, et al. Two-months-off, four-months-on antiretroviral regimen increases the risk of resistance, compared with continuous therapy: a randomized trial involving West African adults. *J Infect Dis* **2009** Jan 1;199(1):66-76.
48. WHO. 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. [Accessed: 2009 July 16]; Available from: [http://www.who.int/child-adolescent-health/New\\_Publications/NUTRITION/consensus\\_statement.pdf](http://www.who.int/child-adolescent-health/New_Publications/NUTRITION/consensus_statement.pdf)
49. Becquet R, Leroy V, Ekouevi DK, et al. Complementary feeding adequacy in relation to nutritional status among early weaned breastfed children who are born to HIV-infected mothers: ANRS 1201/1202 Ditrane Plus, Abidjan, Côte d'Ivoire. *Pediatrics* **2006**;117(4):e701-10.
  50. Cames C, Mouquet C, Ayassou K, et al. A sustainable baby food support for HIV-1-infected mothers. The Kesho Bora study initiative in Bobo Dioulasso, Burkina Faso. Poster N°TUPE0356. In: The XVI International AIDS conference. Toronto, Canada. , **2006**.
  51. Taha TE, Kumwenda NI, Gibbons A, et al. Short postexposure prophylaxis in newborn babies to reduce mother-to-child transmission of HIV-1: NVAZ randomised clinical trial. *Lancet* **2003** 2003/10/11;362(9391):1171-7.
  52. Kilewo C, Karlsson K, Massawe A, et al. Prevention of Mother-to-Child Transmission of HIV-1 through breast-feeding by treating infants prophylactically with Lamivudine in Dar es Salaam, Tanzania: The Mitra Study. *J Acquir Immune Defic Syndr* **2008**;48(3):315-23.
  53. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended Antiretroviral Prophylaxis to Reduce Breast-Milk HIV-1 Transmission. *N Engl J Med* **2008**;359(2):119-29.
  54. Moorthy A, Gupta A, Bhosale R, et al. Nevirapine resistance and breast-milk HIV transmission: effects of single and extended-dose nevirapine prophylaxis in subtype C HIV-infected infants. *PLoS ONE* **2009**;4(1):e4096.
  55. Six Week Extended-Dose Nevirapine (SWEN) Study Team. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet* **2008** Jul 26;372(9635):300-13.
  56. Shearer WT. Breastfeeding and HIV infection. *Pediatrics* **2008** May;121(5):1046-7.
  57. Chasela C, Hudgens M, Jamieson D, et al. Both maternal HAART and daily infant nevirapine (NVP) are effective in reducing HIV-1 transmission during breastfeeding in a randomized trial in Malawi: 28 week results of the Breastfeeding, Antiretroviral and Nutrition (BAN) Study. Abstract WELBC103. . In: The 5th IAS Conference on HIV Pathogenesis and Treatment. Cape Town, South Africa, **2009**.
  58. Lehman DA, Chung MH, John-Stewart GC, et al. HIV-1 persists in breast milk cells despite antiretroviral treatment to prevent mother-to-child transmission. *Aids* **2008** Jul 31;22(12):1475-85.
  59. Kilewo C, Karlsson K, Ngarina M, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers prophylactically with triple antiretroviral therapy in Dar es Salaam, Tanzania - the MITRA PLUS study. In: The Third Conference on HIV Pathogenesis and Treatment. Rio De Janeiro, Brasil, **2005**.
  60. Marazzi MC, Palombi L, Liotta G, et al. Decrease in HIV-1 Mother-to-Child Transmission in Women Receiving Postnatal HAART: 12-Month Follow-up Data. Abstract 668 In: The 15th Conference on Retroviruses and Opportunistic Infections. Boston, USA. , **2008**.
  61. Palombi L, Marazzi MC, Voetberg A, Magid NA. Treatment acceleration program a experience of the DREAM program in prevention of mother-to-child transmission of HIV. *Aids* **2007**;21 Suppl. 4:S65-S71.
  62. Peltier A, Ndayisaba G, Lepage P, et al. Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother-to-child transmission in Rwanda. *Aids* (**in press**).
  63. Shapiro R, Hughes M, Ogwu A, et al. A Randomized Trial Comparing Highly Active Antiretroviral Therapy Regimens for Virologic Efficacy and the Prevention of Mother-to-Child HIV Transmission among Breastfeeding Women in Botswana (The Mma Bana Study). Abstract WELBB101. . In: The 5th IAS Conference on HIV Pathogenesis and Treatment. Cape Town, South Africa, **2009**.
  64. Thomas T, Masaba R, Ndivo R, et al. Prevention of Mother-to-Child Transmission of HIV-1 among Breastfeeding Mothers Using HAART: The Kisumu Breastfeeding Study, Kisumu, Kenya, 2003–2007. Abstract 45aLB. In: The 15th Conference on Retroviruses and Opportunistic Infections. Boston, USA. , **2008**.
  65. Tonwe-Gold B, Ekouevi DK, Viho I, et al. Peripartum and postnatal HIV transmission in West Africa: evaluation of a two-tiered Approach. *PLoS Medicine* **2007**;4(8):e257.
  66. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral Concentrations in Breast-feeding Infants of Mothers Receiving HAART. *Antimicrob Agents Chemother* **2009**;53(3):1170-6.
  67. Bae WH, Wester C, Smeaton LM, et al. Hematologic and hepatic toxicities associated with antenatal and postnatal exposure to maternal highly active antiretroviral therapy among infants. *Aids* **2008** Aug 20;22(13):1633-40.
  68. Thorne C, Newell ML. Safety of agents used to prevent mother-to-child transmission of HIV: is there any cause for concern? *Drug Saf* **2007**;30(3):203-13.
  69. Leroy V, Karon JM, Alioum A, et al. Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS* **2002**;16(4):631-41.
  70. Becquet R, Ekouevi DK, Menan H, et al. Early mixed feeding and breastfeeding beyond six months increase the risk of postnatal HIV transmission: ANRS 1201/1202 Ditrane Plus, Abidjan, Côte d'Ivoire. *Preventive Medicine* **2008**;47(1):27-33.
  71. Leroy V, Ekouevi DK, Becquet R, et al. 18-month effectiveness of short-course antiretroviral regimens combined with alternatives to breastfeeding to prevent HIV mother-to-child transmission. *PLoS ONE* **2008**;3(2):e1645.

72. Rollins NC, Becquet R, Bland RM, Coutoudis A, Coovadia HM, Newell ML. Infant feeding, HIV transmission and mortality at 18 months: The need for appropriate choices by mothers and prioritisation within programs. *AIDS* **2008**;22(17):2349-57.
73. Kuhn L, Aldrovandi GM, Sinkala M, et al. Effects of Early, Abrupt Weaning for HIV-free Survival of Children in Zambia. *N Engl J Med* **2008** Jun 4.
74. Vyankandondera J, Luchters S, Hassink E. Reducing risk of HIV-1 transmission from mother to infant through breastfeeding using antiretroviral prophylaxis in infants (SIMBA-study). Oral communication N°LB7. In: The 2<sup>nd</sup> IAS Conference on HIV Pathogenesis and Treatment. Paris, France. , **2003**.



**Table 1.** 12-24 mother-to-child transmission (MTCT) rates and infant death (95% CI) among breastfed children with the provision of peri-partum short-course antiretroviral (ARV) regimens to the mother during pregnancy/delivery.

Study	ARV intervention		MTCT risk according to baseline maternal CD4 count	Infant infection or death (1 – HIV-free survival) according to baseline maternal CD4 count
	Maternal regimen Infant regimen	Duration	(95% confidence interval)	
Ditrame & Retro-Ci, Côte d'Ivoire [69]	ZDV	from 36-38 weeks of gestation, plus 7 days post-partum	Among women with CD4 <500 cells/mm <sup>3</sup> : 25.6% at 1.5 Mo (17.9-33.3) 29.3% at 6 Mo (31.4-37.2) 38.5% at 12 Mo (29.7-46.3)	Among women with CD4 <500 cells/mm <sup>3</sup> : 28.8% at 1.5 Mo (21.2-36.5) 32.8% at 6 Mo (24.8-40.6) 41.0% at 12 Mo (32.0-50.1)
	no ARV for infants		Among women with CD4 ≥500 cells/mm <sup>3</sup> : 7.7% at 1.5 Mo (3.6-11.8) 8.8% at 6 Mo (4.5-13.1) 9.1% at 12 Mo (4.8-13.4)	Among women with CD4 ≥500 cells/mm <sup>3</sup> : 10.2% at 1.5 Mo (5.5-14.8) 10.8% at 6 Mo (6.0-15.7) 11.6% at 12 Mo (6.7-16.4)
Ditrame Plus, Côte d'Ivoire [70, 71]	ZDV+sdNVP	from 36 weeks of gestation	8.6% at 1.5 Mo (2.9-13.2) 10.1% at 6 Mo (5.5-14.9) 15.9% at 18 Mo (9.6-26.5)	16.8% at 18 Mo (12-24)
	NVP single dose + 7 days of ZDV for infants			
	ZDV/3TC+sdNVP	from 32 weeks of gestation, plus 3 days post-partum	6.2% at 1.5 Mo (3.1-9.9) 6.8% at 6 Mo (3.6-10.7) 13.0% at 18 Mo (3.6-10.7)	13.6% at 18 Mo (9.6-24.5)
	NVP single dose + 7 days of ZDV for infants			
Vertical Transmission Study, South Africa [72]	sdNVP	-	21.0% at 18 Mo (19.0-23.1)	24.0% at 18 Mo (22-27)
ZEBS, Zambia [73]	sdNVP	-	Short-term breastfeeding 21.4% at 24 Mo *	Short-term breastfeeding 32.6% at 24 Mo *
			Long-term breastfeeding 25.8% at 24 Mo *	Long-term breastfeeding 36% at 24 Mo *
MTCT-Plus, Côte d'Ivoire [65]	ZDV/3TC+sdNVP	from 32 weeks of gestation, plus 3 days post-partum	Among women <u>not</u> eligible for ARV therapy: 3.1% at 1 Mo (0.1-6.7) 7.5% at 12 Mo (2.8-12.3)	Among women <u>not</u> eligible for ARV therapy: 12.1% at 12 Mo (6.4-17.9)
	NVP single dose + 7 days of ZDV for infants			

\* Confidence interval was not available. 3TC: lamivudine; sdNVP: single-dose nevirapine; ZDV: zidovudine.

#### Median breastfeeding durations were:

8 months for the Ditrame & Retro-Ci trials; 4 months for the Ditrame Plus study; 6 months for the Vertical Transmission Study; 4 and 16 months in the short-term and long-term breastfeeding groups of the ZEBS study, respectively; 6 months in the MTCT Plus study.

**Table 2.** 18-month postnatal transmission of HIV among children uninfected at 4 weeks of age and according to different thresholds of maternal antenatal CD4 count. Pooled analysis of the Vertical Transmission Study (South Africa, 2001-2007) and the Ditrane Plus Study (Côte d'Ivoire, 2001-2005). N=1151.

Antenatal maternal CD4 count (cells/ml)	N	Number of children HIV-infected through breastfeeding	HIV postnatal transmission (%)	95% confidence interval
< 200	119	15	15.3	9.5-24.2
≥ 200	1032	57	6.2	4.9-8.0
< 250	181	20	11.0	5.3-16.2
≥ 250	970	52	5.4	3.5-6.5
< 350	353	38	12.6	9.3-16.9
≥ 350	798	34	4.8	3.4-6.6
< 200	119	15	15.3	9.5-24.2
200-349	234	23	11.3	7.6-16.5
350-500	320	18	6.3	4.9-9.1
≥ 500	478	16	3.7	2.3-6.0

Adapted from Becquet et al. CROI 2008 [35]

**Table 3.** Mother-to-child transmission (MTCT) rates (95% confidence interval) with the provision of antiretroviral post-exposure prophylaxis to the breastfed infant.

Study	Antiretroviral intervention		MTCT risk (95% confidence interval)
	Maternal regimen	Infant regimen	
SIMBA, Rwanda [74]	ZDV+ddl	daily NVP or 3TC *	6.9% at 1 Mo ** 7.7% at 6 Mo **
	<i>from 36 weeks of gestation to 1 week post-partum</i>	<i>from birth up to 6 months</i>	
MASHI, Botswana [10]	ZDV+sdNVP	daily ZDV	4.6% at 1 Mo ** 9.0% at 7 Mo ** 9.5% at 18 Mo **
	<i>from 36 weeks of gestation to 1 week post-partum</i>	<i>from birth up to 6 months</i>	
MITRA, Tanzania [52]	ZDV+3TC	daily 3TC	3.8% at 1.5 Mo (2.0-5.6) 4.9% at 6 Mo (2.7-7.1)
	<i>from 36 weeks of gestation to 1 week post-partum</i>	<i>from birth up to 6 months</i>	
PEPI, Malawi [53]	sdNVP	daily NVP or NVP/ZDV	<i>Among infants who were HIV-uninfected at birth</i> Infant NVP prophylaxis 5.9% at 9 Mo (3.9-7.0)
		<i>from birth up to 14 weeks</i>	Infant NVP/ZDV prophylaxis 6.4% at 9 Mo (4.9-8.3)
SWEN, Ethiopia, Uganda, India [55]	sdNVP	daily NVP	<i>Among infants who were HIV-uninfected at birth</i> 2.5% at 1.5 Mo ** 6.9% at 6 Mo **
		<i>from birth up to 6 weeks</i>	

\* Similar MTCT rates were observed in both groups.

\*\* Confidence interval was not available.

3TC: lamivudine; ddl: didanosine; sdNVP: single-dose nevirapine; ZDV: zidovudine.

#### Median breastfeeding durations were:

14 weeks in the SIMBA study; unknown in the MASHI study (mothers instructed to wean at 5 months); 18 weeks in the MITRA study; unknown in the PEPI study (most infants were weaned between 6 and 9 months of age); unknown in the SWEN study (most infants were weaned between 14 weeks and 6 months of age).

**Table 4.** 6-12 month mother-to-child transmission (MTCT) rates and infant death (95% confidence interval) with the provision of antiretroviral therapy to the mother during pregnancy and breastfeeding.

Study	Antiretroviral intervention		MTCT risk according to baseline maternal CD4 count	Infant infection or death (1 – HIV-free survival) according to baseline maternal CD4 count
	Maternal regimen Infant regimen	Duration	(95% confidence interval)	
Kisumu, Kenya [64]	ZDV/3TC+NVP *	from 34 weeks of gestation until 6 Mo post-partum	Among women with CD4 <250 cells/mm <sup>3</sup> : 4.3% at 1 Mo (1.8-10.0) 5.2% at 6 Mo (2.4-11.2) 6.7% at 12 Mo (3.2-13.9)	<i>not available</i>
	NVP single dose for infants	but continued if WHO treatment criteria were met	Among women with CD4 ≥250 cells/mm <sup>3</sup> : 3.8% at 1 Mo (2.2-6.3) 4.9% at 6 Mo (3.1-7.7) 5.5% at 12 Mo (3.6-8.4)	
Kesho-Bora, Burkina Faso - Kenya [40, 41]	ZDV/3TC+NVP	from 18-36 weeks of gestation	Among women with CD4 <200 cells/mm <sup>3</sup> : 6.4% at 12 Mo (0.3-12.4)	Among women with CD4 <200: 10.8% at 12 Mo (3.2-18.3)
	NVP single dose for infants			
MTCT-Plus, Côte d'Ivoire [65]	ZDV/3TC+NVP	from 20 weeks of gestation	Among women eligible for ARV therapy: 1.0% at 1 Mo (0.0-3.1) 3.3% at 12 Mo (0.0-6.9)	Among women eligible for ARV therapy: 11.2% at 12 Mo (5.0-17.4)
	NVP single dose + 1 week of ZDV for infants			
AMATA, Rwanda [62]	HAART eligible (CD4<350 or stage IV); D4T+3TC+NVP	Non eligible: from 28 weeks of gestation until 7 Mo post-partum	1.3% at 1 Mo (0.4-4.1%) 1.8% at 1 Mo (0.7-4.8%)	Overall: 5.0% at 9 Mo (3.0-9.0)
	Non eligible ZDV+3TC+EFZ	stop breastfeeding at 6 Mo		
	NVP single-dose + 1 week of ZDV for infants in both strata			
MITRA-PLUS, Tanzania [59]	ZDV/3TC+NVP	from 34 weeks of gestation until 6 Mo postpartum	4.1 % at 1.5 Mo (2.1-6.0) 5.0% at 6 Mo (3.2-7.0)	<i>not available</i>
	1 week of ZDV-3TC for infants	continued if mother eligible for treatment at 6 Mo		
Dream cohort, Mozambique [60, 61]	ZDV/3TC+NVP	from 15 weeks of gestation	Among women eligible for ARV therapy: 1.2% at 1 Mo ** 2.2% at 6 Mo ** 2.8% at 12 Mo **	<i>not available</i>
	NVP single dose for infants			

\* Half-way through the trial, NVP was replaced by nelfinavir among women with CD4 &gt;250 cells/ml.

\*\* Confidence interval was not available. 3TC: lamivudine; sdNVP: single-dose nevirapine; ZDV: zidovudine.

## Online Appendix 1.

The PEPI study, conducted in Malawi, randomised children born to mothers who had received single-dose NVP to receive either a neonatal single-dose of NVP and one week of ZDV (group 1), or 14 weeks of extended daily infant ARV prophylaxis with NVP (group 2) or NVP+ZDV (group 3) [1]. At 9 months of age, the risk of HIV infection was 10.6% in group 1, 5.2% in group 2 and 6.4% in group 3. However, at 18 months, HIV rates were as high as 13.9% in group 1, 10.1% in group 2 and 10.2% in group 3. In the SWEN study, conducted as parallel randomised trials in Ethiopia, India and Uganda, an extended infant post-exposure prophylaxis with daily NVP from birth during six weeks was assessed in breastfed children, and compared to single-dose NVP (all mothers had received single-dose NVP) [2]. The 6-week transmission rate in the extended-NVP arm was 2.5% versus 5.3% in the single-dose NVP arm ( $p=0.009$ ), but the 6-month HIV transmission rate was similar in both study arms: 8.9% in the extended-NVP arm vs. 6.9% in the single-dose NVP arm ( $p=0.16$ ). Moreover, nearly all (92%) infants who became infected in the extended-NVP arm developed NNRTI resistance mutations [3]. In Tanzania, breastfed children received daily 3TC from birth through six months of age, while their mothers received daily ZDV+3TC from the third trimester of pregnancy until one week post-partum [4]. HIV-transmission rates were 3.8% and 4.9% at six weeks and six months of age, respectively. However, the breastfeeding duration was considerably shorter than usual African practices (18 weeks in median), and only 15% of the children were still breastfed at six months of age.

1. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended Antiretroviral Prophylaxis to Reduce Breast-Milk HIV-1 Transmission. *N Engl J Med* 2008;359(2):119-29.
2. Six Week Extended-Dose Nevirapine (SWEN) Study Team. Extended-dose nevirapine to 6 weeks of age for infants to prevent HIV transmission via breastfeeding in Ethiopia, India, and Uganda: an analysis of three randomised controlled trials. *Lancet* 2008 Jul 26;372(9635):300-13.
3. Moorthy A, Gupta A, Bhosale R, et al. Nevirapine resistance and breast-milk HIV transmission: effects of single and extended-dose nevirapine prophylaxis in subtype C HIV-infected infants. *PLoS ONE* 2009;4(1):e4096.
4. Kilewo C, Karlsson K, Massawe A, et al. Prevention of Mother-to-Child Transmission of HIV-1 through breast-feeding by treating infants prophylactically with Lamivudine in Dar es Salaam, Tanzania: The Mitra Study. *J Acquir Immune Defic Syndr* 2008;48(3):315-23.

## Online Appendix 2.

In Kisumu, Kenya, the 12-month transmission rate for children born to mothers with a baseline CD4 count  $>250$  cells/ml and receiving ARV therapy from 34 weeks of gestation until 6 months post-partum was 5.5% [1]. In this study, the overall transmission attributable to breastfeeding was 3.5% at 12 months of age. However maternal HAART was stopped at six months of age if WHO treatment criteria were not met, even if children were still being breastfed. Thus, among women with baseline CD4 count  $>250$  cells/ml, the postnatal transmission risk was 1.7%: 1.1% occurred between months 1 and 6 (i.e. while mothers were on ARV treatment), and 0.6% occurred between six and 12 months of age (i.e. after the maternal HAART was stopped). Among women with a baseline CD4 count  $<250$  cells/ml, the maternal HAART was continued beyond six months of age. The postnatal transmission risk in this higher-risk subgroup was 2.4% between months 1 and 12. In Côte d'Ivoire and Mozambique, although maternal ARV treatment had been provided to HAART-eligible women from the third trimester of pregnancy and throughout the breastfeeding exposure, the cumulative postnatal HIV transmission rate (between 1 and 12 months) was 2.3 and 1.6%, respectively [2-4]. The postnatal transmission risk between months 1 and 6 was estimated at 0.8% in Mozambique [3-4], and 0.9% in Tanzania [5]. Finally, the open-label AMATA trial in Rwanda yielded the lowest transmission rate ever reported after six months of continuous breastfeeding exposure and maternal HAART [6]. More recently, very low transmission rates have also been reported at 6 months post-partum in Botswana among women with CD4  $\geq 200$  cells/ml treated with HAART [7], but more detailed data beyond that age are now expected.

1. Thomas T, Masaba R, Ndivo R, et al. Prevention of Mother-to-Child Transmission of HIV-1 among Breastfeeding Mothers Using HAART: The Kisumu Breastfeeding Study, Kisumu, Kenya, 2003–2007. Abstract 45aLB. In: The 15th Conference on Retroviruses and Opportunistic Infections. Boston, USA, 2008.
2. Tonwe-Gold B, Ekouevi DK, Viho I, et al. Peripartum and postnatal HIV transmission in West Africa: evaluation of a two-tiered Approach. *PLoS Medicine* 2007;4(8):e257.
3. Marazzi MC, Palombi L, Liotta G, et al. Decrease in HIV-1 Mother-to-Child Transmission in Women Receiving Postnatal HAART: 12-Month Follow-up Data. Abstract 668 In: The 15th Conference on Retroviruses and Opportunistic Infections. Boston, USA, 2008.
4. Palombi L, Marazzi MC, Voetberg A, Magid NA. Treatment acceleration program a experience of the DREAM program in prevention of mother-to-child transmission of HIV. *Aids* 2007;21 Suppl. 4:S65-S71.
5. Kilewo C, Karlsson K, Ngarina M, et al. Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers prophylactically with triple antiretroviral therapy in Dar es Salaam, Tanzania - the MITRA PLUS study. In: The Third Conference on HIV Pathogenesis and Treatment. Rio De Janeiro, Brasil, 2005.
6. Peltier A, Ndayisaba G, Lepage P, et al. Breastfeeding with maternal antiretroviral therapy or formula feeding to prevent HIV postnatal mother-to-child transmission in Rwanda. *Aids* (in press).
7. Shapiro R, Hughes M, Ogwu A, et al. A Randomized Trial Comparing Highly Active Antiretroviral Therapy Regimens for Virologic Efficacy and the Prevention of Mother-to-Child HIV Transmission among Breastfeeding Women in Botswana (The Mma Bana Study). Abstract WELBB101. In: The 5th IAS Conference on HIV Pathogenesis and Treatment. Cape Town, South Africa, 2009.