Universal antiretroviral therapy for pregnant and breast-feeding HIV-1-infected women: towards the elimination of mother-to-child transmission of HIV-1 in resource-limited settings.

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Universal antiretroviral therapy for pregnant and breast-feeding HIV-1-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.

MESH Keywords Acquired Immunodeficiency Syndrome ; drug therapy ; immunology ; Antiretroviral Therapy, Highly Active ; Breast Feeding ; adverse effects ; CD4 Lymphocyte Count ; Female ; HIV-1 ; Health Resources ; Humans ; Infectious Disease Transmission, Vertical ; prevention & control ; Pregnancy ; Pregnancy Complications, Infectious ; drug therapy

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 eliminates, 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 (± 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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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 (95% confidence interval)	Infant infection or death (1 – HIV-free survival) according to baseline maternal CD4 count
	Maternal regimen Infant regimen	Duration		
Ditrame & Retro-Ci, Côte d' Ivoire [69]	ZDV no ARV for infants	from 36–38 weeks of gestation, plus 7 days post-partum	Among women with CD4 <500 cells/mm^3 : 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^3 : 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^3 : 28.8% at 1.5 Mo (21.2–36.5) 32.8% at 6 Mo (24.8–40.6) 32.8% at 6 Mo (24.8–40.6) 41.0% at 12 Mo (32.0–50.1) Among women with CD4 ≥500 cells/mm^3 : 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 NVP single dose + 7 days of ZDV for infants ZDV/3TC+sdNVP NVP single dose + 7 days of ZDV for infants	from 36 weeks of gestation from 32 weeks of gestation, plus 3 days post-partum	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) 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)	16.8% at 18 Mo (12–24) 13.6% at 18 Mo (9.6–24.5)
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 * Long-term breastfeeding 25.8% at 24 Mo *	Short-term breastfeeding 32.6% at 24 Mo * Long-term breastfeeding 36% at 24 Mo *
MTCT-Plus, Côte d'Ivoire [65]	ZDV/3TC+sdNVP NVP single dose + 7 days of ZDV for infants	from 32 weeks of gestation, plus 3 days post-partum	Among women not eligible for ARV therapy: 3.1% at 1 Mo (0.1–6.7) 7.5% at 12 Mo (2.8–12.3)	Among women not eligible for ARV therapy: 12.1% at 12 Mo (6.4–17.9)

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

* Similar MTCT rates were observed in both groups.

** Confidence interval was not available.

3TC: Iamivudine; 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 (95% confidence interval)	Infant infection or death (1 – HIV-free survival) according to baseline maternal CD4 count
	Maternal regimen Infant regimen	Duration		
Kisumu, Kenya [64]	ZDV/3TC+NVP * NVP single dose for infants	from 34 weeks of gestation until 6 Mo post-partum but continued if. WHO treatment criteria were met	Among women with CD4 <250 cells/mm^3 : 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) Among women with CD4 ≥250 cells/mm^3 : 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)	not available
Kesho-Bora, Burkina Faso -Kenya [40, 41]	ZDV/3TC+NVP NVP single dose for infants	from 18–36 weeks of gestation	Among women with CD4 <200 cells/mm^3 : 6.4% at 12 Mo (0.3–12.4)	Among women with CD4 <200: 10.8% at 12 Mo (3.2–18.3)
MTCT-Plus, Côte d' Ivoire [65]	ZDV/3TC+NVP NVP single dose + 1 week of ZDV for infants	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)
AMATA, Rwanda [62]	HAART eligible (CD4<350 or stage IV): D4T+3TC+NVP Non eligible ZDV+3TC+EFZ NVP single-dose + 1 week of ZDV for infants in both strata	Non eligible: from 28 weeks of gestation until 7 Mo post-partum stop breastfeeding at 6 Mo	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)
MITRA-PLUS, Tanzania [59]	ZDV/3TC+NVP 1 week of ZDV-3TC for infants	from 34 weeks of gestation until 6 Mo postpartum continued if mother eligible for tretament at 6 Mo	4.1 % at 1.5 Mo (2.1–6.0) 5.0% at 6 Mo (3.2–7.0)	not available
Dream cohort, Mozambique [60, 61]	ZDV/3TC+NVP NVP single dose for infants	from 15 week of gestation	Among women eligible for ARV therapy: 1.2 % at 1 Mo ** 2.2% at 6 Mo ** 2.8% at 12 Mo **	not available

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

** Confidence interval was not available.

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