# 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

Renaud Becquet,[1,2] Didier K. Ekouevi,[1,2,7] Elise Arrive,[1,2] Jeffrey S. A. Stringer,[8,9] Nicolas Meda,[10] Marie-Laure Chaix,[3,4] Jean-Marc Treluyer,[3,5] Valériane Leroy,[1,2] Christine Rouzioux,[3,4] Stéphane Blanche,[3,6] and François Dabis[1,2]

[1]INSERM, Unité 897, Centre de Recherche "Epidémiologie et Biostatistique," and [2]Institut de Santé Publique Epidémiologie Développement (ISPED), Université Victor Segalen Bordeaux 2, Bordeaux, [3]Université Paris Descartes, EA3620, [4]Service de Virologie, Centre Hospitalier Universitaire Necker Enfants Malades, [5]Laboratoire de pharmacologie clinique, Centre Hospitalier Universitaire Cochin-Saint-Vincent-de-Paul, and [6] Unité d'immunologie et hématologie pédiatrique, Centre Hospitalier Universitaire Necker Enfants Malades, Paris, France; [7]ANRS site in Côte d'Ivoire (PAC-CI), Centre Hospitalier Universitaire de Treichville, Abidjan, Côte d'Ivoire; [8]Centre for Infectious Disease Research in Zambia, Lusaka, Zambia; [9]Schools of Medicine and Public Health, University of Alabama, Birmingham, United States; [10]ANRS site in Burkina Faso, Université de Ouagadougou, Ouagadougou, Burkina Faso

**Prevention of mother-to-child transmission (MTCT) of human immunodeficiency virus type 1 (HIV-1) 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 and are also infrequently used. Furthermore, postnatal transmission via breast-feeding is a serious additional threat. Modifications of infant feeding practices aim to reduce HIV-1 transmission through breast milk; replacement feeding is neither affordable nor safe for the majority of African women, and early breast-feeding cessation (eg, prior to 6 months of life) requires substantial care and nutritional counseling to be practiced 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 breast-feeding women, with good efficacy, or single-drug postexposure 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 pediatric AIDS lies in the universal provision of fully suppressive ARV regimens to all HIV-1–infected women through pregnancy, delivery, and the entire breast-feeding period. On the basis of 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 (MTCT) of human immunodeficiency virus type 1 (HIV-1) in breast-feeding 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 program scale-up, though 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 pediatric AIDS worldwide, through the universal use of antiretroviral (ARV) regimens in pregnant and breast-feeding women.

## PREVENTION OF MTCT IN AFRICA: PAST SUCCESSES AND CURRENT PROGRAMMATIC CHALLENGES

MTCT can occur in utero, during delivery, or through breast-feeding and is responsible for the majority of pediatric HIV-1 infections. Each day, an estimated 1600 children become infected with HIV-1 worldwide, 90% of whom live in sub-Sa-

**Table 1. Mother-to-Child Transmission (MTCT) Rates and Infant Death among Breast-Fed Children Whose Mothers Received Peripartum Short-Course Antiretroviral (ARV) Regimens during Pregnancy and/or Delivery**

| Study | ARV intervention | | | Median duration of breast-feeding, months | MTCT risk (95% CI), % | Risk of HIV-1 infection or death (95% CI), % |
|---|---|---|---|---|---|---|
| | Maternal regimen | Infant regimen | Duration | | | |
| Ditrame & Retro-Ci [6], Côte d'Ivoire | ZDV | ... | From 36–38 weeks of gestation, plus 7 days postpartum | 8 | Among women with CD4 <500 cells/mm³: at 1.5 months, 25.6 (17.9–33.3); at 6 months, 29.3 (31.4–37.2); at 12 months, 38.5 (29.7–46.3) | Among women with CD4 <500 cells/mm³: at 1.5 months, 28.8 (21.2–36.5); at 6 months, 32.8 (24.8–40.6); at 12 months, 41.0 (32.0–50.1) |
| Ditrame & Retro-Ci [6], Côte d'Ivoire | ZDV | ... | From 36–38 weeks of gestation, plus 7 days postpartum | 8 | Among women with CD4 ≥500 cells/mm³: at 1.5 months, 7.7 (3.6–11.8); at 6 months, 8.8 (4.5–13.1); at 12 months, 9.1 (4.8–13.4) | Among women with CD4 ≥500 cells/mm³: at 1.5 months, 10.2 (5.5–14.8); at 6 months, 10.8 (6.0–15.7); at 12 months, 11.6 (6.7–16.4) |
| Ditrame Plus [7, 8], Côte d'Ivoire | ZDV plus single-dose NVP | Single-dose NVP plus 7 days of ZDV | From 36 weeks of gestation | 4 | At 1.5 months, 8.6 (2.9–13.2); at 6 months, 10.1 (5.5–14.9); at 18 months, 15.9% (9.6–26.5) | At 18 months, 16.8 (12–24) |
| Ditrame Plus [7, 8], Côte d'Ivoire | ZDV/3TC plus single-dose NVP | Single-dose NVP plus 7 days of ZDV | From 32 weeks of gestation, plus 3 days postpartum | 4 | At 1.5 months, 6.2 (3.1–9.9); at 6 months, 6.8 (3.6–10.7); at 18 months, 13.0 (3.6–10.7) | At 18 months, 13.6 (9.6–24.5) |
| Vertical Transmission Study [9], South Africa | ZDV/3TC plus single-dose NVP | Single-dose NVP | ... | 6 | At 18 months, 21.0 (19.0–23.1) | At 18 months, 24.0 (22–27) |
| ZEBS [10], Zambia | Single-dose NVP | ... | ... | 4 | Short-term breast-feeding: at 24 months, 21.4 | Short-term breast-feeding: at 24 months, 32.6 |
| ZEBS [10], Zambia | Single-dose NVP | ... | ... | 16 | Long-term breast-feeding: at 24 months, 25.8 | Long-term breast-feeding: at 24 months, 36 |
| MTCT-Plus [11], Côte d'Ivoire | ZDV/3TC plus single-dose NVP | Single-dose NVP plus 7 days of ZDV | From 32 weeks of gestation, plus 3 days postpartum | 6 | Among women not eligible for ARV therapy: at 1 month, 3.1 (0.1–6.7); at 12 months, 7.5 (2.8–12.3) | Among women not eligible for ARV therapy: at 12 months, 12.1 (6.4–17.9) |

**NOTE.** 3TC, lamivudine; CI, confidence interval; HIV-1, human immunodeficiency virus type 1; NVP, nevirapine; ZDV, zidovudine.

**Table 2. Eighteen-Month Postnatal Transmission of Human Immunodeficiency Virus Type 1 (HIV-1) among Children Uninfected at 4 Weeks of Age, According to Antenatal Maternal CD4 Count**

| Antenatal maternal CD4 count, cells/mL | No of children | No of children infected through breast-feeding | HIV-1 postnatal transmission (95% CI), % |
|---|---|---|---|
| <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) |

**NOTE.** Pooled analysis of the Vertical Transmission Study (South Africa, 2001–2007) and the Ditrame Plus Study (Côte d'Ivoire, 2001–2005) (N = 1151). Table adapted from Becquet et al [41]. CI, confidence interval.

haran Africa, where vertically-acquired HIV-1 disease remains a major contributor to child mortality [1]. Scientific successes for the prevention of MTCT have been achieved over the past decade with the development of effective ARV interventions. However, this prevention is challenging in Africa [2–5]. This relative failure of MTCT prevention at the public health level is mostly explained by 3 reasons [3]: (1) global coverage of HIV-1 testing and counseling remains unsatisfactorily low, and too few women are offered effective interventions to prevent MTCT; (2) the mainstay intervention of single-dose nevirapine prophylaxis is moderately effective but induces viral drug resistance in HIV-1–infected mothers and infants; and (3) prevention of transmission via breast-feeding has remained largely elusive.

***The need for effective interventions to prevent HIV-1 transmission through breast milk.*** As detailed in Table 1, short-course peripartum prophylaxis with one or more ARV drugs reduces the MTCT risk around delivery [12], but the subsequent risk of postnatal transmission remains high in settings where prolonged breast-feeding is practised [13]. Various infant feeding interventions, such as early breast-feeding cessation or replacement feeding from birth, can reduce or eliminates, respectively the postnatal transmission risk without increasing infant mortality in well-supported research settings [14–16]. 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 [17–19]. 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 3 ARV drugs initiated during pregnancy and continued during lactation might represent an alternative intervention that allows safe breast-feeding, especially when water availability and uninterrupted supplies of breast-milk substitutes are not assured [20]. Indeed, HAART reduces the infectivity of all body secretions and thus lowers the rate of HIV-1 transmission [21, 22]. The safety and efficacy of this strategy is currently being assessed among women in Africa through intervention trials using a variety of ARV regimens. Acceptable, efficient, and safe ARV interventions aimed at preventing HIV-1 transmission for the majority of women, 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-1–infected pregnant mothers and their infants in resource-constrained settings typically involve intrapartum and neonatal single-dose nevirapine and may be supplemented with antenatal zidovudine and/or lamivudine. These regimens produce MTCT risk reductions ranging from 37% to 77%, compared with no intervention [23–29]. However, one-tenth to two-thirds of women who take a single dose of nevirapine will develop viral resistance to the nonnucleoside reverse-transcriptase inhibitors (NNRTIs) [30]. This problem can be substantially reduced by combining the use of single-dose nevirapine with short-courses of lamivudine (with or without zidovudine) for 7 days after delivery [31, 32]. A single intrapartum dose of tenofovir and emtricitabine also reduces the rate of NNRTI resistance by one-half [33]. None of these approaches fully eliminate 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 6 months after exposure to single-dose nevirapine [34, 35]. Previous single doses of nevirapine did not compromise the efficacy of subsequent NNRTI-based HAART started ≥6 months after delivery [34–36]. 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-1 status.*** HIV-1 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-1 test in

2007 [37]. In this context, most women present late in pregnancy or even in the labor ward unaware of their HIV-1 infection status. These women may be offered partially effective ARV regimens, such as single-dose nevirapine, but usually are offered no intervention for preventing postnatal transmission [38]. 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. Interventions that take subsequent treatment of these women into account and strategies to increase the proportion of pregnant women who know their HIV-1 status [39] 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, 37]. 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 breast-feeding cessation [3]. All these prevention strategies must be ARV-based; safe during pregnancy, labor, and lactation; well tolerated; durable; and not inducing of viral drug resistance. Moreover, the ideal drug combinations would also be appropriate in women presenting late for delivery [5, 40].

## THE SCIENTIFIC CHALLENGES OF THE PREVENTION OF MTCT THROUGH BREAST-FEEDING

*Effective PMTCT interventions exist for women eligible for ARV treatment.* The risk of HIV-1 transmission through breast-feeding is 3–10 times higher among women with CD4 counts <200 cells/mL than for those above this threshold [41, 42]. According to WHO guidelines, pregnant women with a low CD4 count are eligible for ARV therapy for their own health. Once initiated, HAART will rap-

idly and constantly reduce the maternal viral load in plasma and breast milk, likely reducing the MTCT risk through breast-feeding [43, 44]. However, at least two-thirds of HIV-1–infected pregnant and breast-feeding women are not ill enough to require ARV therapy for their own health according to the rather restrictive WHO guidelines (CD4 count <200 cells/mL, WHO clinical stage IV, or CD4 count <350 cells/mL and WHO clinical stage III) [45]. Thus, in settings where breast-feeding women with low CD4 counts receive HAART, but 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-1 transmission occurred in women with CD4 count >200 cells/mL [41]. In this pooled analysis, the breast-feeding duration was a median of 4 months (interquartile range, 4.4–12.4 months), 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% confidence interval, 2.2%–12.8%) among children born to mothers with baseline CD4 counts >500 cells/mL who received a short-course of zidovudine antenatally, a single-dose of intrapartum nevirapine, and no postpartum ARV intervention. The median breast-feeding duration was 18 months in this group (interquartile range, 9–25 months ) [46, 47]. Thus, the universal use of maternal HAART regimens throughout the entire breast-feeding 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 breast-feeding.* In a context where all HIV-1–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; international guidelines are currently in revision to adjust to this new evidence [48, 49]. 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 [50].

According to the current WHO recommendations, only pregnant and breast-feeding women who are eligible for ARV therapy because of their own health should continue HAART during the breast-feeding 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 nonpregnant adults have suggested that intermittent, CD4 count–guided HAART (ie, stopping therapy when the CD4 count decreased below 350 cells/mL) was associated with an increased risk of opportunistic disease or death [51, 52]. Similarly, a fixed 2-month off intermittent therapy led to a higher proportion of patients with CD4 counts <350 cells/mL [53].

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 breast-feeding period. Rules for stopping HAART in the fraction of women who are symptom-free and have reached high CD4 counts at the time of breast-feeding cessation (ie, ≥500 cells/mL) will need to be tailored to the evolving knowledge in this field. We strongly advocate for this universal maternal HAART approach, which may allow narrowing the gap with the rapidly evolving treatment guidelines for adults.

*Supporting women to make breast-feeding cessation at 6 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

**Table 3. Mother-to-Child Transmission (MTCT) Rates with the Provision of Antiretroviral Postexposure Prophylaxis to the Breast-Fed Infant**

| Study, location | Antiretroviral intervention | | MTCT risk (95% CI), % |
| | Maternal regimen, duration | Infant regimen | |
| --- | --- | --- | --- |
| SIMBA [62], Rwanda | ZDV plus ddI, from 36 weeks of gestation to 1 week postpartum | Daily NVP or 3TC,[a] from birth up to 6 months | At 1 month, 6.9; at 6 months, 7.7 |
| MASHI [16], Botswana | ZDV plus single-dose NVP, from 36 weeks of gestation to 1 week postpartum | Daily ZDV, from birth up to 6 months | At 1 month, 4.6; at 7 months, 9.0; at 18 months, 9.5 |
| MITRA [58], Tanzania | ZDV plus 3TC, from 36 weeks of gestation to 1 week postpartum | Daily 3TC, from birth up to 6 months | At 1.5 months, 3.8 (2.0–5.6); at 6 months, 4.9 (2.7–7.1) |
| PEPI [59], Malawi | Single-dose NVP | Daily NVP or NVP/ZDV, from birth up to 14 weeks | Among infants who were HIV-1–uninfected at birth: infant NVP prophylaxis at 9 months, 5.9 (3.9–7.0); infant NVP/ZDV prophylaxis at 9 months, 6.4 (4.9–8.3) |
| SWEN [61], Ethiopia, Uganda, India | Single-dose NVP | Daily NVP, from birth up to 6 weeks | Among infants who were HIV-1–uninfected at birth: at 1.5 months, 2.5; at 6 months, 6.9 |

**NOTE.** The median breast-feeding duration was 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), and unknown in the SWEN study (most infants were weaned between 14 weeks and 6 months of age). 3TC, lamivudine; CI, confidence interval; ddI, didanosine; NVP, nevirapine; ZDV, zidovudine.

[a] Similar MTCT rates were observed in both the NVP and 3TC groups.

breast-feeding in the first months of life while minimizing the HIV-1 transmission risk. This needs to be coupled with breast-feeding cessation at ~6 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 who were breast-fed for >6 months than among children who were breast-fed for ≤6 months [41]. Breast-feeding beyond 6 months should therefore be avoided when replacement feeding after breast-feeding cessation can be safely and sustainably provided, as recommended by WHO [54]. Women need to be counseled properly to provide adequate complementary feeding with locally available foods to replace breast milk from 6 months onwards. Adequate feeding practices around the weaning period are indeed crucial for achieving optimal child growth. The study in Côte d'Ivoire showed that inadequate complementary feeding at the age of 6 months was associated with impaired child growth during the following 12

months [55]. In this cohort, the risk of stunting growth was 50% higher in children for whom the dietary diversity was inappropriate in the months following the breast-feeding cessation process, compared with those adequately fed during this crucial period.

Further research will be required to provide HIV-1–infected women with innovative strategies to reduce the risk of postnatal transmission beyond 6 months of age while ensuring postnatal nutritional support for adequate complementary feeding practices [56]. This should be done in addition to and not as an alternative to maternal HAART.

***The maternal versus infant approach to preventing the postnatal MTCT risk.*** ARV drugs can be administered to infants as prophylaxis against HIV-1 exposure. In Malawi, a very short course of nevirapine was administered to newborns of HIV-1–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 [57].

More recently, 3 studies have docu-

mented the efficacy of a more extended ARV prophylaxis in breast-fed infants [58–61] and provide provocative but not entirely satisfactory results (Table 3; Appendix A, which appears only on the online version of the journal).

Thus, the administration of ARV drugs to breast-fed infants is another possible strategy to reduce postnatal HIV-1 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 breast-feeding exposure [63] and should involve drugs that are not as likely as nevirapine to select resistant virus and compromise the future treatment needs of HIV-1–infected children. The BAN study, currently underway in Malawi, is expected to yield more results on this issue [64]. 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).

**Table 4. Mother-to-Child Transmission (MTCT) Rates and Infant Death with the Provision of Antiretroviral Therapy (ARV) to the Mother during Pregnancy And Breast-Feeding**

| Study, location | Antiretroviral intervention | | | MTCT risk (95% CI), % | Risk of HIV-1 infection or death (95% CI), % |
|---|---|---|---|---|---|
| | Maternal regimen | Infant regimen | Duration | | |
| Kisumu [66], Kenya | ZDV/3TC plus NVP[a] | Single-dose NVP | From 34 weeks of gestation until 6 months postpartum but continued if WHO treatment criteria met | Among women with CD4 <250 cells/mm3: at 1 month, 4.3 (1.8–10.0); at 6 months, 5.2 (2.4–11.2); at 12 months 6.7 (3.2–13.9). Among women with CD4 ≥250 cells/mm3: at 6 months, 4.9 (3.1–7.7); at 12 months, 5.5 (3.6–8.4) | Not available |
| Kesho-Bora [46, 47], Burkina Faso-Kenya | ZDV/3TC plus NVP | Single-dose NVP | From 18–36 weeks of gestation | Among women with CD4 <200 cells/mm3: at 12 months, 6.4 (0.3–12.4) | Among women with CD4 <200 cells/mm3: at 12 months, 10.8 (3.2–18.3) |
| MTCT-Plus [11], Côte d'Ivoire | ZDV/3TC plus NVP | Single-dose NVP plus 1 week of ZDV | From 20 weeks of gestation | Among women eligible for ARV therapy: at 1 month, 1.0 (0.0–3.1); at 12 months, 3.3 (0.0–6.9) | Among women eligible for ARV therapy: at 12 months, 11.2 (5.0–17.4) |
| AMATA [67], Rwanda | HAART eligible (CD4 <350 cells/mL or stage IV), D4T plus 3TC plus NVP; not eligible, ZDV plus 3TC plus EFZ | Single-dose NVP plus 1 week of ZDV | Not eligible: from 28 weeks of gestation until 7 months postpartum, stop breast-feeding at 6 months | At 1 month, 1.3 (0.4–4.1); at 9 months, 1.8 (0.7–4.8) | Overall at 9 months, 5.0 (3.0–9.0) |
| MITRA-PLUS [68], Tanzania | ZDV/3TC plus NVP | 1 week of ZDV-3TC | From 34 weeks of gestation until 6 months postpartum, continued if mother eligible for treatment at 6 months | At 1.5 months, 4.1 (2.1–6.0); at 6 months, 5.0 (3.2–7.0) | Not available |
| Dream cohort [69, 70], Mozambique | ZDV/3TC plus NVP | Single-dose NVP | From 15 weeks of gestation | Among women eligible for ARV therapy: at 1 month, 1.2; at 6 months, 2.2; at 12 months, 2.8 | Not available |

**NOTE.** 3TC, lamivudine; D4T, stavudine; EFZ, efavirenz; HAART, highly active antiretroviral therapy; HIV-1, human immunodeficiency virus type 1; NVP, nevirapine; WHO, World Health Organization; ZDV, zidovudine.

[a] Half-way through the trial, NVP was replaced by nelfinavir among women with CD4 counts >250 cells/mL.

*Universal maternal HAART could largely eliminate the overall MTCT risk.* The effect of maternal HAART on HIV-1 load in breast milk has been reported in 3 African studies so far. In Mozambique, ARV treatment had been initiated in the third trimester of pregnancy and continued for a median duration of 3 months [43]. In this study, all HIV-1–infected women treated with HAART had lower cell-free HIV-1 RNA load in breast milk and were less likely to have a detectable breast milk viral load, compared with untreated women. These results are in line with those previously reported in a smaller study conducted in Botswana among women with baseline CD4 counts <200 cells/mL who were treated with HAART before and/or after delivery, with breast-milk samples collected a median of 3 months after HAART initiation [44]. In this study, HAART had no apparent effect on cell-associated HIV-1 DNA load in breast milk [44]. Similarly, a third study recently conducted in Kenya among HAART-treated breast-feeding women showed the suppression of cell-free HIV-1 RNA in breast milk without suppression of HIV-1 DNA in this compartment [65].

As shown in Table 4, HAART in breast-feeding women results in transmission rates generally <5% in breast-feeding populations (Appendix B, which appears only in the online version of the journal) [11, 66–71].

Not negligible in this new perspective is the fact that infants will be exposed to the ARV drugs through breast-feeding [44, 72]. 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 breast-feeding to infants in biologically significant concentrations when their mothers received these drugs [72]. In Mozambique, detectable concentrations of ARV drugs were found in breast milk 1 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 [43]. This result suggests a possible lag in elimination of ARV drugs in breast milk. On the basis of current knowledge, the diffusion of lopinavir/ritonavir and tenofovir in breast milk 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-1–infected children who will receive suboptimal concentrations of ARVs?

The issue of infant toxicities associated with exposure to maternal HAART is of crucial interest. A study in Botswana among breast-fed infants born to HAART-treated women suggests 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 1 month of age [73]. This study also showed that excess infant anemia related to HAART exposure either in utero or during breast-feeding were not detected [73]. Thorne and Newell recently synthesized 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 hematological, mitochondrial, teratogenic, and carcinogenic effects) [74]. They concluded that "the immense benefits of antiretroviral prophylaxis in prevention of mother-to-child transmission far outweigh the potential for adverse effects" [74, p 204]. These adverse effects require additional and longer term monitoring because they are likely to occur later in childhood [74]. Moreover, the extent and effect of infant drug exposure through breast milk should now be well understood to evaluate the benefits and risks of maternal HAART during breast-feeding [72].

## CONCLUSIONS

We suggest the active promotion of the universal maternal HAART approach as a way toward 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-1–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. The strategy should consider breast-feeding cessation around 6 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, 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 breast-feeding women aware of their HIV-1 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-1 testing and counseling among pregnant women, reduce stigma, and favor the overall family care approach. Finally, our suggested approach is also in line with the recently advocated universal voluntary HIV-1 testing with immediate potent ARV treatment [3].

## 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. Curr Opin HIV AIDS **2007**; 2:361–6.

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**. Available at: http://www.msfaccess.org/main/hiv-aids/pmtct-experts-roundtable/. Accessed 16 July 2009.

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**; 22:797–805.

5. UNICEF. Children and AIDS: second stocktaking report. **2008**. Available at: http://www.unicef.org/publications/files/ChildrenAIDS_SecondStocktakingReport.pdf. Accessed 16 July 2009.

6. 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**; 16:631–41.

7. 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 Ditrame Plus, Abidjan, Côte d'Ivoire. Prev Med **2008**; 47:27–33.

8. 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:e1645.

9. Rollins NC, Becquet R, Bland RM, Coutsoudis 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**; 22:2349–57.

10. 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**; 359:130–41.

11. 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:e257.

12. Leroy V, Sakarovitch 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**; 19:1865–75.

13. 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**; 189:2154–66.

14. 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:e17.

15. 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**; 286:2413–20.

16. 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**; 296:794–805.

17. 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**; 83:418–26.

18. 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.". Bull World Health Organ **2006**; 84:90–6.

19. 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**; 80:812–8.

20. Becquet R. Antiretroviral therapy among HIV-infected breastfeeding mothers: a promising strategy to prevent HIV transmission through breastmilk in Africa. Future HIV Therapy **2007**; 1:17–21.

21. 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**; 373:48–57.

22. 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**; 342:921–9.

23. 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: 786–92.

24. 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 Ditrame Plus study, Abidjan, Cote d'Ivoire. AIDS **2005**; 19:309–18.

25. 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**; 354:795–802.

26. Lallemant 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**; 351:217–28.

27. 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**; 359:1178–86.

28. Shaffer N, Chuachoowong R, Mock PA, et al. Short-course zidovudine for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Lancet **1999**; 353: 773–80.

29. 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**; 353:781–5.

30. 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**; 36:1009–21.

31. 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 Ditrame Plus, Abidjan, Cote d'Ivoire. J Infect Dis **2006**; 193:482–7.

32. McIntyre JA, Hopley M, Moodley D, et al. Efficacy of short-course AZT plus 3TC to reduce nevirapine resistance in the prevention of mother-to-child HIV transmission: a randomized clinical trial. PLoS Med **2009**; 6: e1000172.

33. 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**; 370:1698–705.

34. 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**; 351:229–40.

35. Lockman S, Shapiro RL, Smeaton LM, et al. Response to antiretroviral therapy after a single, peripartum dose of nevirapine. N Engl J Med 2007; 356:135–47.

36. 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; 46:611–21.

37. WHO, UNICEF, UNAIDS. Towards universal access. Scaling up priority HIV/AIDS interventions in the health sector. Geneva, Switzerland. 2008.

38. 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; 12: 568–76.

39. 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; 3:e3501.

40. Dabis F, Ekpini ER. HIV-1/AIDS and maternal and child health in Africa. Lancet 2002; 359: 2097–104.

41. Becquet R, Bland R, Leroy V, et al. Duration, pattern of breastfeeding and postnatal transmission of HIV: pooled analysis of individual data from West and South African cohorts. PLoS One 2009; 4:e7397.

42. 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; 17:1493–501.

43. 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; 44:286–91.

44. 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; 192:713–9.

45. 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; 23:1469–74.

46. 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: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). 2008.

47. 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: Program and abstracts of the 5th IAS Conference on HIV Pathogenesis and Treatment (Cape Town, South Africa). 2009.

48. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. N Engl J Med 2009; 360:1815–26.

49. Phillips A. Morbidity and mortality in the HAART era [abstract 8]. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). 2008.

50. 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; 353: 1463–8.

51. 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; 367:1981–9.

52. 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: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). 2008.

53. 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; 199:66–76.

54. 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. Available at: http://www.who.int/child-adolescent-health/New_Publications/NUTRITION/consensus_statement.pdf. Accessed 16 July 2009.

55. Becquet R, Leroy V, Ekouevi DK, et al. Complementary feeding adequacy in relation to nutritional status among early weaned breast-fed children who are born to HIV-infected mothers: ANRS 1201/1202 Ditrame Plus, Abidjan, Côte d'Ivoire. Pediatrics 2006; 117: e701–10.

56. 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 TUPE0356]. In: Program and abstracts of the PXVI International AIDS conference (Toronto, Canada). 2006.

57. 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; 362:1171–7.

58. 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; 48:315–23.

59. Kumwenda NI, Hoover DR, Mofenson LM, et al. Extended antiretroviral prophylaxis to reduce breast-milk HIV-1 transmission. N Engl J Med 2008; 359:119–29.

60. 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:e4096.

61. 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; 372:300–13.

62. 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 LB7]. In: Program and abstracts of the 2nd IAS Conference on HIV Pathogenesis and Treatment (Paris, France). 2003.

63. Shearer WT. Breastfeeding and HIV infection. Pediatrics 2008; 121:1046–7.

64. 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: Program and abstracts of the 5th IAS Conference on HIV Pathogenesis and Treatment (Cape Town, South Africa). 2009.

65. 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; 22:1475–85.

66. 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: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). 2008.

67. 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 2009 [Epub ahead of print].

68. 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: Program and abstracts of the 3rd Conference on HIV Pathogenesis and Treatment (Rio De Janeiro, Brazil). 2005.

69. Marazzi MC, Palombi L, Liotta G, et al. De-

crease in HIV-1 mother-to-child transmission in women receiving postnatal HAART: 12-month follow-up data [abstract 668]. In: Program and abstracts of the 15th Conference on Retroviruses and Opportunistic Infections (Boston). **2008**.

70. 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):S65-71.

71. 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: Program and abstracts of the 5th IAS Conference on HIV Pathogenesis and Treatment (Cape Town, South Africa). **2009**.

72. Mirochnick M, Thomas T, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of mothers receiving HAART. Antimicrob Agents Chemother **2009**; 53:1170–6.

73. 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**; 22:1633–40.

74. 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**; 30:203–13.