Field efficacy of zidovudine, lamivudine and single-dose nevirapine to prevent peripartum HIV transmission.

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* Abstract

Objectives: In Africa, single-dose nevirapine (NVPsd), short regimens of zidovudine (ZDV) or ZDV+lamivudine (3TC) are recommended to prevent peripartum mother-to-child HIV transmission (PMTCT). We evaluated the six-week field efficacy of two more PMTCT drug combinations. **Design:** An open-label intervention cohort in Abidjan. **Methods:** In 2001-2002, consenting women started oral ZDV 300mg bid at ≥36 weeks of gestation, with 600mg of ZDV + 200mg NVPsd orally at beginning of labour. In 2002-2003, the antepartum regimen at ≥32weeks comprised ZDV as previously + 3TC 150mg bid; the labour dose comprised ZDV+NVPsd as previously + 300mg 3TC orally. Neonates received ZDV syrup (2 mg/kg/6 hours) for 7 days + NVPsd syrup (2mg/kg) on Day 2 in both periods. Each woman was assisted to either use breast milk substitutes or breastfeed exclusively. Pædiatric HIV infection was diagnosed by plasma HIV RNA viral load at 4 weeks, confirmed at 6 weeks. The reference group was a cohort receiving a short regimen of ZDV ≥36-38 weeks in 1995-2000 in the same population. **Results:** 1144 HIV-infected pregnant women were included: 351 with ZDV, 420 with ZDV+NVPsd and 373 with ZDV+3TC+NVPsd; 1010 livebirths were eligible for analysis; 79 children were HIV-infected peripartum. Six-week transmission probability was 6.5**%** (95% confidence interval 3.9-9.1**%**) with ZDV+NVPsd, a 72% reduction compared to ZDV alone (52-88%; p=0.0002 adjusted on maternal CD4, clinical stage and breastfeeding). It was 4.7% (2.4-7.0**%)** with ZDV+3TC+NVPsd (p=0.34 compared to ZDV+NVPsd). **Conclusions:** A short-course of ZDV+NVPsd prevents most peripartum HIV transmission in Africa. This regimen could be added to international guidelines.

FIELD EFFICACY OF ZIDOVUDINE, LAMIVUDINE AND SINGLE-DOSE NEVIRAPINE TO PREVENT PERIPARTUM HIV TRANSMISSION

ANRS DITRAME PLUS STUDY, ABIDJAN

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ABSTRACT

Objectives: In Africa, single-dose nevirapine (NVPsd), short regimens of zidovudine (ZDV) or ZDV+lamivudine (3TC) are recommended to prevent peripartum mother-to-child HIV transmission (PMTCT). We evaluated the six-week field efficacy of two more PMTCT drug combinations. **Design:** An open-label intervention cohort in Abidjan. **Methods:** In 2001-2002, consenting women started oral ZDV 300mg bid at ≥36 weeks of gestation, with 600mg of ZDV + 200mg NVPsd orally at beginning of labour. In 2002-2003, the antepartum regimen at ≥32weeks comprised ZDV as previously + 3TC 150mg bid; the labour dose comprised ZDV+NVPsd as previously + 300mg 3TC orally. Neonates received ZDV syrup (2 mg/kg/6 hours) for 7 days + NVPsd syrup (2mg/kg) on Day 2 in both periods. Each woman was assisted to either use breast milk substitutes or breastfeed exclusively. Pædiatric HIV infection was diagnosed by plasma HIV RNA viral load at 4 weeks, confirmed at 6 weeks. The reference group was a cohort receiving a short regimen of ZDV ≥36-38 weeks in 1995-2000 in the same population. **Results:** 1144 HIV-infected pregnant women were included: 351 with ZDV, 420 with ZDV+NVPsd and 373 with ZDV+3TC+NVPsd; 1010 livebirths were eligible for analysis; 79 children were HIV-infected peripartum. Six-week transmission probability was 6.5**%** (95% confidence interval 3.9-9.1**%)** with ZDV+NVPsd, a 72% reduction compared to ZDV alone (52-88%; p=0.0002 adjusted on maternal CD4, clinical stage and breastfeeding). It was 4.7% (2.4-7.0**%)** with ZDV+3TC+NVPsd (p=0.34 compared to ZDV+NVPsd). **Conclusions:** A short-course of ZDV+NVPsd prevents most peripartum HIV transmission in Africa. This regimen could be added to international guidelines.

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APPENDIX

Composition of the ANRS 1201/1202 DITRAME PLUS Study Group

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CONTRIBUTORS

François DABIS was the director and co-primary investigator of the entire project, supervised the epidemiological aspects of the study, wrote the manuscript. Laurence BEQUET was the study coordinator of all aspects of the project on site. Didier Koumavi EKOUEVI was the chief data manager and participated to data analysis and manuscript writing. Ida VIHO was the clinical director and monitored the entire study. François ROUET was responsible for all laboratory aspects of the project on site and contributed to the writing of the manuscript. Charlotte SAKAROVITCH and Laurence DEQUAE-MERCHADOU prepared and conducted data analysis. Apollinaire HORO supervised clinically the antenatal and obstetrical phases of the study. Renaud BECQUET contributed to data monitoring and was particularly in charge of surveillance of adverse events. Patricia FASSINOU supervised clinically the pædiatric phase of the project. Christiane WELFFENS-EKRA was the obstetrician primary investigator of the project. Christine ROUZIOUX supervised the laboratory component of the project and ensured quality control. Valériane LEROY was the co-primary investigator of the project, was reponsible for evaluation of postpartum interventions, participated to manuscript writing.

INTRODUCTION

Mother-to-child transmission (MTCT) of HIV type 1 accounts for most of the 2000 newly acquired pædiatric HIV infections in Africa each day (1). Several antiretroviral (ARV) regimens to prevent MTCT have been successfully evaluated and are recommended by the World Health Organization (WHO) since 2000 (2). Two ARV drugs are thus used in monotherapy: zidovudine (ZDV) and nevirapine (NVP).

ZDV given for the last four weeks of pregnancy plus the labour/delivery period has been evaluated in two placebo-controlled randomized trials in West Africa (3, 4). Transmission risk was 14.7% at six weeks compared to 24.8% with placebo, despite predominant breastfeeding exposure allowing for early HIV postnatal transmission (5). Open-label cohort studies confirmed the field efficacy or effectiveness of this ZDV regimen (6). The efficacy of maternal and neonatal NVP single dose (NVPsd) prophylaxis has been demonstrated first in a randomized controlled trial in Uganda with a six-week transmission rate of 11.8% (7). Another trial in South Africa demonstrated the statistical equivalence at six weeks of a NVP regimen, adding a second postpartum maternal NVP dose to the previous regimen, compared to a dual regimen of ZDV+lamivudine (3TC), 12% versus 9% (8).

Combinations of ARVs may further reduce MTCT in Africa as in Europe and in the USA (9). Although succesufully evaluated in South Africa (8), in a multi-country African trial (10) and in France (11), the ZDV+3TC combination may induce neonatal anemia and viral resistance after ≥2 months of use and thus remains infrequently used.

We conducted a cohort study in Abidjan, Côte d'Ivoire to evaluate the acceptability, tolerance and effectiveness of: 1) a short-course peripartum ZDV regimen combined with NVPsd during labour (ZDV+NVPsd) and followed by a very short neonatal prophylaxis of ZDV+NVPsd; 2) the same regimen with the addition of a maternal short-course of 3TC (ZDV+3TC+NVPsd).

METHODS

Study setting

The ANRS 1201/1202 DITRAME PLUS project was conducted in two districts of Abidjan. HIV counselling and testing services were set up within the antenatal clinics of the Yopougon University Hospital and six community-run health facilities. Two sites served for enrolment and follow-up.

Study design

The study was an open-label intervention cohort. The study protocol was approved by the National Ethical Committee in Côte d'Ivoire and the French Agence Nationale de Recherches sur le SIDA (ANRS). The pooled data of two consecutive series of mother-infant pairs, receiving ZDVin the ANRS 049a trial in 1995-1998 (4) or in a cohort on the same sites in 1999-2000 (6), were used for comparison. This regimen consisted of 300mg ZDV tablets twice a day at ≥36 weeks of gestation, two tablets (600mg) at beginning of labour and one week of maternal ZDV postnatally but no neonatal prophylaxis.

Inclusion procedures

All pregnant women attending the selected clinics were offered pre-test counselling and HIV testing. Those ≥18 years old, at <32 weeks of gestation, living within the city limits and signing an informed consent were eligible. All serum samples were screened on site for HIV antibodies by an immunochromatographic rapid test (Determine ®, Abbott Laboratories, Abbot Park, IL, USA). A negative diagnosis was based on this single test result. Positive samples were immediately confirmed on site by a second rapid test (Genie II ®, Bio-Rad**,** Marnes-La-Coquette, France). Announcement of the seropositive status was made if both test results were positive. Women who tested positive with the two rapids tests or whose test results needed confirmation in the CeDReS reference laboratory (12) were systematically

offered to enter the cohort if hæmoglobinæmia was ≥7 g/deciliter (dl). Eligible women were scheduled for enrolment no later than at beginning of labour.

Study medications

The drug combination regimen evaluated in 2001-2002 consisted of a daily antenatal oral regimen of 300mg ZDV tablets twice a day at ≥36 weeks, two tablets (600mg) of ZDV and a single NVP tablet (200 mg) at beginning of labour. The intrapartum package was given at inclusion. Intra-partum treatment was self-initiated by the woman as soon as the labour had started. A second intra-partum dose was given by the study team if women did not deliver within 48 hours of administration of the first labour dose. In 2002-2003, the antenatal regimen was changed to ZDV 300mg and 3TC 150mg tablets twice a day at ≥32 weeks, followed by two tablets of ZDV (600mg) and 3TC (300mg) at beginning of labour plus NVPsd as previously. The ZDV+3TC maternal regimen was continued for three days post-partum. The neonatal prophylaxis was the same in the two periods. At delivery the mother was given a container with ZDV syrup for her neonate with a mono-dose syringe, four times a day (2 mg/kg) for seven days. Mothers were also asked to attend the study clinic 48-72 hours after birth for directly observed administration of 2 mg/kg of NVPsd syrup to their neonate.

Women were advised at inclusion and during subsequent prenatal visits to either choose artificial feeding from birth (13) or exclusive breastfeeding with initiation of weaning as soon as possible ≥4 months of life (14). Women were given support once their choice made, including free provision of equipment and supplies up to nine months postpartum (15).

Follow-up procedures

Demographic, clinical information, maternal CD4 measured by flow cytometry and HIV-1 RNA plasma viral load were processed at entry in the study. Women were given weekly then bi-weekly prepartum appointments for interview, clinical follow-up, drug distribution, verification of drug intake and tolerance. An appointment was given ≤48 hours after delivery, then a week later at the end of the treatment period, and at weeks 4 and 6 postpartum. The clinical follow-up of the child followed the same schedule. Children's blood samples were obtained for diagnosis of HIV infection and hæmoglobin measurement. Medical and psycho-social support was provided between scheduled visits. All prescribed medications, hospital stays and transportation were provided free of charge.

Study outcomes

Diagnosis of pædiatric HIV infection

Capillary blood was collected in EDTA microtainer tubes in new-borns at day 2; 1-2 ml of peripheral blood was taken at weeks 4 and 6. All samples collected at week 4 were processed for plasma RNA viral load measurement. The bDNA Versant HIV RNA kit version 3.0 (Bayer Diagnostics, Emeryville, CA, USA) was applied to the ZDV cohort. A real time PCR (quantitative Taqman technology) was applied to cohorts with combination drug regimens. Compared to the bDNA assay, the real time PCR has shown 100% sensitivity and specificity (95% lower bounds of 93.7% and 98.3%, respectively) (16, 18). The same techniques were applied to the preceding available sample(s) and to the six-week sample if the first one tested was positive. Both assays were controlled by the ANRS quality assurance

programme. The diagnosis of pædiatric HIV-1 infection was made on the basis of two positive virology tests (17). All samples with plasma HIV RNA >5000 copies/ml were considered positive (16, 18). The first positive test in the series allowed the estimation of the timing of infection: in utero if the day 1-4 specimen was positive, intrapartum / early postpartum if the day 1-4 specimen was negative but the week 4-6 specimen positive and timing of peripartum infection remained unknown in other instances (17). Absence of infection was defined by a negative test at the last time point an assay was done. Those children who had no sample available for testing and could not be followed >6 weeks were considered of definitive unknown HIV status.

Adverse events

Neonatal severe anæmia was defined by hæmoglobinæmia <8 g/dl at week 4. All stillbirths, early neonatal (≤7 days) and neonatal (<28 days) deaths were taken into account. The frequency of maternal and neonatal clinical rash was estimated seven days after delivery/birth.

Statistical analysis

The sample size of the ZDV+NVPsd cohort was calculated to estimate a 6-week MTCT risk of 7.5%, twice lower than with ZDV alone in a predominantly breast-feeding population (5), with a 5% type-I error (two-sided), a 10% type-II error and 10% of ininterpretable observations. This part of the study was terminated when its Scientific Committee after reviewing the available data concluded to the superiority of the ZDV+NVPsd combination compared to ZDV alone. The next regimen, ZDV+3TC+NVPsd, was then evaluated. This part of the study was terminated when highly active antitretroviral combination therapy (HAART) became available on site for the prevention of MTCT. To guarantee statistical independence of observations, we selected the first livebirth when a woman gave multiple livebirths (17). Group comparisons used variance analysis, Student's t-test or non parametric Mann-Whitney test for quantitative variables, Chi-2 test or Fisher's exact test for qualitative variables. The 6-week probability of infection was estimated using the Kaplan-Meier survival technique considering age at infection as the mid-point between the last negative and the first positive test results (17). All factors potentially associated with MTCT were studied in univariate then bivariate analyses adjusted on treatment. Cox multivariate proportional hazards model was used to study the relative effectiveness of each treatment, expressed as one minus the hazard ratio (HR). Multivariate analyses of the effect of treatment used as adjustment variables those with $p<0.25$ in bivariate analyses or $p<0.05$ in the comparison of the treatment groups. The role of interaction terms was investigated. Point estimates of summary statistics are reported with their 95 percent confidence interval (CI).

RESULTS

Study population

Between September 1995 and July 2003, 1144 pregnant women were enrolled: 351 received ZDV alone, 420 ZDV+NVPsd and 373 ZDV+3TC+NVPsd. There were 1120 maternal records available for analysis, of whom 56 women were lost to follow-up prior to delivery (Table 1). After exclusion of the multiple birth outcomes, the total number of births selected was 1064, including 22 stillbirths. Thirty-two eligible livebirths could not be taken into account in the analysis, without any blood sample available (n=17) and death in the first week of life (n=15). The baseline and follow-up characteristics of the cohorts are summarized in Table 2. The proportion of women eligible for HAART according to the 2003 WHO criteria (clinical stage 4 or clinical stage 3 and CD4<350/mm^3 or stage 1-2 and CD4<200/mm^3) (19) was 20.8%, including all the women (14.5%) with CD4<200.

Treatment intake

The median length of antenatal treatment was 21 days with ZDV, 29 with ZDV+NVPsd and 50 with ZDV+3TC+NVPsd (Table 2). The proportion of women taking the ARV labour dose increased from 83% with ZDV alone to 93% with the two drug combinations ($p<10^{-4}$). The postpartum ARV prophylaxis was generally taken. This component could not be compared between the groups as it differed (Table 2). There was no statistical difference between the three groups for place of delivery and frequency of cesærian section, an infrequent practice (Table 2). The proportion of women who chose to breastfeed from birth was 54-66% in the two groups receiving ARV combinations, whereas it was 97.6% in the ZDV group (Table 2).

Tolerance

Maternal tolerance to the three drug regimens was good (Table 3), with a 0.5% incidence of severe anemia in the first month postpartum. One woman, 32 years old, WHO clinical stage 1, 228 CD4/mm^3 and 8.1 g/dL of hæmoglobinemia, initiated ZDV+3TC at 32 weeks of gestation but stopped prophylaxis after four weeks with an hæmoglobinemia of 3.5 g/dL, corrected by a blood transfusion. Her child was infected in utero. There was no report of grade III or IV rash after the maternal NVPsd intake during labour. Severe neonatal anemia was observed in 20 instances (2.2%), always transient. There was no report of grade III or IV rash after the neonatal NVPsd intake. The frequencies of perinatal deaths (stillbirths and early neonatal deaths) and low birthweight were comparable (p=0.17 and 0.28, respectively, tables 1 and 3). All neonatal deaths but two were recorded in the first week of life and their frequency was comparable between the three groups (p=0.74, table 3). All but one remained of indeterminate HIV status, without any relation with infant feeding modality.

Effectiveness

There were 79/1010 neonates for whom the diagnosis of pædiatric HIV infection was made (Table 1). For 29 of them, in utero transmission was considered. In 28 instances, transmission was classified as intrapartum or early postnatal, the 22 other infections remaining of unknown timing. The overall six-week probability of transmission was 6.5% (CI 3.9-9.1%) with ZDV+NVPsd and 4.7% (CI 2.4-7.0%) with ZDV+3TC+NVPsd (p=0.34 after adjustment on maternal CD4 count, plasma HIV-1 RNA, WHO clinical stage, primigravida, duration of prepartum treatment, intrapartum treatment intake, low birthweight and breastfeeding). When using ZDV alone as reference (12.5% transmission at six weeks), the protective effect of the two drug combinations was strong, with an adjusted effectiveness of 72% (45-86%) for ZDV+NVPsd and 76% (52-88%) for ZDV+3TC+NVPsd (p<0.0002 and 0.0001, respectively after adjustment for maternal CD4 count, WHO clinical stage, moderate

anemia, age, primigravida, low birthweight, duration of prepartum treatment, intrapartum treatment intake, cesæerian section and breastfeeding) (Table 4). There was neither an interaction between treatment and maternal CD4 count (p=0.68) nor between treatment and infant feeding (p=0.57). There was no statistical difference in the crude and adjusted risks of transmission at six weeks according to the infant feeding exposure. This adjustment factor never reached statistical significance in multivariate analyses (p=0.10, Table 4). Thus, compared to ZDV alone, the relative effectiveness of the two drug combinations among the 703 breastfed children was 70% for ZDV+NVPsd (p<0.002) and 77% for ZDV+3TC+NVPsd (p<0.003).

We stratified the sample according to the 2003 WHO criteria for HAART indication (p=0.65 for the interaction of this variable with treatment). Among the 212 HAART eligible women, the six-week probability of peripartum infection was 23.6% with ZDV alone, 13.6% with ZDV+NVPsd and 9.1% with ZDV+3TC+NVPsd (p=0.28 and 0.10, respectively for the two comparisons using ZDV as reference). Among the 774 women who had no HAART indication, the six week peripartum transmission probability was 10.9% with ZDV alone, 3.6% with ZDV+NVPsd and 3.5% with ZDV+3TC+NVPsd (p<0.03 for both comparisons using ZDV as reference).

We could not investigate the relationship between the ARV regimens and the timing of acquisition of pædiatric HIV infection as the majority of cases in the ZDV cohort were HIV RNA positive for the first time at ≥Day 7 (Table 1). Finally, the time period of enrolment was not investigated as the study of each drug regimen followed the previous one without any overlap. We verified however that the transmission rate did not vary by calendar year for each period of enrolment (data not shown).

DISCUSSION

We conclude to the high effectiveness of ZDV+NVPsd, reducing by 72% peripartum MTCT compared to ZDV alone (3-6). We cannot demonstrate an additional benefit of adding 3TC to ZDV+NVPsd although starting ZDV+3TC a month earlier than ZDV. It is now internationally recognized that triple drug combinations used together and not sequentially further reduce MTCT, especially for women who need HAART for themselves (20). However, we identified with ZDV+NVPsd a peripartum regimen that is particularly effective when HAART is not indicated, with comparable results to industrialized countries before the HAART era (9, 21). The six-week residual risk was independant of the breastfeeding exposure. The prolonged duration of NVP levels in both the mother and the child over the first weeks of life may have reduced early transmission by breastmilk, an added benefit of NVPsd combined with ZDV or ZDV+3TC. Two-year follow-up is under way to estimate the additional postnatal transmission risk and the cumulative effectiveness of our peripartum and postpartum packages (15).

Comparing directly the different ARV MTCT regimens is difficult. The first African placebo-controlled trials evaluated individual drug regimens (3, 4, 7, 10). Then, equivalence trials were designed (8). Three key parameters have varied from trial to trial and impair the direct comparison of published results. The median maternal CD4 count varied between 545/mmm^3 in West Africa ZDV studies (5) to 370 with ZDV+NVPsd (Table 2), 461 in the Uganda NVPsd trial (7) and 482 in the ZDV+3TC trial (10). The frequency of cesærian section was 30% in South Africa (8), 3-6% in our cohort and exceptionnally elective. We introduced alternatives to prolonged and predominant breastfeeding whereas no neonatal intervention had been proposed in the ZDV reference cohort. Our estimate of the six-week transmission risk includes early postnatal transmission, possibly partly controlled by the

neonatal ZDV+NVPsd prophylaxis but impaired by other risk factors, low maternal CD4 and low frequency of cesærian section. These three factors were controlled for in all analyses. In doing so, our ZDV+NVPsd regimen had the lowest estimate of the residual transmission risk compared to ZDV alone (3, 4), NVPsd (7), ZDV+3TC, except its longest regimen with a residual transmission of 5.7% (10).

The DITRAME PLUS regimens were made of several components, each of them selected based on previous evidence. We did not design the study to investigate their respective contribution as recently done in Thailand in a randomized trial (22). Indeed, their results strengthen our approach of adding NVPsd to a short-course ZDV regimen. This trial suggests also that the neonatal ZDV+NVPsd prophylaxis has an added value, with a 2.0% residual transmission versus 2.8% in the absence of neonatal NVPsd, although the difference remained below statistical significance (22). Neonatal NVPsd together with one week of ZDV has recently been shown to prevent more intrapartum transmission than NVPsd in Malawi when no ARV could be given before delivery/birth (23). This was not the case however when maternal NVPsd had been administered prior to delivery (24). Based on these evidences, WHO recommends as first line regimen the combination of a short-course of ZDV for pregnant women at ≥28 weeks and children, for at least one week, with NVPsd for both (20).

We chose a nonrandomized approach to estimate the treatment effect as we considered there was *a priori* lack of equipoise between ZDV+NVPsd and ZDV alone. Indeed, ethical principles and time constraints can legitimize the use of nonrandomized designs (25). The Thai trial conducted at the same time than our study stopped its ZDV alone arm after its first interim analysis as it was already inferior to the two arms evaluating ZDV+NVPsd combinations (22). We acknowledge that beyond important confounding factors systematically controlled for, e.g. the clinical and immunological stage of HIV disease, the breastfeeding exposure and the duration of the ARV prophylaxis, unconsidered factors could

not be taken into account by our design. Of note, the uptake in the cohorts remained constant over time (26).

Viral resistance has not been a concern with short-course ZDV (27). In the Uganda NVPsd trial, the resistance mutations were transiently diagnosed in 19% of the mothers but were not associated with transmission (28, 29). The acquisition of different patterns of transient resistance by 46% of the infected children in this trial was considered due to the neonatal NVPsd rather than to the transmission of resistant virus (29). Using NVPsd in combination with other drugs, the incidence of viral mutations at six-week postpartum was 15% in industrialized countries (30). Early results of resistance studies within our cohort confirm that NVP resistance occurs at a high frequency among mothers (33%) and children (23%) despite the use of ZDV+NVPsd instead of NVPsd (31). Further studies will determine whether resistance to 3TC has been added to resistance to NVPsd (11, 32) and conversely, if the three-day maternal postpartum ZDV+3TC regimen has influenced or not the occurrence of maternal NVP resistance (33). The consequences of viral resistance after NVPsd exposure on the subsequent response to HAART in women and children should be urgently investigated in Africa like in the Thai trial (34) considering the possible large-scale adverse effect on subsequent treatment options.

The ZDV+3TC+NVPsd regimen we evaluated was selected at a time access to HAART was too limited in Côte d'Ivoire to be considered during pregnancy. Our choice was based on the demonstrated efficacy of short-courses of ZDV+3TC in the ANRS 075 cohort in France (11) and in the PETRA trial in Africa (10). We did not demonstrate an enhanced effectiveness of this regimen compared to ZDV+NVPsd, although our study had limited statistical power, an uneven distribution of confounding variables between the two groups (controlled for in the analysis) and was terminated mid-2003 as soon as HAART became available on site.

The ZDV+NVPsd MTCT prophylactic regimen we evaluated is now part of the list of internationally recommended drug regimens by WHO (20). Once the benefit (effectiveness) / risk (resistance) ratio of the ZDV+3TC+NVPsd combination is known, this regimen may also be considered. Four areas now require further research consideration. First, the uptake of ARV peripartum interventions is critical to obtain a public health impact. ZDV and NVPsd are not easy to use in Africa (35-37). Their combined use will not be necessarily more complex but the challenge is to improve coverage (26). Second, the reduction of the risk of postnatal transmission should be adressed, either with infant feeding strategies (15) or with ARV-based approaches (38). Third, alternatives to NVPsd containing regimens should be investigated as viral resistance and impaired response to subsequent ARV treatment is a serious concern. Finally, the residual transmission we observed with ZDV+NVPsd cannot be considered fully satisfactory. HAART is now universally recommended for pregnant women who fulfill this indication for themselves (20). We demonstrate in a large African cohort, like in a randomized trial in Thailand, that a short-course peripartum ZDV regimen combined with NVPsd is more effective than previously used single drug regimens and will greatly contribute to the prevention of pædiatric HIV infection if rapidly and widely used.

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Table 1. Number of women and children by treatment group in the ANRS 1201/1202 DITRAME PLUS study of prevention of mother-to-child transmission of HIV

	ZDV+3TC+NVPsd (2002-2003)	ZDV+NVPsd (2001-2002)	ZDV (1995-2000)
Women enrolled	373	420	351
Excluded	1	18	5
(HIV-2 infection only)	(1)	(16)	(5)
Women analysed	372 (100%)	402 (100%)	346 (100%)
Lost to follow-up before delivery	23 (6.2%)	22 (5.5%)	11 (3.2%)
Women who gave birth	349	380	335
Multiple birth outcomes excluded	17 †	21 #	4 †
(stillbirth)	(0)	(1)	(0)
Single or first births analysed	349 (100%)	380 (100%)	335 (100%)
Stillbirths	13 (3.7%)	5 (1.3%)	4 (1.2%)
Livebirths analysed	336 *(100%)*	375 *(100%)*	331 *(100%)*
Not tested for paediatric diagnosis	7 *(2.1%)*	14 *(3.7%)*	11 *(3.3%)*
(died before day 8)	(4)	(6)	(5)
Included in the transmission analysis	329 (100%)	361 (100%)	320 (100%)
Tested HIV positive ≤week 6	15 (4.6%)	23 (6.4%)	41 (12.8%)
Confirmed in utero infection (day 1 or 2)	7	10	3
Probable in utero infection (day 3 or 4)	3	4	2
Intra partum or early postnatal infection	3	8	17
Timing of peripartum infection unknown	2	1	19

† second birth among twins; # second birth among 17 twin births, second and third births among two triplets

3TC = lamivudine; NVPsd = single-dose nevirapine during labour; ZDV = zidovudine

Table 2. Baseline and follow-up characteristics of pregnant women and children: ANRS 1201/1202 DITRAME PLUS study

	ZDV+3TC+NVPsd	ZDV+NVPsd	ZDV	P1	P2
Pregnant women enrolled	372	402	346		
Median age in years (IQR)	27 (23-30)	26 (23-30)	25 (22-30)	0.03	0.31
Median parity (IQR)	1 (0-2)	1 (1-3)	1 (0-3)	0.07	0.07
Primigravida (%)	27 (7.3)	39 (9.7)	52 (15.2)	0.002	0.05
Median gestational age (IQR) at enrolment	33 (32-34)	36 (36-37)	36 (36-37)	<0.0001	<0.0001
Median hæmoglobinemia in g/dL (IQR)	9.95 (9.2-10.8)	9.90 (9.0-10.7)	9.30 (8.5-10.3)	<0.0001	0.37
% moderate anaemia (7-10g hæmoglobin / dL)	206 (55.4)	224 (55.7)	233 (68.3)	<0.0001	0.90
Median lymphocyte CD4+ count/mm^3 (IQR)	412 (265-580)	370 (243-552)	502.5 (327-714)	0.0003	0.03
<200 CD4+ cells / mm^3 (%)	53 (14.3)	75 (18.7)	34 (10.1)	0.004	0.10
WHO clinical stage 3-4 (%)	73 (19.6)	126 (31.3)	34 (10.1)	<0.0001	0.0002
WHO clinical stage 4 / AIDS (%)	0	9 (2.2)	5 (1.5)	0.007	0.004
Indication for HAART (2003 WHO criteria) *	75 (20.2)	117 (29.1)	43 (12.4)	<0.0001	0.004
Median log10 HIV-1 RNA plasma viral load at enrolment (IQR)	4.45 (3.94-5.1)	4.40 (3.76-4.88)	**	NA	0.003
Median duration of prepartum treatment in days (IQR)	50 (34-63)	29 (18-40)	21 (13-32)	<0.0001	<0.0001
Women who delivered	349	380	335		
Delivered at home (%)	39 (11.2)	35 (9.2)	41 (12.4)	0.36	0.38
With cesærian section (%)	21 (6.0)	19 (5.0)	10 (3.0)	0.16	0.55
Intrapartum treatment taken (%)	322 (92.5)	354 (93.2)	274 (83.3)	<0.0001	0.75
Women with livebirths analysed	336	375	331		
Maternal postpartum (one week) ZDV (%)	NA	NA	308 (96.3)		
Neonatal ZDV (one week) +NVPsd prophylaxis (%)	298 (88.7)	331 (88.3)	NA	NA	0.86
Children ever breastfed ≤4 weeks (%)	223 (66.1)	203 (54.1)	323 (97.6)	<0.0001	0.0006

p1 test for difference between the three groups ZDV, ZDV+NVPsd, ZDV+3TC+NVPsd
p2 test for difference between the ZDV+NVPsd and ZDV+3TC+NVPsd groups; IQR interquartile range; NA not applicable
3TC = lamivudine; NVPsd = single-dose nevirapine during labour; ZDV = zidovudine
*HAART = highly active antiretroviral therapy if WHO clinical stage 4 or WHO clinical stage 3 and CD4<350 / mm^3 or WHO clinical stage 1/2 and CD4<200 / mm^3
** 4.8 log10 for a sample of transmitting mothers and 3.7 for a sample of non transmitting mothers

Table 3. Maternal and neonatal biological tolerance to treatment, and neonatal mortality : ANRS 1201/1202 DITRAME PLUS study

	ZDV+3TC+NVPsd	ZDV+NVPsd	ZDV	p-value *
Women who delivered	349	380	335	
Women with severe anæmia	0/297	1/341	4/310	0.07
(Hæmoglobinemia <7 g/dL [a])	(0%)	(0.3%)	(1.3%)	
Severe rash <Day 7 postpartum	0	0	0	NA
Children followed ≥1 day	336	375	331	
Children with severe anæmia (%)	4/282	7/329	9/300	0.59
(Hæmoglobinemia <8 g/dL [a])	(1.8%)	(2.1%)	(3.0%)	
Severe rash <Day 7	0	0	0	NA
Low birthweight (<2500 g) (%)	50/332	41/372	42/324	0.28
	(15.1%)	(11.0%)	(13.0%)	
Early neonatal deaths (≤7 days)	6 (1.8%)	6 (1.6%)	7 (2.1%)	0.86
All neonatal deaths (<28 days)	8 (2.4%)	6 (1.6%)	7 (2.1%)	0.74

3TC = lamivudine ; NVPsd = single-dose nevirapine during labour ; ZDV = zidovudine
NA: not applicable
a at day 28 postpartum for ZDV+3TC+NVPsd and ZDV+NVPsd ; at day 45 postpartum for ZDV
* test for difference between the three groups unadjusted for baseline differences

Table 4. Six-week probability of peripartum infection, bivariate and multivariate Cox proportional hazard model for the risk of mother-to-child transmission of HIV according to treatment group (reference: ZDV): ANRS 1201/1202 DITRAME PLUS study

Variables			Crude (Univariate)				Bivariate*			Multivariate**		
	N=986 †	Pr. Inf.§	95% CI	p§§	HR#	95% CI	HR	95% CI	p	HR	95% CI	p
Treatment				0.002								
ZDV	303	12.5	8.7-16.3		1	-		NA		1	-	
ZDV+NVPsd	357	6.5	3.9-9.1		0.54	0.3-0.9				0.28	0.1-0.5	0.0002
ZDV+3TC+NVPsd	326	4.7	2.4-7.0		0.39	0.2-0.7				0.24	0.1-0.5	<0.0001
Maternal CD4 count				0.0005					<0.0001			0.0026
[0-200[	147	15.6	10-22		3.61	1.9-6.9	4.47	2.3-8.6		3.83	1.9-7.7	
[200-350[	232	9.1	6-13		2.00	1.0-3.9	2.45	1.3-4.8		2.31	1.1-4.6	
[350-500[	244	7.5	4-11		1.64	0.8-3.2	1.91	0.9-3.8		1.94	0.96-3.9	
≥ 500	363	4.6	2-7		1	-	1	-		1	-	
WHO clinical stage				0.002					0.0003			0.009
Stage 1-2	779	6.5	5-8		1	-	1	-		1	-	
Stage 3-4	207	13.4	9-19		2.08	1.3-3.3	2.50	1.5-4.1		1.98	1.2-3.3	
Maternal moderate anemia				0.09					0.20			0.91
No	396	5.9	4-8		1	-	1	-		1		
Yes	589	9.3	7-12		1.53	0.9-2.5	1.38	0.8-2.3		0.97	0.6-1.6	
Maternal age (for +10 years)	-	NA	-	0.46	1.17	0.8-1.8	1.25	0.8-1.9	0.29	1.05	0.7-1.6	0.80
Primigravida				0.59					0.4			0.44
No	889	8.1	6-10		1	-	1	-		1	-	
Yes	97	6.5	2-12		0.80	0.3-1.8	0.69	0.3-1.6		0.71	0.3-1.7	
Prepartum treatment				0.13					0.32			0.43
< 7 days	47	16.2	5-27		1	-	1	-		1	-	
[7-20] days	247	8.4	5-12		0.53	0.2-1.2	0.52	0.2-1.2		0.56	0.2-1.4	
≥ 21 days	692	7.3	5-9		0.45	0.2-1.0	0.58	0.3-1.3		0.71	0.3-1.7	
Intrapartum treatment				0.18					0.41			0.67
No	91	11.5	5-18		1	-	1	-		1	-	
Yes	895	7.6	6-10		0.64	0.3-1.2	0.75	0.4-1.5		0.85	0.4-1.8	
Cesærian section				0.16					0.22			0.23
No	939	8.3	7-10		1	-	1	-		1	-	
Yes	47	2.1	0-6		0.27	0.04-2.0	0.29	0.0-2.1		0.30	0.04-2.2	
Low birthweight				0.0002					0.0003			0.0006
No	863	6.8	5-9		1	-	1	-		1	-	
Yes	123	16.0	10-23		2.55	1.5-4.3	2.59	1.5-4.4		2.63	1.5-4.6	
Breastfed				0.96					0.12			0.10
Never	283	7.5	4-11		1	-	1	-		1	-	
Ever	703	8.0	6-10		0.99	0.6-1.6	0.62	0.3-1.1		0.59	0.3-1.1	

* adjusted on treatment ** variables with p<0.25 in bivariate analysis or p≤0.05 in the comparison of the three treatment groups (table 2)

§ Kaplan Meier probability of infection at 6 weeks §§ logrank test # univariate analysis = unadjusted Cox proportional hazards model

† 24 children / 1010 eligible for the transmission analysis (table 1) are excluded for incomplete data

CI confidence interval HR hazard ratio 3TC = lamivudine; NVPsd = single-dose nevirapine during labour; ZDV =zidovudine

Moderate anemia 7≤hæmoglobinemia≤10g/dL Low birthweight <2500g

18 Nov 2004

TO: Prof François Dabis
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Dear Prof Dabis,

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