PMTCT Intelligence Report

prepared by the Bordeaux Working Group *


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Subject Headings/Subheadings
Conference summary
Contraception
Gynaecology
Infant feeding/Breastfeeding
MTCT (Mother-to-Child Transmission)
Obstetrics
PMTCT/ARV (Prevention of Mother-to-Child Transmission/AntiRetroVirals)
Primary prevention of sexual transmission/VCT (Voluntary Counselling and Testing)
Termination of pregnancy/Abortion

Citation format (by alphabetical order of the authors)
Author(s). Title. Source.
Notes (prepared by the Bordeaux Working Group)
Author address, if available (for reprints)
URL, if available (link to author abstract/full text/journal TOC)
Subject Headings

**Notes:** This interesting paper attempts to answer three burning issues concerning the distribution and stability of HIV virus in breastmilk (BM). First, the authors studied the ability of a commercial assay to detect HIV RNA viral load not only in the skim milk portion of BM as it is usually done, but also in whole BM and BM lipid fraction. In the three types of BM samples, an excellent correlation was found between the nominal and the observed copy numbers. Moreover, even if HIV tends to migrate to the milk lipid fraction, it represents such a small proportion of the milk that sample variations in the lipid proportion do not affect the amount of virus detected in whole milk. Second, some factors contained in BM are known to inhibit PCR amplification. The authors demonstrate that these factors generally do not affect the accuracy of the measurement. Third, as access to refrigeration is limited in developing countries, the authors assessed the influence of collection and storage conditions on HIV RNA stability. HIV RNA remained particularly stable even after having been left for up to 30 hours at room temperature (25°C) or at 4°C. Moreover, three consecutive freeze-thaw cycles did not affect HIV RNA levels in BM samples.

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Infant feeding/breastfeeding


**Notes:** This study presents pharmacokinetics of two Protease Inhibitors (PI) during pregnancy: Nelfinavir (n=9) and Indinavir (n=4), with or without Ritonavir (n=2). Nelfinavir pharmacokinetics appeared stable during pregnancy but was highly variable from patient to patient. Metabolic induction of Indinavir occurs during pregnancy and resolves spontaneously postpartum. This induction is offset by concomitant use of Ritonavir. The authors concluded that the impact of Nelfinavir use during pregnancy could not be fully determined.

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PMTCT/ARV


**Notes:** The dynamics of viral turnover in the genital tract and the timing of drug effect on genital virus is poorly documented. The authors conducted a prospective study amongst nonpregnant antiretroviral-naive women in Nairobi to determine the effect of zidovudine (ZDV) on genital and plasma HIV-RNA during the first few days of administration. A total of 42 women were enrolled in this study and completed specimen collection. At baseline, HIV-1 RNA levels in the cervix and vagina were both correlated with plasma viral load (r=0.66, n=33; p<0.001 for cervix and r=0.55, n=26; p=0.001 for vagina). With 7 days of ZDV treatment, plasma HIV-1 RNA decreased from 4.5 to 4.0 log10 copies/ml (p<0.001). Cervical and vaginal HIV-1 RNA also decreased: 2.9 to 1.8 log10 copies/swab (p<0.001) and 2.3 to 1.3 log10 copies/swab (p=0.003), respectively. HIV-1 RNA half-life following ZDV treatment was 4.7, 1.3 and 0.9 days in plasma, cervix and vagina, respectively. This study does not observe a rebound of viremia following drug cessation. The authors emphasised that these results may not apply completely to pregnant women and concluded that further investigations to compare the effects of short-course antiretroviral regimens on genital and breast milk shedding of HIV-1 will be useful to inform the design of the new drug regimens.

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**Notes:** In this concise communication, the authors address the issue of the coverage of PMTCT interventions and explore alternative models for programme implementation in resource-poor countries. They conducted an observational study of HIV-infected pregnant women identified through VCT within the Coast Provincial General Hospital of Mombassa (Kenya). From April 2001 to April 2002, 3 680 women attended a first antenatal visit, 2 516...
were pre-test counselled for HIV and 348 were tested HIV positive (14%). Along the lines of the HIVNET 012 protocol, nevirapine (NVP) (both mother tablet and infant suspension) was provided to HIV-infected women at 34 weeks gestation. Study results show that among HIV-infected women at post-test counselling, only 50% collected NVP and 20% took NVP. Only 30% of women seen for antenatal care at the hospital delivered onsite, most women giving birth in other clinics or at home. Over a 12 month period, the programme avoided 16 perinatal transmissions in 515 HIV-infected women; a 100% coverage of this programme would have prevented 77 infant infections; if intra-partum testing and treatment had been available, 126 infections would have been avoided. Though the 20% coverage of this PMTCT programme is consistent with other studies in Africa, it is still terribly low. Among the critical operational strategies of implementing and integrating the HIVNET 012 regimen, the authors mention: the accessibility to at least one antenatal visit and thus the need to improve the coverage of basic mother-child-health (MCH) services; the need for both pre- and intra-partum VCT as shown to be effective in Thailand, the increase of individual counselling rates both for HIV-infected and HIV-negative women; the need to prescribe NVP earlier in pregnancy. The authors conclude on the critical need for further qualitative research on the determinants of MCH services coverage and compliance. Mother and child follow-up should also urgently be addressed to improve the effectiveness and impact of these single dose NVP-based PMTCT programmes.

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PMTCT/ARV

WHO. WHO reconfirms the support for the use of nevirapine to prevent mother-to-child transmission of HIV.

Notes: WHO has reconfirmed in July 2003 its support for the use of nevirapine (NVP) for PMTCT. This statement was prepared after that the US National Institutes of Health released on the web (http://www.niaid.nih.gov/daids/pdf/012_report.pdf) their March 2003 report on the re-monitoring of the HIVNET 012 trial. This procedure was used in order to obtain NVP Food and Drug Administration (FDA) licensure in the USA for the PMTCT indication. The report concluded that NVP was indeed safe and effective but the study lacked the necessary documentation to support the request to the FDA to consider this study as a stand alone pivotal trial. It is important that WHO reiterates now that NVP is one of the key antiretroviral drugs to be included in the minimum standard package of care for HIV-positive women and their children.

URL: http://www.who.int/reproductive-health/rtis/nevirapine.htm

PMTCT/ARV


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PMTCT was covered in two oral sessions, one controversy session and 85 posters. An institutional symposium was organised by the Ghent-IAS Group entitled "Prevention of HIV transmission through breastfeeding : what next?"(www.ghentgroup.org). In a late breaker session, the preliminary results of the SIMBA trial were presented.

Pathogenesis

Concerning "Treatment issues in Pediatric HIV infection", there were two states of the art talks about early antiretroviral treatment in infants, presented by S. Blanche (France) and K. Luzuriaga (USA). Two clinical studies conducted in developing countries, Côte d'Ivoire and Kenya, were also presented. P. Msellati et al (abstract 31) reported the clinical and biological impact of HAART amongst HIV-infected children. In this cohort, 77 Ivoirian infants received HAART. The authors concluded that HAART treatment of children in Africa is feasible and as effective as in industrialized countries. The Kenyan team (abstract 30) determined patterns and correlates of pediatric HIV viral load and association with disease progression. McIntosh et al (abstract 32) showed that the levels of L phenotypic markers in the first 4 months of life may predict rapid progression in infants and allow identification of slow immunologic progression among those infants who may not need immediate antiretroviral therapy. In this session, Faye on behalf of the French prospective cohort (abstract 33) presented the clinical impact (risk of death, opportunistic infections and encephalopathy) of early treatment (before 6 month of age) of infected newborns. In conclusion, some authors suggest to start HAART early in HIV-infected infants independently of the CD4 percentage, although the debate remains open. Other investigations are probably required to know exactly the advantages of this strategy. One interesting study was presented by the French cohort study group concluding that the MTCT rate of HIV-2 could be estimated at 0.5%. This early paediatric diagnosis is now feasible by PCR technique (abstract 65). In conclusion, all these presentations do not change the current recommendations for the pediatric prescription of antiretrovirals.
Peripartum Interventions
A new result concerning perinatal treatment to prevent MTCT was presented by F. Dabis (abstract 219) on behalf of the ANRS 1201 Ditrame Plus trial, conducted in Abidjan, Côte d'Ivoire. The field-efficacy of a short regimen of Zidovudine (ZDV) + peripartum Nevirapine (NVP) (6% transmission rate at 6 weeks) has been demonstrated in the previous phase of this open-label trial (See CROI report in IR 2003, issue 2). The same team is now reporting preliminary results showing that ZDV+Lamivudine(3TC)+NVP may prevent more peripartum transmission cases (5% MTCT rate, 95% CI:1.7-11.4) a non statistically significant difference with ZDV+NVP, underlying the fact however that all the residual transmission cases happened in women with CD4<500/mm3. An interesting controversy was presented by J. Sullivan, pro use of single-dose NVP, and F. Dabis, pro combination therapy for PMTCT. Concerning post-exposure treatment of infants, M. Lallemant (abstract 62) presented the interim results of the PHPT-2 study in Thailand. This study assessed the safety and efficacy of NVP in addition to ZDV in mother and infant regimens for the prevention of perinatal HIV transmission in the absence of breastfeeding. He concluded that while adding NVP during labour to the oral ZDV prophylaxis significantly decreases HIV transmission down to 3%, the need for the infant NVP dose still needs to be established. Final analysis will be performed by the end of 2003. These trials in Côte d'Ivoire and Thailand lack drug resistance data at the moment, an important limitation for the full understanding of their findings from both scientific and public health points of view. Several posters like McDonald (abstract 1063) in Lusaka, Zambia, Saman (abstract 1052) in Phnom Penh, Cambodia and Lallemant (abstract 1025) in Thailand reported the feasibility and good-acceptance of MTCT interventions in their settings, underlying the site specific difficulties where the efforts have to be concentrated to improve these encouraging results.

Postpartum Interventions
J. Vyankandondera presented the results of the SIMBA randomized open-label trial conducted in Rwanda and Uganda, evaluating in infants born to HIV-infected mothers the efficacy of postnatal prophylaxis with 3TC or nevirapine in the first 6 months of breastfeeding (abstract LB7). This intervention led to a residual postnatal risk of transmission of HIV of 1% in the first 6 months of life in both groups. These preliminary results are encouraging, but further investigations are needed to evaluate the cumulative postnatal risk of transmission at 18 months of age. Furthermore, the background rate of postnatal transmission to which their result should be compared is probably in the range of 3 to 4% considering the limited length of breastfeeding exposure (100 days), the promotion of exclusive breastfeeding and the low frequency of maternal advanced HIV disease. Another approach to counteract the risk of postnatal transmission of HIV consists in the complete avoidance of breastfeeding, with provision of formula feeding. Yet, the feasibility and safety of this intervention in resource-poor settings needs to be further investigated beyond the Nairobi randomised clinical trial. R. Becquet presented the preliminary results of the ANRS 1202 DITRAME PLUS study conducted in Abidjan, Côte d'Ivoire, comparing the mortality in breastfed and formula-fed children born to HIV-infected mothers (abstract 63). In this context of free-provision of formula feeding, close follow-up and intensive counselling from birth, formula feeding looked feasible since there was no excess in mortality in formula-fed children compared to those breastfed. During the Ghent-IAS institutional symposium entitled "Prevention of HIV transmission through breastmilk: what's next?" that was held during the conference (http://www.ghentgroup.org), F. Dabis proposed using formula feeding as a medicine for women at the most advanced stages of HIV disease. Another conceivable option to reduce the risk of postnatal transmission of HIV consists in the promotion of exclusive breastfeeding from birth. Yet, the feasibility of this intervention remains controversial. An interesting study was conducted in Chennai, India to evaluate the exclusivity of breastfeeding in different settings (abstract 1066). In urban compared to rural populations, only 39% (vs 24%) of mothers practiced exclusive breastfeeding with a median duration of 2.8 months (vs 2.6). These results underline that exclusive breastfeeding is quite uncommon especially in rural settings. Thus, intensive counselling is needed to promote this intervention among antenatal clinics attendees. To date, there are conflicting results concerning women mortality according to their feeding practices. Marie-Louise Newell presented the results of the BHITS meta-analysis examining mortality in 4237 HIV-infected African mothers according to child's feeding modality (abstract 221). In multivariate analysis, the 12-month mortality was significantly lower among women that ever breastfed compared to those who never breastfed their children. Yet, this difference was not significant anymore when looking at the 18-month mortality. Further investigations will be conducted excluding from the analysis women who died right after delivery because of obstetrical complications.


Conference summary