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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, well documented (6 figures and 5 tables), presents new data confirming the mitochondrial dysfunction and the persistence of this abnormality in HIV-uninfected children born to seropositive women. The presence of this side effect was screened in a prospective cohort and a notification register for the children was created to explore this side effect. All unexplained symptoms compatible with mitochondrial dysfunction were reported. A total of 2644/4426 children were exposed to antiretrovirals and 26 children presented common conditions including neurological symptoms and abnormal cerebral magnetic resonance imaging (MRI). Evidence of mitochondrial dysfunction was found in 12 children and the 14 other children presented "possible" mitochondrial dysfunction. The 18 months incidence for "established" mitochondrial disease in this prospective cohort was estimated at 0.26% [95% CI, 0.10 - 0.54] in exposed children (born to HIV-infected mothers), whereas in the general population it is estimated at 0.01%. The only factor associated with the mitochondrial dysfunction (possible and established) was the use of combinations of nucleoside analogues (RR=2.5, 95% CI 1.0-6.5; reference group was monotherapy of zidovudine). The mode of infection, the geographical origin of the mother and prematurity were not associated with mitochondrial dysfunction. The originality and one of the strengths of this manuscript is the good documentation of mitochondrial dysfunction in infants exposed to antiretrovirals during pregnancy, with the occurrence of a neurological syndrome being associated with persistent mitochondrial dysfunction. We can define severe mitochondrial dysfunction for this purpose as the association of neurological symptoms (development retardation, seizures and behavioural disturbances), significant abnormalities on cerebral MRI (lesions of the white matter and brainstem) and often hyperlactatemia. The symptomatology and evolution are however relatively variable.

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**Notes:** The editorial accompanying the release of the final report of the HIVNET 012 trial (see Jackson et al in this issue) asks for a shift in PMTCT strategies. Indeed, Beckerman suggests that it is time to move to optimal antiretroviral regimens for PMTCT irrespective of the context, ensuring higher efficacy and lower risk of drug resistance. The author stresses also the need of a continuum of care, in which PMTCT is only one piece and aiming at avoiding maternal and infant death. This may seem common sense but one should realize how rapidly the issue of access to care has grown and PMTCT has greatly contributed to this evolution. With this respect, the HIVNET 012 NVP single dose regimen has created a breakthrough and should continue to be used while other interventions are neither feasible nor accessible for a majority of pregnant women and their neonates in resource-poor settings.

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**Notes:** The authors investigated the validity of several methods aimed at the collection of data on the exclusivity of breastfeeding and its duration. This study was conducted on 130 HIV-infected women and their infants in a rural district of South Africa [previously described in Bland RM et al, IR 2 (8)]. Infant feeding practices were recorded through various approaches, in order to assess whether the children had been exclusively breastfed (EBF) or not:
- 48 hour recall history (weekly from birth to 16 weeks of age, and thrice weekly over the same period for a subset of mother-infant pairs) ;
- 7 day recall history (weekly from birth to 16 weeks of age) ;
- recall on the duration of EBF between 6 and 9 months of age ;
- simple diaries in which women marked the days of non-EBF.
One interesting finding is that the 48 hour recall does not accurately reflect EBF history since birth. Thus, the authors emphasize the importance of collecting prospective, longitudinal data to correlate postnatal HIV transmission and feeding practices. The authors also demonstrate the accuracy of 7 day recall (in comparing it with thrice weekly 48 hour recall) to describe the feeding practices over the past 7 days. Finally, the simple diaries were easy to use and
particularly reliable at identifying EBF infants, and should thus be used in the forthcoming studies to corroborate data collected during interviews.

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**Infant feeding/Breastfeeding**


**Notes:** This paper aimed to measure the additional morbidity in children exposed to HIV according to their mode of feeding, in a vitamin A intervention trial carried out in South Africa. In this trial, women chose to breastfeed or formula feed their infants according to WHO guidelines. Feeding practices and morbidity were recorded at clinic follow-up visits at week 1, 6, month 3 and quarterly thereafter until 15 months of age or cessation of breastfeeding. However, only infants followed-up for at least 9 months were included in the study population. In such conditions, among the 738 mother-child pairs, 305 (41%) were considered lost to follow-up and 49 children died. Among the survivors, it seems that HIV-infected infants who were never breastfed had a poorer outcome than those who were breastfed: 9 (60%) of those who were never breastfed versus 15 (32%) of breastfed children had clinical symptomatology [odds ratio (OR) 4.05, 95% CI 0.91-20.63, p=0.05]. However, there was no adjusted analysis performed according to the CD4 count level or the HIV viral load level. In addition, illness episodes among these HIV-infected children could more likely be due to HIV infection than to feeding practices. These biases should refrain us to conclude to a potential negative effect of avoidance of breastfeeding in order to decrease MTCT of HIV. This study illustrates well the complexity of analysing the relationship between feeding modalities and morbidity in children exposed to HIV taking into account the reverse causality effect.

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**Infant feeding/Breastfeeding**


**Author abstract:** In 1999, we reported safety and efficacy data for short-course nevirapine from a Ugandan perinatal HIV-1 prevention trial when 496 babies were followed up to age 14-16 weeks. Safety and efficacy data are now presented for all babies followed up to 18 months of age. From November, 1997, to April, 1999, HIV-1 infected pregnant women in Kampala, Uganda, were randomly assigned nevirapine (200 mg at labour onset and 2 mg/kg for babies within 72 h of birth; regimen A) or zidovudine (600 mg orally at labour onset and 300 mg every 3 h until delivery, and 4 mg/kg orally twice daily for babies for 7 days, regimen B). Infant HIV-1 testing was done at birth, age 6-8 and 14-16 weeks, and age 12 months by HIV-1 RNA PCR, and by HIV-1 antibody at 18 months. HIV-1 transmission and HIV-1-free survival were assessed using Kaplan-Meier analysis. We recorded adverse experiences through 6-8 weeks postpartum for mothers, and 18 months for babies. Efficacy analyses were by intention to treat. We enrolled 645 mothers to the study: 313 were assigned regimen A, 313 regimen B, and 19 placebo. Eight mothers were lost to follow-up before delivery. 99% of babies were breastfed (median duration 9 months). Estimated risks of HIV-1 transmission in the zidovudine and nevirapine groups were 10.3% and 8.1% at birth (p=0.35); 20.0% and 11.8% by age 6-8 weeks (p=0.0063); 22.1% and 13.5% by age 14-16 weeks (p=0.0064); and 25.8% and 15.7% by age 18 months (p=0.0023). Nevirapine was associated with a 41% (95% CI 16-59) reduction in relative risk of transmission through to age 18 months. Both regimens were well-tolerated with few serious side-effects. Intrapartum/neonatal nevirapine significantly lowered HIV-1 transmission risk in a breastfeeding population in Uganda compared with a short intrapartum/neonatal zidovudine regimen. The absolute 8.2% reduction in transmission at 6-8 weeks was sustained at age 18 months (10.1% [95% CI 3.5-16.6]). This simple, inexpensive, well-tolerated regimen has the potential to significantly decrease HIV-1 perinatal transmission in less-developed countries.
Editorial note: This final report of the HIVNET 012 trial has been awaited for about two years. Without further discussions of this delay and its reasons, it is essential that these data are published to adequately inform the researchers, clinicians, programme planners, implementers and funding bodies. The results are consistent with earlier reports with more safety information. It is unfortunate that the data cannot be broken down by CD4 and/or HIV plasma RNA strata (these two variables are the key ones in the multivariate analysis performed although it did not quite follow international standards). Besides efficacy and safety, NVP resistance in women and children induced by this single dose regimen remains the greatest concern. Data are awaited on the viro-immunological and clinical response of women and children who will initiate highly active antiretroviral therapy after having been exposed to the HIVNET 012 NVP regimen. While the researchers build this evidence, it is essential that the international community is not distracted to make the best possible use of the HIVNET 012 NVP regimen, giving us the opportunity to prevent a great deal of the paediatric HIV pandemic.

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PMTCT/ARV


Notes: Risk factors for mother-to-child transmission were analysed in a hospital-based population of HIV-infected pregnant women (n=297) in Rio de Janeiro, Brazil over a period of six years (January 1996 - December 2001). All patients were treated according to national guidelines at the time of enrolment, zidovudine monotherapy (1996), mono or dual nucleosides (1997) and highly active antiretroviral therapy since 1998. Formula was provided to all mothers, and children were not breastfed. The overall transmission rate was 3.57% and remained constant over time. The authors found a significant association between low birth-weight and the HIV infection status of the infant (p=0.0072) whereas a longer duration of antiretroviral drug prophylaxis during pregnancy was independently associated with a lower risk of transmission (p=0.008). Cruz et al emphasise the importance of diagnosing HIV infection early in pregnancy to provide optimal PMTCT ARV strategies. These results are fairly comparable to what has been achieved in the USA and in Europe.

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PMTCT/ARV


Notes: This short report presents a novel resistance mutation (V106M) associated with nevirapine (NVP) in HIV-infected women with subtype C HIV-1 virus. This mutation was found in 7/141 (5%) women at 6 weeks postpartum, all had received single dose of NVP for PMTCT in South Africa. The authors also found the mutation V106A (3.5%) in the same population. Morris et al suggest to add this novel point resistance V106M in the list of the NVP resistance mutations including already K103N, V106A, Y181C, Y188C and G109A. The monitoring of the antiretroviral resistance should be highlighted in assessing the long term efficacy of NVP for PMTCT.

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PMTCT/ARV


Notes: This article focuses on the feasibility of using short-course zidovudine to prevent mother-to-child transmission of HIV in a rural area of Kenya between 1996 and 1998. Of the 836 mothers interviewed, 825 consented to be included in the programme. The prevalence of HIV infection was 26.2%. Among the 216 HIV positive women diagnosed, 51 (23.6%) took the full prescribed dose, 69 (31.9%) took only the prenatal dose, and the remaining 96 (44.4%) did not take any dose. A shorter gestational period and a lower level of education were associated with not taking the prophylaxis. Non-compliance to the intrapartum dose was associated with mothers
giving birth at home and fear of traditional birth attendants. By the end of the second year, 75 HIV-exposed children (34.7%) and 33 HIV-infected mothers (15.3%) had died. The HIV-free survival of children at 24 months was significantly and positively associated with mother survival ($P < 0.001$) and prenatal ZDV compliance ($P < 0.003$). Despite the fact that the data described here are not very recent, this article highlights two problems of major concern: first, uptake of antiretroviral prophylaxis has to be improved and a way to do so is to focus on socioeconomic and cultural barriers. Second, the child survival is strongly related to maternal health, and it is clear that programmes to prevent mother to child transmission and improve child health should include maternal care to be more efficient.

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**Notes:** This paper is one of the rare well documented reports on the use of HIVNET 012 intrapartum and neonatal single-dose nevirapine (NVP) regimen to reduce the risk of intrapartum transmission of HIV since the original report on this clinical trial in Uganda (see long term efficacy report by Jackson et al in the same issue of the IR). It addresses some of the epidemiological challenges of NVP delivery within the context of an operational PMTCT programme in Zambia and specifically explores how maternal dose timing and/or cord blood drug concentration may be predictors for perinatal HIV transmission.

In this prospective cohort enrolled and followed in two clinics in Lusaka, 430 HIV-infected women were enrolled over a nine-months period in 2000 and 2001. NVP was given to women either at 36 weeks gestation or upon presentation in established labour, and to infants never more than 24h after delivery. Adequate intake was self-reported or observed. HIV transmission data were available for 278 women only (65%), with 31 infants (11.2%) infected at six weeks: six (2.2%) infected intrauterine, 25 infected intrapartum/early postpartum (9%). The HIV transmission rate was essentially identical to the 1999 HIVNET 012 trial findings (11.1). Among the factors associated with HIV transmission were: alcohol use in index pregnancy, report of mixed rather than exclusive breastfeeding (Relative Risk [RR], 5.1; 95% CI 2.5-10.5), viral load greater than the median value for the cohort (RR, 2.4; 95% CI, 1.03-5.5), clinical chorioamnionitis (RR, 4.7; 95% CI 1.7-13) and less than 1 h elapsing between NVP ingestion and delivery (RR, 2.4; 95% CI 1.2-4.8). Late NVP dosing appeared highly predictive of overall transmission [adjusted odds ratio (AOR) 3.7; 95% CI, 1.4-10.1] and intrapartum/early postpartum transmission (AOR, 5.5; 95% CI, 1.9-16). Women who delivered within one hour of drug ingestion had a lower average cord blood NVP concentration than those in whom more than an hour had elapsed (351±805 versus 942±797 ng/ml; $P<0.001$). Unexpectedly, the study did not identify a threshold cord blood NVP concentration below which risk of transmission increased.

These results highlight that appropriate prophylactic drug levels early in labour and prevention of missed doses among women who might deliver at home or at a non participating facility are critical for the efficacy of NVP operational programmes. Policy implications comprise the development of counselling services addressing the recognition of signs of onset of labour, focusing on the importance of prompt drug self-administration once labour is suspected. The authors conclude on the need to increase the number of more effective programmes, i.e. which combine both the distribution of NVP antepartum for self-administration at the onset of labour as well as the provision of NVP in labour room for all women. A repeat dose of neonatal NVP may be necessary if labour lasts one hour or less after the ingestion of the intrapartum NVP dose as suggested also by Mirochnick et al (see IR 3 (9) for a review of this paper). The reader should be aware though that there is no direct evidence that this will further reduce the peripartum transmission rate. It is therefore possible that a single dose given right after birth in this context may give a similar result.

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Notes: In this letter, the authors point out the importance and difficulty to assess real effectiveness of PMTCT programmes in terms of compliance. They propose and have begun in Lusaka, Zambia, an alternative method based on testing cord-blood specimens for nevirapine, and underline that this method needs the development of simpler, cheaper but still sensitive assays to become broadly relevant.

Address:
URL:
PMTCT/ARV


Notes: This non intervention prospective MTCT Cohort was conducted in rural Kenya and investigated the subtype hypothesis on a post-hoc basis. The authors conclude from all their analyses that subtype D of HIV-1 either alone or in the context of recombinant viruses D/A and A/D increased the risk of MTCT after controlling for known risk factors including plasma RNA viral load. They recommend this parameter be measured in further PMTCT intervention trials but do not propose subtype specific interventions to be evaluated. There are limitations to this report. If one believes these conclusions are epidemiologically and clinically important, it should be noted that the D and A/D subtypes were only present in one fourth of the women, making the potential impact of this association limited. Furthermore, three methodological criticisms can be formulated which may seriously influence the conclusions: 38% of the study samples were discarded from analysis due to the impossibility to make an HIV infant diagnosis ; maternal CD4 was unavailable and one knows its independent prognostic value from HIV RNA viral load in MTCT ; finally the definition of peripartum transmission was excessive, with positive PCR up to four months of age and the analytical approach based on logistic regression technique was suboptimal. The viral subtype issue and its implications remain uncertain based on this report and the previous ones.

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MTCT

13th International Conference on STD & AIDS in Africa (ICASA), Nairobi, Kenya. September, 21st - 26th, 2003. Abstracts are not available on the the Web and there is no index in the print edition of the proceedings.

We highlight here first a few oral presentations which provided new research findings.

- Pakker N, et al. Efficacy of postnatal prophylaxis of 3TC or NVP in breastfed children to prevent MTCT through breastfeeding, the SIMBA study. [abstr LB not available]
- Newell ML, et al. Mortality in children born to HIV infected mothers in Africa, the IHMA study [abstr LB 1098982]

Data of seven MTCT intervention trials in largely breastfed populations were pooled for this analysis. Children were categorized as never or never breastfed. Among the 3468 singleton live births, the overall mortality rate was 110‰. HIV-infected children were 12 times more likely to die than HIV uninfected children. Infant death was associated with lower maternal CD4 count and mother's death, but was not associated with the breastfeeding status. Similar results were found after adjustment on infant HIV infection status.


The aim of this study was to validate a new technology, the real time PCR for the diagnosis of HIV infection (plasma RNA) in children. A good correlation (r=0.83) was found between this technique and bDNA assay at different child ages, especially by four weeks of age. The sensitivity and specificity of real time PCR compared to bDNA were 100%, with acceptable lower bound of the CI. This new technology appears thus extremely reliable, easy to use and ten times less costly than commercially available kits.
Selected operational research presentations:

- Ngashi N et al. The place of nevirapine in the Botswana AZT-based PMTCT program. [abstr 371858].
  The Botswana national PMTCT program is implemented since April 1999 and is based on zidovudine (ZDV/AZT) short course. Its overall uptake is 23% (2002 statistics). However, 50% of these women received an inadequate dose of ZDV. The reasons are multifactorial: delay to make a decision to test, delayed return for HIV test result and shortage of staff for counselling and follow-up of women. The use of nevirapine (NVP) in this context could be critical to enhance both the uptake and the efficacy of MTCT interventions in addition to addressing core programmatic issues. Indeed, Botswana has recently added NVP to its PMTCT protocol so as to improve the effectiveness of the PMTCT program.

Challenges in the implementation of PMTCT of HIV interventions in resource poor countries:

- Mulenga D. et al. Assessing the impact of interventions for vertical transmission of HIV. [abstr 516601]
- Kahindo et al. PMCT - Experience from 2 sites in Kenya. [abstr 555524]
- Quaghebeur A et al. Feasibility of the HIVNET012 Regimen in a real life situation. [abstr 559749]
- Kagwire F Experience and challenges of implementation of prevention of mother to child transmission of HIV (PMTCT) project in western Uganda. [abstr 688376].

Pilot projects have shown the effectiveness of PMTCT interventions and now guidelines are needed on how to scale-up these interventions. Various presentations confirmed the low uptake and drop out of PMTCT interventions at each stage, pre-test counselling, HIV testing, post test counselling, ARVs intake or infant follow-up. Presentations listed above highlighted that challenging issues remain to increase the number of infections averted: 1) integrated community-based communication programs; 2) engaging male partners in the PMTCT activities; 3) strengthening infant feeding counselling and support; 4) incorporating comprehensive care services and; 5) strategies to address stigma. Among the suggestions that were pinpointed that need to be considered and/or improved are: "opt-out" testing strategy and effective counselling and client follow-up.

Infant feeding in the context if HIV/AIDS:

- Henderson PL et al. Improving global guidance on infant feeding in the context of HIV/AIDS. [abstr 568697].

Among the possible strategies for the prevention of postnatal mother-to-child transmission of HIV, breastfeeding with abruptly weaning at an appropriate age is seriously considered. Thus, there is a need for technical guidance as well as accurate measurements of infant feeding practices in such programmes, as stressed by Henderson et al. A package of technical and programmatic information and guidelines on infant feeding in the context of HIV/AIDS has been revised by WHO. In this session, updated material aimed for decision-makers and health workers was presented. Main issues considered in these documents are how to assist HIV-positive women in infant feeding while preventing negative impacts on breastfeeding.

Conference summary

Erratum IR 3 (9)

- Nachega J, Notes page 32:
  Read : tuberculosis screening of whom 13 (11%) were found to have active tuberculosis
  Instead of : tuberculosis screening of whom 213 (11%) were found to have active tuberculosis

- Poirier MC, Notes page 33
  Read : levels observed may compromise
  Instead of : levels observed may comprise