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WHO, Reproductive Health and Research

HIV Care & PMTCT in Resource-Limited Settings

Monthly Intelligence Report

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prepared by the Bordeaux Working Group

Members: Elise Arrivé, Renaud Becquet, François Dabis (Coordinator), Valérie Leroy, Dominique Marchand, Evelyne Mouillet (Coordinator), Joanna Orne-Gliemann, Freddy Perez, Charlotte Sakarovitch, Catherine Seyler, Besigin Tonwe-Gold.

Number of citations selected for this issue: 21

Subject headings / Subheadings indexing the selected references (by alphabetical order)

Adults / Women	Eastern Europe	Infant feeding / Breastfeeding	Prevention of Mother-To-Child Transmission (PMTCT) / AntiRetroViral (ARV)	Treatment impact and response
Children	Gynæcology	Infections (Others) / Prophylaxis	Prevention of sexual transmission	Treatment monitoring
Clinical manifestations (Others)	Hepatitis B infection (HBV)	Low Income Countries (LICs) / Africa, Asia, Caribbean, South America	Randomized Controlled Trial (RCT)	Treatment programme
Comprehensive care	Hepatitis C infection (HCV)	Mother-To-Child Transmission (MTCT)	Termination of pregnancy / Abortion	Tuberculosis (TB) / Prophylaxis
Conference summary	Highly Active AntiRetroviral Treatment (HAART)	Natural history	Treatment adherence	Viral resistance
Contraception	Industrialized countries	Obstetrics	Treatment complications	Voluntary Counselling and Testing (VCT)

Citation format (by alphabetical order of the authors): Author(s). **Title**. Source. **Abstr.** (Authors' abstract) or **Notes** (prepared by the Bordeaux Working Group) **Author address**, if available, **Subject Headings**

Editorial

More than twenty years after the discovery of the Human Immunodeficiency Virus (HIV), the scientific literature continues to be produced at a very high speed, with on average 120 to 150 new citations in the Current Contents Life Sciences series each week. Most of these published papers refer now to original studies in the general areas of care and public health, with a diminishing part of basic science publications. The relative proportion of the HIV/AIDS scientific literature directly dedicated to the resource-limited countries increases now regularly.

The Bordeaux Working Group of the Institut de Santé Publique, Epidémiologie et Développement (ISPED, Université Victor Segalen, Bordeaux, France) was solicited in 2001 by the World Health Organization (Department of Reproductive Health and Research, WHO/RH) to produce a monthly bulletin to screen, select and report on the scientific information in the area of the prevention of mother-to-child transmission of HIV (PMTCT). The PMTCT Intelligence Report was thus produced monthly since May 2001 and posted on the WHO web site:

http://www.who.int/reproductive-health/rtis/MTCT/monthly_publications/listing_mtct_reports.htm.

Starting with this issue (January 2005), the Bordeaux Working Group will produce and disseminate a systematic and broader review and selection of the scientific literature in the area of HIV/AIDS, targeting HIV care and PMTCT programmes in resource-limited settings. We aim to select a maximum of 20 references per month on the basis of their clinical and/or public health relevance. An indexation of all the documents selected will use a list of 40 headings and sub-headings.

This new version of the Intelligence Report will be posted monthly on the ISPED web site as well as on the web sites of the sponsors (WHO/RH, Elizabeth Glaser Pediatric AIDS Foundation, International Center for AIDS Care and Treatment Programs (ICAP) at Columbia University Mailman School of Public Health). This document will provide to the web-reader a list of selected references including for each of them the title, list of authors (with e-mail address of the corresponding author), abstract (when available), keywords and link to the site where the full text is accessible (when available).

The cumulative database of the references, including the archives of the PMTCT Intelligence Report, will remain available on the ISPED web site and thus will be accessible free of charge and without registration via a search engine using the keywords.

The target audience of this expanded version of the Intelligence Report is the medical and public health staff involved in HIV programmes in resource-limited countries. If you work on at least one of the three components Care, Treatment, and PMTCT and act at the tertiary or secondary care levels as well as in programme management, you should read the Intelligence Report each month. We hope this new product will please you and remain available for suggestions for improving it.

François DABIS and Evelyne MOUILLET
for the Intelligence Report Bordeaux Working Group

Chappuy H, Treluyer JM, Jullien V, Dimet J, Rey E, Fouche M, Firtion G, Pons G, Mandelbrot L. **Maternal-fetal transfer and amniotic fluid accumulation of nucleoside analogue reverse transcriptase inhibitors in human immunodeficiency virus-infected pregnant women.** *Antimicrobial Agents and Chemotherapy* 2004;48(11):4332-4336.

Abstr. This study was performed to investigate placental transfer of nucleoside analogue reverse transcriptase inhibitors (NRTIs) and their concentrations in amniotic fluid when given to human immunodeficiency virus (HIV)-infected pregnant women. A total of 100 HIV type 1-infected mothers receiving antiretroviral therapy, including one or more NRTIs, for clinical indications at the time of delivery were enrolled. Maternal blood samples and amniotic fluid were obtained during delivery or cesarean section, and paired cord blood samples were obtained by venipuncture immediately after delivery. Drug concentrations were measured by using high-performance liquid chromatography. A significant relationship between concentrations in maternal and cord plasma samples was found for zidovudine, lamivudine, stavudine, and didanosine. The ratio between the concentrations in cord and maternal plasma samples (R) was high for zidovudine (R = 1.22), its glucuronide metabolite (3'-azido-3'-deoxythymidine-beta-D-glucuronide) (R = 1.01), stavudine (R = 1.32), lamivudine (R = 0.93), and abacavir (R = 1.03) and was low for didanosine (R = 0.38). The ratio between the concentrations in amniotic fluid and cord plasma samples was high for zidovudine (R = 2.24), its glucuronide metabolite (R = 2.83), stavudine (R = 4.87), and lamivudine (R = 3.99) and was lower for didanosine (R = 1.14). These findings indicate that most NRTIs cross the placenta by simple diffusion and are concentrated in the amniotic fluid, probably through fetal urinary excretion. The efficacy or toxicity of NRTIs may vary according to placental transfer.

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Adults / Women, Industrialized countries, Obstetrics, PMTCT / ARV

Check E. **Activists and researchers rally behind AIDS drug for mothers.** *Nature* 2004;432(7020):935.

Notes: The debate around the quality of the HIVNET 012 randomized controlled trial has been reopened in the media. We will not cover all the contributions. The Institute of Medicine is currently conducting a review of the available data and its progress report is regularly updated

URL: <http://www4.nationalacademies.org/cp/nsf/Projects+by+PIN/HPDP-H-04-08-A>

Adults / Women, Children, LICs, PMTCT / ARV, RCT

Covington DL, Conner SD, Doi PA, Swinson J, Daniels EM. **Risk of birth defects associated with nelfinavir exposure during pregnancy.** *Obstetrics and Gynecology* 2004;103(6):1181-1189.

Abstr. OBJECTIVE: The objective of this study was to examine the human teratogenic risk of the protease inhibitor, nelfinavir mesylate, used to treat human immunodeficiency virus. METHODS: This study used a subset of data from the Antiretroviral Pregnancy Registry, which was designed to monitor prenatal exposures to antiretroviral therapy and detect a potential increase in the risk of birth defects. The registry uses a prospective exposure-registration cohort design. All records of pregnant women exposed to nelfinavir, used alone or in combination, were extracted and analyzed. The prevalence of birth defects was compared with the Centers for Disease Control and Prevention's (CDC) population-based surveillance system. RESULTS: Through July 2002, the registry had monitored 915 live births exposed to nelfinavir. Among 301 first-trimester exposures, there were 9 birth defects, for a prevalence of 3% (95% confidence interval 1.4, 5.6). This rate is not significantly different from the CDC's system, which had a prevalence of 3.1 per 100 live births (95% confidence interval 3.1, 3.2; P = .99). There was no consistent pattern among reported birth defects. CONCLUSION. Adequate numbers of first-trimester exposures to nelfinavir have been monitored to detect a 2-fold increase in the prevalence of overall birth defects. No such increases have been detected when compared with the CDC rate. However, the numbers are not sufficient to detect any increased rate of specific defects. Although nelfinavir should only be used in pregnancy if the benefits outweigh the potential risks, the findings from this study should provide some assurance. (C) 2004 by The American College of Obstetricians and Gynecologists.

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Children, Clinical manifestations (Others), HAART, Industrialized countries, PMTCT / ARV, Treatment complications

European Collaborative Study. **Levels and patterns of neutrophil cell counts over the first 8 years of life in children of HIV-1-infected mothers.** *AIDS* 2004;18(15):2009-2017.

Abstr. Background: Antiretroviral drugs (ARV) as prophylaxis to prevent mother-to-child transmission of HIV results in decreased haematological parameters during and shortly after exposure, with recent data suggesting a more prolonged inhibition of haematopoiesis until at least 18 months. Design: Data on 156 HIV-infected and 1533 uninfected children in the European Collaborative Study followed from birth until at least 8 years of age.

Methods: Smoothers and splines were used to elucidate patterns over age; linear mixed effects allowed for repeated measurements. Covariates included the child's HIV-1 infection status, prematurity, gender, race, drug withdrawal symptoms at birth and ARV exposure; effects on neutrophil count were quantified in regression analyses using z-scores (SD from mean) of neutrophil counts obtained after modelling untransformed values using the LMS method. For HIV-infected children, progression to AIDS and ARV therapy were also included. Results: After approximately 4 months of age, neutrophil counts were consistently and substantially lower in HIV-infected children than in uninfected children; in both groups, black children had significantly lower counts than white children across the whole age range. In uninfected children, male gender and ARV exposure were associated with reduced neutrophil count until at least 8 years of age. In HIV-infected children, advanced disease and ARV treatment were significantly associated with neutrophil count. Conclusion: A considerably longer effect of exposure to ARV was shown in uninfected children than previously thought and significant associations were shown between race and gender and neutrophil count, as previously observed for lymphocyte counts. The clinical relevance of these reduced levels of neutrophils requires further investigation. (C) 2004 Lippincott Williams Wilkins.

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Children, Industrialized countries, PMTCT / ARV

Farquhar C, Kiarie JN, Richardson BA, Kabura MN, John FN, Nduati RW, Mbori Ngacha DA, John Stewart GC. **Antenatal couple counseling increases uptake of interventions to prevent HIV-1 transmission.** Journal of Acquired Immune Deficiency Syndromes 2004;37(5):1620-1626.

Abstr. To determine effect of partner involvement and couple counseling on uptake of interventions to prevent HIV-1 transmission, women attending a Nairobi antenatal clinic were encouraged to return with partners for voluntary HIV-1 counseling and testing (VCT) and offered individual or couple posttest counseling. Nevirapine was provided to HIV-1-seropositive women and condoms distributed to all participants. Among 2104 women accepting testing, 308 (15%) had partners participate in VCT, of whom 116 (38%) were couple counseled. Thirty-two (10%) of 314 HIV-1-seropositive women came with partners for VCT; these women were 3-fold more likely to return for nevirapine ($P = 0.02$) and to report administering nevirapine at delivery ($P = 0.009$). Nevirapine use was reported by 88% of HIV-infected women who were couple counseled, 67% whose partners came but were not couple counseled, and 45% whose partners did not present for VCT (P for trend = 0.006). HIV-1-seropositive women receiving couple counseling were 5-fold more likely to avoid breast-feeding ($P = 0.03$) compared with those counseled individually. Partner notification of HIV-1-positive results was reported by 138 women (64%) and was associated with 4-fold greater likelihood of condom use ($P = 0.004$). Partner participation in VCT and couple counseling increased uptake of nevirapine and formula feeding. Antenatal couple counseling may be a useful strategy to promote HIV-1 prevention interventions.

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Adults / Women, LICs / Africa, PMTCT / ARV, VCT

Fitzgerald DW, Maxi A, Marcelin A, Johnson WD, Pape JW. **Notification of positive HIV test results in Haiti: Can we better intervene at this critical crossroads in the life of HIV-infected patients in a resource-poor country?** AIDS Patient Care & Stds 2004;18(11):658-664.

Abstr. The current study was conducted in Port au Prince, Haiti, to determine if information collected at HIV notification during voluntary counseling and testing (VCT) can predict patients' future adherence with risk reduction counseling and medical referral. Case histories describe HIV-infected patients with signs of depression during counseling who do not return for medical care, and women afraid of economic ruin and domestic violence who do not notify their sexual partners. Quantitative predictors of seeking medical care include: denial at the announcement of HIV test results (odds ratio [OR] 0.3, 95% confidence interval [CI] 0.1-0.6), belief that HIV can be transmitted by magic (OR 0.6, 95% CI 0.3-0.9), and having symptoms at the time of HIV testing (OR 1.9, 95% CI 1.6-2.3). Predictors of refusal to notify sexual partner of HIV status include: being poor (OR 1.8, 95% CI 1.1-2.5), female (OR 2.1, 95% CI 1.7-2.5), and belief that HIV can be transmitted by magic (OR 2.3, 95% CI 1.9-2.6) In conclusion, information collected during HIV counseling and testing can predict patients' future adherence with counseling and medical referral. Counselors can use information such as signs of severe depression, economic hardship, and denial of HIV disease to identify patients at risk for nonadherence and to provide them with specialized counseling and care.

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Adults, Comprehensive care, LICs / Caribbean, VCT

Hatzakis AE, Touloumi G, Pantazis N, Anastassopoulou CG, Katsarou O, Karafoulidou A, Goedert JJ, Kostrikis LG. **Cellular HIV-1 DNA load predicts HIV-RNA rebound and the outcome of highly active antiretroviral therapy.** AIDS 2004;18(17):2261-2267.

Abstr. Objective: To assess whether cellular HIV-1 DNA prior to highly active antiretroviral therapy (HAART) initiation predicts its outcome. Design and methods: Patients included all 51 hemophiliacs of the Greek component of the Multicenter Hemophilia Cohort Study who had initiated HAART and for whom cryopreserved lymphocyte samples before HAART initiation were available. Cellular HIV-1 DNA quantification was performed by a molecular beacon-based real-time PCR assay in multiple samples per patient with a median (interquartile range) follow-up of 76 (45-102) weeks. Results: The median (range) baseline HIV-1 DNA load was 297 (< 10 to 3468) copies per 1×10^6 peripheral blood mononuclear cells. Baseline HIV-1 DNA load did not predict initial virological response (VR). None of the patients with initial VR and baseline HIV-1 DNA load at or below the median experienced a subsequent virological rebound, while the cumulative probability of virological rebound by week 104 was 55% among those with HIV-1 DNA load greater than the median ($P < 0.008$). Cellular HIV-1 DNA load was the only parameter associated with sustained virological response as shown by univariate or multivariate analyses [adjusted odds ratio (95% confidence interval) 0.197 (0.048-0.801) per 1 log(10) increase in DNA copies, $P = 0.023$]. Conclusion: Low cellular HIV-1 DNA load is a marker of sustained virological response in patients with initial VR and it can reliably predict the long-term success of HAART. (C) 2004 Lippincott Williams Wilkins.

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Adults, HAART, Industrialized countries, Treatment monitoring

Henderson GJ, Hoffman NG, Ping LH, Fiscus SA, Hoffman IF, Kitrinos KM, Banda T, Martinson FEA, Kazembe PN, Chilongozi DA, Cohen MS, Swanstrom R. **HIV-1 populations in blood and breast milk are similar.** Virology 2004;330(1):295-303.

Abstr. Mother-to-child transmission (MTCT) of human immunodeficiency virus type 1 (HIV-1) through breast milk is a significant mechanism of infection in many regions of the world. We compared the HIV-1 populations in paired blood and breast milk samples using a heteroduplex tracking assay (HTA) for the V1/V2 regions of env (V1/V2-HTA). V1/V2-HTA patterns were similar in the eight pairs of samples for which adequate template sampling could be demonstrated. No unique variants existed in either compartment, and differences detected in the relative abundance of variants between compartments were small, occurred among low abundance variants, and were not statistically significant. We also documented the impact of template sampling as a limiting feature in comparing two viral populations. The absence of unique variants and the lack of significant differences in the relative abundance of variants between these compartments support the conclusion that viruses in the blood plasma and breast milk are well equilibrated. (C) 2004 Elsevier Inc. All rights reserved.

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Adults / Women, Infant feeding / Breastfeeding, LICs / Africa, MTCT

Kumarasamy N, Chaguturu S, Mayer KH, Solomon S, Yepthomi HT, Balakrishnan P, Flanigan TP. **Incidence of immune reconstitution syndrome in HIV/tuberculosis-coinfected patients after initiation of generic antiretroviral therapy in India.** Journal of Acquired Immune Deficiency Syndromes 2004;37(5):1574-1576.

Abstr. This paper describes the incidence of immune reconstitution syndrome (IRS) from the developing world and implications for clinicians. Eleven of 144 HIV and tuberculosis (TB)-coinfecting individuals followed for 72 person-years developed IRS within 6 months of initiating generic highly active antiretroviral therapy (HAART). All of the IRS patients were male, with a median age of 29 years; median CD4 at HAART initiation was 123 cells/mm³, and 6-month median CD4 rise was 124 cells/mm³. There was no statistical difference in CD4 rise or CD4 count and duration of TB treatment at HAART initiation between those who did and those who did not develop IRS ($P = 0.8380$). The median time to development of clinical IRS was 42 days (range 10-89 days). The incidence of IRS in this cohort is 15.2 cases per 100 patient-years. With increased coprevalence of opportunistic infections, especially TB, and increasing access to antiretroviral therapy in the developing world, clinicians in these countries must be able to identify IRS and relieve symptoms without compromising clinical care.

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Adults, Clinical manifestations (Others), HAART, LICs / Asia, TB, Treatment complications

Liebeschuetz S, Bamber S, Ewer K, Deeks J, Pathan AA, Lalvani A. **Diagnosis of tuberculosis in South African children with a T-cell-based assay: a prospective cohort study.** *Lancet* 2004;364(9452):2196-2203.

Abstr. Background Childhood tuberculosis often presents non-specifically and is a common differential diagnosis in high prevalence areas. Current diagnostic tools have poor sensitivity and cannot reliably exclude tuberculosis, so overdiagnosis is common. HIV co-infection exacerbates this problem and accounts for an increasing proportion of paediatric tuberculosis worldwide. Methods We assessed the usefulness of a T-cell-based rapid blood test for Mycobacterium tuberculosis infection, the enzyme-linked immunospot assay (ELISPOT), in routine clinical practice. We did a prospective blinded study of 293 African children with suspected tuberculosis in kwaZulu-Natal, a region with high HIV prevalence. Children had full clinical assessment, ELISPOT, and a tuberculin skin test. Test results were compared with final clinical and microbiological diagnoses. Results In children with tuberculosis, sensitivity of ELISPOT was 83% (95% CI 75-89, n=133), significantly higher ($p<0.001$) than the 63% (54-72) sensitivity of tuberculin skin test (n=116). Sensitivity of tuberculin skin test fell significantly in children younger than 3 years (to 51%), with HIV co-infection (36%), or with malnutrition (44%). Sensitivity of ELISPOT, which was not significantly adversely affected by these factors, was 85%, 73%, and 78%, respectively in these subgroups. In 116 children with both test results available, sensitivity of the two tests combined was 91% (85-95). Conclusions Diagnostic sensitivity of ELISPOT is higher than that of the skin test and is less affected by factors frequently associated with childhood tuberculosis in developing countries. Used together with the skin test, ELISPOT provides a clinically useful diagnostic sensitivity in African children with suspected tuberculosis.

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Children, LICs / Africa, Natural history, TB

McClelland RS, Baeten JM, Overbaugh J, Richardson BA, Mandaliya K, Emery S, Lavreys L, Ndinya Achola JO, Bankson DD, Bwayo JJ, Kreiss JK. **Micronutrient supplementation increases genital tract shedding of HIV-1 in women - Results of a randomized trial.** *Journal of Acquired Immune Deficiency Syndromes* 2004;37(5):1657-1663.

Abstr. To test the hypothesis that micronutrient supplementation decreases genital HIV-1 shedding, a double-blind, randomized, placebo-controlled trial of 6 weeks of multivitamin plus selenium supplementation vs. placebo was conducted among 400 HIV-1-seropositive, nonpregnant, antiretroviral-naïve women in Mombasa, Kenya. Primary outcome measures included cervical and vaginal shedding of HIV-1-infected cells and RNA. Secondary outcomes included plasma viral load and CD4 count. Surprisingly, the odds of detection of vaginal HIV-1-infected cells were 2.5-fold higher ($P = 0.001$) and the quantity of HIV-1 RNA in vaginal secretions was 0.37 log₁₀ copies/swab higher ($P = 0.004$) among women who received micronutrients in comparison to placebo, even after adjustment for potential confounders including baseline HIV-1 shedding and CD4 count. The increase in vaginal HIV-1 shedding was greatest among women who had normal baseline selenium levels. Micronutrient supplementation resulted in higher CD4 (+23 cells/ μ L, $P = 0.03$) and CD8 (+74 cells/ μ L, $P = 0.005$) counts compared with placebo but did not alter the plasma viral load. In this randomized trial, micronutrients resulted in higher levels of genital HIV-1 shedding compared with placebo. The potential benefit of micronutrient supplementation in HIV-1-seropositive women should be considered in relation to the potential for increased infectivity.

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Adults / Women, Comprehensive care, LICs / Africa, Natural history, Prevention of sexual transmission, RCT

Olweny CLM, Borok M, Gudza I, Clinch J, Cheang M, Kiire CF, Levy L, Otim Oyet D, Nyamasve J, Schipper H. **Treatment of AIDS-associated Kaposi's sarcoma in Zimbabwe: Results of a randomized quality of life focused clinical trial.** *International Journal of Cancer* 2005;113(4):632-639.

Abstr. Kaposi's sarcoma is currently the most common tumor in Zimbabwe. The purpose of our study is to compare the effectiveness of supportive care vs. 3 intervention approaches, namely oral Etoposide, a 3-drug combination, and radiotherapy using quality of life (QOL) as the primary measure of success. In addition, our study was to determine whether a disease-specific module has greater sensitivity to group differences than a generic QOL questionnaire and to determine the most pragmatic approach to treating epidemic Kaposi's sarcoma (EKS) in Zimbabwe. Histologically confirmed HIV-positive patients with Kaposi's sarcoma were randomized to receive supportive care only or supportive care plus either radiotherapy, oral Etoposide or a 3-drug combination consisting of actinomycin-D, vincristine and bleomycin. No patient received antiretroviral therapy. The primary outcome was QOL measured by the functional living index-cancer (FLI-C) and supplemented by the Kaposi's sarcoma module (KSM). From 1994-1999, 495 EKS patients were accrued, and 470 were evaluable. Of these, 433 are known to be dead, 26 are lost to follow-up and 11 are still alive. The group treated with oral Etoposide

had a significantly better QOL than the radiotherapy group for the total FLI-C score (adjusted mean plus standard error at 3-months 89 +/- 3 vs. 76 +/- 3; p = 0.004) and for the hardship (11 +/- 0.4 vs. 9 +/- 0.4; p = 0.001); social (10 +/- 0.4 vs. 8 +/- 0.4; p = 0.001) and nausea (9 +/- 0.4 vs. 8 +/- 0.4; p = 0.002) subscales. In addition, on the physical and psychological subscales, the Etoposide group had a significantly better QOL than the other 3 treatment groups (p < 0.04). The 3-drug combination, supportive care and radiotherapy groups did not differ significantly from each other with respect to the total FLI-C score or its subscales. There were no group differences with respect to survival. Oral Etoposide therapy resulted in better total FLI-C QOL score than radiotherapy. As well, Etoposide resulted in better physical and psychological subscale scores than radiotherapy, 3-drugs and supportive care. Thus, funds permitting, oral Etoposide is a pragmatic approach to treating EKS in an environment where antiretroviral drugs are not universally available. The study underscores the value of undertaking studies in areas of disease prevalence and the necessity of selecting appropriate outcome measures. (C) 2004 Wiley-Liss, Inc.

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Adults, Clinical manifestations (Others), LICs / Africa, RCT, Treatment impact and response

Pujari SN, Patel AK, Naik E, Patel KK, Dravid A, Patel JK, Mane AA, Bhagat S. **Effectiveness of generic fixed-dose combinations of highly active antiretroviral therapy for treatment of HIV infection in India.** Journal of Acquired Immune Deficiency Syndromes 2004;37(5):1566-1569.

Abstr. Objective: To assess clinical and immunologic effectiveness and acute toxicity to nevirapine (NVP)-based fixed-dose combinations (FDCs) in antiretroviral-naive HIV-1-infected patients in India. Design: Observational study of patients initiated on NVP-based combination therapy delivered as FDCs. Methods: Antiretroviral-naive HIV-1-infected patients initiated on FDCs (zidovudine/lamivudine [3TC]/NVP or stavudine/3TC/NVP) were assessed clinically and with CD4 counts periodically. Adverse events to NVP were assessed clinically and by laboratory markers. Frequency and risk factors for development of adverse events and clinical outcomes were determined. Results: Of the 1291 patients started on therapy, 1253 completed a minimum of 3 months of follow-up. Rash and hepatitis were documented in 6.6% (95% confidence interval [CI]: 5.5-8.3) and 3.2% (95% CI: 2.3-4.8) of patients initiating therapy, respectively. There was significant improvement in CD4 counts over 2 years. Forty-eight patients died, and 186 clinical events were documented in these patients. Tuberculosis was the most common cause of morbidity and mortality. Self-reported adherence was high. Conclusion: Fixed-dose formulations of NVP-based combination therapy are safe and produced durable clinical and immunologic benefit.

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Adults, HAART, LICs / Asia, Treatment adherence, Treatment complications, Treatment impact and response

Safreed Harmon K, Cooper DA, Lange JMA, Duncombe C, Phanuphak P. **The HIV Netherlands Australia Thailand research collaboration: lessons from 7 years of clinical research.** AIDS 2004;18(15):1971-1978.

Notes. An editorial review describing the experience of collaborative therapeutic research in Thailand since 1996.

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HAART, LICs / Asia, RCT

Seipone K, Ntuny R, Smith M, Thuku H, Mazhani L, Creek T, Shaffer N, Kilmarx PH. **Introduction of routine HIV testing in prenatal care - Botswana, 2004 (Reprinted from MMWR, vol 53, pg 1083-1086, 2004).** JAMA 2005;293(2):152-153.

Notes. Routine non-compulsory HIV screening during prenatal care has been suggested as a key strategy to increase the uptake of HIV counselling and testing services provided in the context of PMTCT interventions. Three months after implementing this "opt-out" approach, the acceptability of HIV testing in four clinics of Francistown, the second largest city in Botswana, had increased from 75.3% to 90.5% (p<0.001). The next urgent step for the Botswana Ministry of Health is to introduce rapid HIV tests to increase the number of women being post-test counselled. Indeed, the knowledge of their HIV status is essential for HIV-negative women to maintain safe sex behaviours and for HIV-infected women to access anti-retroviral prophylaxis for MTCT and anti-retroviral treatment for themselves.

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Adults / Women, LICs / Africa, PMTCT / ARV, VCT

Sonnenberg P, Glynn JR, Fielding K, Murray J, Godfrey Faussett P, Shearer S. **How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners.** *Journal of Infectious Diseases* 2005;191(2):150-158.

Abstr. Background. Infection with human immunodeficiency virus (HIV) increases the risk of tuberculosis (TB), but no study has assessed how this risk changes with time since HIV seroconversion. Methods. The incidence of pulmonary TB was estimated in miners with and those without HIV infection in a retrospective cohort study. HIV test results were linked to routinely collected TB, demographic, and occupational data. The rate ratio (RR) for the association between HIV status and TB was estimated by time since HIV seroconversion, calendar period, and age. Results. Of the 23,874 miners in the cohort, 17,766 were HIV negative on entry, 3371 were HIV positive on entry, and 2737 seroconverted during follow-up (1962 had a seroconversion interval of less than or equal to 2 years). A total of 740 cases of TB were analyzed. The incidence of TB increased with time since seroconversion, calendar period, and age. TB incidence was 2.90 cases/100 person-years at risk (pyar) in HIV-positive miners and was 0.80 cases/100 pyar in HIV-negative miners (adjusted RR, 2.9 [95% confidence interval {CI}, 2.5-3.4]). TB incidence doubled within the first year of HIV infection (adjusted RR, 2.1 [95% CI, 1.4-3.1]), with a further slight increase in HIV-positive miners for longer periods, up to 7 years. Conclusion. The increase in the risk of TB so soon after infection with HIV was unexpected. Current predictive models of TB incidence underestimate the effect of HIV infection in areas where TB is endemic.

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Adults, LICs / Africa, Natural history, TB

Steel Duncan JC, Pierre R, Evans Gilbert T, Rodriguez B, Smikle MF, Palmer P, Whorms S, Hambleton I, Figueroa JP, Christie CDC. **Uptake of interventions, outcomes and challenges in caring for HIV exposed infants in Kingston, Jamaica.** *West Indian Medical Journal* 2004;53(5):308-314.

Abstr. Background: In a few Caribbean islands, prevention of mother-to-child transmission (pMTCT) of HIV with zidovudine prophylaxis has reduced transmission rates from 27 - 44% to 5.5 - 9%. Objectives: To highlight the uptake of interventions, preliminary outcomes and challenges in caring for HIV-exposed infants in a pMTCT HIV programme in a resource-limited setting. Method: A cohort of HIV-infected pregnant women were identified at the leading maternity centres in Greater Kingston through HIV counselling and testing and enrolled in the Kingston Paediatric and Perinatal HIV/AIDS Programme. Antiretroviral prophylaxis with zidovudine or nevirapine was given to the HIV-positive women and their newborns along with formula feeding. Some infants were enrolled retrospectively and followed irrespective of whether they had or had not received antiretroviral prophylaxis. A multidisciplinary team at the paediatric centres supervised protocol-driven management of the infants. Infants were followed for clinical progress and definitive HIV-infection status was to be confirmed at 18 months of age by ELISA or the Determine Rapid Test. Results: During September 1, 2002 through August 31, 2003, 132 HIV-exposed infants were identified. For those infants prospectively enrolled (78), 97% received antiretroviral prophylaxis and 90% were not breastfed. For all HIV-exposed children, 90% received cotrimoxazole prophylaxis and 88% continued follow-up care. Ninety-two per cent of all the infants remained asymptomatic and five died; of these deaths one is possibly HIV-related (severe sepsis at 11 weeks). This infant was retrospectively identified, had received no antiretroviral prophylaxis and was breastfed. The main programme challenges, which were overcome, included the impact of stigma, compliance with antiretroviral chemoprophylaxis, breast-milk substitution and follow-up care. Financial constraints and laboratory quality assurance issues limited early diagnosis of HIV infection. Conclusion: Despite the challenges, the expected outcome is to prevent 50 new cases of HIV/AIDS in children living in Greater Kingston per year (300 over six years).

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Adults / Women, Children, Comprehensive care, Infant feeding / Breastfeeding, LICs / Caribbean, PMTCT / ARV

Thorne C, Patel D, Newell ML. **Increased risk of adverse pregnancy outcomes in HIV-infected women treated with highly active antiretroviral therapy in Europe.** *AIDS* 2004;18(17):2337-2339.

Abstr. Highly active antiretroviral therapy (HAART) may be associated with adverse pregnancy outcomes. Among 4372 live births in the European Collaborative Study, the prematurity rate increased to 24.9% in 2000-2004. Antenatal HAART use initiated pre-pregnancy was strongly associated with prematurity (AOR 2.05, 95% CI 1.43, 2.95), particularly severe prematurity. The implication of increased prematurity is evidenced in high neonatal mortality in these groups (0.66% for infants at 34-36 weeks and 7.37% at < 34 weeks' gestation).

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Children, HAART, Industrialized countries, PMTCT / ARV, Treatment complications

van Heeswijk RPG, Khaliq Y, Gallicano KD, Bourbeau M, Seguin I, Phillips EJ, Cameron DW. **The pharmacokinetics of nelfinavir and M8 during pregnancy and post partum.** Clinical Pharmacology and Therapeutics 2004;76(6):588-597.

Abstr. Objective: The objective of this study was to explore the pharmacokinetics of nelfinavir and its active metabolite hydroxy-t-butylamidenelfinavir (M8) during pregnancy and post partum. Methods. Eleven human immunodeficiency virus type 1-infected Pregnant women receiving 1250 mg nelfinavir twice. daily were enrolled. Pharmacokinetics of nelfinavir and M8 were assessed over a 12-hour period during pregnancy (median, 32 weeks' gestation; range, 31-36 weeks) and post partum (median, 8 weeks post partum; range, 6-15 weeks). Drug concentrations were analyzed by HPLC coupled to tandem mass spectroscopy,, and pharmacokinetic parameters were calculated by use of noncompartmental methods. Results: The-median area under the plasma concentration-time curve from 0 to 12 hours (AUC(0-12)), the maximal plasma concentration (C-max), and the concentration at the end of the dosing interval (C-12) for nelfinavir postpartum were 33.5 h . mug/mL, 5.80 mug/mL, and 1.40 mug/mL, respectively. The values for the geometric mean ratio (GMR) (third trimester/post partum) for the nelfinavir AUC(0-12), C-max, and C-12 were 0.76 (90% confidence interval [CI], 0.54-1.06), 0.81 (90% CI, 0.57-1.15), and 0.43 (90% CI, 0.25-0.76), respectively. The GMR values for the M8 AUC(0-12), C-max, and C-12 were 0.32 (90% CI, 0.18-0.55), 0.31 (90% CI, 0.19-0.51), and 0.30 (90% CI, 0.14-0.64), respectively. The median ratio values of the AUC(0-12) of M8 and nelfinavir (M8/nelfinavir) during the third trimester and post partum were 11% and 27%, respectively (GMR, 0.42 [90% CI, 0.33-0.53]). Conclusions: Nelfinavir exposure was reduced during pregnancy, and the reduction was statistically significant for C-12. M8 concentrations were about 70% lower during pregnancy compared with post partum, suggesting either induction of hepatic cytochrome P450 (CYP) 3A4 or inhibition of CYP2C19, or both, during pregnancy. Because 8 of 11 women had subtherapeutic nelfinavir trough concentrations during pregnancy, the safety and efficacy of therapeutic drug monitoring should be investigated.

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Adults / Women, Industrialized countries, PMTCT / ARV

Wade NA, Unadkat JD, Huang S, Shapiro DE, Mathias A, Yasin S, Ciupak G, Watts DH, Delke I, Rathore M, Hitti J, Frenkel L, Samelson R, Smith ME, Mofenson L, Burchett SK. **Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332.** Journal of Infectious Diseases 2004;190(12):2167-2174.

Abstr. This study evaluates the safety, tolerance, and pharmacokinetics of stavudine (d4T) in human immunodeficiency virus (HIV) - infected zidovudine (ZDV) - intolerant/refusing pregnant women and of single-dose d4T in their infants. Women received d4T and lamivudine (3TC) from enrollment until labor. During labor, women received oral 3TC and either intravenous or oral d4T. Infants received ZDV and 3TC for 6 weeks and a single dose of oral d4T at weeks 1 and 6. Mean maternal antenatal d4T pharmacokinetics (terminal plasma half-life [T-1/2], 83.5 +/- 16.8 min; area under the plasma-concentration time curve [AUC(0-infinity)], 81.6 +/- 22.0 mug . min/mL n = 6) were not significantly different from those during labor (T-1/2, 87.3 +/- 24.7 min; AUC(0-infinity), 88.1 +/- 16.6 mug . min/ mL; n = 6). Umbilical-cord and maternal plasma concentrations were not significantly different from one another. The oral clearance of d4T in infants was significantly greater at week 6 versus week 1 (vs. 6.8 +/- 1.0 vs. 5.6 +/- 1.2 mL/min/kg). There were no toxicities, in women or infants, that required discontinuation or modification of the study drug. No infants had positive HIV viral diagnostic tests. d4T with or without 3TC is a potential alternative to ZDV for HIV-infected pregnant women.

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Adults / Women, Children, Industrialized countries, Obstetrics, PMTCT / ARV

WHO. **"3 by 5" Progress report, December 2004.**

Abstr. Based on the right to treatment and building on years of work by governments, donors, and civil society, "3 by 5" aims to help infuse hope and energy into communities that have been largely immobilized by the devastating toll of the epidemic. Further, we were convinced that the entire United Nations System, and especially WHO, could do much more to help countries provide treatment to the poorest, most affected communities. As we present our second progress report, we are witnessing incredible synergy arising from strategic partnerships across a variety of sectors. The global effort to achieve "3 by 5" is gaining momentum and has clearly shifted from vision to reality. Progress in the second half of 2004 has been dramatic, reaching the December milestone of 700 000 people receiving antiretroviral therapy. A remarkable international movement has now gathered behind the "3 by 5" target.

URL: <http://www.who.int/3by5/progressreport05/en>

HAART, LICs, Treatment programme