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## HIV Care & PMTCT in Resource-Limited Settings

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**Citation format** (by alphabetical order of the authors): Author(s). **Title**. Source. **Abstr.** (Authors' abstract) or **Notes** (selection from the paper) **Author address**, if available, **Free full text**, if available

Danel C, Moh R, Anzian A, Abo Y, Chenal H, Guehi C, Gabillard D, Sorho S, Rouet F, Eholie S, Anglaret X. **Tolerance and acceptability of an efavirenz-based regimen in 740 adults (Predominantly women) in West Africa.** *Journal of Acquired Immune Deficiency Syndromes* 2006;42(1):29-35.

**Abstr.** In sub-Saharan Africa, the position of efavirenz as a first-line nonnucleoside reverse transcriptase inhibitor remains to be discussed. We report here the 6-month efficacy and tolerance of all efavirenz-containing highly active antiretroviral therapy regimen in a large cohort of HIV-1-infected adults. Seven hundred forty highly active antiretroviral therapy-naïve adults (74% women; 14% with positive serum HBs antigen and 21% with abnormal baseline transaminase value) started zidovudine + lamivudine + efavirenz. At month 6, 1.2% of them were dead, 87% had undetectable viral load, and 7% had abnormal transaminase value. From months 1 to 6, the percentage of women who were actually using a contraceptive method increased from 58% to 80% (65% intramuscular progesterone and 35% oral estrogen/ progesterone combination). The incidence of pregnancy was 2.6/100 woman-years (95% confidence interval, 0.67-4.51), and 86% of pregnant women voluntarily interrupted the pregnancy with no intervention on our part. Before month 6, only 0.8% of patients permanently discontinued efavirenz for severe adverse effects (neurologic, 0.6%; Cutaneous, 0.1%; and hepatic, 0.1%). The leading cause of severe morbidity was tuberculosis. Considering the very high hepatic and cutaneous tolerance, efavirenz could be considered as a valuable first-line drug for women of childbearing age who agree to use contraception in sub-Saharan Africa, provided that the risk of teratogenicity should be closely monitored.

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Doualla Bell F, Avalos A, Gaolathe T, Mine M, Gaseitsiwe S, Ndwapi N, Novitsky VA, Brenner B, Oliveira M, Moisi D, Moffat H, Thior I, Essex M, Wainberg MA. **Impact of human immunodeficiency virus type 1 subtype C on drug resistance mutations in patients from Botswana failing a nelfinavir-containing regimen.** *Antimicrobial Agents and Chemotherapy* 2006;50(6):2210-2213.

**Abstr.** Among 16 human immunodeficiency virus-infected (subtype C) Botswana patients who failed nelfinavir (NFV)-containing regimens, the most prevalent mutation observed was D30N (54%), followed by L90M (31%). L89I, K20T/I, and E35D polymorphic changes were also identified. These findings suggest that subtype C viruses in Botswana may develop resistance to NFV via subtype-specific pathways.

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Giuliano M, Galluzzo CM, Germinario EAP, Amici R, Bassani L, Deho L, Vyankandondera J, Mmiro F, Okong P, Vella S. **Selection of resistance mutations in children receiving prophylaxis with lamivudine or nevirapine for the prevention of postnatal transmission of HIV** [Letter to the Editor]. *Journal of Acquired Immune Deficiency Syndromes* 2006;42(1):131-133.

**Notes.** NNRTI resistance mutations have been reported in 42% and 46% of infants who were exposed to the regimen of single-dose NVP (mother + child). Therefore, because all infants in our study have been exposed to a minimum of 14 days of NVP as a single drug, a high frequency of NNRTI resistance mutations was expected and indeed found. It is interesting to note that although a reduced fitness of the Y181C-containing viruses has been reported in our study in 6 of 7 children with the Y181C mutation who had a subsequent sample, this mutation was also present several months after the discontinuation of prophylaxis. For 3TC, the emergence of resistance mutations has been shown to be associated with the duration of the administration in studies in which the drug was given in combination with zidovudine. In our study, the administration for 2 weeks of 3TC as a single drug was associated with the emergence of the M184V mutation in most of the infants. This mutation appeared to fade rapidly, confirming data on the rapid reversion to wild-type of the M184V-containing viruses. Our finding of a high percentage of NNRTI-naïve women with NNRTI mutations deserves further studies to assess the prevalence of resistance mutations in a larger number of untreated women in this setting.

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Gray G, Violari A, McIntyre J, Jivkov B, Schnittman S, Reynolds L, Ledine JM. **Antiviral activity of nucleoside analogues during short-course monotherapy or dual therapy: Its role in preventing HIV infection in infants.** *Journal of Acquired Immune Deficiency Syndromes* 2006;42(2):169-176.

**Abstr.** Background: This is the first report on the preliminary efficacy of 4 different short-course nucleoside analogue regimens (stavudine [d4T], didanosine [ddI], d4T+ddI, and zidovudine [ZDV]) for the prevention of mother-to-child transmission of HIV-1 (MTCT) in a resource-limited setting. Design: This prospective open-label, randomized 4-arm study (May 1999 to May 2000) conducted in South Africa enrolled 373 women from 34 weeks of gestation; medication was continued through delivery and for 6 weeks to infants. MTCT rates were ascertained at birth, 6, 12, and 24 weeks of age. Results: Mean maternal HIV-1 RNA levels decreased rapidly on treatment in all groups. At week 4, the mean decrease was 1.91 log<sub>10</sub> copies/mL (c/mL) in the d4T+ddI group,

1.33 log<sub>10</sub> c/mL in the ddI group, 1.12 log<sub>10</sub> c/mL in the d4T group, and 0.76 log<sub>10</sub> c/mL in the ZDV group. Among the 362 evaluable mother-infant pairs, 11 infants in the d4T group, 10 in the ddI group, 5 in the ZDV group, and 4 in the d4T+ddI group were infected by 24 weeks of age. Eleven infections occurred in utero. Treatment with d4T and ddI was not associated with lactic acidosis or hepatic steatosis. Conclusions: The abbreviated use of nucleoside analogues for the prevention of MTCT appears safe and effective.

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Harries AD, Schouten EJ, Libamba E. **Scaling up antiretroviral treatment in resource-poor settings** [Viewpoint]. *Lancet* 2006;367(9525):1870-1872.

**Notes.** We strongly believe that Malawi should continue scaling up use of the first-line stavudine, lamivudine, and nevirapine regimen only, and should provide other first-line and second-line drugs in only a few centres. There is an important public-health consideration to support this view. Because there are many eligible HIV-infected people who are not yet receiving any treatment and because over 80% of patients do well on the first-line regimen priority should be given to provision of first-line treatment to those not yet receiving ART rather than offering better care to the minority already on ART. This approach is based on principles of equity and should result in an improved overall health gain. At present we are working with WHO and the US Centers for Disease Control and Prevention to develop a system in five busy ART sites for yearly monitoring of viral load and viral resistance in patients on the first-line ART regimen. These measurements will give us a national perspective of the effect of treatment and the standard outcomes will provide valuable information about longitudinal survival. There will be continuous pressure from both within and outside Malawi to use advanced laboratory technology. We cannot support this position unless the technology for measurement of viral load and CD4-lymphocyte counts becomes cheaper, more straightforward, and more user friendly. In most health-care facilities in Malawi, essential laboratory services cannot be provided reliably and we think that the introduction of present laboratory technology that supports ART will weaken rather than strengthen general laboratory service delivery. Health-care staff will have to learn to trust their patients and aim to review them every 2–3 months instead of every month. Malawi will have to teach less qualified health-care workers to manage patients and to consider decentralisation to health centres to reduce the load on the hospital clinics and improve access for patients living in rural areas. For national monitoring, there might be a need to simplify the outcome analysis to standard primary outcomes only, because the task of wading through thousands of patients' master cards to report on side-effects and pill counts will become impossible. Some of Malawi's busy clinics use both a manual register and a computer system for monitoring of patients starting ART. Computerisation of all the ART facilities might be possible and we are exploring this option, but Africa is littered with broken computers that have been destroyed by power surges, lightning storms, or electronic viruses and we are not convinced that this is the answer.

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Holmes CB, Zheng H, Martinson NA, Freedberg KA, Walensky RP. **Optimizing treatment for HIV-infected South African women exposed to single-dose nevirapine: Balancing efficacy and cost.** *Clinical Infectious Diseases* 2006;42(12):1772-1780.

**Abstr.** Introduction. Nevirapine (NVP) resistance may decrease the effectiveness of viral suppression with NVP-based antiretroviral therapy (ART) in women infected with human immunodeficiency virus (HIV) with previous exposure to single-dose NVP. However, the alternative lopinavir-ritonavir-based ART regimen is more expensive. Our objectives were to project the tradeoffs regarding life expectancy, cost, and cost-effectiveness of these ART regimens for NVP-exposed, HIV-infected women in South Africa. Methods. We developed a simulation model in which NVP-exposed, HIV-infected South African women received 1 of 5 treatment strategies: HIV care without ART, NVP-based ART, lopinavir-ritonavir-based ART, NVP-based ART followed by lopinavir-ritonavir-based ART, or lopinavir-ritonavir-based ART followed by NVP-based ART. The prevalence of NVP resistance was 39%; other data were obtained from the published literature. Results. Projected life expectancy was 43.7 months for women who did not receive ART, 77.4 months for women who received a single NVP-based regimen, and 84.5 months for women who received a single lopinavir-ritonavir-based regimen. NVP resistance reduced survival time by up to 11.6 months among women who received NVP-based ART. The cost-effectiveness of NVP-based ART was \$800 (US dollars) per year of life saved, compared with no ART, and the cost-effectiveness of lopinavir-ritonavir-based therapy was \$4400 per year of life saved, compared with NVP-based ART. Lopinavir-ritonavir followed by NVP-based ART yielded the greatest life expectancy (105.4 months), had a cost-effectiveness of \$2300 per year of life saved, and, if the efficacy of NVP-based regimens improved 16 months postpartum, further increased survival. Conclusions. NVP resistance substantially decreased the projected survival time associated with NVP-based ART, and lopinavir-ritonavir-based ART resulted in a superior survival time but at higher cost. A sequential regimen starting with lopinavir-

ritonavir-based ART followed by NVP-based ART maximized projected survival and was cost effective in South Africa.

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Homsy J, Kalamya JN, Obonyo J, Ojwang J, Mugumya R, Opio C, Mermin J. **Routine intrapartum HIV counseling and testing for prevention of mother-to-child transmission of HIV in a rural Ugandan hospital.** *Journal of Acquired Immune Deficiency Syndromes* 2006;42(2):149-154.

**Abstr.** Objective: In Africa, prevention of mother-to-child HIV transmission (PMTCT) programs are hindered by limited uptake by women and their male partners. Routine HIV counseling and testing (HCT) during labor has been proposed as a way to increase PMTCT uptake, but little data exist on the impact of such intervention in a programmatic context in Africa. Design and Methods: In May 2004, PMTCT services were established in the antenatal clinic (ANC) of a 200-bed hospital in rural Uganda; in December 2004, ANC PMTCT services became opt-out, and routine opt-out intrapartum HCT was established in the maternity ward. We compared acceptability, feasibility, and uptake of maternity and ANC PMTCT services between December 2004 and September 2005. Results: HCT acceptance was 97% (3591/3696) among women and 97% (104/107) among accompanying men in the ANC and 86% (522/ 605) among women and 98% (176/180) among their male partners in the maternity. Thirty-four women were found to be HIV seropositive through intrapartum testing, representing an 12% (34/278) increase in HIV infection detection. Of these, 14 received their result and nevirapine before delivery. The percentage of women discharged from the maternity ward with documented HIV status increased from 39% (480/1235) to 88% (1395/1594) over the period. Only 2.8% of undocumented women had their male partners tested in the ANC in contrast to 25% in the maternity ward. Of all male partners who presented to either unit, only 48% (51/107) came together and were counseled with their wife in the ANC, as compared with 72% (130/180) in the maternity ward. Couples counseled together represented 2.8% of all persons tested in the ANC, as compared with 37% of all persons tested in the maternity ward. Conclusion: Intrapartum HCT may be an acceptable and feasible way to increase individual and couple participation in PMTCT interventions.

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Kuhn L, Sinkala M, Kankasa M, Kasonde P, Thea DM, Aldrovandi GM. **Nevirapine resistance viral mutations after repeat use of nevirapine for prevention of perinatal HIV transmission** [Letter to the Editor]. *Journal of Acquired Immune Deficiency Syndromes* 2006;42(2):260-262.

**Notes.** Our preliminary data suggest that there is no increase in the detection of viral mutations associated with NNRTI resistance when sdNVP is taken for a second time in a subsequent pregnancy. Although we were able to assemble a unique population of repeat users to compare to first-time users matched by viral load, sample size is small, and the results should be confirmed in larger studies. Because our data are based on population sequencing of detectable resistance mutations at 6 weeks postdelivery, we may have missed other possible changes in the dynamics of viral resistance. Sequential measurements over time and quantification of low-level mutants may provide a more sensitive indicator of the development of resistance mutations with repeat use of NVP. The strong correlation we observed between viral load and genotypic resistance also cautions against uncritical comparisons across studies because the proportions of women with high viral loads may differ substantially between study populations.

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Marazzi MC, Germano P, Liotta G, Guidotti G, Loureiro S, Gomes AD, Blazquez MCV, Narciso P, Perno CF, Mancinelli S, Palombi L. **Safety of nevirapine-containing antiretroviral triple therapy regimens to prevent vertical transmission in an African cohort of HIV-1-infected pregnant women.** *HIV Medicine* 2006;7(5):338-344.

**Abstr.** Objective To assess the incidence and consequences of adverse reactions among African HIV-positive pregnant women treated with fixed-dose combinations of a nevirapine-containing antiretroviral (ARV) triple therapy. Methods A retrospective analysis of the clinical files of 703 HIV-1-positive pregnant women treated with a nevirapine-containing regimen between May 2002 and July 2004 was conducted. Selection criteria for inclusion in the analysis were: (a) taking ARV for more than 14 days; (b) baseline values of transaminases below the threshold of 2.5 times the upper limit of normal (ULN). The women were on a nevirapine-containing regimen for a median of 127 days [interquartile range (IQR) 86-190 days], starting on average at the 27th week of gestation (standard deviation +/- 9.5) and continuing up to a maximum of 6 months after delivery. All women were offered formula milk to feed the babies. Highly active antiretroviral therapy (HAART) was continued beyond 6 months only if the patient qualified on the first visit. The main outcome measures were incidence of hepatotoxicity, skin rashes and Stevens-Johnson syndrome. Multivariate analysis to assess the impact of several factors on the adverse reaction rate was performed. Results As of 1 August 2004, 554 pregnancies reached term, 96 women were still pregnant, and 53 women dropped out of the programme before giving birth. After 2 months

of therapy the percentage of patients with a viral load less than 1000 HIV-1 RNA copies/mL increased to 78.6%; average CD4 cell counts increased from 490 cells/ $\mu$ L before therapy to 630 after therapy. The incidence of grade 3-4 adverse reactions (hepatotoxicity, skin rashes and Stevens-Johnson syndrome) was 6.5, 2.4 and 1.1%, respectively. Five women died during pregnancy (0.88%). Only one of the deaths could be associated with ARV treatment. Conclusion Nevirapine-containing regimens in pregnant woman, at all CD4 cell count levels, appear to be safe in African settings.

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Palmer S, Boltz V, Martinson N, Maldarelli F, Gray G, McIntyre J, Mellors J, Morris L, Coffin J. **Persistence of nevirapine-resistant HIV-1 in women after single-dose nevirapine therapy for prevention of maternal-to-fetal HIV-1 transmission.** Proceedings of the National Academy of Sciences of the United States of America 2006;103(18):7094-7099.

**Abstr.** Single-dose nevirapine (sdNVP) for prevention of mother-to-child transmission of HIV-1 can select nevirapine (NVP)-resistant variants, but the frequency, duration, and clinical significance of this resistance is not well defined. We used a sensitive allele-specific PCR assay to assess the emergence and persistence of NVP-resistant variants in plasma samples from 22 women with HIV-1 subtype C infection who participated in a study of sdNVP for prevention of mother-to-child transmission of HIV-1. The women were categorized into three groups on the basis of detection of NVP resistance by standard genotype analysis. Group 1 (n = 6) had NVP resistance detected at 2 and 6 mo after sdNVP, but not at 12 mo. Group 2 (n = 9) had NVP resistance detected at 2 mo, but not 6 mo. Group 3 (n = 7) had no NVP resistance detected at any time point. Allele-specific PCR analysis for the two most common NVP resistance mutations (K103N and Y181C) detected NVP-resistant variants in most (16 of 21) samples that were negative for NVP resistance by standard genotype, at levels ranging from 0.1% to 20% 1 yr after treatment. The frequency of NVP-resistant mutations decreased over time, but persisted above predose levels for more than 1 yr in  $\geq$  23% of the women. These findings highlight the urgent need for studies assessing the impact of sdNVP on the efficacy of subsequent antiretroviral therapy containing NVP or other nonnucleoside reverse transcriptase inhibitors.

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Ramachandran G, Hemanthkumar AK, Rajasekaran S, Padmapriyadarsini C, Narendran G, Sukumar B, Sathishnarayan S, Raja K, Kumaraswami V, Swaminathan S. **Increasing nevirapine dose can overcome reduced bioavailability due to rifampicin coadministration.** Journal of Acquired Immune Deficiency Syndromes 2006;42(1):36-41.

**Abstr.** We studied the effect of rifampicin on steady-state pharmacokinetics of nevirapine and the impact of increasing the dose of nevirapine on its peak (C-max) and trough (C-min) levels in 13 HIV-infected patients on regular antiretroviral treatment with nevirapine-containing regimens (200 mg twice daily). A baseline pharmacokinetic study was conducted and repeated after 1 week of daily rifampicin (450/600 mg). The study was repeated in 7 of 8 patients who had subtherapeutic C-min nevirapine levels after increasing nevirapine dose to 300 mg twice daily. Liver function was monitored. Rifampicin caused significant reductions in C-max (42%), C-min (53%), and exposure (46%) of nevirapine (P < .01). The C-min of nevirapine fell below the therapeutic range of 3  $\mu$ g/mL in 8 of 13 patients. An increase of nevirapine to 300 mg twice daily raised C-min to therapeutic range in all 7 patients without exceeding the toxic level of 12  $\mu$ g/mL. There were no clinical or laboratory adverse events. Our findings suggest that decreased bioavailability of nevirapine because of rifampicin coadministration could be overcome by increasing the dose of nevirapine from 200 to 300 mg twice daily without short-term adverse events. Further studies to evaluate the long-term safety of higher dose of nevirapine are required.

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Soorapanth S, Sansom S, Bulterys M, Besser M, Theron G, Fowler MG. **Cost-effectiveness of HIV rescreening during late pregnancy to prevent mother-to-child HIV transmission in South Africa and other resource-limited settings.** Journal of Acquired Immune Deficiency Syndromes 2006;42(2):213-221.

**Abstr.** A decision analysis model, from a health care system perspective, was used to assess the cost-effectiveness of HIV rescreening during late pregnancy to prevent perinatal HIV transmission in South Africa, a country with high HIV prevalence and incidence among pregnant women. Because new HIV prenatal prophylactic and pediatric antiretroviral therapy (ART) regimens are becoming more widely available, the study was carried out with different combinations of the two. With an estimated HIV incidence during pregnancy of 2.3 per 100 person-years, HIV rescreening would prevent additional infant infections and result in net savings when zidovudine plus single-dose nevirapine or single-dose nevirapine is used for perinatal HIV prevention, and ART was available to treat perinatally HIV-infected children. The cost savings were robust over a wide range of

parameter values when ART was available to treat perinatally HIV-infected children but were more sensitive to variations around the baseline when ART was not available. The minimum time interval between the initial and repeat screens would be from 3 to 18 weeks, depending on prophylactic and treatment regimens, for HIV rescreening to be cost saving. Overall, HIV rescreening late in pregnancy in high-prevalence, resource-limited settings such as South Africa would be a cost-effective strategy for reducing mother-to-child transmission.

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Townsend CL, Tookey PA, Cortina Borja M, Peckham CS. **Antiretroviral therapy and congenital abnormalities in infants born to HIV-1-infected women in the United Kingdom and Ireland, 1990 to 2003.** *Journal of Acquired Immune Deficiency Syndromes* 2006;42(1):91-94.

**Abstr.** Antiretroviral therapy (ART) in pregnancy substantially reduces the risk of mother-to-child transmission of HIV, but concerns exist about the potential for teratogenic effects. This analysis was undertaken to explore the relation between ART in pregnancy and birth defects in infants born to HIV-infected women in the United Kingdom and Ireland between 1990 and 2003. Comprehensive obstetric and pediatric HIV surveillance is carried out through the National Study of HIV in Pregnancy and Childhood. Congenital abnormalities were reported in 101 of 3172 infants (100 of 3120 pregnancies). There was no statistically significant association between the prevalence of congenital abnormalities and exposure to ART overall: 3.4% (90 of 2657 pregnancies) in exposed pregnancies and 2.2% (10 of 463 pregnancies) in nonexposed pregnancies ( $P = 0.166$ ); prevalence was similar whether or not exposure occurred in the first trimester: 3.7% (20 of 541 pregnancies) after early exposure and 3.1% (80 of 2579 pregnancies) without early exposure ( $P = 0.476$ ). There was also no significant association with type of ART in early pregnancy (ie, highly active antiretroviral therapy [HAART] vs. mono- or dual therapy, HAART with protease inhibitor and/or nonnucleoside reverse transcriptase inhibitor). The lack of association was maintained after adjustment for potential confounding factors. These findings are reassuring, but continued monitoring is essential in view of the increasing number of women on therapy at conception and the likely continuing diversity of drug regimens.

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