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prepared by the Bordeaux Working Group

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Chaix ML, Ekouevi DK, Peytavin G, Rouet F, Tonwe Gold B, Viho I, Bequet L, Amani Bosse C, Menan H, Leroy V, Rouzioux C, Dabis F. **Impact of nevirapine (NVP) plasma concentration on selection of resistant virus in mothers who received single-dose NVP to prevent perinatal human immunodeficiency virus type 1 transmission and persistence of resistant virus in their infected children.** *Antimicrobial Agents and Chemotherapy* 2007;51(3):896-901.

Abstr. Nonnucleoside reverse transcriptase inhibitor resistance following the use of single-dose nevirapine (sdNVP) for the prevention of mother-to-child transmission (PMTCT) remains a concern. In the ANRS-1201/1202 Ditrane study, conducted in Abidjan, Cote d'Ivoire, a short-course regimen of zidovudine was associated with sdNVP for PMTCT. In this study, we estimate the frequency of NVP resistance and its relationship with NVP concentration in mothers. Genotypic resistance analysis was performed on mothers' plasma samples at week 4 postpartum (PP) and on human immunodeficiency virus (HIV) DNA in peripheral blood mononuclear cells (PBMC) when an NVP resistance mutation was detected. The same tests were performed for the infected children at week 4, month 3, and month 12. Mothers' NVP plasma concentrations were measured at 48 h PP. Twenty-one (33%) of the 63 women selected had NVP-resistant (NVP-R) virus at week 4 PP. The median plasma NVP concentration was 598 ng/ml for the mothers without NVP-R virus compared to 851 ng/ml for the mothers harboring NVP-R virus ($P = 0.014$). NVP-R mutations were detected in the HIV DNA of 15/20 women. Plasma NVP-R mutations were detectable in 6 of 26 infected children at week 4. All 6 children had detectable NVP-R mutations in HIV DNA of PBMC. Blood samples taken at month 3 (1 child) and month 12 (1 child) revealed the persistence of NVP-R mutations in plasma and cells. Emergence of NVP-R virus in mothers is strongly correlated with a high level of plasma NVP concentration, owing to a prolonged postpartum period of viral replication under NVP selective pressure. The follow-up of the cohort demonstrates the prolonged archive of resistant virus.

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Coovadia HM, Rollins NC, Bland RM, Little K, Coutsooudis A, Bennish ML, Newell ML. **Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study.** *Lancet* 2007;369(9567):1107-1116.

Abstr. Background Exclusive breastfeeding, though better than other forms of infant feeding and associated with improved child survival, is uncommon. We assessed the HIV-1 transmission risks and survival associated with exclusive breastfeeding and other types of infant feeding. Methods 2722 HIV-infected and uninfected pregnant women attending antenatal clinics in KwaZulu Natal, South Africa (seven rural, one semiurban, and one urban), were enrolled into a non-randomised intervention cohort study. Infant feeding data were obtained every week from mothers, and blood samples from infants were taken monthly at clinics to establish HIV infection status. Kaplan-Meier analyses conditional on exclusive breastfeeding were used to estimate transmission risks at 6 weeks and 22 weeks of age, and Cox's proportional hazard was used to quantify associations with maternal and infant factors. Findings 1132 of 1372 (83%) infants born to HIV-infected mothers initiated exclusive breastfeeding from birth. of 1276 infants with complete feeding data, median duration of cumulative exclusive breastfeeding was 159 days (first quartile [Q1] to third quartile [Q3], 122-174 days). 14.1% (95% CI 12.0-16.4) of exclusively breastfed infants were infected with HIV-1 by age 6 weeks and 19.5% (17.0-22.4) by 6 months; risk was significantly associated with maternal CD4-cell counts below 200 cells per mu L (adjusted hazard ratio [HR] 3.79; 2.35-6.12) and birthweight less than 2500 g (1.81, 1.07-3.06). Kaplan-Meier estimated risk of acquisition of infection at 6 months of age was 4.04% (2.29-5.76). Breastfed infants who also received solids were significantly more likely to acquire infection than were exclusively breastfed children (HR 10.87, 1.51-78.00, $p=0.018$), as were infants who at 12 weeks received both breastmilk and formula milk (1.82, 0.98-3.36, $p=0.057$). Cumulative 3-month

mortality in exclusively breastfed infants was 6.1% (4.74-7.92) versus 15.1% (7.63-28.73) in infants given replacement feeds (HR 2.06, 1.00-4.27; p=0.051). Interpretation The association between mixed breastfeeding and increased HIV transmission risk, together with evidence that exclusive breastfeeding can be successfully supported in HIV-infected women, warrant revision of the present UNICEF, WHO, and UNAIDS infant feeding guidelines.

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Forna F, Liechty CA, Solberg P, Asiimwe F, Were W, Mermin J, Behumbiize P, Tong T, Brooks JT, Weidle PJ. **Clinical toxicity of highly active antiretroviral therapy in a home-based AIDS care program in rural Uganda.** Journal of Acquired Immune Deficiency Syndromes 2007;44(4):456-462.

Abstr. Background: We evaluated clinical toxicity in HIV-infected persons receiving antiretroviral therapy (ART) in Uganda. Methods: From May 2003 through December 2004, adults with a CD4 cell count \leq 250 cells/ μ L or World Health Organization stage 3/4 HIV disease were prescribed ART. We calculated probabilities for time to toxicity and single-drug substitution as well as multivariate-adjusted hazard ratios for development of toxicity. Results: ART (stavudine plus lamivudine with nevirapine [96%] or efavirenz [4%]) was prescribed for 1029 adults, contributing 11,268 person-months of observation. Toxicities developed in 543 instances in 411 (40%) patients (incidence rate = 4.47/100 person-months): 36% peripheral neuropathy (9% severe); 6% rash (2% severe); 2% hypersensitivity reaction; \leq 0.5% acute hepatitis, anemia, acute pancreatitis, or lactic acidosis; and 13% other. Probabilities of remaining free from any toxicity 6, 12, and 18 months were 0.76, 0.59, and 0.47 and from any severe toxicity at 6, 12, and 18 months were 0.92, 0.86, and 0.85, respectively. For 217 patients (21%), 222 single-drug substitutions were made, mostly because of peripheral neuropathy or rash. Conclusions: Clinical toxicities were common, but no patients discontinued ART because of toxicity. The most common toxicities, peripheral neuropathy and rash, were managed with single-drug substitutions. In resource-limited settings, toxicity from ART regimens containing stavudine or nevirapine is manageable but more tolerable regimens are needed.

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Holmes WR, Savage F. **Exclusive breastfeeding and HIV [Comment].** Lancet 2007;369(9567):1065-1066.

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Jackson DJ, Chopra M, Doherty TM, Colvin MSE, Levin JB, Willumsen JF, Goga AE, Moodley P. **Operational effectiveness and 36 week HIV-free survival in the South African programme to prevent mother-to-child transmission of HIV-1.** AIDS 2007;21(4):509-516.

Abstr. Objective: Previous studies on the operational effectiveness of programmes to reduce transmission of HIV from mother-to-child (PMTCT) in Africa have generally been hospital-based pilot studies with short follow-up periods. Method: Prospective cohort study to evaluate the routine operational effectiveness of the South African National PMTCT Programme, primarily measured by HIV-free survival at 36 weeks post-delivery. Three of eighteen pilot sites participating in the programme were selected as they reflected differences in circumstances, such as HIV prevalence, socioeconomic status and rural-urban location. A total of 665 HIV-positive mothers and their infants were followed.

Results: HIV-free survival at 36 weeks varied significantly across sites with 84% in Paarl, 74% in Umlazi and 65% in Rietvlei (P=0.0003). Maternal viral load was the single most important factor associated with HIV transmission or death [hazard ratio (HR), 1.54; 95% confidence interval (CI), 1.21-1.95]. Adjusting for health system variables (fewer than four antenatal visits and no antenatal syphilis test) explained the difference between Rietvlei and Paarl (crude HR, 2.27; 95% CI, 1.36-3.77; adjusted HR, 1.81; 95% CI, 0.93-3.50). Exposure to breastmilk feeding explained the difference between Umlazi and Paarl (crude HR, 1.74; 95% CI, 1.06-2.84; adjusted HR, 1.41; 95% CI, 0.81-2.48). Conclusion: Ever breastfeeding and underlying inequities in healthcare quality within South Africa are predictors of PMTCT programme performance and will need to be addressed to optimize PMTCT effectiveness.

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Notes: We are commenting here on the above study published in AIDS looking at the operational effectiveness of PMTCT programmes in South Africa. This article is particularly interesting in the fact that most previous operational studies looking at the effectiveness of PMTCT programmes have been centred on pilot programmes which were often hospital based, showing short term follow up (6-16 weeks) and which did not measure HIV transmission and or infant death. In this research, sites were operational rural or urban sites and the study was designed to look at the longer term follow up of PMTCT programmes with the main outcome of interest being HIV free survival at 36 weeks. Secondly the results of this study suggest that if benefits of PMTCT programmes are to be realised then attention must be focused on also strengthening the health care infrastructure especially in disadvantaged areas with low resources and poorly functioning health services.

This recently published research was carried out in 3 chosen sites among 18 pilot sites of the South African PMTCT program following 665 HIV positive mothers and infants. The sites were chosen to reflect difference in circumstances (prevalence of antenatal HIV prevalence, socio-economic status and rural or urban settings). An urban-periurban with relatively high socio-economic profile and a relatively well functioning public health care system (Paarl) with an antenatal HIV prevalence of 9% was compared to a rural site in one of the poorest regions with a antenatal HIV prevalence of 28% (Rietvlei) and a periurban site considered as intermediate with an antenatal HIV prevalence of 47% (Umlazi).

The authors reported substantial differences across sites with regard to maternal and infant characteristics, quality of care and infant feeding practices with the rural site in the poorest region showing as expected the poorest indicators in terms of quality of care as measured by antenatal visits, syphilis screening, postnatal visits and immunisation rates. When the authors looked at the outcome of interest the differences seen in cumulative HIV transmission at 36 weeks across sites were not statistically significant (P=0.07) but infant mortality was significantly higher in the rural resource poor site (P=0.0005).

The composite indicator was significantly different across sites for HIV free survival rates at 36 weeks of age of 84% for the most advantaged site, 73% for the intermediate site and 64% for the poor rural site (P=0.0003). Only two independent risk factors for HIV free survival transmission and or infant death in the multivariate analysis were found; maternal viral load and prematurity. But even after controlling for these two factors, the site difference still remained statistically different. This led the authors to conclude that established risk factors ¹ do not explain differences in HIV free survival rates between sites (maternal viral load was actually highest at the site with the best HIV survival rate). When they used models to analyse this data, regression analysis suggested that a mother in the most disadvantaged site with similar viral load, gestational aged baby and infant feeding practices was still more than twice as likely to have an HIV positive infant or see her child die by 9 months. This led the authors to suggest that the difference across sites in HIV transmission and or infant death could only be explained by the difference in quality of healthcare system services As it has been suggested by McCoy ² when describing the pitfalls of rapidly expanding ART programs or by Peeling et al ³ when

looking at the uptake of syphilis screening in Haiti in maternal services, their findings also suggest that the addition of new vertically led interventions such as PMTCT programmes to already under-resourced and poorly functioning health systems may not lead to improved HIV related health indicators. Recently MSF⁴ has made a well publicized appeal to donors recommending that adequate human capacity is essential for the success of ART programmes in low income countries and that health care systems need to be strengthened and specific attention given to the provision of additional resources such as adequately paid staff and funding to poor-functioning health care systems in disadvantage areas whilst avoiding to divert resources from other important public health issues.

The authors conclude by suggesting that new programmes such as PMTCT should be designed from the start for “active catalysis” of broader health system development rather than a narrow vertical intervention.

References:

1. Leroy et al AIDS 2005; 19:1865-1875
2. MCoy et al Am J Public Health 2005;95:18-22
3. Peeling et al Lancet 2004;364:1561-1563
4. MSF <http://www.msf.org/msfinternational>

Jamisse L, Balkus J, Hitti J, Gloyd S, Manuel R, Osman N, Djedje M, Farquhar C. **Antiretroviral-associated toxicity among HIV-1-seropositive pregnant women in Mozambique receiving nevirapine-based regimens.** Journal of Acquired Immune Deficiency Syndromes 2007;44(4):371-376.

Abstr. Objective: To assess toxicities associated with highly active antiretroviral therapy (HAART) among HIV-1-infected pregnant women treated with nevirapine-based regimens according to Mozambican national guidelines. Study Design: Prospective cohort study. Methods: HIV-1-infected antiretroviral-naive pregnant women with CD4 counts \leq 350 cells/ μ mL were initiated on nevirapine, lamivudine, and stavudine or zidovudine and followed monthly. Severe hepatotoxicity was defined as aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels \geq 5-fold the upper limit of normal. Analyses were stratified by baseline CD4 Count ($<$ 250 vs. 250-350 cells/ μ mL). Results: Among 146 pregnant women, 75 (52%) began nevirapine, lamivudine, and zidovudine and 71 (48%) began nevirapine, lamivudine, and stavudine. Overall, 79 (54%) women had CD4 counts $<$ 250 cells/ μ mL, 7 (5%) had grade II hepatotoxicity, and 4 (3%) had severe (grade III or IV) hepatotoxicity. All 4 women with severe hepatotoxicity had baseline CD4 counts \geq 250 cells/ μ mL ($P = 0.02$). Rates of skin toxicity, anemia, and peripheral neuropathy did not differ by CD4 cell count group. Overall, 12 (8%) women changed or discontinued HAART as a result of drug toxicity. Conclusions: Severe hepatotoxicity from nevirapine-containing HAART in this cohort of pregnant women was more common at higher CD4 counts (6% vs. 0% among women with CD4 counts \geq 250 cells/ μ mL and CD4 counts $<$ 250 cells/ μ mL, respectively), suggesting that laboratory monitoring is necessary when administering nevirapine-containing regimens to pregnant women with CD4 counts \geq 250 cells/ μ mL.

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Notes: We are commenting here on an article published in the april 2007 issue of JAIDS where Jamisse et al provide data regarding toxicity associated with highly active antiretroviral therapy (HAART) among HIV-1 infected pregnant women treated with NVP based regimens in Mozambique. The authors found that the occurrence of hepatotoxicity was rather high with 8% of the 146 women developing more than grade II hepatotoxicity and 3% developing severe grade III/IV hepatotoxicity. They also found that there was a significantly higher rate of hepatotoxicity among women with higher CD4 counts $>$ 250 cell/ μ mL (6% compared to 0% in women with CD4 $<$ 250 cells/ μ mL) suggesting that laboratory monitoring of pregnant women under NVP containing HAART might be necessary especially in those with higher CD4s.

In the light of the 2006 WHO revised guidelines¹ for PMTCT recommending that HAART be considered for pregnant women with CD4 count <350cell/microl, this recent study is interesting in the midst of continuing debate over NVP based toxicity in pregnant women needing treatment for their own health.

In the past several years, contradictory studies have been published. Hitti et al² in 2004 described in the Pediatric AIDS Clinical Trial Group Protocol (PACTG) a prospective study on 38 ART naive pregnant women randomised to either NVP or Nelfinavir based HAART. They reported rather worrisome results with high incidence rates of treatment limiting hepatic or cutaneous toxicity in pregnant women with higher than 250 CD4 cells. Furthermore in South Africa, Sanne et al³ reported data demonstrating a high risk (17%) of early hepatotoxicity associated with the use of nevirapine mainly in African (non pregnant) women with relatively high baseline CD4+ cell counts (mean, 398 cells/mm³) and they also found an association with low body-mass index (BMI) <18.5 as an independent risk factor. All these alarming studies brought about a notification from the manufacturer Boehringer Ingelheim⁴ which declared that due to the 12 fold increased risk of severe hepatotoxicity in women with CD4 counts higher than 250 cells/microl, they issued a warning on the risk of using NVP based HAART without close monitoring in pregnant women with high CD4 cell counts. However recently in 2006, a Brazilian study⁵ on 197 pregnant women treated with NVP based HAART reported 6% of hepatotoxicity with no severe grade III/IV hepatotoxicity.

Observations regarding NVP induced toxicity are important, because nevirapine is commonly used as a component of first-line therapy in resource-limited settings, especially in women. These findings need to be taken into account in future international WHO recommendations and as the authors point out, it might be important for programs in resource poor settings to consider monitoring of ALT/AST levels during the first months of therapy in order to identify early, and potentially reversible, drug-induced hepatotoxicity.

References:

1. WHO 2006 PMTCT guidelines Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: towards universal access. Accessed at <http://www.who.int/hiv/pub/mtct/pmtct/en>
2. Hitti et al JAIDS 2004; 36:772-776
3. Sanne et al J Inf Dis 2005; 191:825-829
4. Boehringer notification Accessed at: <http://www.Bidocs.com/renetnt:/Notifications/Dear+HCP+Itr+Feb+2004.pdf>
5. Joao et al Am J Obstet Gynecol 2006;194:199-202.

Katlama C, Esposito R, Gatell JM, Goffard JC, Grinsztejn B, Pozniak A, Rockstroh J, Stoehr A, Vetter N, Yeni P, Parys W, Vangeneugdenk T. **Efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients: 24-week results of POWER 1.** AIDS 2007; 21(4): 395-402.

Abstr. Background: The ongoing phase IIb POWER 1 (TMC114-C213) trial is designed to assess efficacy and safety of the protease inhibitor (PI) TMC114 (darunavir) in treatment-experienced HIV-1-infected patients. Design: This randomized, partially blinded, 24-week dose-finding study compared efficacy and safety of four doses of TMC114 plus low-dose ritonavir (TMC114/r) with investigator-selected control PI(s) (CPI[s]). Methods: Patients with one or more primary PI mutation and HIV RNA > 1000 copies/ml received optimized background therapy, plus TMC114/r 400/100 mg once daily, 800/100 mg once daily, 400/100 mg twice daily or 600/100 mg twice daily, or CPI(s). The primary endpoint (intent-to-treat) compared proportions of patients achieving viral load reduction $\geq 1.0 \log_{10}$ copies/ml from baseline. Results: In total, 318 patients were treated. Baseline mean viral load was $4.48 \log_{10}$ copies/ml; median CD4 cell count was 179 cells/ μ l. In the CPI arm 62% of patients discontinued (virological failure: 54%); 10% of TMC114/r patients discontinued. More TMC114/r (69-77%) than CPI patients (25%) reached the primary endpoint (P < 0.001); 43-53% of TMC114/r patients and 18% of the CPI arm achieved viral load < 50 copies/ml (P <

0.001). TMC114/r demonstrated greater mean CD4 cell count increases versus CPI(s) (68-124 versus 20cells/ μ l; $P < 0.05$). TMC114/r 600/100 mg twice daily demonstrated the highest virological and immunological responses. Adverse event incidence was similar between treatments; headache and diarrhoea were more common with CPI(s). Conclusions: TMC114/r demonstrated statistically higher 24-week virological response rates and CD4 cell count increases than CPI(s). TMC114/r 600/100 mg twice daily has received regulatory approval in treatment-experienced patients.

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World Health Organisation, UNAIDS. **Guidance on provider-initiated HIV testing and counselling in health facilities.** May 2007.

Address: WHO. hiv-aids@who.int

Free Full Text: http://www.who.int/hiv/who_pitc_guidelines.pdf

World Health Organisation, UNAIDS, UNCEF. **Towards Universal Access. Scaling up priority HIV/AIDS interventions in the health sector.** Progress Report, April 2007.

Address: WHO. hiv-aids@who.int

Free Full Text:

http://www.who.int/hiv/mediacentre/universal_access_progress_report_en.pdf