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ELIZABETH GLASER PEDIATRIC AIDS FOUNDATION



ICAP
Columbia University
MAILMAN SCHOOL
OF PUBLIC HEALTH

HIV Care & PMTCT in Resource-Limited Settings

Monthly Intelligence Report

2006, Vol 2, Issue 2

[Available on line](#)

prepared by the Bordeaux Working Group

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Number of citations selected for this issue: 13

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, **Free full text**, if available

Chaix ML, Ekouevi DK, Rouet F, Tonwe Gold B, Viho I, Bequet L, Peytavin G, Toure H, Menan H, Leroy V, Dabis F, Rouzioux C. **Low risk of nevirapine resistance mutations in the prevention of mother-to-child transmission of HIV-1: Agence Nationale de Recherches sur le SIDA Ditrane Plus, Abidjan, Cote d'Ivoire.** Journal of Infectious Diseases 2006;193(4):482-487.

Abstr. The frequency of resistance mutations was estimated in the cohort of Agence Nationale de Recherches sur le SIDA Ditrane Plus, a study that evaluated the combination of short-course zidovudine (ZDV) plus lamivudine (3TC) and single-dose nevirapine (SD-NVP) followed by 3 days of postpartum ZDV plus 3TC for the prevention of mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1). The frequency with which resistance mutations were detected in mothers at week 4 postpartum was 1.14% (95% confidence interval [CI], 0.03% - 6.17%) for NVP and 8.33% (95% CI, 3.66% - 15.76%) for 3TC. In multivariate analysis, 3TC resistance was associated with a longer duration of ZDV plus 3TC prepartum prophylaxis (P = .009). This regimen, which is feasible in resource-limited settings, prevents most peripartum HIV-1 transmission and minimizes the development of NVP resistance.

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Chiappini E, Galli L, Gabiano C, Tovo PA, de Martino M. **Early triple therapy vs mono or dual therapy for children with perinatal HIV infection [letter].** Journal of the American Medical Association 2006;295(6):626-628.

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De Cock KM, Bunnell R, Mermin J. **Unfinished business - Expanding HIV testing in developing countries [Perspectives].** New England Journal of Medicine 2006;354(5):440-442.

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Eshleman SH, Hoover DR, Hudelson SE, Chen S, Fiscus SA, Piwowar Manning E, Jackson JB, Kumwenda NI, Taha TE. **Development of nevirapine resistance in infants is reduced by use of infant-only single-dose nevirapine plus zidovudine postexposure prophylaxis for the prevention of mother-to-child transmission of HIV-1.** Journal of Infectious Diseases 2006;193(4):479-481.

Abstr. We analyzed the development of nevirapine (NVP) resistance in human immunodeficiency virus type 1 (HIV-1)-infected Malawian infants who received regimens containing singledose NVP (SD-NVP) for the prevention of mother-to-child transmission (MTCT) of HIV-1. All infants received SD- NVP, and some randomly received zidovudine (ZDV) as well. Mothers did or did not receive SD- NVP on the basis of when they arrived at the hospital for delivery. In infants 6 - 8 weeks of age, NVP resistance was less frequent when infants had received SD- NVP plus ZDV and mothers had not received SD- NVP than when infants had received SD- NVP alone and mothers had received SD- NVP (4/15 [27%] vs. 20/23 [87%]; P < .001). The risk of MTCT of HIV- 1 was comparable with these regimens. Infant-only prophylaxis also eliminates the development of NVP resistance in mothers.

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Gallant JE, DeJesus E, Arribas JR, Pozniak AL, Gazzard B, Campo RE, Lu B, McColl D, Chuck S, Enejosa J, Toole JJ, Cheng AK. **Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV.** New England Journal of Medicine 2006;354(3):251-260.

Abstr. BACKGROUND: Durable suppression of replication of the human immunodeficiency virus (HIV) depends on the use of potent, well-tolerated antiretroviral regimens to which patients can easily adhere. METHODS: We conducted an open-label, noninferiority study involving 517 patients with HIV infection who had not previously received antiretroviral therapy and who were randomly assigned to receive either a regimen of tenofovir disoproxil fumarate (DF), emtricitabine, and efavirenz once daily (tenofovir-emtricitabine group) or a regimen of fixed-dose zidovudine and lamivudine twice daily plus efavirenz once daily (zidovudine-lamivudine group). The primary end point was the proportion of patients without baseline resistance to efavirenz in whom the HIV RNA level was less than 400 copies per milliliter at week 48 of the study. RESULTS: Through week 48, significantly more patients in the tenofovir-emtricitabine group reached and maintained the primary end point of less than 400 copies of HIV RNA per milliliter than did those in the zidovudine-lamivudine group (84 percent vs. 73 percent, respectively; 95 percent confidence interval for the difference, 4 to 19 percent; P=0.002). This difference excludes the inferiority of the tenofovir DF, emtricitabine, and efavirenz regimen, indicating a significantly greater response with this regimen. Significant differences were also seen in the proportion of patients with HIV RNA levels of less than 50 copies per milliliter (80 percent in the tenofovir-emtricitabine group vs. 70 percent in the zidovudine-lamivudine group; 95 percent confidence interval for the difference, 2 to 17 percent; P=0.02) and in increases in CD4 cell counts (190 vs. 158 cells per cubic millimeter,

respectively; 95 percent confidence interval for the difference, 9 to 55; P=0.002). More patients in the zidovudine-lamivudine group than in the tenofovir-emtricitabine group had adverse events resulting in discontinuation of the study drugs (9 percent vs. 4 percent, respectively; P=0.02). In none of the patients did the K65R mutation develop. **CONCLUSIONS:** Through week 48, the combination of tenofovir DF and emtricitabine plus efavirenz fulfilled the criteria for noninferiority to a fixed dose of zidovudine and lamivudine plus efavirenz and proved superior in terms of virologic suppression, CD4 response, and adverse events resulting in discontinuation of the study drugs.

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Goujard C, Bonarek M, Meyer L, Bonnet F, Chaix ML, Deveau C, Sinet M, Galimand J, Delfraissy JF, Venet A, Rouzioux C, Morlat P. **CD4 cell count and HIV DNA level are independent predictors of disease progression after primary HIV type 1 infection in untreated patients.** *Clinical Infectious Diseases* 2006;42(5):709-715.

Abstr. Background. Treatment initiation at the time of primary human immunodeficiency virus (HIV) type 1 (HIV-1) infection has become less frequent in recent years. Methods. In the French prospective PRIMO Cohort, in which patients are enrolled at the time of primary HIV-1 infection, 30% of the 552 patients recruited during 1996-2004 did not start receiving antiretroviral treatment during the first 3 months after diagnosis. We analyzed the patients' clinical and immunological outcomes and examined potential predictors of disease progression. Progression was defined as the occurrence of an acquired immunodeficiency syndrome (AIDS)-related clinical event or a CD4 cell count < 350 cells/mm³. Results. Fifty-six (34%) of the untreated patients experienced immunological progression during a median duration of follow-up of 24 months, and 1 of these patients had an AIDS-related event. The estimated risks of progression were 25%, 34%, and 42% at 1, 2, and 3 years after enrollment, respectively. Compared with patients who did not have progression, those with progression had significantly lower CD4 cell counts at diagnosis (455 vs. 738 cells/mm³), higher plasma HIV RNA levels (4.9 vs. 4.5 log₁₀ copies/mL), and higher HIV DNA levels (3.3 vs. 3.0 log₁₀ copies/10⁶ peripheral blood mononuclear cells [PBMCs]). All 3 parameters were significantly associated with progression in univariate analysis. In multivariate analysis, only the CD4 cell count and HIV DNA level were independently predictive of disease progression (relative hazard for CD4 cell count, 1.84 per decrease of 100 cells/mm³; relative hazard for HIV DNA level, 2.73 per increase of 1 log₁₀ copies/10⁶ PBMCs). Conclusions. Both a low initial CD4 cell count and a high HIV DNA level are predictive of rapid progression of untreated primary HIV-1 infection. Affected patients may therefore benefit from close clinical and laboratory monitoring and/or early administration of treatment.

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Jackson JB, Parsons T, Musoke P, Nakabiito C, Donnell D, Fleming T, Mirochnick M, Mofenson L, Fowler MG, Mmro F, Guay L. **Association of cord blood nevirapine concentration with reported timing of dose and HIV-1 transmission.** *AIDS* 2006;20(2):217-222.

Abstr. Background: To correlate nevirapine presence and concentration in cord bloods of infants born to HIV-1 infected women with report of timing of dose and HIV-1 transmission at 6 weeks of age. Methods: All available cord blood samples from the infants of mothers enrolled in the HIVNET 012 trial who were randomly assigned to receive either nevirapine or zidovudine at the onset of labor were tested for a nevirapine concentration. Results: Nevirapine was detected in the cord blood of 244 of 259 (94%) infants whose mothers reported they took nevirapine in labor more than 1 h before delivery and in 12 of 13 (92%) infants whose mothers reported they took nevirapine less than 1 h before delivery. The median nevirapine cord blood concentration was 1238 ng/ml [interquartile range (IQR), 905-1474 ng/ml] and 122 ng/ml (IQR, 64-321 ng/ml) for women who reported taking nevirapine more or less than 1 h before delivery, respectively (P < 0.001). The median nevirapine cord blood concentration of infants who were HIV-1 negative at birth, but positive at 6-8 weeks of age (n = 11), was 916 ng/ml (IQR, 737-1245 ng/ml) compared with 1192 ng/ml (IQR, 875-1471 ng/ml) for uninfected infants (n = 236). Conclusions: Cord blood nevirapine concentration correlated well with report of nevirapine administration and timing of dose before delivery. The nevirapine cord blood concentration was modestly lower in infected infants, although the number of infants infected between birth and 6-8 weeks of age was small (n = 11). The high adherence rate in the HIVNET 012 study supports the efficacy, simplicity and deliverability of this regimen.

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Kilaru KR, Kumar A, Sippy N, Carter AO, Roach TC. **Immunological and virological responses to highly active antiretroviral therapy in a non-clinical trial setting in a developing Caribbean country.** HIV Medicine 2006;7(2):99-104.

Abstr. Objective Few data exist on the efficacy of antiretroviral therapy in individuals infected with HIV in the Caribbean. We evaluated the virological and immunological responses of HIV-infected adults starting highly active antiretroviral therapy (HAART). Design This was a prospective observational cohort study. Methods A total of 158 antiretroviral-naïve patients who initiated HAART between January 2002 and March 2003, and completed at least 6 months of treatment and follow up, were included in the analysis. The response to therapy was assessed by changes in CD4 cell counts and viral loads from baseline. The mean increase in CD4 cell count, the rate of virological success (a viral load of < 50 HIV-1 RNA copies/mL) and the rate of immunological success (an increase in CD4 cell count of \geq 50 cells/ μ L over the baseline value) after commencing HAART were measured. Results In total, 82% of patients (123 of 150) achieved viral loads of < 50 copies/mL after 6 months of therapy. Viral success rate after 6 months of HAART was similar irrespective of gender, pre-HAART CD4 cell count and pre-HAART viral load. However, patients older than 40 years were significantly more likely to achieve virological success than those younger than 40 years. At 6 months after starting HAART, 79.5% of patients were estimated to have achieved immunological success and 17.9% had an increase in CD4 cell count of \geq 200 cells/ μ L over the baseline value. The median increase in CD4 cell count for the 156 patients who had CD4 cell counts at baseline and at 6 months of therapy was 122 cells/ μ L. Conclusion In this cohort of antiretroviral-naïve HIV-infected adults, there was a high rate of virological and immunological success after 6 months of HAART, irrespective of the pre-HAART viral load and CD4 cell count.

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Mbulaitye SM, Katabira ET, Wabinga H, Parkin DM, Virgo P, Ochai R, Workneh M, Coutinho A, Engels EA. **Spectrum of cancers among HIV-infected persons in Africa: The Uganda AIDS-cancer registry match study.** International Journal of Cancer 2006;118(4):985-990.

Abstr. Although more than 25 million people in sub-Saharan Africa have human immunodeficiency virus (HIV) infection, little is known regarding their cancer risk. We investigated cancer risk among persons with HIV/AIDS in Uganda using record-linkage. We linked records of 12,607 HIV-infected persons attending The AIDS Support Organization (TASO) in Kyadondo County from October 1988 through December 2002 to the Kampala Cancer Registry. We calculated standardized incidence ratios (SIRs) to identify increased cancer risks in the early (4-27 months after TASO registration), late (28-60 months), or combined (4-60 months) incidence periods. We identified 378 cancers (181 prevalent, 197 incident) among TASO participants. Of incident cancers, 137 (70%) were AIDS-defining cancers. Risk was increased in the early-incident period, compared to the general population, for the AIDS-defining cancers: Kaposi sarcoma (SIR 6.4, 95%CI 4.8-8.4), non-Hodgkin lymphoma (6.7, 1.8-17), and cervical carcinoma (2.4, 1.1-4.4). These three cancers were also increased in the combined periods. Risks of five non-AIDS-defining cancers were increased in the combined periods: Hodgkin lymphoma (5.7, 1.2-17) and cancers of the conjunctiva (SIR 4.0; 1.5-8.7), kidney (16, 1.8-58), thyroid (5.7, 1.1-16), and uterus (5.5, 1.5-14). Cancers of the breast, nasopharynx, and lung were increased either in the early or late incident periods only. Among 407 children, seven cancers were observed, of which five were Kaposi sarcoma. The application of a record-linkage design in Africa broadens the repertoire of epidemiological tools for studying HIV-infected populations. We confirm the increased risks of AIDS-defining cancers and report increased risks of a few non-AIDS-defining cancers.

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Nombela N, Kouadio B, Toure S, Seyler C, Flori YA, Anglaret X. **Nonantiretroviral drug consumption by CD4 cell count in HIV-infected adults - A 5-year cohort study in Cote d'Ivoire.** Journal of Acquired Immune Deficiency Syndromes 2006;41(2):225-231.

Abstr. We followed a cohort of 592 HIV-infected adults during 1292 person-years in Abidjan before the highly active antiretroviral therapy (HAART) era. On the basis of the exhaustive monitoring of nonantiretroviral drugs actually delivered to the patients and of the real cost of drugs at the cohort center's pharmacy during the study period, we estimated the mean cost of drugs per person per year (MCPY) overall, by drug characteristics, and by patients' baseline CD4 cell count. The MCPY was \$198 US overall and \$83 US, \$101 US, \$186 US, \$233 US, and \$459 US in patients with a baseline CD4 count \geq 500 cells/mm³, 350 to 499 cells/mm³, 200 to 349 cells/mm³, 100 to 199 cells/mm³, and < 100 cells/mm³, respectively. The most costly classes of drugs were the antibacterial (MCPY \$30 US), the antifungal (\$16 US), and the analgesic (\$6 US) classes in patients ;with a baseline CD4 count \geq 500 cells/mm³ versus the antifungal (\$208 US), the antibacterial (\$49 US), and the antiparasitic (\$31 US) classes in patients with a baseline CD4 count < 100 cells/mm³. These data could be used in further cost-effectiveness analyses that seek to prioritize health interventions. Meanwhile, they roughly

suggest that successful antiretroviral treatment, which would stabilize the CD4 count above 500 cells/mm³, could reduce by 5-fold the cost of nonantiretroviral drugs in HIV-infected adults in Abidjan.

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Toni TD, Masquelier B, Lazaro E, Dore Mbami M, Ba Gomis FO, Tea Diop Y, Kouakou K, Diby J, Sia E, Soppi S, Essien S, Schrive MH, Pinson P, Chenal H, Fleury HJ. **Characterization of nevirapine (NVP) resistance mutations and HIV type 1 subtype in women from Abidjan (Cote d'Ivoire) after NVP single-dose prophylaxis of HIV type 1 mother-to-child transmission.** AIDS Research and Human Retroviruses 2005;21(12):1031-1034.

Abstr. Nevirapine (NVP) single dose is widely used in developing countries to prevent HIV-1 mother-to-child transmission. However, this regimen selects key drug resistance mutations that can impair further HAART efficacy. We studied the HIV-1 reverse transcriptase genotype from 29 Ivoirian women 1 month after an NVP single-dose prophylaxis. NVP resistance mutations were observed in six (20.7%) women. The majority of the isolates were CRF02_AG. These results confirm previous studies and suggest the need for different prophylaxis regimens in this setting.

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Vezenia HE, Henry K, Ravindran GD, Kurpad AV, Raj TDS, Fox K, Weller D, Brundage RC, Cavert W, Balfour HH. **A randomized crossover study to determine bioequivalence of generic and brand name nevirapine, zidovudine, and lamivudine in HIV-negative women in India** Journal of Acquired Immune Deficiency Syndromes 2006;41(2):131-136.

Abstr. Low-cost generic antiretroviral drugs are available in resource-limited settings for treatment of HIV infections. However, few bioequivalence data in specific populations in which these generics are likely to be used are available. We conducted a randomized crossover bioequivalence study of generic and brand name formulations of nevirapine, zidovudine, and lamivudine in HIV-negative Indian women using US Food and Drug Administration (FDA) criteria. Subjects took single doses of all formulations separated by a 14-day washout period. Plasma concentrations were measured over 96 hours during each study period. Average bioequivalence was determined using natural log-transformed maximum concentration (C-max) and area-under-the-concentration-time curve (AUC) mean ratio data. Fifteen Indian women were enrolled. The 90% confidence intervals for nevirapine (14 subjects) and lamivudine (15 subjects) C-max, AUC from 0 to the last measurable time point (AUC(0-t)), and AUC from 0 to infinity (AUC(0-infinity)) mean ratios and zidovudine (15 subjects) AUC(0-t) and AUC(0-infinity) mean ratios were all within 0.80 to 1.25. However, the 90% confidence interval for zidovudine C-max mean ratio was 0.70 to 1.46. Generic and brand name nevirapine and lamivudine met FDA average bioequivalence criteria. Lack of average bioequivalence for zidovudine was found for C-max but is not expected to be clinically significant, because the total AUC values were similar between formulations.

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Zachariah R, Teck R, Buhendwa L, Labana S, Chinji C, Humblet P, Harries AD. **How can the community contribute in the fight against HIV/AIDS and tuberculosis? An example from a rural district in Malawi.** Transactions of the Royal Society of Tropical Medicine and Hygiene 2006;100(2):167-175.

Abstr. This paper describes (a) the experience of initiating community involvement in HIV/AIDS and tuberculosis (TB) activities in a rural district in Malawi and (b) some of the different ways in which the community is contributing in the fight against these two diseases and the outcomes of their involvement. During a 2-year period, a total of 21358 (41%) of 52510 HIV tests performed at voluntary counselling and HIV testing (VCT) sites in the district were conducted by lay community counsellors. A team of 465 community volunteers, 1362 trained family caregivers and 9 community nurses provided care and support to 5106 HIV-positive individuals, of whom 2006 (39%) were in WHO stage III or IV. All those in WHO stage III or IV were on cotrimoxazole prophylaxis and 895 (45%) of these were also on antiretroviral treatment. A total of 2714_B patients, of whom 1627 (60%) were HIV-positive, also received care and support. A total of 1694 orphans were trained in vocational skills. Twelve vegetable gardens and three maize farms were set up, and pre-school activities were organised for 900 orphans. Communities can play an important contributory role in reducing the burden of HIV/AIDS and TB and in mitigating its impact. Despite this, community resources in most settings are often under-exploited and their role remains undefined.

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