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ICAP
Columbia University
MAILMAN SCHOOL
OF PUBLIC HEALTH

HIV Care & PMTCT in Resource-Limited Settings

Monthly Intelligence Report

2006, Vol 2, Issue 3

[Available on line](#)

prepared by the Bordeaux Working Group

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Number of citations selected for this issue: 15

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

Boerma JT, Stanecki KA, Newell ML, Luo C, Beusenberg M, Garnett GP, Little K, Calleja JG, Crowley S, Kim JY, Zaniewski E, Walker N, Stover J, Ghys PD. **Monitoring the scale-up of antiretroviral therapy programmes: methods to estimate coverage.** Bulletin of the World Health Organization 2006;84(2):145-150.

Abstr. This paper reviews the data sources and methods used to estimate the number of people on, and coverage of, antiretroviral therapy (ART) programmes in low- and middle-income countries and to monitor the progress towards the "3 by 5" target set by WHO and UNAIDS. We include a review of the data sources used to estimate the coverage of ART programmes as well as the efforts made to avoid double counting and over-reporting. The methods used to estimate the number of people in need of ART are described and expanded with estimates of treatment needs for children, both for ART and for cotrimoxazole prophylaxis. An estimated 6.5 million people were in need of treatment in low- and middle-income countries by the end of 2004, including 660 000 children under age 15 years. The mid-2005 estimate of 970 000 people receiving ART in low- and middle-income countries (with an uncertainty range 840 000-1 100 000) corresponds to a coverage of 15% of people in need of treatment.

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Braitstein P, Brinkhof MWG, Dabis F, Schechter M, Boule A, Miotti P, Wood R, Laurent C, Sprinz E, Seyler C, Bangsberg DR, Balestre E, Sterne JAC, May M, Egger M. **Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries.** Lancet 2006;367(9513):817-824.

Abstr. Background Highly active antiretroviral therapy (HAART) is being scaled up in developing countries. We compared baseline characteristics and outcomes during the first year of HAART between HIV-1-infected patients in low-income and high-income settings. Methods 18 HAART programmes in Africa, Asia, and South America (low-income settings) and 12 HIV cohort studies from Europe and North America (high-income settings) provided data for 4810 and 22 217, respectively, treatment-naïve adult patients starting HAART. All patients from high-income settings and 2725 (57%) patients from low-income settings were actively followed-up and included in survival analyses. Findings Compared with high-income countries, patients starting HAART in low-income settings had lower CD4 cell counts (median 108 cells per μ L vs 234 cells per μ L), were more likely to be female (51% vs 25%), and more likely to start treatment with a non-nucleoside reverse transcriptase inhibitor (NNRTI) (70% vs 23%). At 6 months, the median number of CD4 cells gained (106 cells per μ L vs 103 cells per μ L) and the percentage of patients reaching HIV-1 RNA levels lower than 500 copies/mL (76% vs 77%) were similar. Mortality was higher in low-income settings (124 deaths during 2236 person-years of follow-up) than in high-income settings (414 deaths during 20 532 person-years). The adjusted hazard ratio (HR) of mortality comparing low-income with high-income settings fell from 4.3 (95% CI 1.6-11.8) during the first month to 1.5 (0.7-3.0) during months 7-12. The provision of treatment free of charge in low-income settings was associated with lower mortality (adjusted HR 0.23; 95% CI 0.08-0.61). Interpretation Patients starting HAART in resource-poor settings have increased mortality rates in the first months on therapy, compared with those in developed countries. Timely diagnosis and assessment of treatment eligibility, coupled with free provision of HAART, might reduce this excess mortality.

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Fawzi WW. **The benefits and concerns related to vitamin A supplementation [Editorial commentary].** Journal of Infectious Diseases 2006;193(6):756-759.

See the article by Humphrey et al

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French MA. **'Tuberculosis' after commencing antiretroviral therapy in HIV patients from countries where Mycobacterium tuberculosis infection is common [Letter].** AIDS 2006;20(3):473-474.

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Humphrey JH, Iliff PJ, Marinda ET, Mutasa K, Moulton LH, Chidawanyika H, Ward BJ, Nathoo KJ, Malaba LC, Zijenah LS, Zvandasara P, Ntozini R, Mzengeza F, Mahomva AI, Ruff AJ, Mbizvo MT, Zunguza CD. **Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality.** Journal of Infectious Diseases 2006;193(6):860-871.

Abstr. Background. Low maternal serum retinol level is a risk factor for mother-to-child transmission (MTCT) of human immunodeficiency virus (HIV). Multiple-large-dose vitamin A supplementation of HIV-positive children reduces mortality. The World Health Organization recommends single-large-dose vitamin A supplementation for postpartum women in areas of prevalent vitamin A deficiency; neonatal dosing is under

consideration. We investigated the effect that single-large-dose maternal/neonatal vitamin A supplementation has on MTCT, HIV-free survival, and mortality in HIV-exposed infants. **Methods.** A total of 14,110 mother-infant pairs were enrolled ≤ 96 h after delivery, and both mother and infant, mother only, infant only, or neither received vitamin A supplementation in a randomized, placebo-controlled trial with a factorial design. All but 4 mothers initiated breast-feeding. A total of 4495 infants born to HIV-positive women were included in the present analysis. **Results.** Neither maternal nor neonatal vitamin A supplementation significantly affected postnatal MTCT or overall mortality between baseline and 24 months. However, the timing of infant HIV infection modified the effect that supplementation had on mortality. Vitamin A supplementation had no effect in infants who were polymerase chain reaction (PCR) negative for HIV at baseline. In infants who were PCR negative at baseline and PCR positive at 6 weeks, neonatal supplementation reduced mortality by 28% ($P = .01$), but maternal supplementation had no effect. In infants who were PCR negative at 6 weeks, all 3 vitamin A regimens were associated with similar to 2-fold higher mortality ($P \leq .05$). **Conclusions.** Targeted vitamin A supplementation of HIV-positive children prolongs their survival. However, postpartum maternal and neonatal vitamin A supplementation may hasten progression to death in breast-fed children who are PCR negative at 6 weeks. These findings raise concern about universal maternal or neonatal vitamin A supplementation in HIV-endemic areas.

See the editorial commentary by Fawzi

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Joseph P, Severe P, Ferdinand S, Goh KS, Sola C, Haas DW, Johnson WD, Rastogi N, Pape JW, Fitzgerald DW. **Multidrug-resistant tuberculosis at an HIV testing center in Haiti.** *AIDS* 2006;20(3):415-418.

Abstr. Objective: Tuberculosis is the major opportunistic infection of HIV/AIDS in developing countries. We investigated the prevalence rate of multidrug-resistant (MDR) tuberculosis at an HIV voluntary counseling and testing (VCT) center in Port-au-Prince, Haiti. Design and methods: A cross-sectional prevalence study of MDR-tuberculosis was conducted at a VCT Center. All patients reporting at least 5 days of cough were screened for tuberculosis, including sputum culture. All Mycobacteria tuberculosis isolates underwent drug susceptibility testing. Results: Between January 2000 and December 2002, isolates from 330 patients underwent drug susceptibility testing. MDR-tuberculosis was documented in 16 (6%) of 281 patients with primary tuberculosis and 10 (20%) of 49 patients with recurrent tuberculosis. In patients with primary disease, 11 (10%) of 115 HIV-infected patients had MDR-tuberculosis compared with five (3%) of 166 HIV-negative patients, (risk ratio 3.2; 95% confidence interval 1.1-8.9; $P = 0.0331$). Conclusion: Multidrug resistance was prevalent among patients found to have pulmonary tuberculosis at an HIV testing center in Port-au-Prince. Patients with primary pulmonary tuberculosis who were HIV-co-infected were more likely to have multidrug resistance than HIV-negative patients. Assiduous attention to tuberculosis infection control measures at HIV testing centers in developing countries is critical to prevent nosocomial MDR-tuberculosis transmission. Measures may include appropriate ventilation, outdoor seating, ultra-violet lights, and rapid on-site screening for tuberculosis.

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Laufer MK, van Oosterhout JJG, Thesing PC, Thumba F, Zijlstra EE, Graham SM, Taylor TE, Plowe CV. **Impact of HIV-associated immunosuppression on malaria infection and disease in Malawi.** *Journal of Infectious Diseases* 2006;193(6):872-878.

Abstr. Background. Human immunodeficiency virus (HIV) infection and malaria coexist in much of Africa. Previous studies differ in their findings on the interactions between the 2 infections. **Methods.** Adults living with HIV infection in Blantyre, Malawi, were enrolled in a longitudinal observational study from September 2002 to August 2004. Malaria blood smears were obtained monthly and for any illness suggestive of malaria. Complete evaluations of all illness episodes were conducted, regardless of malaria smear results. **Results.** The incidence of clinical malaria episodes was higher in participants with CD4 cell counts < 200 cells/mm³ than in those with CD4 cell counts 1500 cells/mm³. The trend was preserved when increasingly specific definitions of malaria disease were used. The prevalence of malaria infection was not associated with CD4 cell count. In per-visit analysis, lower CD4 cell counts were associated with higher incidences of pneumonia, sepsis, and tuberculosis but not of malaria. Severe malaria was rare, with only 3 cases in 591 person-years of observation. Parasite density and CD4 cell count were independent risk factors for fever. **Conclusions.** Profoundly immunosuppressed adults with HIV infection require more-frequent treatment for uncomplicated malaria, but malaria infection and disease are less strongly associated with HIV-associated immunosuppression than are other opportunistic infections. Where malaria is common, the high incidence of fever found among immunosuppressed adults may lead to misclassification of illness episodes as malaria.

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Lawn SD, Bekker LG, Middelkoop K, Myer L, Wood R. **Impact of HIV infection on the epidemiology of tuberculosis in a peri-urban community in South Africa: the need for age-specific interventions.** *Clinical Infectious Diseases* 2006;42(7):1040-1047.

Abstr. Background. In August 2005, the World Health Organization declared the tuberculosis (TB) epidemic in Africa to be a regional emergency. Current TB-control measures are failing, largely as a result of the human immunodeficiency virus (HIV) epidemic. Evaluation of additional control interventions requires detailed understanding of the epidemiological relationship between these diseases at the community level. Methods. We examined age- and sex-specific trends in TB notifications and their association with the prevalence of HIV infection in a peri-urban township in South Africa during 1996 - 2004. Denominators for TB notifications were derived from population census data. The local TB-control program used the World Health Organization directly observed treatment, short-course (DOTS) strategy. Results. TB notification rates increased 2.5-fold during the period, reaching a rate of 1468 cases per 100,000 persons in 2004 (, by test for trend); the estimated population prevalence of HIV infection increased $P = .007$ from 6% to 22% during the same period. After stabilization of prevalence of HIV infection, the TB notification rate continued to increase steeply, indicating ongoing amplification of the TB epidemic. In 2004, at least 50% of children aged 0 - 9 years who developed TB were HIV infected. Annual TB notification rates among adolescents increased from 0 cases in 1996 - 1997 to 436 cases per 100,000 persons in 2003 - 2004, and these increases were predominantly among female. However, 20-39- year-old persons were affected most, with TB notification rates increasing from 706 to 2600 cases per 100,000 persons among subjects in their 30s. In contrast, TB rates among persons aged 150 years did not change. Conclusions. HIV infection is driving the TB epidemic in this population, and use of the DOTS strategy alone is insufficient. TB notifications have reached unprecedented levels, and additional targeted, age- specific interventions for control of TB and HIV infection in such populations are needed.

See the editorial commentary by Whalen

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Levine AM, Karim R, Mack W, Gravink DJ, Anastos K, Young M, Cohen M, Newman M, Augenbraun M, Gange S, Watts DH. **Neutropenia in human immunodeficiency virus infection - Data from the Women's Interagency HIV Study.** *Archives of Internal Medicine* 2006;166(4):405-410.

Abstr. Background: Neutropenia is well described in individuals infected with human immunodeficiency virus (HIV) and occurs in approximately 10% to 50% of cases. Neither the effect of highly active antiretroviral therapy (HAART) on neutrophil counts nor the significance of neutropenia in terms of survival has previously been evaluated. Methods: The prevalence of neutropenia among 1729 HIV-infected women, followed up as part of the Women's Interagency HIV Study, was evaluated. The CD4 lymphocyte counts, HIV-1 RNA levels, and complete blood cell counts, including absolute neutrophil counts, were obtained at 6-month intervals. Results: Neutropenia was common among HIV-infected women; at baseline, 4% had neutrophil counts less than 2000/ μ L, whereas 7% had counts less than 1000/ μ L. During 7.5 years of follow-up, neutrophil counts less than 2000/ μ L occurred on at least 1 occasion in 79%, whereas absolute neutrophil counts less than 1000/ μ L were documented in 31%. Worsening HIV disease parameters, such as lower CD4 cell counts ($P < .001$) and higher HIV-1 RNA levels ($P < .001$), were associated with development of neutropenia. Resolution of neutropenia was associated with higher CD4 cell counts ($P < .001$) and use of HAART ($P = .007$). We found that HAART, without zidovudine, was associated with protection against development of neutropenia. On multivariate analysis, neutropenia was not found to be associated with decreased survival among HIV-infected women. Conclusions: Worsening HIV disease parameters are associated with neutropenia in HIV-infected women. Treatment with HAART, without zidovudine in the regimen, protects against development of neutropenia, whereas HAART use and higher CD4 cell counts are associated with resolution of neutropenia. Neutropenia is not associated with decreased survival in HIV-infected women.

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Mootsikapun P, Chetchotisakd P, Anunnatsiri S, Boonyaprawit P. **Efficacy and safety of indinavir/ritonavir 400/100 mg twice daily plus two nucleoside analogues in treatment-naive HIV-1-infected patients with CD4(+) T-cell counts < 200 cells/mm(3): 96-week outcomes.** *Antiviral Therapy* 2005;10 (8):911-916.

Abstr. Objective: To evaluate the efficacy and safety of indinavir/ritonavir 400/100 mg plus stavudine and lamivudine twice daily in antiretroviral-therapy-naive Thai HIV-1-infected patients. Methods: This was an open-label, non-randomized single arm study. Antiretroviral-naive patients (n=80) with CD4(+) cell count < 200x10⁶/l were started on stavudine and lamivudine plus indinavir/ritonavir 400/100mg twice daily. CD4(+) cell count and HIV RNA were determined at week 0, 12, 24, 48 and 96. HIV RNA was measured to a level of 50 copies/ml by RT-PCR assay. Primary analysis was statistically performed as intent to treat. The primary endpoint was the percentage of patients with plasma HIV RNA below 50 copies/ml at week 96. Result: Eighty

antiretroviral-therapy-naïve patients with median CD4(+) cell count $19 \times 10^6/l$ (range: $2-197 \times 10^6/l$) and median baseline plasma HIV RNA of 174,000 copies/ml (range 16,800-750,000 copies/ml) were enrolled. In the intent-to-treat analysis at week 96, the proportion of patients with HIV RNA of < 50 copies/ml was 68.8% (95% confidence interval [CI]: 68.3-69.3), whereas it was 88.7% (95% CI: 88.1-89.3) in the on-treatment analysis at week 96. The regimen was well tolerated. Hyperglycaemia, hypercholesterolaemia and hypertriglyceridaemia were found in 8.3, 33.3 and 37.0% of the patients, respectively. Treatment was stopped in 18 patients; two from intolerance, two switched therapy, four as a result of serious adverse event-related death, and ten were lost to follow-up. Conclusion: Our study demonstrates that indinavir/ritonavir 400/100 mg plus stavudine and lamivudine twice daily, the least expensive boosted protease inhibitor, appears to be effective and safe up to 96 weeks despite high baseline viraemia and low CD4(+) cell count in antiretroviral-naïve patients.

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Newell ML, Patel D, Goetghebuer T, Thorne C. **CD4 cell response to antiretroviral therapy in children with vertically acquired HIV infection: Is it associated with age at initiation?** Journal of Infectious Diseases 2006;193(7):954-962.

Abstr. Background. Considerable uncertainty remains as to whether early initiation of antiretroviral therapy (ART) in children with vertically acquired human immunodeficiency virus (HIV) infection increases the benefit in terms of immunological response. Methods. The association between immunological outcome and early initiation of and/or more-potent ART was investigated, using age-standardized z scores for CD4 cell counts (hereafter, "CD4 z scores"), in 131 HIV-infected children enrolled in the European Collaborative Study, a birth cohort study. Results. Median age at initiation of the most-potent ART was 4 years (range, 0.1-15.5 years). Initiation of treatment after 5 months of age resulted in nonsignificantly lower CD4 z scores 6 months after initiation. Time to a 20% increase in CD4 z score was associated with age at initiation of the most-potent ART (adjusted hazard ratios [AHRs], 0.37 [$P < .01$] and 0.43 [$P = .05$] for 5 months-5 years of age and > 5 years of age, respectively, compared with < 5 months of age), ethnicity (AHR, 0.48 [$P = .01$], for black vs. white), and highly active ART (HAART) with or without prior ART (AHRs, 3.16 [$P < .01$] and 3.95 [$P < .001$], vs. mono or dual ART, respectively). The risk of subsequent deterioration of CD4 z score was similar for children who initiated ART in different age groups ($\chi^2 = 0.824$; $P = .82$). Conclusions. We confirm the effectiveness of HAART with respect to the recovery of CD4 cell count and suggest a benefit of initiating ART before the age of 5 months. Age at initiation of the most-potent ART was not associated with the likelihood of sustaining the recovery of CD4 cell count.

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Resino S, Resino R, Micheloud D, Gutierrez DG, Leon JA, Ramos JT, Ciria L, de Jose I, Mellado J, Munoz Fernandez A. **Long-term effects of highly active antiretroviral therapy in pretreated, vertically HIV type 1-infected children: 6 years of follow-up.** Clinical Infectious Diseases 2006;42(6):862-869.

Abstr. Background. Several studies of children with human immunodeficiency virus (HIV) type 1 infection have demonstrated sustained increases in CD4(+) cell count, even when virological failure has occurred after receipt of highly active antiretroviral therapy (HAART), but these studies were of limited duration. Moreover, the CD4(+) cell count threshold at which antiretroviral treatment should be initiated is still unsettled. The aim of this study was to define the long-term impact of HAART on CD4(+) cell percentage and viral load according to CD4(+) cell percentages before HAART was initiated. Methods. We conducted a retrospective study of 113 pretreated HIV-1-infected children stratified by pre-HAART CD4(+) cell percentage ($< 5\%$, $5\% - 15\%$, $15\% - 25\%$, and $> 25\%$). The inclusion criteria were as follows: initiating HAART with a protease inhibitor, having 6 years of follow-up after starting HAART, having a CD4(+) cell count or viral load recorded before initiation of HAART, and having received mono- or dual-nucleoside therapy before starting HAART. Results. During the first 2 years of HAART, HIV-1-infected children experienced a significant increase in CD4(+) cell percentage and a decrease in viral load ($P < .05$). During their last 4 years of receiving HAART, we found a significant decrease in viral load but not an increase in CD4(+) cell percentage, because the CD4(+) cell percentage reached a plateau after the second year of HAART. Moreover, children with CD4(+) cell percentages of $< 5\%$ at baseline did not achieve CD4(+) cell percentages of $> 25\%$ after 6 years of HAART. Children with CD4(+) cell percentages of $5\% - 25\%$ at baseline had a strong negative association with achieving CD4(+) cell percentages of $> 30\%$ for at least 6 and 12 months but not with achieving CD4(+) cell percentages of $> 30\%$ for at least 24 months. Conclusions. Long-term HAART allowed for restoration of CD4(+) cell counts and control of viral loads in HIV-1-infected children. However, initiating HAART after severe immunosuppression has occurred is detrimental for the restoration of the CD4(+) cell count.

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Abstr. The aim of this study is to assess whether HIV-related illness and World Health Organization (WHO) clinical stage can be used to guide initiation of antiretroviral therapy (ART) in rural Rakai District, Uganda. A retrospective cohort analysis of 910 HIV-seroprevalent individuals randomly sampled from a community cohort was conducted. The associations between HIV-related clinical illness and HIV viral loads > 55,000 copies/mL and death were evaluated as a guide for initiation of ART. Reporting one or more HIV-related illnesses was associated with high specificity for identifying HIV viral load > 55,000 copies/mL and predicting death within 30 months. There were more deaths in those with one symptom at baseline (16.3%) and two or more symptoms (25.0%) than in those reporting no symptoms (9.6%; P = 0.001). HIV-related illness and WHO stage predicted disease progression. The specificity of clinical illness to predict viral load > 55,000 copies/mL was high and could be used to rule in HIV disease requiring ART.

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Vasan A, Renjifo B, Hertzmark E, Chaplin B, Msamanga G, Essex M, Fawzi W, Hunter D. **Different rates of disease progression of HIV type 1 infection in Tanzania based on infecting subtype.** Clinical Infectious Diseases 2006;42(6):843-852.

Abstr. Background. Many different subtypes of human immunodeficiency virus (HIV) type 1 have been identified, particularly in sub-Saharan Africa. However, much remains unknown regarding the relative pathogenicity of these subtypes and their influence on the clinical progression of HIV infection. We examined prospectively the associations between HIV-1 subtypes A, C, and D and recombinant viruses, as well as the rates of disease progression in a cohort of seropositive women from Dar es Salaam, Tanzania. Methods. A total of 428 pregnant mothers participating in a larger controlled trial of the effect of vitamin supplements were selected for DNA sequencing of their HIV-1 subtype. Plasma viral load was measured at baseline, and CD4(+) cell counts was assessed at baseline and at regular intervals throughout the follow-up period. Proportional hazards regression (hazards ratio [HR]) analysis was used to measure the association between viral subtype and the rate of disease progression. Results. Relative to patients with subtype A, patients with subtype D experienced the most rapid progression to death (HR, 2.27; 95% confidence interval [CI], 1.46-3.52) or to the World Health Organization stage 4 of illness (HR, 1.94; 95% CI, 1.20-3.14) and to a CD4(+) cell count of < 200 cells/mm³ (HR, 2.12; 95% CI, 1.42-3.17). After adjustment for viral load, CD4(+) cell count, and other baseline covariates, the associations remained similar. Conclusions. We observed heterogeneity in the rates of disease progression of HIV-1 disease in infected persons, on the basis of the infecting subtype. Subtype D was associated with the most rapid progression of the disease, relative to the other 3 categories of viruses in our cohort.

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Whalen CC. **Failure of directly observed treatment for tuberculosis in Africa: A call for new approaches [Editorial commentary].** Clinical Infectious Diseases 2006;42(7):1048-1050.

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