HIV Care & PMTCT in Resource-Limited Settings

Monthly Intelligence Report
2009, Vol 5, Issue 10

Back Issues on Line

prepared by the Bordeaux Working Group

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Number of citations selected for this issue: 17

Citation format (by alphabetical order of the authors): Author(s). Title. Source. Abstr. (Authors' text) or Introduction (Authors' text) or Selection (Selected sections of the paper) or Notes or Abstr. Edited (Written by the Bordeaux Working Group). Author Address, if available, Free Full Text, if available


Abstr. As a result of the scale-up of antiretroviral treatment (ART) programmes and substantial financial support worldwide, an increasing number of HIV-infected individuals in low-income and middle-income countries (LIMCs) now have access to ART. Despite this progress, important questions remain on the best use of ART and how patients should be maintained on a successful regimen. This Review addresses some of the issues faced by those managing the epidemic in LMICs, including when to start treatment, choice of first-line ART, and when to switch regimens. Although the first priority must be continued expansion of access to ART, there should be a move towards starting ART earlier to treat individuals before they reach advanced stages of disease, to reduce early mortality, and to build support for improved monitoring of treatment failure. There is also a need for more randomised controlled studies to identify the long-term outcomes, cost-effectiveness of ART, and use of virological monitoring in LMICs.

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Notes. Introduction of Social Science & Medicine, Part Special Issue: Women, Mothers and HIV Care in Resource Poor Settings, Edited by Alice Desclaux, Philippe Msellati and Saskia Walentowitz.

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Abstr. A wide clinical spectrum of renal diseases affects individuals with HIV. These conditions include acute kidney injury, electrolyte and acid-base disturbances, HIV-associated glomerular disease, acute-onchronic renal disease and adverse side effects related to treatment of HIV. Studies employing varying criteria for diagnosis of kidney disease have reported a variable prevalence of these diseases in patients with HIV in sub-Saharan Africa: 6% in South Africa, 38% in Nigeria, 26% in Cote d'Ivoire, 28% in Tanzania, 25% in Kenya, 20-48.5% in Uganda and 33.5% in Zambia. Results from these studies also suggest that a broader spectrum of histopathological lesions in HIV-associated kidney disease exists in African populations than previously thought. Strategies to prevent or retard progression to end-stage renal disease of HIV-associated kidney conditions should include urinalysis and measurement of kidney function of all people with HIV at presentation. Renal replacement in the form of dialysis and transplantation should be implemented as appropriate. This Review focuses on the available evidence of renal diseases in patients with HIV infection in sub-Saharan Africa and offers practical guidelines to treat these conditions that also take into consideration challenges and obstacles that are specific to sub-Saharan Africa.

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Abstr. To reduce mother-to-child transmission of human immunodeficiency virus (HIV) in resource-poor settings, the World Health Organization recommends exclusive breast-feeding for 6 months,
followed by rapid weaning if replacement feeding is affordable, feasible, available, safe, and sustainable. In the Kisumu Breastfeeding Study (trial registration: Clinicaltrials.gov identifier NCT00146380), infants of HIV-infected mothers who received antiretroviral therapy experienced high rates of diarrhea at weaning. To address this problem, mothers in the Kisumu Breastfeeding Study were given safe water storage vessels, hygiene education, and bleach for household water treatment. We compared the incidence of diarrhea in infants enrolled before (cohort A) and after (cohort B) implementation of the intervention. Cohort B infants experienced less diarrhea than cohort A infants, before and after weaning (P < .001 and P = .047, respectively); however, during the weaning period, there were no differences in the frequency of diarrhea between cohorts (P = 0.89). Testing of stored water in cohort B homes indicated high adherence (monthly range, 80%-95%) to recommended chlorination practices. Among infants who were weaned early, provision of safe water may be insufficient to prevent weaning-associated diarrhea.

See Kuhn editorial below

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**Edited Abstr.** Introduction: The HIV-1 epidemic in African countries is largely due to non-B HIV-1 subtypes. Patterns and frequency of antiretroviral drug resistance mutations observed in these countries may differ from those in the developed world, where HIV-1 subtype B predominates. Methods: HIV-1 subtype and drug resistance mutations were assayed among Nigerian patients with treatment failure on first-line therapy (plasma HIV RNA > 1000 copies/mL). Criteria for inclusion in this study were: (1) virological failure (2) adherence (defined as adhering to scheduled drug pickups 3 months before failure) (4) presence of one or more reverse transcriptase resistance mutations. Sequence analysis of the reverse transcriptase and protease gene revealed drug resistance mutations and HIV-1 viral subtype. Specific patterns of mutations and clinical characteristics are described in patients with the K65R mutation. Results: Since 2005, 338 patients were evaluated. The most prevalent subtypes were CRF02_AG [152 of 338 (44.9%)] and G [128 of 338 (37.9%)]. Three hundred seven of 338 (90.8%) patients had previously received stavudine and/or lamivudine + efavirenz or nevirapine; 41 of 338 (12.1%) had received tenofovir (TDF). The most common nucleoside reverse transcriptase inhibitor mutations observed were M184V (301, 89.1%) and K70R (91, 26.9%). The K65R mutation was present in 37 of 338 patients (10.9%). In this selected sample, K65R mutation was present in 24/41 (58.5%) patients receiving TDF-containing first line regimen and 13/307 (4.2%) patients not receiving TDF. The Q151M (P < 0.05), K219R, and T69del (P < 0.01) mutations were more common in patients with K65R who had not received TDF. Conclusions: The K65R mutation is increasingly recognized and is a challenging finding among patients with non-B HIV subtypes, whether or not they have been exposed to TDF. Use of TDF in first line regimens in resource limited settings may lead to high rates of resistance.

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**Abstr.** Objective To investigate trends in adult mortality in a population serviced by a public-sector antiretroviral therapy (ART) programme in rural South Africa using a demographic surveillance system. Methods Verbal autopsies were conducted for all 7930 deaths observed between January 2000 and December 2006 in a demographic surveillance population of 74 500 in the Umkhanyakude district of northern KwaZulu-Natal province, South Africa. Age-standardized mortality rate ratios (SMRRs) were calculated for adults aged 25 to 49 years, the group most affected by HIV, for the 2 years before 2004 and the 3 subsequent years, during which ART had been available. Findings Between 2002-2003 (the period before ART) and 2004-2006 (the period after ART), HIV-related age-standardized mortality declined significantly, from 22.52 to 17.58 per 1000 person-years in women 25-49 years of age (P < 0.001; SMRR: 0.780; 95% confidence interval, CI: 0.691-0.881), and from 26.46 to 18.68 per 1000
person-years in men 25-49 years of age (P < 0.001; SMRR: 0.706; 95% CI: 0.615-0.811). On sensitivity analysis the results were robust to the possible effect of misclassification of HIV-related deaths. Conclusion Overall population mortality and HIV-related adult mortality declined significantly following ART roll-out in a community with a high prevalence of HIV infection. A clear public health message of the benefits of treatment, as revealed by these findings, should be part of a multi-faceted strategy to encourage people to find out their HIV serostatus and seek care.

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Abstr. We aimed in this study to describe efavirenz concentration-time courses in treatment-naive children after once-daily administration to study the effects of age and body weight on efavirenz pharmacokinetics and to test relationships between doses, plasma concentrations, and efficacy. For this purpose, efavirenz concentrations in 48 children were measured after 2 weeks of didanosine-lamivudine-efavirenz treatment, and samples were available for 9/48 children between months 2 and 5 of treatment. Efavirenz concentrations in 200 plasma specimens were measured using a validated high-performance liquid chromatography method. A population pharmacokinetic model was developed with NONMEM. The influence of individual characteristics was tested using a likelihood ratio test. The estimated minimal and maximal concentrations of efavirenz in plasma (C-min and C-max, respectively) and the area under the concentration-time curve (AUC) were correlated to the decrease in human immunodeficiency virus type 1 RNA levels after 3 months of treatment. The threshold C-min (and AUC) that improved efficacy was determined. The target minimal concentration of 4 mg/liter was considered for toxicity. An optimized dosing schedule that would place the highest percentage of children in the interval of effective and nontoxic concentrations was simulated. The pharmacokinetics of efavirenz was best described by a one-compartment model with first-order absorption and elimination. The mean apparent clearance and volume of distribution for efavirenz were 0.211 liter/h/kg and 4.48 liters/kg, respectively. Clearance decreased significantly with age. When the recommended doses were given to 46 of the 48 children, 19% (44% of children weighing less than 15 kg) had C(min)s below 1 mg/liter. A significantly higher percentage of children with C(min)s of > 1.1 mg/liter or AUCs of > 51 mg/liter . h than of children with lower values had viral load decreases greater than 2 log(10) copies/ml after 3 months of treatment. Therefore, to optimize the percentage of children with C(min)s between 1.1 and 4 mg/liter, children should receive the following once-daily efavirenz doses: 25 mg/kg of body weight from 2 to 6 years, 15 mg/kg from 6 to 10 years, and 10 mg/kg from 10 to 15 years. These assumptions should be prospectively confirmed.

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Abstr. Background. As highly active antiretroviral therapy (ART) is introduced into areas of the world in which hepatitis B virus (HBV) infection is highly endemic, it is important to determine the influence of HBV on persons with human immunodeficiency virus (HIV) and HBV coinfection who are receiving ART. Methods. We studied 1564 HIV-infected patients in Jos, Nigeria, who initiated ART. Participants with HIV-HBV coinfection had hepatitis B e antigen (HBeAg) and HBV DNA status determined. CD4(+) T cell count and HIV load at ART initiation were compared between individuals with HIV monoinfection and those with HIV-HBV coinfection with use of univariate methods. Regression analyses were used to determine if HBeAg status or HBV DNA at ART initiation were associated with baseline HIV parameters or ART response. Results. The median CD4(+) T cell count of the 262 participants with HIV-HBV coinfection (16.7%) was 107 cells/mL, compared with 130 cells/mL for participants with HIV monoinfection at ART initiation (P < .001). Participants with HIV-HBV coinfection also had higher HIV
loads than did patients with HIV monoinfection (4.96 vs 4.75 log(10) copies/mL; p = .02). Higher HBV DNA and detectable HBeAg levels were independently associated with lower CD4(+) T cell counts at ART initiation but not with higher HIV loads. In a multivariable model, HBeAg-positive patients were less likely than HBeAg-negative patients to suppress HIV replication to <= 400 copies/mL (odds ratio, 0.54; P = .03) at 24 weeks, but they had similar CD4(+) T cell increases. At 48 weeks, there was no significant effect of HBeAg status on ART response. Conclusions. Among HIV-infected Nigerian individuals, HBV coinfection, especially among those with high levels of HBV replication, was associated with lower CD4(+) T cell counts at ART initiation, independent of HIV RNA level. Patients with HBeAg-positive status had a slower virological response to ART, compared with HBeAg-negative patients. Further work is needed to understand the effects of HBV on CD4(+) T cells.

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Abstr. Background: Access to free antiretroviral therapy in sub-Saharan Africa has been steadily increasing, and the success of large-scale antiretroviral therapy programs depends on early initiation of HIV care. However, little is known about the stage at which those infected with HIV present for treatment in sub-Saharan Africa. Methods: We conducted a cross-sectional analysis of initial visits to the Immune Suppression Syndrome Clinic of the Mbarara University Teaching Hospital, including patients who had their initial visit between February 2007 and February 2008 (N = 2311). Results: The median age of the patients was 33 years (range 16-81 years), and 64% were female. More than one third (40%) were categorized as late presenters, that is, World Health Organization disease stage 3 or 4. Male gender, age 46-60 years (vs. younger), lower education level, being unemployed, living in a household with others, being unmarried, and lack of spousal HIV status disclosure were independently associated with late presentation, whereas being pregnant, having young children, and consuming alcohol in the prior year were associated with early presentation. Conclusions: Targeted public health interventions to facilitate earlier entry into HIV care are needed, as well as additional study to determine whether late presentation is due to delays in testing vs. delays in accessing care.

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Abstr. Background: To increase access to antiretroviral therapy in resource-limited settings, several experts recommend "task shifting" from doctors to clinical officers, nurses and midwives. This study sought to identify task shifting that has already occurred and assess the antiretroviral therapy training needs among clinicians to whom tasks have shifted. Methods: The Infectious Diseases Institute, in collaboration with the Ugandan Ministry of Health, surveyed health professionals and heads of antiretroviral therapy clinics at a stratified random sample of 44 health facilities accredited to provide this therapy. A sample of 265 doctors, clinical officers, nurses and midwives reported on tasks they
performed, previous human immunodeficiency virus training, and self-assessment of knowledge of human immunodeficiency virus and antiretroviral therapy. Heads of the antiretroviral therapy clinics reported on clinic characteristics. Results: Thirty of 33 doctors (91%), 24 of 40 clinical officers (60%), 16 of 114 nurses (14%) and 13 of 54 midwives (24%) who worked in accredited antiretroviral therapy clinics reported that they prescribed this therapy (p < 0.001). Sixty-four percent of the people who prescribed antiretroviral therapy were not doctors. Among professionals who prescribed it, 76% of doctors, 62% of clinical officers, 62% of nurses and 51% of midwives were trained in initiating patients on antiretroviral therapy (p = 0.457); 73%, 46%, 50% and 23%, respectively, were trained in monitoring patients on the therapy (p = 0.017). Seven percent of doctors, 42% of clinical officers, 35% of nurses and 77% of midwives assessed that their overall knowledge of antiretroviral therapy was lower than good (p = 0.001). Conclusion: Training initiatives should be an integral part of the support for task shifting and ensure that antiretroviral therapy is used correctly and that toxicity or drug resistance do not reverse accomplishments to date.

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Abstr. Background: Although HIV program evaluations focusing on mortality on ART provide important evidence on treatment effectiveness, they do not assess overall HIV program performance because they exclude patients who are eligible but not started on ART for whatever reason. The objective of this study was to measure mortality that occurs both pre-ART and during ART among HIV-positive children enrolled in two HIV-programs in Cambodia. Methods: Retrospective cohort study on 1168 HIV-positive children < 15 years old registered in two HIV-programs over a four-year period. Mortality rates were calculated for both children on treatment and children not started on ART. Results: Over half (53%) of children were 5 years or above and only 69(6%) were < 18 months. Overall, 9% (105/1168) of children died since the set-up of the programs. By the end of the observation period, 66(14.5%) patients not on ART had died compared to 39(5.5%) of those under treatment, and 100(22%) who did not start ART were lost-to-follow-up compared to 13(2%) on ART. 66/105 (62.8%) of all in-program deaths occurred before starting ART, of which 56% (37/66) and 79% (52/66) occurred within 3 and 6 months of enrolment respectively. Mortality rate ratio between children not on ART and children on ART was 4.1 (95% CI: 2.7-6.2) (P < 0.001). The most common contributing cause of death in first 3 months of treatment and in first 3 months of program enrollment was tuberculosis. 41/52 (79%) children who died within 6 months of enrollment had met the ART eligibility criteria before death. Conclusion: HIV-positive children experienced a high mortality and loss-to-follow-up rates before starting ART. These program outcomes may be improved by a more timely ART initiation. Measuring overall in-program mortality as opposed to only mortality on ART is recommended in order to more accurately evaluate pediatric HIV-programs performance.

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Abstr. Background: Immune reconstitution inflammatory syndrome (IRIS) after initiating highly active antiretroviral therapy (HAART) has not been widely studied in children, especially in resource-poor settings. Methods: Retrospective cohort study of HIV-infected children initiating HAART between 2001 and 2006 at a tertiary pediatric hospital in Lima, Peru. Charts were reviewed for 1 year after HAART initiation. IRIS was defined as a HAART-associated adverse event caused by an infectious or inflammatory condition in patients with documented virologic or immunologic success. Results: Ninety-one children (52% female) received HAART for at least 1 year. Median age at initiation was 5.7 years; 91% were ART naive and 73% had CDC stage C disease. The incidence of IRIS was 19.8 events per 100 person years (95% CI: 11.5-28.0). Median time to IRIS was 6.6 weeks after HAART initiation (range: 2-32 weeks). There were 18 IRIS events, 11 unmasking and 7 paradoxical. These included associations with Mycobacterium tuberculosis in 4 cases, Bacillus Calmette Guerin lymphadenitis in 1 case, varicella zoster virus in 6 cases and herpes simplex labialis in 6 cases. Children who developed IRIS had a higher baseline HIV viral load (P = 0.02) and an indicator of malnutrition (P = 0.007) before HAART initiation. Conclusion: IRIS occurred in 20% of HIV-infected children starting HAART in Peru and was associated with more advanced disease and malnutrition. Future research is needed to examine specific risk factors associated with pediatric IRIS to allow prompt identification and treatment of IRIS.

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