HIV Care & PMTCT in Resource-Limited Settings

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Back Issues on Line

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**Abstr.** Objective: Each year, intrauterine growth retardation (IUGR) affects 20-30 million neonates worldwide, mostly in resource-limited settings. Increased perinatal and infant mortality has been associated with IUGR. Some studies have suggested that HIV infection could increase the risk of IUGR. To confirm this hypothesis, we examined the association between HIV-related factors and the risk of IUGR in Thailand. Patients and Methods: Data from a cohort of 1436 HIV-infected pregnant women enrolled in the "Perinatal HIV Prevention Trial-1", a clinical trial conducted from 1997 to 1999 in Thailand, were analyzed using a logistic regression, adjusting for risk factors usually associated with IUGR. Results: The rate of IUGR was 7.6%. Adjusting for a short maternal height, low body mass index, small weight gain during pregnancy, and infant female sex, a low maternal CD4 percentage was independently associated with IUGR (odds ratio 0.96, per 1% increment, 95% confidence interval 0.93 to 0.99, P = 0.03). Conclusions: The current World Health Organization recommendation to initiate combination antiretroviral therapy for immunocompromised women as early as possible during pregnancy for their own health and for the prevention of HIV mother-to-child transmission is likely to also decrease the incidence of IUGR. Encouraging immunocompromised HIV-infected women who plan to become pregnant to wait until immune restoration has been achieved may help to reduce the risk of IUGR.

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**Abstr.** Background: There is growing concerti about the human resources needed to care for increasing numbers of patients receiving antiretroviral therapy in resource-limited settings. We evaluated all alternative model, community-based, comprehensive antiretroviral program staffed primarily by peer health workers and nurses. Methods: We conducted a retrospective cohort study of patients receiving antiretroviral therapy during the first 10 months of program enrollment beginning in late 2003. Virologic, immunologic, clinical, and adherence data were collected. Results: Of 360 patients started on treatment, 258 (72%) were active and on therapy approximately 2 years later. Viral load testing demonstrated that 86% of active patients (211/246 tested) had a viral load < 400 copies per milliliter. The median CD4 increase for active patients was 197 cells per cubic millimeter (interquartile range, 108346). Patients with either a history of antiretroviral use or lack of CD4 response were more likely to experience virologic failure. Survival was 84% at 1 year and 82% at 2 years. World Health Organization stage 4 was predictive of both not sustaining therapy and increased mortality. Conclusions: A community-based antiretroviral treatment program in a resource-limited setting can provide excellent AIDS care over at, least a 2-year period. A comprehensive program based upon peer health workers and nurses provides an effective alternative model for AIDS care.

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**Abstr.** Objective: Thailand began a national antiretroviral (ARV) treatment program in 2000, and all government and some private and university hospitals now provide treatment to eligible HIV-infected patients. We describe program scale-up and patient outcomes from 2000 to 2007. Methods: Data from 839 hospitals in all 76 provinces of Thailand were included in this analysis. Outcomes were assessed for patients initiating ARV treatment from January 2000 to December 2005. Follow-up data through March 2007 were included; lost to follow-up was defined as >3 months late for a follow-up visit. A Cox proportional hazard model was used to assess risk factors for death; the Kaplan-Meier method was used to estimate survival probabilities. Results: Outcome data are reported for 58,008 patients. Among these, 52.2% were male; at treatment initiation, the median age was 34 years, the median CD4 count was 41 cells per cubic millimeter, and 50.5% had AIDS. The initial regimen was nevirapine and 2 nonnucleoside reverse transcriptase inhibitors for 92.4% of patients; median follow-up time was 1.6 years (interquartile range = 0.8-2.4 years). Lost to follow-up occurred in 8.8% of patients. Overall 1-year survival was 0.89 (95% confidence interval = 0.88 to 0.89). Death was significantly associated with male sex, age >40 years, baseline CD4 Count <100 cells per cubic millimeter, symptomatic HIV or AIDS, receipt of services at a district or community hospital, and treatment initiation before 2005. Conclusions: National ARV treatment programs can be scaled up rapidly with good patient outcomes. Treatment outcomes among patients in Thailand are comparable to those reported in smaller cohorts in other countries, and Survival rates have improved since 2004.

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**Abstr.** Objective: In the absence of treatment, rapid progression to AIDS Occurs in approximately 20%. of HIV-1-infected infants over the first year of life. The prognosis of these children has considerably improved with highly active antiretroviral therapy. As data from well resourced countries are lacking, the objective of this collaborative study was to evaluate the impact of early treatment in vertically infected infants. Design: Children born to HIV-infected mothers between 1 September 1996 and 31 December 2004, who were diagnosed with HIV and free of AIDS before 3 months, were eligible. Demographics and pregnancy data, details of antiretroviral therapy, and clinical outcome were collected from 11 European Countries. Methods: The risk of AIDS or death, by whether or not an infant started treatment before 3 months of age, was estimated by Kaplan-Meier survival analysis and Cox proportional hazards models. Results: Among 210 children, 21 developed AIDS and three died. Baseline characteristics of the-124 infants treated before 3 months were similar to those of the 86 infants treated later. The risk of developing AIDS/death at 1 year was 1.6 and 11.7%, in the two groups, respectively (P<0.001). Deferring treatment was associated with increased risk of progression [crude hazard ratio 5.0; 95% confidence interval (CI) 2.0-12.6; P = 0.001] that persisted after adjusting for cohort in multivariate models (adjusted hazard ratio 3.0; 95% CI 1.2 - 7.9; P = 0.021). Conclusion: In HIV-1 vertically infected infants, starting antiretroviral therapy before the age of 3 months is associated with a significant reduction in progression to AIDS and death.

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**Abstr.** In view of the lack of suitable paediatric antiretroviral formulations on the market, a novel fixed dose combination (FDC) tablet containing 300 mg zidovudine (AZT) and 160 mg lamivudine (3TC) was developed to improve dosing accuracy and allow flexible drug dosing in function of the body weight of paediatric HIV patients as recommended by WHO. Rectangular tablets with multiple fraction bars were designed and each tablet can be broken into 8 subunits, each subunit containing a drug dose corresponding to a body weight of 5 kg. These fast-disintegrating subunits can easily be administered to children after dispersion in a liquid or mixing with food. In vitro quality control of the FDC tablets was performed and a crossover bioavailability study using 18 adult volunteers was performed after oral administration of the novel FDC tablet and a Duovir tablet. The results of the study showed that the novel tablets as well as its subunits disintegrated fast (<20 s). After 30 min dissolution, AZT and 3TC released from Duovir (R) and the novel tablets was above 95%, the similarity factors Q were above 50 for both AZT and 3TC. A tablet breakability test showed low weight variability (125.1 +/- 5 mg, R.S.D. = 4.4%), with limited weight loss (0.3%). There was no significant difference in pharmacokinetic parameters (C-max, t(max) and AUC(0-12) (h) values) between Duovir and the novel tablets formulated for paediatric applications.

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**Abstr.** Objective To measure the clinical and immunological outcomes of HIV positive adult patients receiving combination antiretroviral therapy in conflict affected northern Uganda. Design Prospective cohort study. Setting Gulu District, northern Uganda. Participants 1625 adults (aged over 14 years) receiving combination antiretroviral therapy. Main outcome measures Primary outcome: all cause mortality. Secondary outcomes: impact of covariates (sex, age, CD4 count at start, adherence, tuberculosis at start, duration of treatment, and internally displaced person status) on mortality. Results Sixty nine (4.2%) patients died during follow-up. The mortality incidence rate was 3.48 (95% confidence interval 2.66 to 4.31) per 100 person years. Patients started treatment with a median CD4 count of 157 (interquartile range 90-220) cells/µl; most (1009; 63%) had World Health Organization stage 2 defined illness. Sixty two patients had pulmonary tuberculosis at the start of treatment. Of the 1521 patients with adherence data, 118 (7.8%) had adherence of less than 95% and 1403 (92.2%) had adherence of 95% or above. Conclusion Patients receiving combination antiretroviral therapy in conflict affected northern Uganda had a mortality comparable to that of patients in peaceful, low income settings and better adherence than patients in higher income settings. These favourable findings highlight the need to expand access to combination antiretroviral therapy in populations affected by armed conflict.

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**Abstr.** Objective: Cryptococcal meningitis is one of the most important HIV-related opportunistic infections, especially in the developing world. In order to help develop global strategies and priorities for prevention and treatment, it is important to estimate the burden of cryptococcal meningitis. Design: Global burden of disease estimation using published studies. Methods: We used the median incidence rate of available studies in a geographic region to estimate the region-specific cryptococcal meningitis incidence; this was multiplied by the 2007 United Nations Programme on HIV/AIDS HIV population estimate for each region to estimate cryptococcal meningitis cases. To estimate deaths, we assumed a 9% 3-month case-fatality rate among high-income regions, a 55% rate among low-income and middle-income regions, and a 70% rate in sub-Saharan Africa, based on studies published in these areas and expert opinion. Results: Published incidence ranged from 0.04 to 12% per year among persons with HIV. Sub-Saharan Africa had the highest yearly burden estimate (median incidence 3.2%, 720,000 cases; range, 144,000-1.3 million). Median incidence was lowest in Western and Central Europe and Oceania (<= 0.1% each). Globally, approximately 957,900 cases (range, 371,700-1,544,400) of cryptococcal meningitis occur each year, resulting in 62,470 deaths (range, 125,000-1,124,900) by 3 months after infection. Conclusion: This study, the first attempt to estimate the global burden of cryptococcal meningitis, finds the number of cases and deaths to be very high, with most occurring in sub-Saharan Africa. Further work is needed to better define the scope of the problem and track the epidemiology of this infection, in order to prioritize prevention, diagnosis, and treatment strategies.

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**Abstr.** Setting: Rifampicin may reduce plasma efavirenz concentrations by inducing the expression of the cytochrome P450 2B6, which metabolizes efavirenz. However, there is no data in pediatric patient populations. Methods: We measured plasma efavirenz concentrations in 15 children during and after rifampicin-based antitubercular treatment. They were receiving standard doses of efavirenz as part of antiretroviral treatment. Trough concentration (C-min) was estimated by extrapolation of the log-linear concentration-time line to 24 hours after the previous dose. Results: Wide interpatient variation and marked bimodality of efavirenz concentrations were observed. Efavirenz C-min was not significantly different during vs. after antitubercular treatment (median 0.83 mg/L interquartile range 0.59-6.57 vs. median 0.86 mg/L interquartile range 0.61-3.56; P = 0.125). Nine (60%) and 8 (53%) children had subtherapeutic C-min (<1 mg/L) during and after antitubercular treatment, respectively. Conclusions: Concomitant rifampicin-based antitubercular treatment was not an important determinant of efavirenz concentrations. The substantial proportion of participants with estimated C-min <1 mg/L could result in the rapid emergence of efavirenz-resistant mutations and treatment failure.

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**Abstr.** Objectives: Assessments of population-level effects of antiretroviral therapy (ART) programmes in Africa are rare. We use data from burial sites to estimate trends in adult AIDS mortality and the mitigating effects of ART in Addis Ababa. ART has been available since 2003, and for free since 2005. Methods: To substitute for deficient vital registration, we use surveillance of burials at all cemeteries. We present trends in all-cause mortality, and estimate AIDS mortality (ages 20-64 years) from lay reports of causes of death. These lay reports are first used as a diagnostic test for the true cause of death. As reference standard, we use the cause of death established via verbal autopsy interviews conducted in 2004. The positive predictive value and sensitivity are subsequently used as anchors to estimate the number of AIDS deaths for the period 2001-2007. Estimates are compared with Spectrum projections. Results: Between 2001 and 2005, the number of AIDS deaths declined by 21.9 and 9.3% for men and women, respectively. Between 2005 and 2007, the number of AIDS deaths declined by 38.2 for men and 42.9% for women. Compared with the expected number in the absence of ART, the reduction in AIDS deaths in 2007 is estimated to be between 56.8 and 63.3%, depending on the coverage of the burial surveillance. Conclusion: Five years into the ART programme, adult AIDS mortality has been reduced by more than half. Following the free provision of ART in 2005, the decline accelerated and became more sex balanced. Substantial AIDS mortality, however, persists.

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**Abstr.** Two years after the introduction of free antiretroviral therapy (ART) in Tanzania and in spite of the logistical support provided to facilitate clinic attendance, a considerable level of attrition from the program was identified among clients from a semi-rural ward. Qualitative research on ART patients' health-seeking behavior identified factors affecting sustained attendance at treatment clinics. A mix of methods was used for data collection including semi-structured interviews with 42 clients and 11 service providers and 4 participatory group activities conducted with members of a post-test group between October and December 2006. A socio-ecological framework guided data analysis to categorize facilitators and barriers into individual, social, programmatic, and structural level influences, and subsequently explored their interaction and relative significance in shaping ART clients' behavior. Our findings suggest that personal motivation and self-efficacy contribute to program retention, and are affected by other individual-level experiences such as perceived health benefits or disease severity. However, these determinants are influenced by others' opinions and beliefs in the community, and constrained by programmatic and structural barriers. Individuals can develop the requisite willingness to sustain strict treatment requirements in a challenging context, but are more likely to do so within supportive family and community environments. Effectiveness and sustainability of ART roll-out could be strengthened by strategic intervention at different levels, with particular attention to community-level factors such as social networks' influence and support.

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Abstr. Objectives. In September 1999, the Elizabeth Glaser Pediatric AIDS Foundation initiated a multicountry, service-based programmatic effort in the developing world to reduce perinatally acquired HIV infection. We review 6 1/2 years of one of the world's largest programs for the prevention of mother-to-child transmission (PMTCT) of HIV. Methods. Each PMTCT facility records patient data in antenatal clinics and labor and delivery settings about counseling, testing, HIV status, and antiretroviral prophylaxis and submits the data to foundation staff. Results. More than 2.6 million women have accessed foundation-affiliated services through June 2006. Overall, 92.9% of women who received antenatal care or were eligible for PMTCT services in labor and delivery have been counseled, and 82.8% of those counseled accepted testing. Among women identified as HIV positive, 75.0% received antiretroviral prophylaxis (most a single dose of nevirapine), as did 45.6% of their infants. Conclusions. The foundation's experience has demonstrated that opt-out testing, supplying mothers with medication at time of diagnosis, and providing the infant dose early have measurably improved program efficiency. PMTCT should be viewed as an achievable paradigm and an essential part of the continuum of care.

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Abstr. Objective. The aim of our study was to develop, on the basis of simple clinical data, predictive short-term risk equations for AIDS or death in Asian patients infected with human immunodeficiency virus (HIV) who were included in the TREAT Asia HIV Observational Database. Methods. Inclusion criteria were highly active antiretroviral therapy initiation and completion of required laboratory tests. Predictors of short-term AIDS or death were assessed using Poisson regression. Three different models were developed: a clinical model, a CD4 cell count model, and a CD4 cell count and HIV RNA level model. We separated patients into low-risk, high-risk, and very high-risk groups according to the key risk factors identified. Results. In the clinical model, patients with severe anemia or a body mass index (BMI; calculated as the weight in kilograms divided by the square of the height in meters) \( \leq 18 \) were at very high risk, and patients who were aged \( \leq 40 \) years or were male and had mild anemia were at high risk. In the CD4 cell count model, patients with a CD4 cell count <50 cells/\( \mu L \), severe anemia, or a BMI \( \leq 18 \) were at very high risk, and patients who were aged \( \leq 40 \) years or were male and had mild anemia were at high risk. In the CD4 cell count and HIV RNA level model, patients with a CD4 cell count <50 cells/\( \mu L \), a detectable viral load, severe anemia, or a BMI similar to 18 were at very high risk, and patients with a CD4 cell count of 51-200 cells/\( \mu L \) and mild anemia were at high risk. The incidence of new AIDS or death in the clinical model was 1.3, 4.9, and 15.6 events per 100 person-years in the low-risk, high-risk, and very high-risk groups, respectively. In the CD4 cell count model the respective incidences were 0.9, 2.7, and 16.02 events per 100 person-years; in the CD4 cell count and HIV RNA level model, the respective incidences were 0.8, 1.8, and 6.2 events per 100 person-years. Conclusions. These models are simple enough for widespread use in busy clinics and should allow clinicians...

**Abstr.** Objective: To explore the rate of reported congenital abnormalities in infants exposed to antiretroviral therapy in utero. Design: Comprehensive national surveillance study in the UK and Ireland. Methods: Births to diagnosed HIV-infected women are reported to the National Study of HIV in Pregnancy and Childhood. Infants born between 1990 and 2007 were included. Results: The rate of reported major and minor congenital abnormality was 2.80% (232/8242) overall, and there was no significant difference by timing of ART exposure: 2.81% (14/498) in unexposed infants, 2.7% (147/5427) following second or third trimester exposure, and 3.1% (53/1708) following first trimester exposure (P = 0.690). There was no difference in abnormality rates by class of ART exposure in the first trimester (P = 0.363), and no category of abnormality was significantly associated with timing of ART, although numbers in these groups were small. There was no increased risk of abnormalities in infants exposed to efavirenz (P = 0.672) or didanosine (P = 0.816) in the first trimester. Conclusion: These findings, based on a large, national, unselected Population provide further reassurance that ART in utero does not pose a major risk of fetal anomaly.

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