HIV Care & PMTCT in Resource-Limited Settings

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**Abstr.** Objective. - We studied the evolution of drug combinations used, as well as the clinical and immunological profile of patients at initiation of highly active antiretroviral therapy (HAART) between 1996 and 2006 in West Africa. Settings and method. - IeDEA West Africa is a network of HIV care programs established in 2006. We analyzed data from 12 clinical centers treating adults in five countries: Benin, Cote d'Ivoire, Senegal, Gambia, and Mali. Patients 16 years of age or over were included in the study and the following was documented: sex, date of birth and date of initiation of HAART. Results. - We included 14,496 adult patients having started HAART, among these 55 % had started HAART between 2005-2006. The proportion of HIV-infected women increased from 46 % in 1996-2000 to 63 % in 2005-2006. The median age at HAART initiation remained constant: 35 years for women and 40 years for men. The proportion of patients having started HAART with a CD4 count <200 cells/μL was 54 % in 1996-2000, and 64% in 2005-2006. The most frequently prescribed HAART was: AZT/3TC (or d4T/DDI)/IDV (27%) in 1996-2000; d4T (or AZT)/3TC/EFV (49 %) in 2003-2004, and d4T/3TC/NVP (49 %) in 2005-2006. Conclusion. - The first line HAART regimen recommended by WHO was initiated in 83% of cases in 2005-2006. New approaches to an earlier initiation of ART should be explored to reduce mortality in HIV-infected patients on HAART. (C) 2009 Elsevier Masson SAS. All rights reserved.

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**Abstr.** Background. The World Health Organization (WHO) recommends cough as the trigger for tuberculosis screening in human immunodeficiency virus (HIV)-infected patients, with acid-fast bacillus (AFB) smear as the initial diagnostic test. Our objective was to assess the yield and cost of a more intensive tuberculosis screening in HIV-infected patients starting antiretroviral therapy (ART) in Durban, South Africa. Methods. We prospectively enrolled adults, regardless of tuberculosis signs/symptoms, who were undergoing ART training from May 2007 to May 2008. After the symptom screen, patients expectorated sputum for AFB smear, tuberculosis polymerase chain reaction (PCR), and mycobacterial culture. Sensitivity and specificity of different symptoms and tests, alone and in combination, were compared with the reference standard of 6-week tuberculosis culture results. Program costs included personnel, materials, and cultures. Results. Of 1035 subjects, 487 (59%) were female; median CD4 cell count was 100 cells/μL. A total of 210 subjects (20%) were receiving tuberculosis treatment and were excluded. Of the remaining 825 subjects, 158 (19%) had positive sputum cultures, of whom 14 (9%) had a positive AFB smear and 82 (52%) reported cough. The combination of cough, other symptoms, AFB smear, and chest radiograph had 93% sensitivity (95% confidence interval, 88%-97%) and 15% specificity (95% confidence interval, 13%-18%). The incremental cost of intensive screening including culture was $360 per additional tuberculosis case identified. Conclusions. Nearly 20% of patients starting ART in Durban, South Africa, had undiagnosed, culture-positive pulmonary tuberculosis. Despite WHO recommendations, neither cough nor AFB smear were adequately sensitive for screening. Tuberculosis sputum cultures should be performed before ART initiation, regardless of symptoms, in areas with a high prevalence of HIV and tuberculosis.

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**Abstr.** Background. Management of pregnant women with human immunodeficiency virus (HIV) type 2 infection remains unclear because of its low prevalence and important differences from HIV-1. Methods. Pregnant women monoinfected with HIV-2 or HIV-1 and their infants enrolled in the prospective, national, multicenter French Perinatal Cohort between 1986 and 2007. Results.
Overall, 2.6% (223/8660) of mothers were infected with HIV-2, and they accounted for 3.1% (367/11841) of the total births. Most were born in sub-Saharan Africa. A higher proportion of HIV-2-infected mothers than HIV-1-infected mothers had no symptoms, had received no antiretroviral therapy at conception (85.9% vs 66.7%), and had received no antiretroviral therapy during pregnancy (42.8% vs 19.9%), particularly highly active antiretroviral therapy (HAART) (79.7% vs 46.1%), and they had higher CD4 cell counts near delivery (median, 574 vs 452 cells/mm³; P < .01). If antiretroviral therapy was used, it was started at a later gestational age for HIV-2-infected mothers (median, 28 vs 25 weeks; P < .01). HIV-2-infected mothers were more likely to deliver vaginally (67.9% vs 49.3%) and to breastfeed (3.6% vs 0.6%; P < .01), and their infants less frequently received postexposure prophylaxis. In the period 2000-2007, the proportion with viral load <100 copies/mL at delivery was 90.5% of HIV-2-infected mothers, compared with 76.2% of HIV-1-infected mothers (P = .1). There were 2 cases of transmission: 1 case in 1993 occurred following maternal primary infection, and the other case occurred postnatally in 2002 and involved a mother with severe immune deficiency. The mother-to-child transmission rate for HIV-2 was 0.6% (95% confidence interval, 0.07%-2.2%). Conclusions. Care for HIV-2-infected pregnant women rests on expert opinion. The mother-to-child transmission residual rate (0.07%-2.2%) argues for systematic treatment: protease inhibitor-based HAART for women requiring antiretroviral therapy or for primary infection and simplified prevention of mother-to-child transmission in other instances.

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Abstr. Context Protease inhibitor (PI)-based therapy is recommended for infants infected with human immunodeficiency virus (HIV) who were exposed to nevirapine for prevention of mother-to-child HIV transmission. However, there are limitations of continuing PI-based therapy indefinitely and reuse of nevirapine has many advantages. Objective To test whether nevirapine-exposed infants who initially achieve viral suppression with PI-based therapy can maintain viral suppression when switched to nevirapine-based therapy. Design, Setting, and Patients Randomized trial conducted between April 2005 and May 2009 at a hospital in Johannesburg, South Africa, among 195 children who achieved viral suppression less than 400 copies/mL for 3 or more months from a cohort of 323 nevirapine exposed children who initiated PI-based therapy before 24 months of age. Interventions Control group children continued to receive ritonavir-boosted lopinavir, stavudine, and lamivudine (n=99). Switch group children substituted nevirapine for ritonavir-boosted lopinavir (n=96). Main Outcome Measures Children were followed up for 52 weeks after randomization. Plasma HIV-1 RNA of greater than 50 copies/mL was the primary end point. Confirmed viremia greater than 1000 copies/mL was used as a criterion to consider regimen changes for children in either group (safety end point). Results Plasma viremia greater than 50 copies/mL occurred less frequently in the switch group (Kaplan-Meier probability, 0.438; 95% CI, 0.334-0.537) than in the control group (0.576; 95% CI, 0.470-0.668) (P=.02). Confirmed viremia greater than 1000 copies/mL occurred more frequently in the switch group (0.201; 95% CI, 0.125-0.289) than in the control group (0.022; 95% CI, 0.004-0.069) (P<.001). CD4 cell response was better in the switch group (median CD4 percentage at 52 weeks, 34.7) vs the control group (CD4 percentage, 31.3) (P=.04). Older age (relative hazard [RH], 1.71; 95% CI, 1.08-2.72) was associated with viremia greater than 50 copies/mL in the control group. Inadequate adherence (RH, 4.14; 95% CI, 1.18-14.57) and drug resistance (RH, 4.04; 95% CI, 1.40-11.65) before treatment were associated with confirmed viremia greater than 1000 copies/mL in the switch group. Conclusion Among HIV-infected children previously exposed to nevirapine, switching to nevirapine-based therapy after achieving viral suppression with a ritonavir-boosted lopinavir regimen resulted in lower rates of viremia greater than 50 copies/mL than maintaining the primary ritonavir-boosted lopinavir regimen.

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Abstr. Objective: Little is known about the temporal impact of the rapid scale-up of large antiretroviral therapy (ART) services on programme outcomes. We describe patient outcomes [mortality, loss-to-follow-up (LTFU) and retention] over time in a network of South African ART cohorts. Design: Cohort analysis utilizing routinely collected patient data. Methods: Analysis included adults initiating ART in eight public sector programmes across South Africa, 2002-2007. Follow-up was censored at the end of 2008. Kaplan-Meier methods were used to estimate time to outcomes, and proportional hazards models to examine independent predictors of outcomes. Results: Enrolment (n = 44,177, mean age 35 years; 68% women) increased 12-fold over 5 years, with 63% of patients enrolled in the past 2 years. Twelve-month mortality decreased from 9% to 6% over 5 years. Twelve-month LTFU increased annually from 1% (2002/2003) to 13% (2006). Cumulative LTFU increased with follow-up from 14% at 12 months to 29% at 36 months. With each annual addition on ART, failure to retain participants was increasingly attributable to LTFU compared with recorded mortality. At 12 and 36 months, respectively, 80 and 64% of patients were retained. Conclusion: Numbers on ART have increased rapidly in South Africa, but the programme has experienced deteriorating patient retention over time, particularly due to apparent LTFU. This may represent true loss to care, but may also reflect administrative error and lack of capacity to monitor movements in and out of care. New strategies are needed for South Africa and other low-income and middle-income countries to improve monitoring of outcomes and maximize retention in care with increasing programme size.
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Abstr. Background. Mother-to-child transmission of human immunodeficiency virus (HIV) infection was extremely common in southern Africa during the 1990s, and a substantial minority of infected infants have survived to reach adolescence undiagnosed. Studies have shown a high prevalence of HIV infection in hospitalized adolescents who have features associated with long-standing HIV infection, including stunting and frequent minor illnesses. We therefore investigated the epidemiology of HIV infection at the primary care level. Methods. Adolescents (aged 10-18 years) attending two primary care clinics underwent HIV and Herpes simplex virus-2 (HSV-2) serological testing, clinical examination, and anthropometry. All were offered routine HIV counseling and testing. Patients attending for acute primary care (APC) who were HIV infected were asked about their risk factors. Results. Five hundred ninety-four participants were systematically recruited (97% participation), of whom 88 (15%) were attending for antenatal care. HIV infection prevalence was higher among APC attendees than among antenatal care attendees (17% vs 6%; P < .007), but for the prevalence of HSV-2 infection, a marker of sexually acquired HIV, the converse was true (4% vs 14%; P < .002). Seventy (81%) of 86 HIV-positive APC attendees were previously undiagnosed. They had a broad range of presenting complaints, with a median CD4 cell count of 329 cells/μL (interquartile range, 176-485 cells/μL) and a high prevalence of stunting, compared with the corresponding prevalence among HIV-negative attendees (40% vs 12%; P < .001). Maternal transmission was considered to be likely by 69 (80%) of the 86 HIV-positive APC attendees, only one of whom was HSV-2 positive. Conclusions. Unrecognized HIV infection was a common cause of primary care attendance. Routine HIV counseling and testing implemented at the primary care level may provide a simple and effective way of identifying older long-term survivors of mother-to-child transmission before the onset of severe immunosuppression and irreversible complications.
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Abstr. Objective: To assess the mutational patterns and factors associated with baseline drug-resistant HIV-1 present at initiation of first-line antiretroviral therapy (ART) at 3 sites in Lusaka, Zambia, in 2007-2008. Methods: Population sequencing of the HIV-1 pol gene was performed in the PharmAccess African Studies to Evaluate Resistance Monitoring cohort. Drug resistance-associated mutations (DRMs) were identified using the WHO 2009 Surveillance DRM list. Multiple logistic regression was used to assess factors associated with baseline resistance. Results: The overall prevalence of baseline resistance was 5.7% [31 of 548 participants; 95% confidence interval (CI): 3.9 to 7.9]; the prevalence of DRMs associated with nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors was 1.1%, 4.0%, and 1.1%, respectively. Resistance prevalence was 5.2% (27 of 523) in antiretroviral-naive and 16.0% (4 of 25) in antiretroviral-experienced (ie, previous use of ART or antiretroviral prophylaxis for prevention of mother-to-child transmission) participants (P = 0.022). Dual-class resistance to NRTIs and NNRTIs was observed in 0.6% of participants. HIV-1 subtype C was identified in 98.0% (537 of 548) of participants. Prior antiretroviral experience (odds ratio: 4.32, CI: 1.34 to 14.0, P = 0.015) and hemoglobin level (highest tertile versus lowest tertile odds ratio: 2.74, CI: 1.09 to 6.89, P = 0.033) were independently associated with baseline resistance. Conclusions: Baseline resistance may compromise the response to standard NNRTI-based first-line ART in 6% of patients in Lusaka, Zambia. Continuous resistance monitoring is warranted to maintain individual and population-level ART effectiveness.

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Abstr. The Centre for the AIDS Program of Research in South Africa (CAPRISA) 004 trial assessed the effectiveness and safety of a 1% vaginal gel formulation of tenofovir, a nucleotide reverse transcriptase inhibitor, for the prevention of HIV acquisition in women. A double-blind, randomized controlled trial was conducted comparing tenofovir gel (n = 445 women) with placebo gel (n = 444 women) in sexually active, HIV-uninfected 18- to 40-year-old women in urban and rural KwaZulu-Natal, South Africa. HIV serostatus, safety, sexual behavior, and gel and condom use were assessed at monthly follow-up visits for 30 months. HIV incidence in the tenofovir gel arm was 5.6 per 100 women-years (person time of study observation) (38 out of 680.6 women-years) compared with 9.1 per 100 women-years (60 out of 660.7 women-years) in the placebo gel arm (incidence rate ratio = 0.61; P = 0.017). In high adherers (gel adherence > 80%), HIV incidence was 54% lower (P = 0.025) in the tenofovir gel arm. In intermediate adherers (gel adherence 50 to 80%) and low adherers (gel adherence < 50%), the HIV incidence reduction was 38 and 28%, respectively. Tenofovir gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence. No increase in the overall adverse event rates was observed. There were no changes in viral load and no tenofovir resistance in HIV seroconverters. Tenofovir gel could potentially fill an important HIV prevention gap, especially for women unable to successfully negotiate mutual monogamy or condom use.

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Undiagnosed Active Tuberculosis in HIV-Infected Patients Commencing Antiretroviral Therapy [Editorial Commentary]. Clinical Infectious Diseases 2010;51(7):830-832.

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Abstr. Stavudine is no longer recommended for use in first-line antiretroviral therapy (ART), but it remains in high demand worldwide because it is affordable. We report the clinical presentation and incidence of severe hyperlactatemia (SL) in HIV-infected adults who initiated ART between April 2005 and May 2009 in Cote d’Ivoire, West Africa. In a prospective cohort study at the HIV care center affiliated with the National Centre for Blood Transfusion, we used standardized forms to record baseline and follow-up data. We measured serum lactate levels for all adults on ART who showed signs of hyperlactatemia. SL was defined as serum lactate >2.5 mmol/liter. Overall, 806 adults initiated ART. Among the 591 patients (73%) on stavudine-containing regimens, 394 were women (67%); the median pre-ART CD4 count was 150/mm(3) and the median body mass index was 20.9 kg/m(2). These patients were followed for a median of 28 months. We detected SL only among patients taking stavudine. The incidence of SL was 0.55/100 person-years (PY) (95% CI 0.47-0.63) overall and 0.85/100 PY among women (95% CI 0.75-0.95). Among the eight patients with SL, 100% lost >9% of body weight before diagnosis, 100% had serum lactate >4mmol/liter (range 4.2-12.1), 50% had pre-ART BMI >25 kg/m(2), and three patients died (38%), accounting for 6.4% of deaths among patients taking stavudine. As long as HIV clinicians continue to use stavudine in sub-Saharan Africa, they should watch out for acute unexplained weight loss in patients taking ART, particularly among women and patients with high pre-ART BMI.

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Abstr. Point-of-care (POC) CD4 testing was implemented at a stand-alone HIV voluntary testing and counseling centre in Harare, Zimbabwe. To validate the use of this new technology, paired blood samples were collected from 165 patients either by a nurse or a laboratory technician and tested using POC and conventional laboratory CD4 machines. Finger prick (capillary) blood was collected directly into the PIMA POC CD4 Analyzer cartridges and tested immediately, whereas venous blood collected into evacuated tubes was used for CD4 enumeration on a Becton Dickinson FACSCalibur. There was no significant difference in mean absolute CD4 counts between the POC PIMA and Becton Dickinson FACSCalibur platforms (+7.6 cells/mu L; P = 0.72). Additionally, there was no significant difference in CD4 counts between the platforms when run by either a nurse (+18.0 cells/mu L; P = 0.49), or a laboratory technicians (-3.1 cells/mu L; P = 0.93). This study demonstrates that POC CD4 testing can be conducted in a voluntary testing and counseling setting for staging HIV-positive clients. Both nurses and laboratory technicians performed the test accurately, thereby increasing the human resources available for POC CD4 testing. By producing same-day results, POC CD4 facilitates immediate decision-making, patient management and referral and may help improve patient care and retention. POC CD4 may also alleviate testing burdens at traditional central CD4 laboratories, hence improving test access in both rural and urban environments.

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Abstr. Objective: To analyze the critical factors favoring the retention of patients under antiretroviral therapy (ART) in KwaZulu-Natal (KZN), South Africa. Design and Methods: This retrospective study was based on the review of a representative sample of patients who began ART
between March 2004 and May 2006 in 32 public sector sites and were followed up to July 1, 2007. Extended Cox proportional hazard models were used to identify the factors which significantly influenced treatment retention during the first 2 years of treatment. Kaplan-Meyer provided the probabilities of remaining on ART if these factors were present. Results: The 2835 sampled patients corresponded to about 10% of the universe of patients under ART in the 32 sites; 929 (33%) were males, and the median age of the sampled patients was 34 (interquartile range: 28-41). The analysis identified factors that significantly decreased the probability of remaining on ART. Patients’ risk factors were initial CD4 <100 cells per microliter, lack of a telephone contact number, and being male. Sites’ risk factors were the presence of a part time (PT) versus a full time (FT) senior professional nurse, a PT versus FT doctor, and intakes of 200 or more new patients per doctor per year. The probability of remaining on ART declined significantly for each increasing level of workload, but having a FT versus a PT doctor made a significant difference only for level of workload of 200 or more new patients per year. Conclusions: The analysis has identified the conditions influencing retention of ART patients in KZN. This has provided a method to estimate absorption capacity of the ART delivery sites, which is of added value for a sustainable expansion of the ART coverage.

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Abstr. Objective: Cotrimoxazole preventive therapy (CPT) reduces morbidity and mortality in HIV-infected children. The WHO recommends prolonged daily CPT for HIV-infected infants and children. In adults, intermittent CPT has been associated with less adverse events than daily, with increased tolerability and equal efficacy. We investigated the efficacy and tolerability of intermittent CPT compared with daily CPT in HIV-infected children over a 5-year period. Design: A prospective randomized controlled study. Methods: HIV-infected children aged at least 8 weeks were randomized to thrice weekly or daily CPT. Outcome measures were mortality, bacterial infections, hospitalizations and adverse events. Results: Three hundred and twenty-four children (median age 23 months) were followed for 672 child-years; 165 (51%) were randomized to intermittent CPT. Most children (287, 89%) were Centers for Disease Control and Prevention clinical category B or C; 207 (64%) received HAART during the study. Mortality (53 deaths, 16%) was similar in the intermittent CPT compared with the daily CPT group (24 (14%) vs. 29 (18%), hazard ratio 0.75 [95% confidence interval (CI) 0.44-1.29]). The predominant causes of death in both groups were sepsis (17, 32%), pneumonia (13, 25%) or diarrhoea (8, 15%). Intermittent CPT was associated with more bacteraemias [incidence rate ratio 2.36 (95% CI 1.21-4.86)]. Children receiving intermittent CPT also spent more days in hospital [incidence rate ratio 1.15 (95% CI 1.04-1.28)]. The rate of serious adverse events was similar between groups [incidence rate ratio 1.07 (95% CI 0.58-2.02)]. Conclusion: Intermittent CPT was associated with more invasive bacterial disease than daily CPT, but survival was similar. Both regimens were well tolerated. On balance, daily CPT remains preferable to intermittent therapy for HIV-infected children.

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