HIV Care & PMTCT in Resource-Limited Settings

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Back Issues on Line

prepared by the Bordeaux Working Group

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**Abstr.** Background: Stakeholders in HIV/AIDS care currently use different programmes for provision of antiretroviral therapy (ART) in Uganda. It is not known which of these represents the best value for money. Objective: To compare the cost effectiveness of home-based care (HBC), facility-based care (FBC) and mobile clinic care (MCC) for provision of ART in Uganda. Methods: Incremental cost-effectiveness analysis was performed using decision and Markov modeling of adult AIDS patients in WHO Clinical Stage 3 and 4 from the perspective of the Ugandan healthcare system. The main outcome measures were cost (year 2008 values), life expectancy in life-years (LY) and the incremental cost-effectiveness ratio (ICER) measured as cost per QALY or LY gained over 10 years. Results: Ten-year mean undiscounted life expectancy was lowest for FBC (3.6 LY), followed by MCC (4.3 LY) and highest for HBC (5.3 LY), while the mean discounted QALYs were also lowest for FBC (2.3), followed by MCC (2.9) and highest for HBC (3.7). The 10-year mean costs per patient were lowest for FBC ($US3212), followed by MCC ($US4782) and highest for HBC ($US7033). The ICER was lower for MCC versus FBC ($US2241 per LY and $US2615 per QALY) than for HBC versus MCC ($US2251 per LY and $US2814 per QALY). FBC remained cost effective in univariate and probabilistic sensitivity analyses. Conclusions: FBC appears to be the most cost-effective programme for provision of ART in Uganda. This analysis supports the implementation of FBC for scale-up and sustainability of ART in Uganda. HBC and MCC would be competitive only if there is increased access, increased adherence or reduced cost.

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**Abstr.** Objectives: To determine the prevalence and type of birth defects among infants following exposure to efavirenz-based antiretroviral therapy (EFV-based ART) during pregnancy. Methods: A Pregnancy Registry was established to enable prospective follow-up of women taking EFV-based ART. In women who conceived on EFV-based ART, EFV was switched with another drug if they presented during the first trimester but was continued if they presented at or after 14 weeks' gestation. Pregnant women needing lifelong ART were commenced on EFV-based ART from 14 weeks' gestation onwards. Infants were followed up for 6 weeks after birth. Results: Between January 2006 and December 2008, 623 ART-naive pregnant women initiated EFV-based ART in the second/third trimester and 195 women conceived on EFV-based ART. Birth defects were observed in 16 of 623 live births [2.60%; 95% confidence interval (CI) 1.5-4.2] and in six of 184 live births (3.3%; 95% CI 1.2-7.0) from women exposed to EFV in the second/third trimester and first trimester, respectively. The prevalence of birth defects was not significantly different between the first and second/third trimester EFV exposure (prevalence ratio 1.27; 95% CI 0.50-3.20; \( P=0.301 \)). Conclusion: No significant increase in the prevalence of birth defects following exposure to EFV-based ART in the first trimester was observed in this cohort. However, the limited number of first trimester EFV-exposed infants precludes definitive conclusions on the teratogenicity or safety of EFV.

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**Abstr.** Context: Introduction of highly active antiretroviral therapy has significantly decreased mortality in HIV-1-infected adults and children. Although an increase in non-HIV-related mortality has been noted in adults, data in children are limited. Objectives: To evaluate changes in causes and risk factors for death among HIV-1-infected children in Pediatric AIDS Clinical Trials Group 219/219C. Design, Setting, and Participants: Multicenter, prospective cohort study designed to evaluate long-term
outcomes in HIV-1-exposed and infected US children. There were 3553 HIV-1-infected children enrolled and followed up between April 1993 and December 2006, with primary cause of mortality identified in the 298 observed deaths. Main Outcome Measures: Mortality rates per 100 child-years overall and by demographic factors; survival estimates by birth cohort; and hazard ratios for mortality by various demographic, health, and antiretroviral treatment factors were determined. Results: Among 3553 HIV-1-infected children followed up for a median of 5.3 years, 298 deaths occurred. Death rates significantly decreased between 1994 and 2000, from 7.2 to 0.8 per 100 person-years, and remained relatively stable through 2006. After adjustment for other covariates, increased risk of death was identified for those with low CD4 and AIDS-defining illness at entry. Decreased risks of mortality were identified for later birth cohorts, and for time-dependent initiation of highly active antiretroviral therapy (hazard ratio 0.54, P < 0.001). The most common causes of death were "End-stage AIDS" (N = 48, 16%) and pneumonia (N = 41, 14%). The proportion of deaths due to opportunistic infections (OIs) declined from 37% in 1994-1996 to 24% after 2000. All 01 mortality declined during the study period. However, a greater decline was noted for deaths due to Mycobacterium avium complex and cryptosporidium. Deaths from "End-stage AIDS," sepsis and renal failure increased. Conclusions: overall death rates declined from 1993 to 2000 but have since stabilized at rates about 30 times higher than for the general US pediatric population. Deaths due to OIs have declined, but non-AIDS-defining infections and multiorgan failure remain major causes of mortality in HIV-1-infected children.

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Abstr. Objective: To evaluate clinical, immunological and virological consequences of CD4-guided antiretroviral therapy (ART) planned treatment interruptions (PTIs) compared with continuous therapy in children with chronic HIV infection in the Paediatric European Network for Treatment of AIDS 11 trial. Design: This was a multicentre, 72-week, open, randomized, phase 11 trial. Methods: One hundred and nine children with HIV-RNA below 50 copies/ml and CD4% of at least 30% (2-6 years) or at least 25% and CD4 cell count of at least 500 cells/mu l (7-15 years) were randomized to continuous therapy (53) or PTI (56). In PTI, ART was restarted if confirmed CD4% was less than 20% or more than 48 weeks had been spent off ART. The primary outcome was Centers for Disease Control and Prevention (CDC) stage C event, death or CD4% less than 15% (and CD4 cell count less than 200 cells/mu l for children aged 7-15years). Results: At baseline, median (interquartile range) age was 9 (6-12) years, CD4% 37% (33-41), CD4 cell count 966 (793-11258) cells/mu l, nadir CD41/0 before combination ART 18% (10-27), time on ART 6 (3-6) years and 26% were CDC stage C. After median (range) 130 (33-180) weeks of follow-up, 4 versus 48% of time was spent off ART in continuous therapy and PTI, respectively. No child died or had a new CDC stage C event; one (2%) continuous therapy versus four (7%) PTI children had a primary outcome based on CD4%/cell count (P=0.2). Lower nadir CD4% predicted faster CD4% decline after stopping ART. Younger age and higher nadir CD4% predicted being off ART for at least 48 weeks and better CD4% recovery following PTI. Conclusion: In this first paediatric trial of PTI, there were no serious clinical outcomes. Younger children had better CD4% recovery after PTIs. Immunology substudies and long-term follow-up in Paediatric European Network for Treatment of AIDS 11 trial are ongoing. Further research into the role of treatment interruption in children is required, particularly, as guidelines now recommend early ART for all infected infants.

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**Abstr.** Background Directly observed therapy has been recommended to improve adherence for patients with HIV infection who are on highly active antiretroviral therapy, but the benefit and cost-effectiveness of this approach has not been established conclusively. We did a systematic review and meta-analysis of randomised trials of directly observed versus self-administered antiretroviral treatment. Methods We did duplicate searches of databases (from inception to July 27, 2009), searchable websites of major HIV conferences (up to July, 2009), and lay publications and websites (March-July, 2009) to identify randomised trials assessing directly observed therapy to promote adherence to antiretroviral therapy in adults. Our primary outcome was virological suppression at study completion. We calculated relative risks (95% CIs), and pooled estimates using a random-effects method. Findings 12 studies met our inclusion criteria; four of these were done in groups that were judged to be at high risk of poor adherence (drug users and homeless people). Ten studies reported on the primary outcome (n=1862 participants); we calculated a pooled relative risk of 1.04 (95% CI 0.91-1.20, p=0.55), and noted moderate heterogeneity between the studies (I-2= 53.8%, 95% CI 0-75.7, p=0.0247) for directly observed versus self-administered treatment. Interpretation Directly observed antiretroviral therapy seems to offer no benefit over self-administered treatment, which calls into question the use of such an approach to support adherence in the general patient population.

**Notes:** See Myers editorial

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**Abstr.** To evaluate the virological response and to describe the resistance profiles in the case of failure after 6 months of first-line highly active antiretroviral therapy (HAART) in HIV-1-infected children living in resource-limited settings. Ninety-seven HIV-1-infected children who started two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) (mainly zidovudine/lamivudine/nevirapine) in Mali were prospectively studied. Virological failure (VF) was defined as loss to follow-up, death or HIV-1 RNA viral load (VL) of > 400 copies/mL at 6 months. When VL was > 50 copies/mL, a genotypic resistance test was performed. Among the 97 children, median age at antiretroviral initiation was 31 months and the majority were in WHO clinical (77.3%) and immunological (70.1%) stage III or IV. At month 6, 44% of children had VL > 400 copies/mL (61% VF). Among the children with detectable VL, 30/37 genotypic resistance tests were available, 8 with wild-type viruses and 22 with resistance mutations (73%): 19 M184V/I, 21 NNRTI mutations and only 3 thymidine analogue mutations (TAMs) (K70R, D67N and L210W in three distinct viruses). At failure, 6/8 children with wild-type viruses had a VL of < 1000 copies/mL whereas 21/22 with resistant viruses had a VL of > 1000 copies/mL. Under NNRTI-based regimens, early detection of VF could allow the reinforcement of adherence when VL was < 1000 copies/mL, because in most of these cases no resistance mutations were detected, or a change to a protease inhibitor-based regimen if VL was > 1000 copies/mL. The low frequency of TAMs suggests that most NRTIs can be used in a second-line regimen after early failure.

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**Abstr.** Despite the enormous progress made in scaling up antiretroviral therapy (ART) in sub-Saharan Africa, many challenges remain, not least of which are the identification and management of patients who have failed first-line therapy. Less than 3% of patients are receiving second-line treatment at present, whereas 15-25% of patients have detectable viral loads 12 months or more into treatment, of
whom a substantial proportion might have virological failure. We discuss the reasons why virological ART failure is likely to be under-diagnosed in the routine health system, and address the current difficulties with standard recommended second-line ART regimens. The development of new diagnostic tools for ART failure, in particular a point-of-care HIV viral-load test, combined with simple and inexpensive second-line therapy, such as boosted protease-inhibitor monotherapy, could revolutionise the management of ART failure in resource-limited settings.

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**Selection of the text:** In developing countries, breast-feeding is both the cornerstone of child survival and the cause of about one-third of all infant HIV infections. Moreover, the same economic and development inequities that make breast-feeding so critical to infant survival in these settings also make formula feeding inaccessible, unfeasible, unaffordable, unsustainable, and unsafe (ie, not AFASS) for most families. This poignant dilemma has resulted in emotive and sometimes polarising debate within the public health community as we have wrestled to quantify these competing risks, test interventions to reduce them, and modify policy as our understanding improves. Four articles in this issue of the JAIDS shed new light on this issue.

These articles demonstrate that in these settings, provision of feeding interventions for HIV-exposed infants focused only during the first few months of life is not long enough; breast-feeding continues to provide substantial protective benefits against gastroenteritis and mortality into the second year of life.


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**Abstr.** Background Identification of new ways to increase access to antiretroviral therapy in Africa is an urgent priority. We assessed whether home-based HIV care was as effective as was facility-based care. Methods We undertook a cluster-randomised equivalence trial in Jinja, Uganda. 44 geographical areas in nine strata, defined according to ratio of urban and rural participants and distance from the clinic, were randomised to home-based or facility-based care by drawing sealed cards from a box. The trial was integrated into normal service delivery. All patients with WHO stage IV or late stage III disease or CD4-cell counts fewer than 200 cells per μL who started antiretroviral therapy between Feb 15, 2005, and Dec 19, 2006, were eligible, apart from those living on islands. Follow-up continued until Jan 31, 2009. The primary endpoint was virological failure, defined as RNA more than 500 copies per mL after 6 months of treatment. The margin of equivalence was 9% (equivalence limits 0.69-1.45). Analyses were by intention to treat and adjusted for baseline CD4-cell count and study stratum. This
trial is registered at http://isrctn.org, number ISRCTN 17184129. Findings 859 patients (22 clusters) were randomly assigned to home and 594 (22 clusters) to facility care. During the first year, 93 (11%) receiving home care and 66 (11%) receiving facility care died, 29 (3%) receiving home and 36 (6%) receiving facility care withdrew, and 8 (1%) receiving home and 9 (2%) receiving facility care were lost to follow-up. 117 of 729 (16%) in home care had virological failure versus 80 of 483 (17%) in facility care: rates per 100 person-years were 8.19 (95% CI 6.84-9.82) for home and 8.67 (6.96-10.79) for facility care (rate ratio [RR] 1.04, 0.78-1.40; equivalence shown). Two patients from each group were immediately lost to follow-up. Mortality rates were similar between groups (0.95 [0.71-1.28]). 97 of 857 (11%) patients in home and 75 of 592 (13%) in facility care were admitted at least once (0.91, 0.64-1.28). Interpretation This home-based HIV-care strategy is as effective as is a clinic-based strategy, and therefore could enable improved and equitable access to HIV treatment, especially in areas with poor infrastructure and access to clinic care.

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Notes. Special issue devoted to "Learning and doing: operational research and access to HIV treatment in Africa"

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Abstr. Background: The objective of the study was to evaluate whether providing antiretroviral therapy (ART) integrated in antenatal care (ANC) clinics resulted in a greater proportion of treatment-eligible women initiating ART during pregnancy compared with the existing approach of referral to ART. Analysis design and methods: The evaluation used a stepped-wedge design and included all HIV-infected, ART-eligible pregnant women in eight public sector clinics in Lusaka district, Zambia. Main outcome indicators were the proportion of treatment-eligible pregnant women enrolling into HIV care within 60 days of HIV diagnosis, and of these, the proportion initiating ART during pregnancy. Adjusted odds ratios (AORs) and confidence intervals (CIs) for enrollment and initiation proportions were estimated through a logistic regression model accounting for clinical site Cluster and time effects. Results: Between 16 July 2007 and 31 July 2008, 13 917 women started antenatal care more than 60 days before the intervention rollout and constituted the control cohort; 17619 started antenatal care after ART integrated into ANC and constituted the intervention cohort. Of the 1566 patients found eligible for ART, a greater proportion enrolled while pregnant and within the 60 days of HIV diagnosis in the intervention cohort (376/846, 44.41%) compared with the control cohort (181/716, 25.3%), AOR 2.06, 95% CI (1.27-3.34); and initiated ART while pregnant in the intervention cohort (278/846, 32.9%) compared with the control cohort (103/716, 14.4%), AOR 2.01, 95%, CI (1.37-2.95). Conclusion: An integrated ART in ANC strategy doubled the proportion of treatment-eligible women initiating ART while pregnant.

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Abstr. Background. Early weaning has been recommended to reduce postnatal human immunodeficiency virus (HIV) transmission. We evaluated the safety of stopping breast-feeding at different ages for mortality of uninfected children born to HIV-infected mothers. Methods. During a trial of early weaning, 958 HIV-infected mothers and their infants were recruited and followed up from birth to 24 months postpartum in Lusaka, Zambia. One-half of the cohort was randomized to wean abruptly
at 4 months, and the other half of the cohort was randomized to continue breast-feeding. We examined associations between uninfected child mortality and actual breast-feeding duration and investigated possible confounding and effect modification. Results. The mortality rate among 749 uninfected children was 9.4% by 12 months of age and 13.6% by 24 months of age. Weaning during the interval encouraged by the protocol (4-5 months of age) was associated with a 2.03-fold increased risk of mortality (95% confidence interval [CI], 1.13-3.65), weaning at 6-11 months of age was associated with a 3.54-fold increase (95% CI, 1.68-7.46), and weaning at 12-18 months of age was associated with a 4.22-fold increase (95% CI, 1.59-11.24). Significant effect modification was detected, such that risks associated with weaning were stronger among infants born to mothers with higher CD4(+) cell counts (1350 cells/μL). Conclusion. Shortening the normal duration of breast-feeding for uninfected children born to HIV-infected mothers living in low-resource settings is associated with significant increases in mortality extending into the second year of life. Intensive nutritional and counseling interventions reduce but do not eliminate this excess mortality.

Notes: See Shapiro editorial

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Abstr. Background. Despite poor primary health care systems, free antiretroviral therapy (ART) has been available in China for >5 years. Virologic outcomes in Chinese patients receiving ART have not been described on a national level. Methods. A multistage cluster design was used in 8 provinces to randomly select patients who had been receiving first-line ART for at least 6 months, who were stratified into 3 treatment-duration groups. Viral load testing and patient interviews were conducted, and data were linked with national treatment database information. Collected data were analyzed for association with viral suppression by means of multivariate modeling. Adequate viral suppression was defined as a viral load of <400 copies/mL. Results. Of 5256 patients receiving ART, 3984 met the eligibility criteria, among whom 1153 were analyzed. Overall, 72% demonstrated viral suppression, and 82%, 73%, and 67% of the participants receiving ART for 6-11, 12-23, and >= 24 months, respectively, experienced viral suppression (P < .001). In a multivariate model, treatment given at locations other than county-level hospitals was less likely to achieve viral suppression, with greater odds for inadequate virologic response found at village clinics (odds ratio [OR], 5.4; 95% confidence interval [CI], 2.9-10.1), township health centers (OR, 3.1; 95% CI, 1.7-5.6), and public health clinics (OR, 3.1; 95% CI, 1.7-5.6). Patients receiving didanosine-based regimens were more likely to experience an inadequate virologic response than were those receiving lamivudine-based regimens (OR, 3.9; 95% CI, 2.7-5.7). Conclusions. China's national ART program is largely successful at suppressing viral load. Care received outside of hospitals and regimens containing didanosine were associated with less favorable virologic outcomes.

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Abstr. Objective: To determine the rates and causes of first antiretroviral treatment changes in HIV-infected adults in Cote d'Ivoire. Methods: We evaluated adults who initiated antiretroviral treatment in an outpatient clinic in Abidjan. We recorded baseline and follow-up data, including drug prescriptions and reasons for changing to alternative first-line regimens (drug substitution for any reason but failure) or second-line regimens (switch for failure). Results: Two thousand and twelve HIV-infected adults (73%, women) initiated antiretroviral treatment. At baseline, 9% of all patients were on treatment for tuberculosis and 3% of women were pregnant. First-line antiretroviral treatment consisted of two nucleoside reverse transcriptase inhibitors (58% stavudine-lamivudine, 42%, zidovudine-lamivudine)
and efavirenz (63%), nevirapine (32%) or indinavir (5%). Median follow-up time was 16.9 months. During this time, 205 (10%) patients died and 261 (13%) were lost to follow-up. Overall, the rate of treatment modifications was 20.7/100 patient-years. The most common modifications were drug substitutions for intolerance (12.4/100 patient-years), pregnancy (4.5/100 patient-years) and tuberculosis (2.5/100 patient-years). The rates of intolerance-related substitutions were 17.9/100 patient-years for stavudine, 3.9/100 patient-years for zidovudine and 0.1/100 patient-years for efavirenz. Twenty percent of efavirenz substitutions resulted from pregnancy and 18% of nevirapine Substitutions were related to tuberculosis treatment. Conclusion: During the first months following antiretroviral treatment initiation, a third of all treatment changes occurred for reasons other than intolerance to the drug or treatment failure. In Africa, drug forecasting is crucial to ensuring the success of HIV treatment programmes. Drugs that do not require interruptions during pregnancy or tuberculosis treatment should be made more readily available as first-line drugs in sub-Saharan Africa.

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**Abstr.** Background HIV antiretroviral therapy (ART) is often managed without routine laboratory monitoring in Africa; however, the effect of this approach is unknown. This trial investigated whether routine toxicity and efficacy monitoring of HIV-infected patients receiving ART had an important long-term effect on clinical outcomes in Africa. Methods In this open, non-inferiority trial in three centres in Uganda and one in Zimbabwe, 3321 symptomatic, ART-naïve, HIV-infected adults with CD4 counts less than 200 cells per μL starting ART were randomly assigned to laboratory and clinical monitoring (LCM; n=1659) or clinically driven monitoring (CDM; n=1662) by a computer-generated list. Haematology, biochemistry, and CD4-cell counts were done every 12 weeks. In the LCM group, results were available to clinicians; in the CDM group, results (apart from CD4-cell count) could be requested if clinically indicated and grade 4 toxicities were available. Participants switched to second-line ART after new or recurrent WHO stage 4 events in both groups, or CD4 count less than 100 cells per μL (LCM only). Co-primary endpoints were new WHO stage 4 HIV events or death, and serious adverse events. Non-inferiority was defined as the upper 95% confidence limit for the hazard ratio (HR) for new WHO stage 4 events or death being no greater than 1.18. Analyses were by intention to treat. This study is registered, number ISRCTN13968779. Findings Two participants assigned to CDM and three to LCM were excluded from analyses. 5-year survival was 87% (95% CI 85-88) in the CDM group and 90% (88-91) in the LCM group, and 122 (7%) and 112 (7%) participants, respectively, were lost to follow-up over median 4.9 years’ follow-up. 459 (28%) participants receiving CDM versus 356 (21%) LCM had a new WHO stage 4 event or died (6.94 [95% CI 6.33-7.60] vs 5.24 [4.72-5.81] per 100 person-years; absolute difference 1.70 per 100 person-years [0.87-2.54]; HR 1.31 [1.14-1.51]; p=0.0001). Differences in disease progression occurred from the third year on ART, whereas higher rates of switch to second-line treatment occurred in LCM from the second year. 283 (17%) participants receiving CDM versus 260 (16%) LCM had a new serious adverse event (HR 1.12 [0.94-1.32]; p=0.19), with anaemia the most common (76 vs 61 cases). Interpretation ART can be delivered safely without routine laboratory monitoring for toxic effects, but differences in disease progression suggest a role for monitoring of CD4-cell count from the second year of ART to guide the switch to second-line treatment. Funding UK Medical Research Council, the UK Department for International Development, the Rockefeller Foundation, GlaxoSmithKline, Gilead Sciences, Boehringer-Ingelheim, and Abbott Laboratories.

**Notes:** See Phillips editorial

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Abstr. Background. We investigated virological response and the emergence of resistance in the Nevirapine or Abacavir (NORA) substudy of the Development of Antiretroviral Treatment in Africa (DART) trial. Methods. Six hundred symptomatic antiretroviral-naive human immunodeficiency virus (HIV)-infected adults (CD4 cell count, <200 cells/mm(3)) from 2 Ugandan centers were randomized to receive zidovudine-lamivudine plus abacavir or nevirapine. Virology was performed retrospectively on stored plasma samples at selected time points. In patients with HIV RNA levels >1000 copies/mL, the residual activity of therapy was calculated as the reduction in HIV RNA level, compared with baseline. Results. Overall, HIV RNA levels were lower in the nevirapine group than in the abacavir group at 24 and 48 weeks (P < .001), although no differences were observed at weeks 4 and 12. Virological responses were similar in the 2 treatment groups for baseline HIV RNA level <100,000 copies/mL. The mean residual activity at week 48 was higher for abacavir in the presence of the typically observed resistance pattern of thymidine analogue mutations (TAMs) and M184V (1.47 log(10) copies/mL) than for nevirapine with M184V and nonnucleoside reverse-transcriptase inhibitor mutations, whether accompanied by TAMs (0.96 log(10) copies/mL) or not (1.18 log(10) copies/mL). Conclusions. There was more extensive genotypic resistance in both treatment groups than is generally seen in resource-rich settings. However, significant residual activity was observed among patients with virological failure, particularly those receiving zidovudine-lamivudine plus abacavir.

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Abstr. Background. Symptomatic hyperlactataemia and lactic acidosis (SHLA) are potentially life-threatening complications associated with stavudine (d4T), an antiretroviral therapy (ART) drug widely used in developing countries. Methods. Cases comprised all symptomatic patients with measured lactates >= 5 mmol/L referred to a South African hospital between August 2003 and November 2005. Matched controls were selected according to facility and duration on ART. Results. Seventy-one cases and 142 controls were included in the study. The majority of cases presented between 6 and 18 months on ART. Female sex (adjusted odds ratio (AOR) 23.4; 95% confidence interval (CI) 4.0-136.6), a baseline weight between 60 and 75 kg (AOR 4.5; 95% CI 1.4-14.1) or, in particular, >= 75 kg (AOR 19.4; 95% CI 4.1-82.5) at ART initiation and gaining >= 6 kg in the first 3 months on therapy (AOR 3.5; 95% CI 1.3-9.5) were independent risk factors identifying patients who may subsequently develop SHLA. Weight loss of >= 2 kg (AOR 6.1; 95% CI 2.0-18.3), a rise in alanine aminotransferase (ALT) >= 10 U/L (AOR 3.1; 95% CI 1.1-8.9), the presence of at least one of three major symptoms (vomiting, nausea and abdominal pains) of SHLA (AOR 12.6; 95% CI 3.3-47.2) and peripheral neuropathy (AOR 3.4; 95% CI 1.1-9.8) were the clinical parameters that were most able to identify patients with early manifestations of SHLA. Conclusions. This is the first case-control study for SHLA in Southern Africa. Given these findings, we advise that stavudine is avoided in overweight women. Weight loss, a rise in ALT, peripheral neuropathy and/or gastrointestinal symptoms should prompt healthcare workers to assess for SHLA, especially at between 6 and 18 months on ART.

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Abstr. Objective: To estimate whether HIV-infected pregnant women were at an increased risk of hepatotoxicity when taking nevirapine (NVP)-containing regimens compared with HIV-infected pregnant women taking antiretroviral therapy (ART) not containing NVP. Methods: This analysis
included HIV-infected pregnant women on ART from two multicenter, prospective cohorts: the Women and Infants Transmission Study and the International Maternal Pediatric Adolescent AIDS Clinical Trials protocol P1025. Multivariate Cox proportional hazards regression models were used to investigate the association between NVP use and hepatotoxicity. NVP use was dichotomized as use or no use and further categorized according to ART exposure history. We investigated two Outcomes: any liver enzyme elevation (LEE) (grade 1–4) and severe LEE (grade 3–4). Results: A total of 1229 women with ART use during pregnancy were studied, 218 (17.71%) of whom received NVP. Among the women receiving NVP, 137 (62.8%) were NVP naive. Twenty-nine women (13.31%) who received NVP developed any LEE and one (0.5%) developed severe LEE. Of the 1011 women on non-NVP regimens, 145 (14.3%) developed any LEE and 14 (1.4%) developed severe LEE. There were no maternal deaths. In univariate models, LEE was not significantly associated with CD4(+) cell count above 250 cells/μl or NVP use. In adjusted multivariate models, no significant increased risk of LEE (any or severe) in women taking NVP was detected as compared to those taking other ART regardless of prior exposure history. Conclusion: We did not observe an increased risk of hepatotoxicity among HIV-infected pregnant women on NVP versus other ART, including women who were ART naive.

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Abstr. Background: Pregnancy-limited antiretroviral therapy (PLAT) drastically reduces HIV-1 transmission to the newborn, but may select for antiretroviral drug resistance mutations in mothers. Methods: We evaluated antiretroviral-naive, HIV-1-infected pregnant women who received PLAT between 1998 and 2005, and had 2-month or 6-month postpartum plasma samples available with HIV-1 RNA levels more than 500 copies/ml. Postpartum drug resistance mutation rates were assessed blindly using population sequencing and allele-specific PCR (ASPCR) of the M184V, K103N and D30N mutations. Factors associated with selection of drug resistance mutations were investigated. Results: One hundred and forty-six women were included. All women received zidovudine and lamivudine during pregnancy; 76% also received nelfinavir and 8.2% nevirapine. Resistance data were available from 114 women (78%). Postpartum rates of single-class, dual-class, and triple-class resistance were, respectively, 43, 6.1 and 0% (63.2, 10.5 and 1.7% by ASPCR). In women receiving dual or triple PLAT, respectively, postpartum M184V/1 rates were 65% (95% by ASPCR) and 28.7% (51.6% by ASPCR), respectively (P<0.01). Postpartum nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance rates among women receiving nevirapine were 25% for K103N (37.5% by ASPCR) and 12.5% for Y188C. Protease inhibitor resistance rates in women receiving nelfinavir were 1.1% for D30N (1.1%, by ASPCR) and 1.1%, for L90M. Dual versus triple PLAT and prolonged zidovudine exposure were associated with selection of M184V. Nevirapine use and length of zidovudine and lamivudine exposure were associated with selection of K103N. Conclusion: PLAT is associated with frequent selection of resistance to drugs with low-genetic barrier. Routine postpartum genotypic resistance testing may be useful to guide future treatment decisions in mothers.

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Abstr. Cryptococcosis is a global invasive mycosis associated with significant morbidity and mortality. These guidelines for its management have been built on the previous Infectious Diseases Society of America guidelines from 2000 and include new sections. There is a discussion of the management of cryptococcal meningoencephalitis in 3 risk groups: (1) human immunodeficiency virus (HIV)-infected individuals, (2) organ transplant recipients, and (3) non-HIV-infected and nontransplant hosts. There are specific recommendations for other unique risk populations, such as children, pregnant women, persons in resource-limited environments, and those with Cryptococcus gattii infection.
Recommendations for management also include other sites of infection, including strategies for pulmonary cryptococcosis. Emphasis has been placed on potential complications in management of cryptococcal infection, including increased intracranial pressure, immune reconstitution inflammatory syndrome (IRIS), drug resistance, and cryptococcomas. Three key management principles have been articulated: (1) induction therapy for meningoencephalitis using fungicidal regimens, such as a polyene and flucytosine, followed by suppressive regimens using fluconazole; (2) importance of early recognition and treatment of increased intracranial pressure and/or IRIS; and (3) the use of lipid formulations of amphotericin B regimens in patients with renal impairment. Cryptococcosis remains a challenging management issue, with little new drug development or recent definitive studies. However, if the diagnosis is made early, if clinicians adhere to the basic principles of these guidelines, and if the underlying disease is controlled, then cryptococcosis can be managed successfully in the vast majority of patients.

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Abstr. Objectives: We assessed mortality associated with immunologic and virologic patterns of response at 6 months of highly active antiretroviral therapy (HAART) in HIV-infected individuals from resource-limited countries in Africa and South America. Methods: Patients who initiated HAART between 1996 and 2007, aged 16 years or older, and had at least 1 measurement (HTV-1 RNA plasma viral load or CD4 cell count) at 6 months of therapy (3-9 month window) were included. Therapy response was categorized as complete, discordant (virologic only or immunologic only), and absent. Associations between 6-month response to therapy and all-cause mortality were assessed by Cox proportional hazards regression. Robust standard errors were calculated to account for intrasite correlation. Results: A total of 7160 patients, corresponding to 15,107 person-years, were analyzed. In multivariable analysis adjusted for age at HAART initiation, baseline clinical stage and CD4 cell count, year of HAART initiation, clinic, occurrence of an AIDS-defining condition within the first 6 months of treatment, and discordant and absent responses were associated with increased risk of death. Conclusions: Similar to reports from high-income countries, discordant immunologic and virologic responses were associated with intermediate risk of death compared with complete and no response in this large cohort of HIV-1 patients from resource-limited countries. Our results support a recommendation for wider availability of plasma viral load testing to monitor antiretroviral therapy in these settings.
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**Abstr.** Background: The HIV prevalence in Malawi is 12% and Kamuzu Central Hospital (KCH), in the capital Lilongwe, is the main provider of adult and paediatric HIV services in the central region. The Lighthouse at KCH offers opt-in HIV testing and counselling (HTC) for adults and children. In June 2004, Lighthouse was the first clinic to provide free antiretroviral treatment (ART) in the public sector, but few children accessed the services. In response, provider-initiated HIV testing and counselling (PITC) and an ART clinic were introduced at the paediatric department at KCH in Quarter 4 (Q4) 2004.

**Methods:** We analysed prospectively collected, aggregated data of quarterly reports from Q1 2003 to Q4 2006 from HTC centre registers, ART registers and clinic registrations at the ART clinics of both Lighthouse and the paediatric department. By comparing data of both facilities before (Q1 2003 to Q3 2004), and after the introduction of the services at the paediatric department (Q4 2004 to Q4 2006), we assessed the effect of this intervention on the uptake of HIV services for children at KCH.

**Results:** Overall, 3971 children were tested for HIV, 2428 HIV-infected children were registered for care and 1218 started ART. Between the two periods, the median (IQR) number of children being tested, registered and starting ART per quarter rose from 101 (53-109) to 358 (318-440), 56 (50-82) to 226 (192-234) and 18 (8-23) to 139 (115-150), respectively. The median proportion of tested clients per quarter that were children rose from 3.8% (2.7-4.3) to 9.6% (8.8 to 10.0) \((p = 0.0009)\) and the proportion of ART starters that were children rose from 6.9% (4.9-9.3) to 21.1% (19.2-24.2) \((p = 0.0036)\). The proportion of registered children and adults starting ART each quarter increased similarly, from 26% to 53%, and 20% to 52%, respectively. Conclusions: Implementation of PITC and integration of ART services within the paediatric ward are likely to be the main reasons for improved access to HTC and ART for children at KCH, and can be recommended to other hospitals with paediatric inpatients in resource limited settings with high HIV prevalence.

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