HIV Care & PMTCT in Resource-Limited Settings

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prepared by the Bordeaux Working Group

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Abstr. Objective: To describe the spectrum of central nervous system (CNS) disease during the first year of antiretroviral therapy (ART) and to determine the contribution of neurological immune reconstitution inflammatory syndrome (IRIS). Design: A prospective observational cohort study conducted over a 12-month period at a public sector referral hospital in South Africa. Methods: HIV-seropositive patients who developed new or recurrent neurological or psychiatric symptom(s) or sign(s) within the first year of starting ART were enrolled. We used the number of patients starting ART in the referral area in the preceding year as the denominator to calculate the incidence of referral for neurological deterioration. Patients with delirium and peripheral neuropathy were excluded. Outcome at 6 months was recorded. Results: Seventy-five patients were enrolled. The median nadir CD4(+) cell counts was 64 cells/µl. Fifty-nine percent of the patients were receiving antituberculosis treatment. The incidence of referral for CNS deterioration in the first year of ART was 23.3 cases [95% confidence interval (CI), 18.3-29.2] per 1000 patient-years at risk. CNS tuberculosis (n = 27, 36%), cryptococcal meningitis (n = 18, 24%), intracerebral space occupying lesions (other than tuberculoma) (n = 10, 13%) and psychosis (n = 9, 12%) were the most frequent diagnoses. Paradoxical neurological IRIS was diagnosed in 21 patients (28%), related to tuberculosis in 16 and cryptococcosis in five. At 6 months, 23% of the patients had died and 20% were lost to follow-up. Conclusion: Opportunistic infections, notably tuberculosis and cryptococcosis, were the most frequent causes for neurological deterioration after starting ART. Neurological IRIS occurred in over a quarter of patients.


Abstr. OBJECTIVE To describe how district-wide access to HIV/AIDS care was achieved and maintained in Thyolo District, Malawi. METHOD In mid-2003, the Ministry of Health and Medecins Sans Frontieres developed a model of care for Thyolo district (population 587 455) based on decentralization of care to health centres and community sites and task shifting. RESULTS After delegating HIV testing and Counseling to lay counsellors, uptake of testing increased from 1300 tests per month in 2003 to 6500 in 2009. Shifting responsibility for antiretroviral therapy (ART) initiations to non-physician clinicians almost doubled ART enrolment, with a majority of initiations performed in peripheral health centres. By the end 2009, 23 261 people had initiated ART of whom 11 042 received ART care at health-centre level. By the end of 2007, the universal access targets were achieved, with nearly 9000 patients alive and on ART. The average annual cost for achieving these targets was (sic)2.6 per inhabitant/year. CONCLUSION The Thyolo programme has demonstrated the feasibility of district-wide access to ART in a setting with limited resources for health. Expansion and decentralization of HIV/AIDS service-capacity to the primary care level, combined with task shifting, resulted in increased access to HIV services with good programme outcomes despite staff shortages.

**Abstr.** Background. There are scarce data on the long-term survival of human immunodeficiency virus (HIV)-infected children receiving antiretroviral therapy (ART) in lower-middle income countries beyond 2 years of follow-up. Methods. Previously untreated children who initiated ART on meeting immunological and/or clinical criteria were followed in a prospective cohort in Thailand. The probability of survival up to 5 years from initiation was estimated using Kaplan-Meier methods, and factors associated with mortality were assessed using Cox regression analyses. Results. Five hundred seventy-eight children received ART; of these, 111 (19.2%) were followed since birth. At start of ART (baseline), the median age was 6.7 years, 128 children (22%) were aged <2 years, and the median CD4 cell percentage was 7%. Median duration of follow-up was 53 months; 42 children (7%) died, and 38 (7%) were lost to follow-up. Age <12 months, low CD4 cell percentage, and low weight-for-height z score at ART initiation were independently associated with mortality (P < .001). The probability of survival among infants aged < 12 months at baseline was 84.3% at 1 year and 76.7% at 5 years of ART, compared with 95.7% and 94.8%, respectively, among children aged >= 1 year. Low CD4 cell percentage and wasting at baseline had a strong association with mortality among older children but weak or no association among infants. Conclusions. Children who initiated ART as infants after meeting immunological and/or clinical criteria had a high risk of mortality which persisted beyond the first year of therapy. Among older children, those with severe wasting or low CD4 cell percentage at treatment initiation were at high risk of mortality during the first 6 months of therapy. These findings support the scale-up of early HIV diagnosis and immediate treatment in infants, before advanced disease progression in older children.

**HATIP.** New joint guidelines on IPT and intensified case-finding from WHO. Decembre 21, 2010(170).

**Abstr.** New guidelines on prevention of TB in people with HIV through use of isoniazid preventive therapy and intensified case-finding.


**Abstr.** OBJECTIVES: To estimate the rates and timing of mother to infant transmission of HIV associated with breast feeding in mothers who seroconvert postnatally, and their breast milk and plasma HIV loads during and following seroconversion, compared with women who tested HIV positive at delivery. DESIGN: Prospective cohort study. SETTING: Urban Zimbabwe. PARTICIPANTS: 14 110 women and infants enrolled in the Zimbabwe Vitamin A for Mothers and Babies (ZVITAMBO) trial (1997-2001). MAIN OUTCOME MEASURES: Mother to child transmission of HIV, and breast milk and maternal plasma HIV load during the postpartum period. RESULTS: Among mothers who tested HIV positive at baseline and whose infant tested HIV negative with polymerase chain reaction (PCR) at six weeks (n=2870), breastfeeding associated transmission was responsible for an average of 8.96 infant infections per 100 child years of breast feeding (95% CI 7.92 to 10.14) and varied little over the breastfeeding period. Breastfeeding associated transmission for mothers who seroconverted postnatally (n=334) averaged 34.56 infant
infections per 100 child years (95% CI 26.60 to 44.91) during the first nine months after maternal infection, declined to 9.50 (95% CI 3.07 to 29.47) during the next three months, and was zero thereafter. Among women who seroconverted postnatally and in whom the precise timing of infection was known (<=90 days between last negative and first positive test; n=51), 62% (8/13) of transmissions occurred in the first three months after maternal infection and breastfeeding associated transmission was 4.6 times higher than in mothers who tested HIV positive at baseline and whose infant tested HIV negative with PCR at six weeks. Median plasma HIV concentration in all mothers who seroconverted postnatally declined from 5.0 log(10) copies/mL at the last negative enzyme linked immunosorbent assay (ELISA) to 4.1 log(10) copies/mL at 9-12 months after infection. Breast milk HIV load in this group was 4.3 log(10) copies/mL 0-30 days after infection, but rapidly declined to 2.0 log(10) copies/mL and <1.5 log(10) copies/mL by 31-90 days and more than 90 days, respectively. Among women whose plasma sample collected soon after delivery tested negative for HIV with ELISA but positive with PCR (n=17), 75% of their infants were infected or had died by 12 months. An estimated 18.6% to 20.4% of all breastfeeding associated transmission observed in the ZVITAMBO trial occurred among mothers who seroconverted postnatally. CONCLUSIONS: Breastfeeding associated transmission is high during primary maternal HIV infection and is mirrored by a high but transient peak in breast milk HIV load. Around two thirds of breastfeeding associated transmission by women who seroconvert postnatally may occur while the mother is still in the “window period” of an antibody based test, when she would test HIV negative using one of these tests. Trial registration Clinical trials.gov

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Abstr. We aimed to assess the patterns and dynamics of mobile phone usage amongst an antiretroviral treatment (ART) cohort in rural Uganda and ascertain its feasibility for improving clinic attendance. A cross-sectional study of clients on ART exploring their access to mobile phones and patterns of use was employed. Clinic attendances for antiretroviral drug refills were then monitored prospectively over 28 weeks in 176 patients identified in the cross-sectional survey who had access to mobile phones and had given consent to be contacted. Patients were contacted via voice calls or text messages to remind them about their missed clinic appointments. Of the 276 patients surveyed, 177 (64%) had access to mobile phones with all but one willing to be contacted for missed visits reminders. Of the 560 total scheduled clinic appointments 62 (11%) were missed visits. In 79% of episodes in which visits were missed, patients presented for treatment within a mean duration of 2.2 days (SD = 1.2 days) after mobile phone recall. Access to mobile phones was high in this setting. Privacy and confidentiality issues were not considered deterrents. Mobile phones have a potential for use in resource-constrained settings to substantially improve the clinical management of HIV/AIDS.


Abstr. Background: Ukraine has the highest HIV prevalence (1.6%) and is facing the fastest growing epidemic in Europe. Our objective was to describe the clinical, immunological and virological characteristics, treatment and response in vertically HIV-
infected children living in Ukraine and followed from birth. Methods: The European Collaborative Study (ECS) is an ongoing cohort study, in which HIV-1 infected pregnant women are enrolled and followed in pregnancy, and their children prospectively followed from birth. ECS enrolment in Ukraine started in 2000 initially with three sites, increasing to seven sites by 2009. Results: A total of 245 infected children were included in the cohort by April 2009, with a median age of 23 months at most recent follow-up; 33% (n = 77) had injecting drug using mothers and 85% (n = 209) were infected despite some use of antiretroviral prophylaxis for prevention of mother-to-child transmission. Fifty-five (22%) children had developed AIDS, at a median age of 10 months (IQR = 6-19). The most prevalent AIDS indicator disease was Pneumocystis jiroveci pneumonia (PCP). Twenty-seven (11%) children had died (median age, 6.2 months). Overall, 108 (44%) children had started highly active antiretroviral treatment (HAART), at a median 18 months of age; median HAART duration was 6.6 months to date. No child discontinued HAART and 92% (100/108) remained on their first-line HAART regimen to date. Among children with moderate/severe immunosuppression, 36% had not yet started HAART. Among children on HAART, 71% (69/97) had no evidence of immunosuppression at their most recent visit; the median reduction in HIV RNA was 4.69 log10 copies/mL over a median of 10 months treatment. From survival analysis, an estimated 94%, 84% and 81% of children will be alive and AIDS-free at 6, 12 and 18 months of age, respectively. However, survival increased significantly over time: estimated survival rates to 12 months of age were 87% for children born in 2000/03 versus 96% for those born in 2004/08. Conclusion: One in five children had AIDS and one in ten had died. The half of children who received HAART has responded well and survival has significantly improved over time. Earlier diagnosis and prompt initiation of HAART remain key challenges.

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Abstr. Background: The concurrent use of nevirapine-based antiretroviral therapy (ART) and rifampin-containing anti-tuberculosis regimens for the treatment of HIV and tuberculosis (TB) is common in resource-limited countries. Long-term outcomes of this concurrent treatment are unknown. Methods: Seventy HIV-infected patients receiving rifampin for active TB (TB group) and 70 HIV-monoinfected patients (control group) were enrolled to receive nevirapine 400 mg/day-based ART. All were followed through 4 years of ART. Plasma HIV-1 RNA and CD4 cell counts were monitored every 12 weeks until 96 weeks, and every 24 weeks thereafter. Results: Of the 140 patients, the median (interquartile range (IQR)) CD4 count was 31 (14-79) cells/mm(3) and median (IQR) plasma HIV-1 RNA was 5.6 (5.2-5.9) log copies/ml at baseline. Thirty-nine (55.7%) patients in the TB group were diagnosed with extrapulmonary/disseminated TB. The median duration of concurrent administration of nevirapine and rifampin was 5.4 (4.6-6.1) months. By intention-to-treat analysis, the percentage of patients who achieved HIV-1 RNA <50 copies/ml was 52.9% in the TB group and 50% in control group (p = 0.866; odds ratio 1.121, 95% confidence interval 0.578-2.176); median (IQR) CD4 counts were 352 (271-580) cells/mm(3) and 425 (308-615) cells/mm(3) in the corresponding groups (p = 0.238). The proportion of ART discontinuation due to any reason at 1, 2, 3, and 4 years was 21%, 34%, 37%, and 46% in the TB group and 21%, 36%, 43%, and 49% in the control group, respectively (p = 0.651). The 4-year mortality rate was 6.4% in both groups. Conclusions: Nevirapine-based ART is an option for HIV-infected patients who receive rifampin in resource-limited countries or those who cannot tolerate efavirenz.

**Abstr.** Objectives: To evaluate the effect of extended antenatal triple antiretroviral therapy (ART) on infant outcomes. Design: Retrospective cohort study using pooled data from health clinics in Malawi and Mozambique from July 2005 to December 2009. Methods: Computerized records of 3273 HIV-infected pregnant women accessing Drug Resource Enhancement Against AIDS and Malnutrition centers were reviewed. ART regimens consisted of nevirapine-based HAART as of 14-25 weeks gestation until 6 months postpartum. Infant infection was determined at 1, 6 and 12 months of age by branched DNA. Results: A total of 3071 pregnancies resulted in 3148 live births. Lost to follow-up, infant deaths and HIV-1 infection rates at 1 and 12 months were 1.3 and 11.5, 0.8 and 6.7 and 0.8 and 2.0, respectively. Infant HIV-1-free survival at 12 months was 92.5%. Mother-to-child transmission and/or infant deaths correlated with length of maternal antenatal ART by multivariate analysis at 1, 6 and 12 months: 14% in women with more than 30 days of triple antenatal ART and 6.9% in mothers receiving at least 90 days of antenatal ART, P=0.001. Fifty percent of 54 episodes of transmission occurred in women with higher CD4 cell counts (>350 cells/μl). Infant mortality was 67/1000, lower than background rates (78-100/1000). Growth failure (weight-for-age Z score < -2) was present in 8% of infants around birth, 6% at 6 months, 23% at 12 months (lower than country-specific rates). Conclusion: Extended antenatal ART is protective against adverse infant outcomes up to 12 months of age even in children born to mothers with higher CD4 cell counts.


**Abstr.** Background: In countries with high rates of chronic HBV, the World Health Organization recommends screening all HIV-infected adults for hepatitis B surface antigen (HBsAg) before initiating antiretroviral therapy (ART), and starting HIV-HBV-coinfected patients on regimens containing lamivudine (3TC) or emtricitabine (FTC) plus tenofovir disoproxil fumarate (TDF). Here, we estimated the prevalence of untreated HIV-infected adults with negative serum HBsAg and detectable plasma HBV DNA in Cote d'Ivoire. Methods: This was a cross-sectional survey. We tested all untreated HIV type-1 (HIV-1)-infected adults with negative serum HBsAg and detectable plasma HBV DNA in Cote d'Ivoire. Methods: This was a cross-sectional survey. We tested all untreated HIV type-1 (HIV-1)-infected adults with CD4(+) T-cell counts <500 cells/mm(3) for HBsAg, hepatitis B core antibodies (anti-HBc) and HBsAg antibodies (anti-HBs). We measured plasma HBV DNA in patients who tested positive for HBsAg and/or anti-HBc. Results: We included 495 adults, of whom 73% were women. Median CD4(+)-T-cell count was 329 cells/mm(3) and median HIV RNA was 4.9 log(10) copies/ml. Overall, 63 (13%) patients had chronic hepatitis B (HBsAg-positive), 115 (23%) had never been exposed to HBV (HBsAg-negative, anti-HBc-negative and anti-HBs-negative), 108 (22%) had signs of cured infection (anti-HBc-positive and anti-HBs-positive) and 209 (42%) had isolated anti-HBc (HBsAg-negative, anti-HBc-positive and anti-HBs-negative). Of these, 51 (10%) had detectable HBV DNA. Median HBV DNA level was 5.2 log(10) copies/ml (interquartile range [IQR] 3.2-8.8) for patients with chronic hepatitis and 2.2 log(10) copies/ml (IQR 1.8-2.7) for those with occult HBV infection. Conclusions: Among ART-naive HIV-1-infected African adults, 13% were HBsAg-positive and 42% had isolated anti-HBc, including 10% who had occult HBV. The clinical implications of high occult HBV prevalence are unknown. Future studies should assess the benefits of routine use of 3TC or FTC plus TDF as first-line ART in African settings, where HBV DNA tests are unavailable.

Abstr. Objective The aim of the study was to evaluate the evolution of plasma adipokines and lipodystrophy in protease inhibitor-naive vertically HIV-infected children on highly active antiretroviral therapy (HAART). Patients and methods We carried out a multicentre retrospective study of 27 children during 48 months on HAART. Every 3 months, CD4+ T-cells, CD8+ T-cells, viral load (VL), cholesterol, triglycerides, lipoproteins and adipokines were measured. Diagnoses of lipodystrophy were based on clinical examinations. Results We found hypercholesterolaemia (>200 mg/dL) in 9.5, 30.4, 21.7, 14.3 and 13.3% of the subjects at months 0, 12, 24, 36 and 48, respectively, and hypertriglyceridaemia (>170 mg/dL) in 14.3, 8.3, 13, 4.5 and 0% at the same time-points. During follow-up, and especially at the end of the study, we found an increase in plasma resistin levels and significant increases in total plasminogen activator inhibitor type 1, adiponectin, and leptin levels (P<0.05). We also observed slight increases in the leptin/adiponectin ratio, homeostatic model assessment, and C-peptide values during the first months of treatment followed by a moderate decrease or stabilization after 24 months on HAART. At the end of the study, 12 of the 27 children (44.4%) had lipodystrophy, 10 (37%) had lipoatrophy, and 11 (40.7%) had lipohypertrophy; and only three of the 27 children (11.1%) were diagnosed with lipoatrophy and lipohypertrophy with scores >= 2. Conclusions HIV-infected children showed an increase in serum adipokine levels, but this was not associated with the emergence of lipodystrophy during 48 months on HAART.


Abstr. Background: The identification and management of first-line antiretroviral therapy (ART) failure is a key challenge for HIV programs in resource-limited settings. In 2008, the National AIDS Control Organisation, India piloted a national strategy to provide second-line ART. We assessed the National AIDS Control Organisation second-line ART evaluation algorithm. Methods: Adult patients who had received 6 months or more of standard first-line ART were referred for second-line ART evaluation if they demonstrated CD4 decline to pre-ART values, CD4 drop to less than 50% of peak on-treatment value, failure to achieve CD4 greater than 100 c/mm(3), or development of a new World Health Organization Stage 3 or 4 AIDS-defining illness. Patients received HIV RNA testing, and those with HIV RNA 10,000 c/mL or greater qualified to switch to second-line ART. World Health Organization-defined clinical and CD4 criteria for ART failure were compared against virologic failure criteria. Results: Between January and June 2008, 154 patients met criteria for evaluation. Of 122 (79%) patients who had HIV RNA testing, 87 (71%) had viral load 10,000 c/mL or greater and were recommended to start second-line ART, 29 (24%) had viral load less than 400 c/mL, and six (5%) had viral load between 400 and 10,000 c/mL. The positive predictive value of World Health Organization clinical/immunologic criteria to detect virologic failure was 71% (95% confidence interval, 63% to 79%). Conclusions: Second-line ART was initiated in the public sector in India using an approach combining clinical and immunologic evaluation with confirmation of virologic failure. Almost 25% of patients who met clinical/immunologic failure criteria demonstrated virologic suppression. Inclusion of targeted HIV RNA testing in the evaluation of treatment failure can prevent unnecessary switches to second-line ART.
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Abstr. HIV has increased the incidence of tuberculosis (TB) by up to sevenfold in African countries, but antiretroviral therapy (ART) reduces the incidence of AIDS-related TB. We use a mathematical model to investigate the short-term and long-term impacts of ART on the incidence of TB, assuming that people are tested for HIV once a year, on average, and start ART at a fixed time after HIV seroconversion or at a fixed CD4(+) cell count. We fit the model to trend data on HIV prevalence and TB incidence in nine countries in sub-Saharan Africa. If HIV-positive people start ART within 5 y of seroconversion, the incidence of AIDS-related TB in 2015 will be reduced by 48% (range: 37-55%). Long-term reductions depend sensitively on the delay to starting ART. If treatment is started 5, 2, or 1 y after HIV seroconversion, or as soon as people test positive, the incidence in 2050 will be reduced by 66% (range: 57-80%), 95% (range: 93-96%), 97.7% (range: 96.9-98.2%) and 98.4% (range: 97.8-98.9%), respectively. In the countries considered here, early ART could avert 0.71 +/- 0.36 [95% confidence interval (CI)] million of 3.4 million cases of TB between 2010 and 2015 and 5.8 +/- 2.9 (95% CI) million of 15 million cases between 2015 and 2050. As more countries provide ART at higher CD4(+) cell counts, the impact on TB should be investigated to test the predictions of this model.