HIV Care & PMTCT in Resource-Limited Settings

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Back Issues on Line

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Abstr. Background. The efficacy of various antiretroviral (ARV) therapy regimens for human immunodeficiency virus type 2 (HIV-2) infection remains unclear. HIV-2 is intrinsically resistant to the nonnucleoside reverse-transcriptase inhibitors and to enfuvirtide and may also be less susceptible than HIV-1 to some protease inhibitors (PIs). However, the mutations in HIV-2 that confer ARV resistance are not well characterized. Methods. Twenty-three patients were studied as part of an ongoing prospective longitudinal cohort study of ARV therapy for HIV-2 infection in Senegal. Patients were treated with nucleoside reverse-transcriptase inhibitor (NRTI)- and PI (indinavir)-based regimens. HIV-2 pol genes from these patients were genotyped, and themutations predictive of resistance in HIV-2 were assessed. Correlates of ARV resistance were analyzed. Results. Multiclass drug-resistance mutations (NRTI and PI) were detected in strains in 30% of patients; 52% had evidence of resistance to at least 1 ARV class. The reverse-transcriptase mutations M184V and K65R, which confer high-level resistance to lamivudine and emtricitabine in HIV-2, were found in strains from 43% and 9% of patients, respectively. The Q151M mutation, which confers multinucleoside resistance in HIV-2, emerged in strains from 9% of patients. HIV-1 - associated thymidine analogue mutations (M41L, D67N, K70R, L210W, and T215Y/F) were not observed, with the exception of K70R, which was present together with K65R and Q151M in a strain from 1 patient. Eight patients had HIV-2 with PI mutations associated with indinavir resistance, including K7R, I54M, V62A, I82F, L90M, L99F; 4 patients had strains with multiple PI resistance - associated mutations. The duration of ARV therapy was positively associated with the development of drug resistance (P = .02). Nine (82%) of 11 patients with HIV-2 with detectable ARV resistance had undetectable plasma HIV-2 RNA loads (<1.4 log(10) copies/mL), compared with 3 (25%) of 12 patients with HIV-2 with detectable ARV resistance (P = .009). Patients with ARV-resistant virus had higher plasma HIV-2 RNA loads, compared with those with non-ARV-resistant virus (median, 1.7 log(10) copies/mL [range, <1.4 to 2.6 log(10) copies/mL] vs. <1.4 log(10) copies/mL [range, <1.4 to 1.6 log(10) copies/mL], P = .003). Conclusions. HIV-2-infected individuals treated with ARV therapy in Senegal commonly have HIV-2 mutations consistent with multiclass drug resistance. Additional clinical studies are required to improve the efficacy of primary and salvage treatment regimens for treating HIV-2 infection.

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Abstr. Background: In HIV type-1-infected patients starting highly active antiretroviral therapy (HAART), the prognostic value of haemoglobin when starting HAART, and of changes in haemoglobin levels, are not well defined. Methods: We combined data from 10 prospective studies of 12,100 previously untreated individuals (25% women). A total of 4,222 patients (35%) were anaemic: 131 patients (1.1%) had severe (<8.0 g/dl), 1,120 (9%) had moderate (male 8.0-<11.0 g/dl and female 8.0-<10.0 g/dl) and 2,971 (25%) had mild (male 11.0-<13.0 g/dl and female 10.0-<12.0 g/dl) anaemia. We separately analysed progression to AIDS or death from baseline and from 6 months using Weibull models, adjusting for Cl T-cell count, age, sex and other variables. Results:
During 48,420 person-years of follow-up 1,448 patients developed at least one AIDS event and 857 patients died. Anaemia at baseline was independently associated with higher mortality: the adjusted hazard ratio (95% confidence interval) for mild anaemia was 1.42 (1.17-1.73), for moderate anaemia 2.56 (2.07-3.18) and for severe anaemia 5.26 (3.55-7.81). Corresponding figures for progression to AIDS were 1.60 (1.37-1.86), 2.00 (1.66-2.40) and 2.24 (1.46-3.42). At 6 months the prevalence of anaemia declined to 26%. Baseline anaemia continued to predict mortality (and to a lesser extent progression to AIDS) in patients with normal haemoglobin or mild anaemia at 6 months. Conclusions: Anaemia at the start of HAART is an important factor for short- and long-term prognosis, including in patients whose haemoglobin levels improved or normalized during the first 6 months of HAART.

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Abstr. Background Highly active antiretroviral therapy (HAART) is reported to cause insulin resistance among adults, but effects on children are less clear. We attempted to describe the prevalence of insulin resistance among HIV-infected children receiving HAART. Methods Insulin resistance was assessed at 96 weeks of treatment with nonnucleoside reverse transcriptase inhibitor (NNRTI)-based HAART (nevirapine or efavirenz with stavudine and lamivudine) among children in Chiang Mai, Thailand. Insulin resistance was defined as homeostasis model assessment for insulin resistance (HOMA-IR) >= 3.16, fasting c-peptide >= 4.40 ng/mL or fasting insulin >= 25.0 μU/mL. Impaired fasting glucose (IFG) was defined as glucose >= 110 mg/dL. Measurements were analysed for associations with age, lipodystrophy, treatment regimen and clinical data. Results The prevalence of insulin resistance was 6.5%; no child had IFG. Those with insulin resistance were older with higher body mass index. Children >= 10 years had higher IIOMA-IR, c-peptide and insulin, but no difference was seen in the frequency of insulin resistance. No associations between insulin resistance and lipodystrophy or treatment regimen were detected. Conclusions Insulin resistance is uncommon among children receiving NNRTI-based HAART and is unrelated to lipodystrophy.

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Abstr. Background: Prevention of Mother-to-Child Transmission of HIV (PMTCT) is among the key HIV prevention strategies in Zimbabwe. A decrease in use of antenatal care (ANC) services with an increase in home deliveries is affecting the coverage of PMTCT interventions in a context of accelerated economic crisis. The main objective was to evaluate acceptability and feasibility of reinforcing the role of traditional birth attendants (TBAs) in family and child health services through their participation in PMTCT programmes in Zimbabwe. Methods: A community based cross-sectional survey was undertaken using multistage cluster sampling in two rural districts through interviews and focus group discussions among women who delivered at home with a TBA, those who had an institutional delivery and TBAs. Results: 45% of TBAs interviewed knew the principles of PMTCT and 8% delivered a woman with known HIV-positive status in previous year. Of the complete package of PMTCT services, more than 75% of TBAs
agreed to participate in most activities with the exception of performing a blood test (17%), accompanying new-borns to closest health centre to receive medication (15%) and assisting health centres in documentation of the link ANC-PMTCT services (18%). Women who delivered at home were less likely to have received more than one ANC service or have had contact with a health centre compared to women who delivered in a health centre (91.0% vs 72.6%; P < 0.001). Also, 63.6% of the women who delivered in a health centre had the opportunity to choose the place of delivery compared to 39.4% of women who delivered at home (P < 0.001). More than 85% of women agreed that TBAs could participate in all activities related to a PMTCT programme with the exception of performing a blood test for HIV. Concerns were highlighted regarding confidentiality of the HIV-serostatus of women. Conclusion: Although the long-term goal of ANC service delivery in Zimbabwe remains the provision of skilled delivery attendance, PMTCT programmes will benefit from complementary approaches to prevent missed opportunities. TBAs are willing to expand their scope of work regarding activities related to PMTCT. There is a need to reinforce their knowledge on MTCT prevention measures and better integrate them into the health system.

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**Abstr.** The combination of one non-nucleoside reverse transcriptase inhibitor (NNRTI) with two nucleoside reverse transcriptase inhibitors is a validated first-line antiretroviral (ARV) therapy. The once-daily combination of lamivudine, tenofovirDF and nevirapine has not been evaluated in a clinical trial. Randomized, open-label, multicentre, non-inferiority trial comparing lamivudine, tenofovirDF and nevirapine once daily (Group 2) with zidovudine/lamivudine and nevirapine twice daily (Group 1), in naive HIV-1-infected patients with a CD4 count < 350/mm(3). We planned to enrol 250 patients. As of May 2006, 71 patients had been enrolled (35 in Group 1 and 36 in Group 2) and an unplanned interim analysis was done. The groups were comparable at baseline: median CD4 count was 195 and 191/mm(3) and median plasma viral load was 4.9 log(10) and 5.01 log(10), respectively, in Groups 1 and 2. Eight early non-responses (22.2%) were observed, all in Group 2, while two later viral rebounds occurred. Resistance genotypes for the nine Group 2 failing patients showed the mutations M184V/I (n = 3), K65R (n = 6), one or more NNRTI resistance mutations in all cases. At baseline, the nine Group 2 patients who failed had higher median plasma viral load (5.4 log(10)) and lower median CD4 count (110/mm(3)) than the other Group 2 patients (4.7 log(10), P = 0.002 and 223/mm(3), P = 0.004). Nevirapine trough concentrations were not different between the two groups, nor between patients with full viral suppression or those who failed in Group 2. Due to slow recruitment, and those results, the steering committee decided to stop the trial at 12 months. In ARV-naive HIV-1-infected patients, the once-daily lamivudine, tenofovirDF and nevirapine regimen resulted in a high rate of early virological failures. The reasons for the failures remain unclear.

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**Abstr.** Background: Recently, a new tablet formulation of the widely used HIV protease inhibitor lopinavir/ritonavir was licensed. Here, we present a pilot study of the pharmacokinetics of the new adult tablet formulation taken once daily in children. Methods: Lopinavir pharmacokinetics of the new adult tablet formulation were evaluated in 15 HIV type-1-infected children between 4 and 15 years of age. A target dose of 460/115 mg/m(2) was administered once daily. Plasma concentrations of lopinavir over the course of 24 h were determined with a validated HPLC method. Results: The median lopinavir dose was 498 mg/m(2) (range 424-548). The mean +/- SD for lopinavir area under the 24 h curve was 217.9 +/- 44.9 mg/l center dot h, the maximum concentration was 14.8 +/- 2.4 mg/l and the concentration 24 h after intake was 3.1 +/- 2.6 mg/l. The half-life of lopinavir was 5.8 +/- 4.5 h and the median time to maximum concentration was 5.8 h (range 1.8-12.2). Overall, the tablet formulation resulted in greater exposure to lopinavir with less variability compared with the soft-gel capsule formulation. All children treated with the new adult tablet formulation had undetectable viral loads (<50 copies/ml) during 24 weeks follow-up. Conclusions: The tablet formulation could probably result in improved lopinavir dosing and increases the feasibility of once-daily lopinavir/ritonavir-based regimens in children.

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CROI 2009. A lower-income country perspective. Adapted from NAM ([http://www.aidsmap.com](http://www.aidsmap.com)).

The conference started this year with an opening symposium on “The Global Epidemic” and the 3rd Ngaly-Mann Lecture delivered by Glenda Gray and James McIntyre (Perinatal HIV Research Unit, University of the Witwatersrand, Soweto, South Africa). All these presentations are available as webcast sessions ([http://www.retroconference.org/2009/data/files/webcast.htm](http://www.retroconference.org/2009/data/files/webcast.htm)).

The following abstracts highlight some of the key studies reported this year at CROI and that are relevant from a lower-income country perspective (All abstracts are available at [http://www.retroconference.org/AbstractSearch/Default.aspx?Conf=18](http://www.retroconference.org/AbstractSearch/Default.aspx?Conf=18)).

For the first time, a microbicide reduces HIV infections by 30% in the HPTN 035 trial. (Abstract 48LB) This randomized trial used the candidate microbicide PRO2000 (polynaphthalene sulphonate) and involved 3099 women in Malawi, South Africa, Zambia, Zimbabwe and the USA. PRO2000 prevented about a third of potential infections in women who used PRO2000, compared with women who used a placebo gel or no gel at all. These results were not statistically significant. Investigators could therefore only call the microbicide ‘promising’ rather than ‘effective’. Other trial results are due later this year.

Nearly half of new infant HIV infections in Botswana may result from mothers infected during pregnancy or after delivery (Abstract 91). This represents an enormous opportunity for further testing and prevention interventions that are currently being missed. The authors recommendations based on their study findings include routine retesting for HIV-negative pregnant women and provision of late PMTCT. However, the best interventions for such late maternal HIV infections are unknown, and need to be investigated.
ART use in mothers with low CD4 cell counts reduces breastfeeding transmission five-fold after a 14-week course of infant HIV prophylaxis was stopped, according to a study performed in Malawi. However, ART use did not significantly reduce transmission risk in mothers with CD4 cell counts above 250 cells/mm³ (Abstract 92). Maternal resistance to nevirapine following a single dose of this drug is reduced by AZT/ddI or one month’s ART. Two Thai studies (Abstracts 95aLB and 95bLB) have provided further evidence that short courses of more than one antiretroviral drug after delivery almost eliminate the risk of nevirapine resistance in mothers when it is used to prevent mother-to-child transmission, thus preserving nevirapine as an option for maternal treatment when eventually needed.

Kaletra-based ART is superior to nevirapine-based ART for women already exposed to single-dose nevirapine. An antiretroviral regimen based on the boosted protease inhibitor lopinavir/ritonavir (Kaletra, or Aluvia) was indeed significantly more effective than a nevirapine-containing regimen in mothers previously exposed to single-dose nevirapine, according to results from the randomised Optimum Combination Therapy After Nevirapine Exposure (OCTANE) study that was designed to determine whether nevirapine-based ART would be effective in women previously exposed to single-dose nevirapine, or whether a regimen using Kaletra would prove more effective. OCTANE enrolled 243 HIV-positive women in seven African countries. However the difference in response to the two regimens was less pronounced among women who started treatment at a longer interval after exposure to single-dose nevirapine. There was no difference in the risk of treatment failure between the regimens among women who started ART more than two years after exposure to single-dose nevirapine (Abstract 94LB).

Antiretroviral treatment is associated with a lower risk of heterosexual HIV transmission in African serodiscordant couples, according to findings from Uganda, Rwanda and Zambia. In a new study from Rakai, Uganda, (Abstract 52a) based on stable, mixed-status heterosexual couples, sexual transmission was greatly reduced in those who were on ART. Similar data from larger cohorts in the cities of Lusaka and Kigali (abstract 52bLB) with a total of 2993 serodiscordant couples followed up between 2002 and late 2008 concluded that three- to fivefold lower rates of HIV transmission were seen in mixed-status heterosexual couples on ART. However, both presenters also stressed that ART should not be considered a primary means of HIV prevention, but part of a combination approach to prevention. In addition, most HIV-positive persons in Africa are either not aware of their status, or are not on ART because they do not qualify (based on CD4 cell counts).

Oral fluconazole prophylaxis safely prevents invasive cryptococcal disease (meningitis) in people with advanced HIV, according to a randomised, double-blind, placebo-controlled trial conducted in over 1500 participants in rural Uganda (Abstracts 32 and 36cLB). Corticosteroid therapy improves outcomes in people who develop tuberculosis (TB)-immune reconstitution inflammatory syndrome (TB-IRIS) after starting ART using a four-week course of the anti-inflammatory corticosteroid, prednisone without causing an excess of steroid side-effects or other infections, according to a randomised placebo-controlled trial conducted in Cape Town (Abstract 34).

People on TB treatment who started a once-daily ART regimen of nevirapine/ddI/3TC were significantly more likely to fail ART than those who started on a once-daily regimen of efavirenz/ddI/3TC, according to a randomised prospective study from Chennai, India. In fact, the nevirapine arm performed so poorly that the study’s Data Safety and Monitoring Board ended accrual to that study arm and closed the study ahead of schedule (Abstract 35).

Doubling the dose of lopinavir/ritonavir (Kaletra) in children with HIV on rifampicin-based TB treatment fails to provide adequate lopinavir concentrations, according to a drug interaction study conducted in Cape Town, South Africa (Abstract 98). Findings from two Ugandan studies suggest that home-based HIV counselling and testing may augment traditional HIV counselling and testing services in important ways both by increasing acceptance and uptake of HIV testing, but also by impacting attitudes toward HIV at a population level (Abstracts 138 and 139).
Longitudinal surveillance of a poor rural community in Kwazulu-Natal, South Africa (Abstract 173), indicates that HIV incidence remained high from 2003 through 2007, despite prevention activities in the region, with almost half of all new infections occurring in people who had already received one negative test result through local voluntary testing and counselling services. The high rate of seroconversions in young people indicated a need to reach young people while still at school, although results of trials of such interventions in Tanzania have failed to show a reduction in HIV incidence (Abstract 170LB).

Finally, two collaborative cohort studies (Abstracts 71 and 72LB) have examined the value of early HIV antiretroviral treatment with only partial coherence. Publications in high-quality journal are due in April and will be presented later in the Intelligence Report.