HIV Care & PMTCT in Resource-Limited Settings

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Back Issues on Line

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**Abstr.** Objective: Viral resistance occurs with a high frequency after single-dose nevirapine. We aimed to evaluate the tolerance and resistance profiles of a combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) given to HIV-1-infected delivering women and their newborns. Design: An open-label phase I/II trial in Cambodia, Cote d'Ivoire and South Africa. Methods: HIV-1-infected pregnant women received zidovudine from the enrollment until the beginning of labor, when single-dose nevirapine and two tablets of TDF/FTC were given. One daily tablet of TDF/FTC was then administered for 7 days postpartum. All infants received single-dose nevirapine with single-dose TDF (13 mg/kg) and single-dose FTC (2 mg/kg) and 1 week of zidovudine. Mothers and infants were followed for 2 months. Serious adverse events, kinetic of maternal plasma HIV-1 RNA, pediatric HIV infection and genotypic resistance and viral subtype were assessed. Results: Thirty-six HIV-1-infected pregnant women were enrolled: median age 28 years (interquartile range: 26-31 years), median CD4 cell count 462 cells/μl (interquartile range: 376-632) and median HIV-1 RNA 3.7 log(10) copies/ml (interquartile range: 2.95-4.11). Two infants had clinical serious adverse events, including one who died (neonatal sepsis). One transient grade 3 neutropenia and two grade 3/4 hyperbilirubinemia were also reported in neonates. One HIV pediatric in-utero infection was diagnosed (2.8%; 95% confidence interval 0-15.4%). Genotypic viral resistance to nevirapine was detected in one mother out of 34 (2.9%) at one month postpartum, but was also detectable at enrollment. Conclusion: The combination of TDF/FTC to delivering women and their neonates appears well tolerated and to minimize the occurrence of nevirapine viral resistance.


**Abstr.** Many children in sub-Saharan Africa die from AIDS, not having accessed HIV testing and care. Children of adult antiretroviral therapy (ART) patients are a target group for HIV testing in order to increase access to care, but the HIV test coverage of this group in Malawi is unknown. In a cross-sectional survey of 832 patients at a large urban ART clinic in Blantyre, we found that 81.2% of 1223 children and 37.7% of 488 spouses of adult ART patients were reportedly not HIV tested. Wives of male patients were significantly less frequently HIV tested than husbands of female patients (53.0% vs. 72.4%, p<0.0001). Children under the age of 8 years (adjusted odds ratios [aOR] 2.76), children of female patients (aOR 2.53) and of patients whose partner had been HIV tested (aOR 2.87) were significantly more likely to have been tested for HIV. More attention needs to be given to provider initiated testing of children and spouses of ART patients.


**Abstr.** Background: KwaZulu-Natal is the South African province worst affected by HIV and the focus of early modeling studies investigating strategies of antiretroviral treatment (ART) delivery. The reality of antiretroviral roll-out through primary care has differed from that anticipated and real world data are needed to inform the planning of further scaling up of services. We investigated the factors associated with uptake of antiretroviral treatment through a primary healthcare system in rural South Africa.
Methods: Detailed demographic, HIV surveillance and geographic information system (GIS) data were used to estimate the proportion of HIV positive adults accessing antiretroviral treatment within northern KwaZulu-Natal, South Africa in the period from initiation of antiretroviral roll-out until the end of 2008. Demographic, spatial and socioeconomic factors influencing the likelihood of individuals accessing antiretroviral treatment were explored using multivariable analysis. Results: Mean uptake of ART among HIV positive resident adults was 21.0% (95%CI 20.1-21.9). Uptake among HIV positive men (19.2%) was slightly lower than women (21.8%, P = 0.011). An individual's likelihood of accessing ART was not associated with level of education, household assets or urban/rural locale. ART uptake was strongly negatively associated with distance from the nearest primary healthcare facility (aOR = 0.728 per square-root transformed km, 95%CI 0.658-0.963, P = 0.002). Conclusions: Despite concerns about the equitable nature of antiretroviral treatment rollout, we find very few differences in ART uptake across a range of socio-demographic variables in a rural South African population. However, even when socio-demographic factors were taken into account, individuals living further away from primary healthcare clinics were still significantly less likely to be accessing ART.


Abstr. OBJECTIVE To describe the frequency of diagnosis of cryptococcosis among HIV-infected patients in Phnom Penh, Cambodia, at programme entry, to investigate associated risk factors, and to determine the incidence of cryptococcal meningitis. METHODS We analysed individual monitoring data from 11 970 HIV-infected adults enrolled between 1999 and 2008. We used Kaplan-Meier naive methods to estimate survival and retention in care and multiple logistic regression to investigate associations with individual-level factors. RESULTS Cryptococcal meningitis was diagnosed in 12.0% of the patients: 1066 at inclusion and 374 during follow-up. Incidence was 20.3 per 1000 person-years and decreased over time. At diagnosis, median age was 33 years, median CD4 cell count was 8 cells/µl, and 2.4% of patients were receiving combined antiretroviral therapy; 38.7% died and 34.6% were lost to follow-up. Of 750 patients alive and in care after 3 months of diagnosis, 85.9% received secondary cryptococcal meningitis prophylaxis and 13.7% relapsed in median 5.7 months [ interquartile range 4.1-8.8] after cryptococcal meningitis diagnosis (relapse incidence = 5.7 per 100 person-years; 95% CI 4.7-6.9). Cryptococcal meningitis was more common in men at programme entry (adjusted OR = 2.24, 95% CI 1.67-3.00) and fell with higher levels of CD4 cell counts (P < 0.0001). CONCLUSIONS Cryptococcal meningitis remains an important cause of morbidity and mortality in Cambodian HIV-infected patients. Our findings highlight the importance of increasing early access to HIV care and cryptococcal meningitis prophylaxis and of improving its diagnosis in resource-limited settings.

HATIP. Managing MDR-TB in the community: from presentation to cure or end-of-life care. October 18th 2010(167).

**Abstr.** Objective: In South Africa, many HIV-infected patients experience delays in accessing antiretroviral therapy (ART). We examined pretreatment mortality and access to treatment in patients waiting for ART. Design: Cohort of HIV-infected patients assessed for ART eligibility at 36 facilities participating in the Comprehensive HIV and AIDS Management (CHAM) program in the Free State Province. Methods: Proportion of patients initiating ART, pre-ART mortality and risk factors associated with these outcomes were estimated using competing risks survival analysis. Results: Forty-four thousand, eight hundred and forty-four patients enrolled in CHAM between May 2004 and December 2007, of whom 22 083 (49.2%) were eligible for ART; pre-ART mortality was 53.2 per 100 person-years [95% confidence interval (CI) 51.8-54.7]. Median CD4 cell count at eligibility increased from 87 cells/μl in 2004 to 101 cells/μl in 2007. Two years after eligibility an estimated 67.7% (67.1-68.4%) of patients had started ART, and 26.2% (25.6-26.9%) died before starting ART. Among patients with CD4 cell counts below 25 cells/μl at eligibility, 48% died before ART and 51% initiated ART. Men were less likely to start treatment and more likely to die than women. Patients in rural clinics or clinics with low staffing levels had lower rates of starting treatment and higher mortality compared with patients in urban/peri-urban clinics, or better staffed clinics. Conclusions: Mortality is high in eligible patients waiting for ART in the Free State Province. The most immunocompromised patients had the lowest probability of starting ART and the highest risk of pre-ART death. Prioritization of these patients should reduce waiting times and pre-ART mortality.


**Abstr.** Background: Cervical cancer prevention should be provided as part of primary healthcare services for HIV-infected women but conventional screening programs are difficult to implement in low-resource settings. Here, we evaluate the efficacy among HIV-infected women of a simpler, screen-and-treat strategy in which all women with a positive screening test are treated with cryotherapy. Methods: We conducted a randomized clinical trial of two screen-and-treat strategies among 6555 women in Cape Town, South Africa, among whom 956 were HIV-positive. Women were randomized to screen-and-treat utilizing either human papillomavirus DNA testing or visual inspection with acetic acid as the screening method or to a control group. Women were followed for up to 36 months after randomization with colposcopy and biopsy to determine the study endpoint of cervical intraepithelial neoplasia grade 2 or higher. Results: In the control group, HIV-positive women had higher rates of cervical intraepithelial neoplasia grade 2 or higher detected by 36 months (14.9%) than HIV-negative women (4.6%) (P = 0.0006). Screen-and-treat utilizing human papillomavirus DNA testing significantly reduced cervical intraepithelial neoplasia grade 2 or higher through 36 months in both HIV-positive (relative risk = 0.20, 95% confidence interval 0.06-0.69) and HIV-negative women (relative risk = 0.31, 95% confidence interval 0.20-0.50). Reductions in the visual inspection with acetic acid-and-treat group were less marked. Complications of cryotherapy were mostly minor and did not differ in frequency between HIV-positive and HIV-negative women. Conclusion: Screen-and-treat using human papillomavirus testing is a simple and effective method to reduce high-grade cervical cancer precursors in HIV-infected women.

Abstr. Objective To estimate rates of completion of CD4+ lymphocyte testing (CD4 testing) within 12 weeks of testing positive for human immunodeficiency virus (HIV) at a large HIV/AIDS clinic in South Africa, and to identify clinical and demographic predictors for completion. Methods In our study, CD4 testing was considered complete once a patient had retrieved the test results. To determine the rate of CD4 testing completion, we reviewed the records of all clinic patients who tested positive for HIV between January 2008 and February 2009. We identified predictors for completion through multivariate logistic regression. Findings Of the 416 patients who tested positive for HIV, 84.6% initiated CD4 testing within the study timeframe. Of these patients, 54.3% were immediately eligible for antiretroviral therapy (ART) because of a CD4 cell count <= 200/mu l, but only 51.3% of the patients in this category completed CD4 testing within 12 weeks of HIV testing. Among those not immediately eligible for ART (CD4 cells >200/mu l), only 14.9% completed CD4 testing within 12 weeks. Overall, of HIV+ patients who initiated CD4 testing, 65% did not complete it within 12 weeks of diagnosis. The higher the baseline CD4 cell. count, the lower the odds of completing CD4 testing within 12 weeks. Conclusion Patient losses between HIV testing, baseline CD4 cell count and the start of care and ART are high. As a result, many patients receive ART too late. Health information systems that link testing programmes with care and treatment programmes are needed.


Abstr. BACKGROUND Peripartum administration of single-dose nevirapine reduces mother-to-child transmission of human immunodeficiency virus type 1 (HIV-1) but selects for nevirapine-resistant virus. METHODS In seven African countries, women infected with HIV-1 whose CD4+ T-cell counts were below 200 per cubic millimeter and who either had or had not taken single-dose nevirapine at least 6 months before enrollment were randomly assigned to receive antiretroviral therapy with tenofovir-emtricitabine plus nevirapine or tenofovir-emtricitabine plus lopinavir boosted by a low dose of ritonavir. The primary end point was the time to confirmed virologic failure or death. RESULTS A total of 241 women who had been exposed to single-dose nevirapine began the study treatments (121 received nevirapine and 120 received ritonavir-boosted lopin-avir). Significantly more women in the nevirapine group reached the primary end point than in the ritonavir-boosted lopinavir group (26% vs. 8%) (adjusted P = 0.001). Virologic failure occurred in 37 (28 in the nevirapine group and 9 in the ritonavir-boosted lopinavir group), and 5 died without prior virologic failure (4 in the nevirapine group and 1 in the ritonavir-boosted lopinavir group). The group differences appeared to decrease as the interval between single-dose nevirapine exposure and the start of antiretroviral therapy increased. Retrospective bulk sequencing of baseline plasma samples showed nevirapine resistance in 33 of 239 women tested (14%). Among 500 women without prior exposure to single-dose nevirapine, 34 of 249 in the nevirapine group (14%) and 36 of 251 in the ritonavir-boosted lopinavir group (14%) had virologic failure or died. CONCLUSIONS In women with prior exposure to peripartum single-dose nevirapine (but not in those without prior exposure), ritonavir-boosted lopinavir plus tenofovir-emtricitabine was superior to nevirapine plus tenofovir-emtricitabine for initial antiretroviral therapy.

Abstr. Background. Fixed-dose combination scored dispersible stavudine, lamivudine, and nevirapine minitablets (Triomune Baby and Junior; Cipla Ltd) are simpler and cheaper than liquid formulations and have correct dose ratios for human immunodeficiency virus-infected children. However, they cannot be used for dose escalation (DE) of nevirapine. Methods. Children were randomized to initiate antiretroviral therapy with full-dose (FD) nevirapine (Triomune Baby or Junior in the morning and evening) versus DE (half-dose nevirapine for 14 days [Triomune in the morning and stavudine-lamivudine {Lamivir-S} in the evening], then FD), in accordance with World Health Organization weight-band dosing tables. The primary end point was nevirapine-related clinical or laboratory grade 3 or 4 adverse events (AEs). Results. In total, 211 children (median [interquartile range {IQR}] age, 5 [2-9] years; median [IQR] CD4 cell percentage, 13% [8%-18%]) were enrolled and followed up for a median (IQR) of 92 (68-116) weeks. There were 31 grade 3 or 4 AEs that were definitely/probably or uncertainly related to nevirapine in the FD group (18.0 per 100 child-years), compared with 29 in the DE group (16.5 per 100 child-years) (incidence rate ratio, 1.09; 95% confidence interval, 0.63-1.87; P = .74). All were asymptomatic; 11 versus 3 were single grade 3 or 4 elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels, all of which resolved without a change in nevirapine dose or interruption. Thirteen (12%) FD versus 2 (2%) DE children had grade 1 (2 in FD) or grade 2 (11 in FD and 2 in DE) rashes. Three (2 in FD and 1 in DE) substituted efavirenz, 3 (FD) continued FD nevirapine, and 9 (8 in FD and 1 in DE) temporarily interrupted nevirapine, followed by successful DE. Predictors of nevirapine rash were older age (P = .003) and higher CD4 cell count for age (P = .03). Twenty-two children died (12 in FD and 10 in DE), 1 FD and 5 DE children at >4 weeks; none were considered to be drug related by independent review. Conclusions. Rash was more frequent with FD nevirapine, but 88% had no clinical toxicity; elevated AST or ALT levels were transient and resolved spontaneously, suggesting that routine laboratory monitoring has limited value. Dual pediatric stavudine-lamivudine minitablets are preferred for safe and simple DE; if unavailable, initiating FD Triomune requires timely review for rash, which could be managed by temporary reduction to half-dose Triomune or efavirenz substitution.


Abstr. Objective To determine the incidence of loss to follow up in a treatment programme for people living with human immunodeficiency virus (HIV) infection in Kenya and to investigate how loss to follow-up is affected by gender. Methods Between November 2001 and November 2007, 50,275 HIV-positive individuals aged >= 14 years (69% female; median age: 36.2 years) were enrolled in the study. An individual was lost to follow-up when absent from the HIV treatment clinic for >3 months if on combination antiretroviral therapy (cART) or for >6 months if not. The incidence of loss to follow-up was calculated using Kaplan-Meier methods and factors associated with loss to follow-up were identified by logistic and Cox multivariate regression analysis. Findings Overall, 8% of individuals attended no follow-up visits, and 54% of them were lost to follow-up. The overall incidence of loss to follow-up was 25.1 per 100 person-years. Among the 92% who attended at least one follow-up visit, the incidence of loss to follow-up before and after starting cART was 27.2 and 14.0 per 100 person-years, respectively. Baseline factors associated with loss to follow-up included younger age, a long travel time to the
clinic, patient disclosure of positive HIV status, high CD4+ lymphocyte count, advanced-stage HIV disease, and rural clinic location. Men were at an increased risk overall and before and after starting cART. Conclusion The risk of being lost to follow-up was high, particularly before starting cART. Men were more likely to become lost to follow-up, even after adjusting for baseline sociodemographic and clinical characteristics. Interventions designed for men and women separately could improve retention.


Abstr. BACKGROUND Single-dose nevirapine is the cornerstone of the regimen for prevention of mother-to-child transmission of human immunodeficiency virus (HIV) in resource-limited settings, but nevirapine frequently selects for resistant virus in mothers and children who become infected despite prophylaxis. The optimal antiretroviral treatment strategy for children who have had prior exposure to single-dose nevirapine is unknown. METHODS We conducted a randomized trial of initial therapy with zidovudine and lamivudine plus either nevirapine or ritonavir-boosted lopinavir in HIV-infected children 6 to 36 months of age, in six African countries, who qualified for treatment according to World Health Organization (WHO) criteria. RESULTS are reported for the cohort that included children exposed to single-dose nevirapine prophylaxis. The primary end point was virologic failure or discontinuation of treatment by study week 24. Enrollment in this cohort was terminated early on the recommendation of the data and safety monitoring board. Results A total of 164 children were enrolled. The median percentage of CD4+ lymphocytes was 19%; a total of 56% of the children had WHO stage 3 or 4 disease. More children in the nevirapine group than in the ritonavir-boosted lopinavir group reached a primary end point (39.6% vs. 21.7%; weighted difference, 18.6 percentage-points; 95% confidence interval, 3.7 to 33.6; nominal P = 0.02). Baseline resistance to nevirapine was detected in 18 of 148 children (12%) and was predictive of treatment failure. No significant between-group differences were seen in the rate of adverse events. CONCLUSIONS Among children with prior exposure to single-dose nevirapine for perinatal prevention of HIV infection, antiretroviral treatment consisting of zidovudine and lamivudine plus ritonavir-boosted lopinavir resulted in better outcomes than did treatment with zidovudine and lamivudine plus nevirapine. Since nevirapine is used for both treatment and perinatal prevention of HIV infection in resource-limited settings, alternative strategies for the prevention of HIV transmission from mother to child, as well as for the treatment of HIV infection, are urgently required.

Spaulding A, Rutherford GW, Siegfried N. **Tenofovir or zidovudine in three-drug combination therapy with one nucleoside reverse transcriptase inhibitor and one non-nucleoside reverse transcriptase inhibitor for initial treatment of HIV infection in antiretroviral-naive individuals - art. no. CD008740.** Cochrane Database of Systematic Reviews 2010(10):8740-8740.

Abstr. Background The introduction of highly active antiretroviral therapy (ART) as treatment for HIV infection has greatly improved mortality and morbidity for adults and children living with HIV around the world. Two of the most common medications given in first-line ART are the nucleoside reverse transcriptase inhibitor (NRTI) zidovudine (AZT) and the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir (TDF). Objectives To assess the efficacy, safety, and tolerability of TDF compared with AZT in combination with one NRTI and one non-nucleoside reverse transcriptase inhibitor (NNRTI) as part of first-line ART for HIV-infected people in resource-limited settings Search strategy
Standard Cochrane methods were used to search electronic databases and conference proceedings with relevant search terms without limits to language. Selection criteria Randomised controlled trials of HIV-infected patients aged 5 years and older were included. Primary outcomes of interest included mortality, serious adverse events, virologic response to ART, and adherence/tolerance/retention. Secondary outcomes included immunologic response to ART, development of ART drug resistance, and prevention of sexual transmission of HIV. Data collection and analysis Two authors assessed each reference for inclusion and exclusion criteria established a priority. Data were abstracted independently using a standardised abstraction form. Main results Two randomised controlled trials contributed to this literature, enrolling 586 participants, and found no critical difference between TDF and AZT in regards to serious adverse events or virologic response. The trials did find higher rates of adherence and immunologic response in TDF-containing regimens compared with those containing AZT. The quality of the literature to support this conclusion is moderate to high. Drug resistance was more common for TDF than AZT, but the quality of this literature is low, with only one study reporting this outcome. It should be noted that the two studies compared two different drugs in addition to TDF and AZT; one had lamivudine (3TC) and nevirapine (NVP) and the other had emtricitabine (FTC) and efavirenz (EFV). Authors' conclusions We conclude that for the critical outcomes of virologic response and serious adverse events, initial ART regimens containing TDF are equivalent to those containing AZT. However, TDF is superior to AZT in terms of immunologic response and adherence and less frequent emergence of resistance. How much the other drugs in the regimens contributed to these findings is unclear, and true head-to-head trials are still warranted. The role of each drug in initial ART likely will be driven by their specific toxicities.


Abstr. Background: Early cessation of breastfeeding increases morbidity and mortality of children born to HIV-infected mothers in resource-limited settings. However, data on whether breastfeeding reduces the risk of malaria in HIV-exposed and HIV-infected children is limited. Methods: We prospectively followed 99 HIV-unexposed children, 202 HIV-exposed children, and 45 HIV-infected children in a high malaria transmission area in Uganda. All children were given insecticide-treated bednets. HIV-exposed and HIV-infected children were given trimethoprim-sulfamethoxazole prophylaxis. Malaria diagnosis was based on fever and a positive blood smear. Date of breastfeeding cessation was determined through monthly questionnaires. Associations between breastfeeding and the risk of malaria were modeled through binomial generalized estimating equations using multivariate analysis adjusting for repeated measures, age, and location of residence. Analyses were stratified according to mothers' and children's HIV status. Results: Breastfeeding was associated with a significantly lower risk of malaria in 6-15 months old HIV-exposed children (relative risk [RR] = 0.62; P = 0.008) and 6-15 months old HIV-infected children (RR = 0.31; P = 0.002). However, breastfeeding was not protective against malaria for >15-24 months old HIV-unexposed (RR = 1.14; P = 0.21) or >15-24 months old HIV-infected children (RR = 1.11; P = 0.75). Conclusions: HIV-infected mothers should be counseled about the importance of breastfeeding and trimethoprim-sulfamethoxazole prophylaxis to protect their young children and themselves against malaria.


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.