HIV Care & PMTCT in Resource-Limited Settings

Monthly Intelligence Report
2008, Vol 4, Issue 7-8

Back Issues on Line

prepared by the Bordeaux Working Group

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**Number of citations selected for this issue:** 30

**Citation format** (by alphabetical order of the authors): Author(s). Title. Source. Abstr. (Authors' text) or Introduction (Authors' text) or Selection (Selected sections of the paper) or Notes or Abstr. Edited (Written by the Bordeaux Working Group). Author Address, if available, Free Full Text, if available

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Abstr. Background UNICEF/WHO recommends that infants born to HIV-infected mothers who do not have access to acceptable, feasible, affordable, sustainable, and safe replacement feeding should be exclusively breastfed for at least 6 months. The aim of three trials in Ethiopia, India, and Uganda was to assess whether daily nevirapine given to breastfed infants through 6 weeks of age can decrease HIV transmission via breastfeeding. Methods HIV-infected women breastfeeding their infants were eligible for participation. Participants were randomly assigned to receive either single-dose nevirapine (nevirapine 200 mg to women in labour and nevirapine 2 mg/kg to newborns after birth) or 6 week extended-dose nevirapine (nevirapine 200 mg to women in labour and nevirapine 2 mg/kg to newborn babies after birth plus nevirapine 5 mg daily from days 8-42 for the infant). The randomisation sequences were generated by computer at a central data coordinating Centre. The primary endpoint was HIV infection at 6 months of age in infants who were HIV PCR negative at birth. Analyses were by modified intention to treat, excluding infants with missing specimens and those with indeterminate or confirmed HIV infection at birth. These studies are registered with ClinicalTrials.gov, numbers NCT00074399, NCT00061321, and NCT00639938. Findings 2024 liveborn infants randomised in the study had at least one specimen tested before 6 months of age (1047 infants in the single-dose group and 977 infants in the extended-dose group). The modified intention-to-treat population included 986 infants in the single-dose group and 901 in the extended-dose group. At 6 months, 87 children in the single-dose group and 62 in the extended-dose group were infected with HIV (relative risk 0.80, 95% CI 0.58 - 1.0; p=0.16). At 6 weeks of age, 54 children in the single-dose group and 25 in the extended-dose group were HIV positive (0.54, 0.34 - 0.85; p=0.009). 393 infants in the single-dose group and 346 in the extended-dose group experienced grade 3 or 4 serious adverse events during the study (p=0.54). Interpretation Although a 6-week regimen of daily nevirapine might be associated with a reduction in the risk of HIV transmission at 6 weeks of age, the lack of a significant reduction in the primary endpoint-risk of HIV transmission at 6 months-suggests that a longer course of daily infant nevirapine to prevent HIV transmission via breast milk might be more effective where access to affordable and safe replacement feeding is not yet available and where the risks of replacement feeding are high. Funding US National Institutes of Health; US National Institute of Allergy and Infectious Diseases; Fogarty International Center.

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Abstr. Context Rifampicin- based antitubercular therapy reduces the plasma concentrations of nevirapine and efavirenz. The virological consequences of these interactions are not well described. Objective To assess the effectiveness and tolerability of concomitant efavirenz- or nevirapine-based combination antiretroviral therapy and rifampicin- based antitubercular therapy. Design, Setting, and Participants Cohort analysis of prospectively collected routine clinical data in a community - based South
African antiretroviral treatment program. Antiretroviral treatment-naive adults enrolled between May 2001 and June 2006 were included in the analysis, and were followed up until the end of 2006. Interventions Patients starting antiretroviral therapy with or without concurrent antitubercular therapy received either efavirenz or nevirapine at standard doses. Patients developing tuberculosis while taking antiretroviral therapy that included nevirapine were either changed to efavirenz or continued taking nevirapine. Main Outcome Measures Viral load of 400 copies/mL or more after 6, 12, and 18 months of antiretroviral therapy; time to the first viral load of 400 copies/mL or more; time to confirmed virological failure (2 consecutive values >= 5000 copies/mL); time to death; and time to treatment-limiting toxicity were assessed. Results The analysis included 2035 individuals who started antiretroviral therapy with efavirenz (1074 with concurrent tuberculosis) and 1935 with nevirapine (209 with concurrent tuberculosis). There were no differences in time to death or substitution of either antiretroviral drug for toxicity with and without concurrent tuberculosis. Patients starting nevirapine with concurrent tuberculosis were at a higher risk of elevated viral load most notably at 6 months (16.3%; 95% confidence interval [CI], 10.6%-23.5%) than those without tuberculosis (8.3%; 95% CI, 6.7%-10.0%); adjusted odds ratio [OR], 2.1; 95% CI, 1.2-3.4; and in the combined estimate, adjusted OR, 1.7; 95% CI, 1.2-2.6). In the time-to-event analysis of confirmed virological failure (2 consecutive values of >= 5000 copies/mL), patients starting nevirapine with concurrent tuberculosis developed virological failure sooner (adjusted hazard ratio [HR] 2.2; 95% CI, 1.3-3.7). There were no differences between patients starting efavirenz with and without concurrent tuberculosis (adjusted OR, 1.1; 95% CI, 0.8-1.5 [combined estimate] and adjusted HR, 1.1; 95% CI, 0.6-2.0, respectively). There was no difference in time to virological rebound in patients free of tuberculosis and those developing tuberculosis during follow-up while taking nevirapine (adjusted HR, 1.0; 95% CI, 0.5-2.0) or efavirenz (adjusted HR, 0.8; 95% CI, 0.4-1.7). Conclusion In this cohort study, virological outcomes were inferior when nevirapine-based antiretroviral therapy was commenced while taking antitubercular treatment (vs without concurrent tuberculosis) but comparable when starting efavirenz-based antiretroviral therapy (vs without concurrent tuberculosis) or when tuberculosis developed while taking established nevirapine- or efavirenz-based therapies.

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Abstr. Objective To analyse the early loss of patients to antiretroviral therapy (ART) programmes in resource-limited settings. Methods Using data on 5491 adult patients starting ART (median age 35 years, 46% female) in 15 treatment programmes in Africa, Asia and South America with >=12 months of follow-up, we investigated risk factors for no follow-up after treatment initiation, and loss to follow-up or death in the first 6 months. Findings Overall, 211 patients (3.8%) had no follow-up, 880 (16.0%) were lost to follow-up and 141 (2.6%) were known to have died in the first 6 months. The probability of no follow-up was higher in 2003-2004 than in 2000 or earlier (odds ratio, OR: 5.06; 95% confidence interval, CI: 1.28-20.0), as was loss to follow-up (hazard ratio, HR: 7.62; 95% CI: 4.55-12.8) but not recorded death (HR: 1.02; 95% CI: 0.44-2.36). Compared with a baseline CD4-cell count >= 50 cells/μl, a count < 25 cells/μl was associated with a higher probability of no follow-up (OR: 2.49; 95% CI: 1.43-4.33), loss to follow-up (HR: 1.48; 95% CI: 1.23-1.77) and death (HR: 3.34; 95% CI: 2.10-5.30). Compared to free treatment, fee-for-service programmes were associated with a higher probability of no follow-up (OR: 3.71; 95% CI: 0.97-16.05) and higher mortality (HR: 4.64; 95% CI: 1.11-19.41). Conclusion Early patient losses were increasingly common when programmes were scaled up and were associated with a fee for service.
and advanced immunodeficiency at baseline. Measures to maximize ART programme retention are required in resource-poor countries.

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**Free Full Text:** http://www.scielosp.org/pdf/bwho/v86n7/a16v86n7.pdf


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**Abstr.** Background We evaluated the efficacy of raltegravir and the development of viral resistance in two identical trials involving patients who were infected with human immunodeficiency virus type 1 (HIV-1) with triple-class drug resistance and in whom antiretroviral therapy had failed. Methods We conducted subgroup analyses of the data from week 48 in both studies according to baseline prognostic factors. Genotyping of the integrase gene was performed in raltegravir recipients who had virologic failure. Results Virologic responses to raltegravir were consistently superior to responses to placebo, regardless of the baseline values of HIV-1 RNA level; CD4 cell count; genotypic or phenotypic sensitivity score; use or nonuse of darunavir, enfuvirtide, or both in optimized background therapy; or demographic characteristics. Among patients in the two studies combined who were using both enfuvirtide and darunavir for the first time, HIV-1 RNA levels of less than 50 copies per milliliter were achieved in 89% of raltegravir recipients and 68% of placebo recipients. HIV-1 RNA levels of less than 50 copies per milliliter were achieved in 69% and 80% of the raltegravir recipients and in 47% and 57% of the placebo recipients using either darunavir or enfuvirtide for the first time, respectively. At 48 weeks, 105 of the 462 raltegravir recipients (23%) had virologic failure. Genotyping was performed in 94 raltegravir recipients with virologic failure. Integrase mutations known to be associated with phenotypic resistance to raltegravir arose during treatment in 64 patients (68%). Forty-eight of these 64 patients (75%) had two or more resistance-associated mutations. Conclusions When combined with an optimized background regimen in both studies, a consistently favorable treatment effect of raltegravir over placebo was shown in clinically relevant subgroups of patients, including those with baseline characteristics that typically predict a poor response to antiretroviral therapy: a high HIV-1 RNA level, low CD4 cell count, and low genotypic or phenotypic sensitivity score.

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**Abstr.** Background Sub-Saharan Africa has a high rate of HIV infection, most of which is attributable to heterosexual transmission. Few attempts have been made to assess the extent of HIV transmission within marriages, and HIV-prevention efforts remain focused on abstinence and non-marital sex. We aimed to estimate the proportion of heterosexual transmission of HIV which occurs within married or cohabiting couples in urban Zambia and Rwanda each year. Methods We used population-based data from Demographic and Health Surveys (DHS) on heterosexual behaviour in Zambia in 2001-02 and in Rwanda in HIV Care&PMTCT 2008; 4 (7-8) 57
2005. We also used data on the HIV serostatus of married or cohabiting couples and non-cohabiting couples that was collected through a voluntary counselling and testing service for urban couples in Lusaka, in Zambia, and Kigali, in Rwanda. We estimated the probability that an individual would acquire an incident HIV infection from a cohabiting or non-cohabiting sexual partner, and then the proportion of total heterosexual HIV transmission which occurs within married or cohabiting couples in these settings each year. Findings We analysed DHS data from 1739 Zambian women, 540 Zambian men, 1176 Rwandan women, and 606 Rwandan men. Under our base model, we estimated that 55.1% to 92.7% of new heterosexually acquired HIV infections among adults in urban Zambia and Rwanda occurred within serodiscordant marital or cohabiting relationships, depending on the sex of the index partner and on location. Under our extended model, which incorporated the higher rates of reported condom use that we found with non-cohabiting partners, we estimated that 60.3% to 94.2% of new heterosexually acquired infections occurred within marriage or cohabitation. We estimated that an intervention for couples which reduced transmission in serodiscordant urban cohabiting couples from 20% to 7% every year could avert 35.7% to 60.3% of heterosexually transmitted HIV infections that would otherwise occur. Interpretation Since most heterosexual HIV transmission for both men and women in urban Zambia and Rwanda takes place within marriage or cohabitation, voluntary counselling and testing for couples should be promoted, as should other evidence-based interventions that target heterosexual couples. Funding US National Institute of Mental Health, National Institute of Child Health and Human Development, National Institute of Allergy and Infectious Diseases, Fogarty AIDS International Training and Research Program, Emory Center for AIDS Research, and the International AIDS Vaccine Initiative.

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Abstr. Context The availability of new antiretroviral drugs and formulations, including drugs in new classes, and recent data on treatment choices for antiretroviral- naive and - experienced patients warrant an update of the International AIDS Society - USA guidelines for the use of antiretroviral therapy in adult human immunodeficiency virus (HIV) infection. Objectives To summarize new data in the field and to provide current recommendations for the antiretroviral management and laboratory monitoring of HIV infection. This report provides guidelines in key areas of antiretroviral management: when to initiate therapy, choice of initial regimens, patient monitoring, when to change therapy, and how best to approach treatment options, including optimal use of recently approved drugs (maraviroc, raltegravir, and etravirine) in treatment- experienced patients. Data Sources and Study Selection A 14- member panel with expertise in HIV research and clinical care was appointed. Data published or presented at selected scientific conferences since the last panel report (August 2006) through June 2008 were identified. Data Extraction and Synthesis Data that changed the previous guidelines were reviewed by the panel (according to section). Guidelines were drafted by section writing committees and were then reviewed and edited by the entire panel. Recommendations were made by panel consensus. Conclusions New data and considerations support initiating therapy before CD4 cell count declines to less than 350/mu L. In patients with 350 CD4 cells/mu L or more, the decision to begin therapy should be individualized based on the presence of comorbidities, risk factors for progression to AIDS and non- AIDS diseases, and patient readiness for treatment. In addition to the prior recommendation that a high plasma viral load (eg, > 100 000 copies/ mL) and rapidly declining CD4 cell count (> 100/mu L per year) should prompt treatment initiation, active hepatitis B or C virus coinfection, cardiovascular disease risk, and HIV- associated nephropathy increasingly prompt earlier therapy. The initial regimen must be individualized,
particularly in the presence of comorbid conditions, but usually will include efavirenz or a ritonavir-boosted protease inhibitor plus 2 nucleoside reverse transcriptase inhibitors (tenofovir/emtricitabine or abacavir/lamivudine). Treatment failure should be identified and managed promptly, with the goal of therapy, even in heavily pretreated patients, being an HIV-1 RNA level below assay detection limits.

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**Abstr.** Background Combination antiretroviral therapy has led to significant increases in survival and quality of life, but at a population-level the effect on life expectancy is not well understood. Our objective was to compare changes in mortality and life expectancy among HIV-positive individuals on combination antiretroviral therapy. Methods The Antiretroviral Therapy Cohort Collaboration is a multinational collaboration of HIV cohort studies in Europe and North America. Patients were included in this analysis if they were aged 16 years or over and antiretroviral-naive when initiating combination therapy. We constructed abridged life tables to estimate life expectancies for individuals on combination antiretroviral therapy in 1996-99, 2000-02, and 2003-05, and stratified by sex, baseline CD4 cell count, and history of injecting drug use. The average number of years remaining to be lived by those treated with combination antiretroviral therapy at 20 and 35 years of age was estimated. Potential years of life lost from 20 to 64 years of age and crude mortality rates were also calculated. Findings 18 587, 13 914, and 10 854 eligible patients initiated combination antiretroviral therapy in 1996-99, 2000-02, and 2003-05, respectively. 2056 (4.7%) deaths were observed during the study period, with crude mortality rates decreasing from 16.3 deaths per 1000 person-years in 1996-99 to 10.0 deaths per 1000 person-years in 2003-05. Potential years of life lost per 1000 person-years also decreased over the same time, from 366 to 189 years. Life expectancy at age 20 years increased from 36.1 (SE 0.6) years to 49.4 (0.5) years. Women had higher life expectancies than did men. Patients with presumed transmission via injecting drug use had lower life expectancies than did those from other transmission groups (32.6 [1.1] years vs 44.7 [0.3] years in 2003-05). Life expectancy was lower in patients with lower baseline CD4 cell counts than in those with higher baseline counts (32.4 [1.1] years for CD4 cell counts below 100 cells per μL vs 50.4 [0.4] years for counts of 200 cells per μL or more). Interpretation Life expectancy in HIV-infected patients treated with combination antiretroviral therapy increased between 1996 and 2005, although there is considerable variability between subgroups of patients. The average number of years remaining to be lived at age 20 years was about two-thirds of that in the general population in these countries. Funding UK Medical Research Council, GlaxoSmithKline.

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Abstr. Background The provision of highly active antiretroviral therapy (HAART) in resource-limited settings follows a public health approach, which is characterised by a limited number of regimens and the standardisation of clinical and laboratory monitoring. In industrialized countries doctors prescribe from the full range of available antiretroviral drugs, supported by resistance testing and frequent laboratory monitoring. We compared virologic response, changes to first-line regimens, and mortality in HIV-infected patients starting HAART in South Africa and Switzerland. Methods and Findings We analysed data from the Swiss HIV Cohort Study and two HAART programmes in townships of Cape Town, South Africa. We included treatment-naive patients aged 16 or older who had started treatment with at least three drugs since 2001, and excluded intravenous drug users. Data from a total of 2,348 patients from South Africa and 1,016 patients from the Swiss HIV Cohort Study were analysed. Median baseline CD4(+) T cell counts were 80 cells/µl in South Africa and 204 cells/µl in Switzerland. In South Africa, patients started with one of four first-line regimens, which was subsequently changed in 514 patients (22%). In Switzerland, 36 first-line regimens were used initially, and these were changed in 539 patients (53%). In most patients HIV-1 RNA was suppressed to 500 copies/ml or less within one year: 96% (95% confidence interval [CI] 95% - 97%) in South Africa and 96% (94% - 97%) in Switzerland, and 26% (22% - 29%) and 27% (24% - 31%), respectively, developed viral rebound within two years. Mortality was higher in South Africa than in Switzerland during the first months of HAART: adjusted hazard ratios were 5.90 (95% CI 1.81 - 19.2) during months 1 - 3 and 1.77 (0.90 - 3.50) during months 4 - 24. Conclusions Compared to the highly individualised approach in Switzerland, programmatic HAART in South Africa resulted in similar virologic outcomes, with relatively few changes to initial regimens. Further innovation and resources are required in South Africa to both achieve more timely access to HAART and improve the prognosis of patients who start HAART with advanced disease.

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http://medicine.plosjournals.org/archive/1549-1676/5/7/pdf/10.1371_journal.pmed.0050148-L.pdf


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Abstr. Background: The effects of short-course antiretrovirals given to reduce mother-to-child transmission (MTCT) on temporal patterns of cell-associated HIV-1 RNA and DNA in breast milk are not well defined. Methods: Women in Kenya received short-course zidovudine (ZDV), single-dose nevirapine (sdNVP), combination ZDV/sdNVP or short-course highly active antiretroviral therapy (HAART). Breast milk samples were collected two to three times weekly for 4-6 weeks. HIV-1 DNA was quantified by real-time PCR. Cell-free and cell-associated RNA levels were quantified by the Gen-Probe HIV-1 viral load assay. Results: Cell-free HIV-1 RNA levels in breast milk were significantly suppressed by sdNVP, ZDV/sdNVP or HAART therapy compared with ZDV between day 3 and week 4 postpartum (P <= 0.03). Breast milk HIV-1 DNA levels (infected cell levels)
were not significantly different between treatment arms at any timepoint during the 4-6-week follow-up. At 3 weeks postpartum, when the difference in cell-free RNA levels was the greatest comparing HAART directly with ZDV (P = 0.0001), median log(10) HIV-1 DNA copies per 1 x 10(6) cells were 2.78, 2.54, 2.69, and 2.31 in the ZDV, sdNVP, ZDV/sdNVP and HAART arms, respectively (P = 0.23). Cell-associated HIV-1 RNA levels were modestly suppressed in HAART versus ZDV/sdNVP during week 3 (3.37 versus 4.02, P = 0.04), as well as over time according to a linear mixed-effects model. Conclusion: Cell-free and, to a lesser extent, cell-associated HIV-1 RNA levels in breast milk were suppressed by antiretroviral regimens used to prevent MTCT. However, even with HAART, there was no significant reduction in the reservoir of infected cells, which could contribute to breast milk HIV-1 transmission.

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**Abstr.** Background: Good adherence is essential for successful antiretroviral therapy (ART) provision, but simple measures have rarely been validated in Africa. Methods: This was an observational analysis of an open multicenter randomized HIV/AIDS management trial in Uganda and Zimbabwe. At 4-weekly clinic visits, ART drugs were provided and adherence measured through pill usage and questionnaire. Viral load response was assessed in a subset of patients. Drug possession ratio (percentage of drugs taken between visits) defined complete (100%) and good (>= 95%) adherence. Results: In 2957 patients, 90% had pill counts at every visit. Good adherence increased from 87%, 4 weeks after ART initiation, to 94% at 48 weeks, but only 1454 (49%) patients achieved good adherence at every visit in the first year. Complete adherence was associated with 0.32 greater reduction in log(10) viral load (95% confidence interval 0.05, 0.60 P = 0.02) and was independently associated with higher baseline CD4 count, starting ART later in the trial, reporting a single regular sexual partner, clinical center, and time on ART. Conclusions: Population level adherence improved over time suggesting an association with clinical experience. Most patients had at least one visit in the year on which they reported not having good adherence, showing the need for continued adherence interventions.

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**Abstr.** Objectives: Infants infected with HIV-1 perinatally despite single-dose nevirapine progress rapidly. Data on treatment outcome in sub-Saharan African infants exposed to single-dose nevirapine are urgently required. This feasibility study addresses efficacy of infant antiretroviral therapy in this setting. Methods: HIV-infected infants in Durban, South Africa, received randomized immediate or deferred (when CD4 cell count reached < 20%) four-drug antiretroviral therapy (zidovudine/lamivudine/nelfinavir/nevirapine). Genotyping for non-nucleoside reverse transcriptase inhibitor (NNRTI) resistance was undertaken pre-antiretroviral therapy. Monthly follow-up to 1-year post-antiretroviral therapy included viral load, CD4 cell count and verbal/measured adherence monitoring. Results: All 63 infants were exposed to single-dose nevirapine. Twenty-one out of 51 (39%) infants with baseline genotyping results had NNRTI resistance (most frequently Y181C; 20%). Forty-three infants were randomized to immediate antiretroviral therapy (ART): three withdrew pre-antiretroviral therapy; 36 out of 40 completed 1-year of ART. Twenty infants received deferred ART: 17 reached CD4 cell counts less than 20% (median d99) and 13 out of 17 started antiretroviral therapy in year 1. Verbal and measured adherence was 99% and 95%, respectively. One-year post-ART, 49 out of 49 (100%) infants had a viral load less than 400 copies/ml; 46 out of 49 (94%) had viral load less than 50 copies/ml. Ten infants (20%) required second-line ART due to virological failure or tuberculosis treatment, therefore 39 out of 49 (80%) achieved viral load less than 400 copies/ml by intention-to-treat. Time to viral load less than 50 copies/ml correlated with maternal CD4 cell count (r = -0.42; P = 0.005) and infant pre-ART viral load (r=0.64; P < 0.001). NNRTI mutations had no significant effect on virological suppression. Infants starting immediate compared with deferred ART had fewer illness episodes (P=0.003), but no significant difference in virological suppression. Conclusion: Excellent adherence and virological suppression are achievable in infants, despite high-frequency NNRTI mutations and rapid disease progression. Infants remain relatively neglected in roll-out programmes and ART provision must be expanded.

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**Abstr.** Objectives: To determine short- and long-term efficacy of modified directly observed therapy (m-DOT) on antiretroviral adherence. Design: Randomized controlled trial. Setting and Analytic Approach: From September 2003 to November 2004, 234 HIV-infected adults were assigned m-DOT (24 weeks of twice weekly health center visits for nurse-observed pill ingestion, adherence support, and medication collection) or standard care. Follow-up continued until week 72. Self-reported and pill-count adherence and, secondarily, viral suppression and body mass index measures are reported. Generalized estimating equations adjusted for intraclient clustering and covariates were used. Results: During weeks 1-24, 9.1% (9/99) of m-DOT participants reported missing doses compared with 19.1% (20/105) of controls (P = 0.04) and 96.5% (517/531) of m-DOT pill-count measures were; >= 95% compared with 86.1% (445/517) in controls [adjusted odds ratio = 4.4; 95% confidence interval (CI) = 2.6 to 7.5; P < 0.001. Adherence with m-DOT was 4.8 times greater (95% CI = 2.7 to 8.6; P < 0.001) with adjustment for depression and HIV-related hospitalization. In weeks 25-48, adherence with m-DOT (488/589) was similar to controls (507/630). Viral suppression at 48 weeks was 2.0 times (95% CI = 0.8 to 5.2; P = 0.13) as likely in m-DOT participants as controls. M-DOT patients had larger body mass index increases at 24 weeks (2.2 vs 1.4 kg/m(3); P = 0.014). Viral suppression was more likely at week 48 (21/25 vs 13/22; P =
and week 72 (27/30 vs 15/23; \( P = 0.027 \)) among depressed participants receiving m-DOT. Conclusions: M-DOT increased adherence, most notably among depressed participants.

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**Abstr.** Background and Methods: Highly active antiretroviral therapy with efavirenz (EFV) has been prescribed to HIV-positive pregnant women in Rwanda (HIV status I and CD4 cell count > 350 cells/mm\(^3\)) during the last trimester of pregnancy and for 6 months after delivery. The EFV concentrations in maternal plasma, breast milk and in newborns' plasma of 13 women and their children between 6 weeks and 6 months postpartum are reported. Results: Results show a mean EFV plasma concentration of 6.55 mg/L in maternal plasma, 3.51 mg/L in skim milk, and 0.85 mg/L in infant plasma. Significant linear correlations between maternal plasma and skim milk (\( r = 0.8666, P < 0.0001 \)) and between skim milk and infant plasma (\( r = 0.6646, P < 0.02 \)) were found, but no significant correlation was observed between maternal and infant plasma concentrations (\( P > 0.05 \)). Conclusions: After 6 months of breast-feeding, no child out of the 13 had been infected with HIV and all had good psychomotor and growth development. Our results suggest that EFV may be an alternative to nevirapine (NVP) during the third trimester of pregnancy and during the breast-feeding period. Further studies on larger groups of newborns will be necessary to get a better understanding of possible prophylactic protection of the newborns by highly active antiretroviral therapy with EFV given to the mothers.

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**Abstr.** Background Raltegravir (MK-0518) is an inhibitor of human immunodeficiency virus type 1 (HIV-1) integrase active against HIV-1 susceptible or resistant to older antiretroviral drugs. Methods We conducted two identical trials in different geographic regions to evaluate the safety and efficacy of raltegravir, as compared with placebo, in combination with optimized background therapy, in patients infected with HIV-1 that has triple-class drug resistance in whom antiretroviral therapy had failed. Patients were randomly assigned to raltegravir or placebo in a 2:1 ratio. Results In the combined studies, 699 of 703 randomized patients (462 and 237 in the raltegravir and placebo groups, respectively) received the study drug. Seventeen of the 699 patients (2.4%) discontinued the study before week 16. Discontinuation was related to the study treatment in 13 of these 17 patients: 7 of the 462 raltegravir recipients (1.5%) and 6 of the 237 placebo recipients (2.5%). The results of the two studies were consistent. At week 16, counting noncompletion as treatment failure, 355 of 458 raltegravir recipients (77.5%) had HIV-1 RNA levels below 400 copies per milliliter, as compared with 99 of 236 placebo recipients (41.9%, \( P<0.001 \)). Suppression of HIV-1 RNA to a level below 50 copies per milliliter was achieved at week 16 in 61.8% of the raltegravir recipients, as compared with 34.7% of placebo recipients, and at week 48 in 62.1% as compared with 32.9% (\( P<0.001 \) for both comparisons). Without adjustment for the length of follow-up, cancers were detected in 3.5% of raltegravir recipients and in 1.7% of placebo recipients.
The overall frequencies of drug-related adverse events were similar in the raltegravir and placebo groups. Conclusions In HIV-infected patients with limited treatment options, raltegravir plus optimized background therapy provided better viral suppression than optimized background therapy alone for at least 48 weeks.

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**Abstr.** Many underdeveloped countries with poor health-care systems and limited resources are not capable of providing optimal treatment for HIV/AIDS to the millions of patients in need. The purpose of this study was to compare the adherence profile, adverse events and storage methods of patients in Zambia after switching from the lopinavir/ritonavir soft-gelatin capsule (SGC) to the LPV/r tablet. Twenty patients who had been taking LPV/r SGC 133.3 mg/33.3 mg twice daily for at least one month and who switched to LPV/r tablet 200 mg/50 mg, while maintaining the same nucleoside backbone, were surveyed. Results showed that patients adhered similarly to both formulations of LPV/r. However, 50% of patients taking the LPV/r SGC reported doing so without food on at least one occasion. Fifty-five percent of patients taking the LPV/r tablet reported rare or no diarrhoea compared with 15% of those taking the LPV/r SGC. Patients reported either foregoing refrigeration of the LPV/r SGC or adapting their lifestyles to fit the storage requirements of the SGC. These survey data demonstrate the advantage of using the LPV/r tablet over the LPV/r SGC in resource-limited countries such as Zambia.

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**Abstr.** Objectives: To determine the main causes of acid-fast bacillus sputum smear-negative pneumonia in Asian and African HIV-infected patients Design and setting: A prospective multicenter study (ANRS 1260) of consecutive hospitalized patients in tertiary hospitals in Phnom Penh, Ho Chi Minh City, Bangui and Dakar. Intervention: Use of the same clinical, radiological and biological methods at the four sites; regular quality controls of participating laboratories; final review of medical records by experts. Similar criteria used to establish diagnoses. Results: In all 462 patients were enrolled, 291 in Asia and 171 in Africa. The median CD4 cell count was 25 cells/μl. Radiological opacities were diffuse in 42% of patients and localized in 45%. Fiberoptic bronchoscopy
was performed in 354 patients, at similar rates in the four sites. A definite and/or probable diagnosis was obtained in 375 patients (81%). Pneumocystis jiroveci pneumonia, bacterial pneumonia, AFB sputum smear-negative tuberculosis and other infections (fungi, parasites, atypical mycobacteria) were diagnosed in respectively 47, 30, 17 and 12% of Asian patients and 3, 48, 26 and 5% of African patients. Conclusion: In South-east Asia, acid-fast bacillus smear-negative pneumonia is caused by a wide variety of pathogens. When possible, fiberoptic bronchoscopy must be performed rapidly if clinical data are not highly suggestive of bacterial pneumonia, Pneumocystis jiroveci pneumonia or tuberculosis. In contrast, in Africa, bacterial pneumonia and tuberculosis are responsible for the large majority of cases. Fiberoptic bronchoscopy should be restricted to patients with clinical and/or radiological findings not suggestive of bacterial pneumonia or tuberculosis, antibiotic failure, and three consecutive negative sputum smears.

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**Abstr.** Background: Estimation of the number of people in need of antiretroviral therapy (ART) in resource-limited settings requires information on the time from seroconversion to ART eligibility and from ART eligibility to death. Objectives: To estimate duration from seroconversion to different ART eligibility criteria and from ART eligibility to death in HIV-infected adults in low-income and middle-income countries. Methods: Participants with documented seroconversion from five cohorts (two cohorts from Uganda, two from Thailand and one from Cote d'Ivoire) were analysed. We used Weibull survival models and Bayesian simulation methods to model true (unobserved) first time of treatment eligibility. We set a consistency constraint so that the mean duration from seroconversion to death was equal to the mean from seroconversion to ART eligibility plus the mean from eligibility to death. Results: We analysed data from 2072 participants, 16 157 person-years of follow-up and 794 deaths. For the criterion CD4 T-lymphocyte count < 200 cells x10(6)/l, the median duration from seroconversion to ART eligibility was 6.1 years (95% credibility interval 3.3-10.4) for all studies and 7.6 years (95% credibility interval 3.4-15.2) for all but the Thai cohorts. Corresponding estimates for the time from CD4 T-lymphocyte count < 200 cells x10(6)/l to death were 2.1 years (0.7-4.8) and 2.7 years (0.8-8.4). When including all cohorts, the mean time from seroconversion to CD4 T-
lymphocyte count, < 200 cells x10(6)/l and from CD4 T-lymphocyte count < 200 cells x10(6)/l to death represented 66% (38-87%) and 34% (13-62%), respectively of the total survival time. Conclusions: The duration of different ART eligibility criteria to death was longer than the estimates used in previous calculations of the number of people needing ART. However, uncertainty in estimates was considerable and heterogeneity across cohorts important.

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## 17th International AIDS Conference. Feedback from the conference.

The 17th International AIDS Conference was held in Mexico from 3rd to 8th August 2008. Here below are a selection of abstracts related to HIV/AIDS prevention and care in resource-limited settings and that fit with the Monthly Intelligence Report.

**Access and coverage to ARV therapy**

The need to increase access and coverage to ARV therapy in resource-limited settings was extensively discussed (Abstract session TUAB03). In Thyolo, a rural district in Malawi, the implementers managed to achieve the universal coverage target of providing ART to 80% of 11,250 individuals in urgent need of ART. For this, they implemented a single first-line ART regimen and standardized treatment protocols, clinical eligibility criteria for ART initiation, decentralized ART access, task-shifting and active community involvement. This experience emphasises that sustaining universal access faces the challenges of lack of human resources, ensuring quality services and providing adequate coverage for patients requiring second-line therapy.

- Massaquoi M et al. Achieving universal access to antiretroviral therapy in a rural district in Malawi: how was it done? [abstract TUAB0303].

**Children and scaling-up of ARV therapy**

An abstract-driven session addressed the specific case of children in the scaling-up of ARV treatment (Abstract session THAB01). A study conducted in Zambia showed that the integration of paediatric HIV care within existing services at primary care level was still a daily challenge in resource-limited settings. Although HIV guidelines were included in the Integrated Management of Child Illness (IMCI) algorithm, and training provided, they were not utilized by health workers and therefore, many children eligible for HIV/ART services may not have been identified.

An interesting case study conducted in Kenya was presented on the demand-side barriers (it is usually the supply-side barriers that are documented) restricting paediatric ART access, especially health-seeking behaviours of parents/guardians on behalf of young children. This study described the burden of additional costs that are faced by patients receiving free ART, including transport, consultation fees, and ancillary medications, and how this resulted in delayed care seeking and increased morbidity and mortality. Attitudinal barriers including fear and hopelessness also deter caregivers from seeking paediatric HIV care (belief that an HIV-positive child is a “lost cause”). Interventions addressing not only the ineffectiveness of clinic services but also households economic status and knowledge levels are needed to encourage paediatric HIV service uptake.

- Mugala N et al. Barriers to implementation of the HIV guidelines in the IMCI algorithm. [abstract THAB0106].
- Schenk K et al. “If you build it, will they come?“: community perceptions of pediatric HIV testing and treatment in Kenya. [abstract THAB0103].

**Retention in care / ART and loss to follow-up**

Recent studies have shown that patients with a CD4 count ≤100/µL had a high mortality in the first three months after start of ART. This group of patients must be considered as a “high-risk group” and should be seen more frequently for the first three months after...
starting ART. Braitstein et al. reported on a new model in Kenya for providing care to people starting ART in which most of the burden for seeing patients is shifted to nurses and supervised by a physician named "express care". The express care system comprises weekly visits by nurses for three months to patients starting ART with CD4 ≤100. Sick patients are referred to clinicians when required. The main aims of this strategy were to reduce mortality in HIV-infected adults with CD4 cell counts ≤100 when initiating ART, reduce losses to follow-up and increase clinic capacity without increasing cost. Results of the retrospective analysis show that of the 2601 eligible patients included in the study, 14.6% were given express care. The remainder received routine care of monthly clinic visits. This new strategy confirmed a 50% reduced risk of death (adjusted hazard ratio 0.54, 95% CI 0.31-0.94) and a reduced risk of death or loss to follow-up (0.58, 95% CI 0.40-0.84) among patients with CD4 cell ≤100 cell/mm3.

Braitstein P. et al. Early survival and clinic retention among high risk HIV-infected patients initiating combination antiretroviral treatment (cART) in a pilot express care system compared to routine care in Western Kenya. 1 [abstract TUAB0204].

Models of care for HIV-treatment: task shifting and decentralized care
Shortage of health workers is one of the major constraints to deliver HIV care in resource-limited settings. Task shifting is one way to address this issue. It is the process of delegation by which tasks are moved, where appropriate, to less specialized health workers (for example, nurses are trained to prescribe first-line treatment) so as to improve health care coverage by making more efficient use of the human resources already available. Successful implementation programmes of task shifting from physicians to non-physicians in areas with a shortage of doctors were reported at the conference.

Gimbel-Sherr et al. evaluated the quality of care in Mozambique provided by non-physicians, including nurses and paramedics, in areas of doctor shortage between 2004 and 2007. During the study period, 70% of 6000 patients were initiated on ART by mid-level clinical providers and 30% with a similar profile were under care of physicians. Compared with patients under physician care, those under care by non-physicians were 28% more likely to have their CD4 levels measured at 6 months and 44% less likely to be lost to follow-up. Furthermore, there was no difference between the groups in CD4 counts at 12 months or in mortality. The authors conclude that mid-level providers should be widely used to staff ART expansion.

In a prospective cohort study conducted by Humphreys et al. in rural South Africa, mortality rates and loss to follow-up among HIV-positive patients were significantly lower while satisfaction rates were greater among patients attending nurse-led clinics rather than specialist hospital-based centres.

Gimbel-Sherr K et al. Task shifting to mid-level clinical health providers: an evaluation of quality of ART provided by tecnicos de medicina and physicians in Mozambique. [abstract WEAX0105].

Humphreys C et al. Effectiveness and safety of nurse led primary-care based antiretroviral treatment in a resource constrained setting [abstract WEAB0206].

Clinical issues in HIV-infected children and those exposed to ARV in utero
As part of a session on "Clinical Issues in HIV-Infected Children" chaired by Dr. L Mofenson (NIH), Waja et al. reported on a South African study showing that younger children who begin ART do not appear to be as likely to suppress viral load as children who begin treatment at a later age. Of the 1179 children who started ART, 49-57% had viral load results available at 3, 6 and 18 months. The suppression rate at three and six months was significantly lower (p<0.0001 and 0.0349, respectively) in children who began treatment before the age of 18 months. Among the possible reasons highlighted were intolerance of the ART formulation, concurrent TB or TB treatment and poor socio-economical circumstances. This study did not report on the baseline immune status of these children and was unable to analyse the immunological response to ART. Further
studies are required regarding the relationship between age at initiation of ART and time to virological suppression to elucidate the underlying causes that make the younger age group more vulnerable to suppression failure. The authors highlight the need to identify intervention strategies that ensure the success of ART in children in resource-poor settings.

- Waja N et al. Virological suppression in children receiving ART in an urban South African setting. [abstract HIV treatment and TB]

**Tuberculosis**

TB is the biggest single cause of illness and death in people with HIV worldwide. There has been debate on the right time to start HIV treatment for people with a low CD4 cell count and who are receiving TB treatment. Preventive therapy is one of the ways of preventing TB in HIV-positive people with a high risk of disease. Wide-scale implementation has been limited in many resource-poor settings because of concerns on the ability to monitor drug toxicity and the ability to screen for active TB disease. Diero et al. presented a study undertaken in Kenya showing that an isoniazid prophylaxis can be successfully delivered through HIV treatment programmes after TB screening (history, clinical examination and chest x-ray). The key endpoints recorded were either isoniazid preventive therapy (IPT) completion or premature discontinuation (before 9 months). Between 2004 and 2007, IPT was provided to almost 10,000 HIV-positive patients. The authors found that over three-quarters of patients completed IPT, with a low rate of TB in those who took it. The report concludes that IPT within a large HIV treatment program in sub-Saharan Africa appears both feasible and effective in preventing incident episodes of active TB.

- Diero L et al. The experience and outcomes of isoniazid preventive therapy in an HIV treatment program in Western Kenya. [abstract MOAB0306].

**Combination prevention**

During the conference, it was acknowledged that there was no “magic bullet” for HIV prevention (Symposia TUSY08). The concept of “combination prevention” was advocated during the whole conference and specifically during the special session on the Lancet Series on HIV prevention (Special Session TUSS02). It is now acknowledged that people’s lives and risks are too complex to solve with single interventions, and that it is critical to take into account the behavioural, structural and political issues that affect people’s ability to protect themselves. Combination prevention combines biomedical, behavioural, and social/structural prevention, and treatment and prevention for HIV-infected persons. This means the promotion of condom use and fewer sexual partners; circumcision; the prevention of mother-to-child transmission; treatment, not just of HIV disease but also of other sexually transmitted infections; and social policies to fight poverty and defend human rights.

- Piot P. Coming to terms with complexity: A call to action for HIV prevention. [abstract TUSS0206].
- Coates T. Combination prevention and getting the science right: the future of behavioral interventions for HIV prevention. [abstract CDC0466].

**Operational research**

There was also a special session on scaling-up operations research in resource-limited settings, “the science of better, to implement better” (K De Cock) (Special session MOSS01) to reflect on the state of operations research, the topics addressed and neglected.
For more coverage on the Mexico conference

Webcast of specific sessions: http://www.kaisernetwork.org/aids2008

Scaling up Comprehensive Prevention of Mother-to-child Transmission Programmes: Challenges and Lessons Learned from Adapting Global Recommendations to Country Situation:
http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=2859

Learning by Doing: Scaling up HIV Operations Research in Resource-Limited Settings:
http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=2871

The Lancet Series on HIV. Prevention:
http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=2895

New Frontiers in HIV Prevention Sciences:
http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=2904

Aidsmap Information on HIV and AIDS. IAC Mexico 2008 - Conference News: