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International Center for AIDS
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WHO. Dpt of HIV/AIDS

HIV Care & PMTCT in Resource-Limited Settings

Monthly Intelligence Report
2007, Vol 3, Issue 11

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prepared by the Bordeaux Working Group

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Number of citations selected for this issue: 22

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** (Written by the Bordeaux Working Group). **Author Address**, if available, **Free Full Text**, if available

Abrams EJ, Myer L, Rosenfield A, El Sadr WM. **Prevention of mother-to-child transmission services as a gateway to family-based human immunodeficiency virus care and treatment in resource-limited settings: rationale and international experiences.** American Journal of Obstetrics and Gynecology 2007;197(3) Suppl. 1:S101-S106.

Abstr. In many developing countries, services to prevent the mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) operate with limited contact with HIV care and treatment programs, despite significant advances in the accessibility of both services. There is a need to deliver more complex multidrug PMTCT interventions that extend beyond single-dose nevirapine, particularly for pregnant women with advanced HIV disease who are at high risk of transmitting HIV to their children and require rapid initiation of life-long highly active antiretroviral therapy. We argue for strengthened ties between PMTCT services and HIV care and treatment programs in resource-limited settings, viewing PMTCT programs as a gateway to family-based HIV care and treatment. Existing experiences from the multicountry MTCT-Plus Initiative suggest that close ties between PMTCT services and HIV care and treatment programs are feasible and can lead to significant advances in reducing the vertical transmission of HIV and promoting the health of HIV-infected women, children, and families.

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Bassett IV, Giddy J, Nkera J, Wang B, Losina E, Lu Z, Freedberg KA, Walensky RP. **Routine voluntary HIV testing in Durban, South Africa - The experience from an outpatient department.** Journal of Acquired Immune Deficiency Syndromes 2007;46(2):181-186.

Abstr. Objective: To evaluate the yield of a routine voluntary HIV testing program compared with traditional provider-referred voluntary counseling and testing (VCT) in a hospital-affiliated outpatient department (OPD) in Durban, South Africa. Design and Methods: In a prospective 14-week "standard of care" period, we compared OPD physician logs documenting patient referrals to the hospital VCT site with HIV test registers to measure patient completion of HIV test referral. The standard of care period was followed by a 12-week intervention during which all patients who registered at the OPD were given an educational intervention and offered a rapid HIV test at no charge as part of routine care. Results: During the standard of care period, OPD physicians referred 435 patients aged ≥ 18 years for HIV testing; 137 (31.5%) of the referred patients completed testing at the VCT site within 4 weeks. Among those tested, 102 (74.5%) were HIV infected. During the intervention period, 1414 adults accepted HIV testing and 1498 declined. Of those tested, 463 (32.7%, 95% confidence interval: 30.3 to 35.3) were HIV infected. Routine HIV testing in the OPD identified 39 new HIV cases per week compared with 8 new cases per week with standard of care testing based on physician referral to a VCT site ($P < 0.0001$). Conclusions: Routine voluntary HIV testing in an OPD in South Africa leads to significantly higher rates of detection of HIV disease. This strategy should be implemented more widely in high HIV prevalence areas where treatment is available.

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Bell DJ, Kapitaoy Y, Sikwese R, van Oosterhout JJ, Lalloo DG. **Adherence to antiretroviral therapy in patients receiving free treatment from a government hospital in Blantyre, Malawi.** Journal of Acquired Immune Deficiency Syndromes 2007;45(5):560-563.

Abstr. Objectives: To compare 3 measures of adherence to antiretroviral therapy (ART) in HIV-positive adults receiving free treatment from a public hospital in Malawi. Methods: Adherence was measured over 1 month by pill count (PC), self-report, and a medication event monitoring system (MEMS). Results: Data from 80 patients were available for analysis. The mean patient age was 38.6 years, and 57.5% were female. The mean

adherence using the MEMS cap (MC) was 88.1%. Forty-six (57.5%) patients had MC adherence $\geq 95\%$, and 13 (16.2%) had $<80\%$ adherence. There was no association between MC adherence and time on ART. Mean PC adherence was 98.6%, significantly higher than MC adherence ($P < 0.001$). There was no clear relation between PC and MC adherence: 4 patients had MC adherence $<20\%$ but PC adherence of 100%. Self-reports of missing a tablet did not correlate with poor MC adherence. Conclusions: The study shows the complexities of measuring adherence and probable overestimation of adherence by PC and self-report. Because these are the main methods used in developing countries, this raises concerns about the development of drug resistance. Improved methods are needed to detect nonadherence in developing countries, and validation of MC data with drug levels and virologic Outcome in this setting is important.

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Boulle A, Orrell C, Kaplan R, Van Cutsem G, McNally M, Hilderbrand K, Myer L, Egger M, Coetzee D, Maartens G, Wood R. **Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort.** *Antiviral Therapy* 2007; 12 (5): 753-760.

Abstr. Introduction: The patterns and reasons for antiretroviral therapy (ART) drug substitutions are poorly described in resource-limited settings. Methods: Time to and reason for drug substitution were recorded in treatment-naïve adults receiving ART in two primary care treatment programmes in Cape Town. The cumulative proportion of patients having therapy changed because of toxicity was described for each drug, and associations with these changes were explored in multivariate models. Results: Analysis included 2,679 individuals followed for a median of 11 months. Median CD4(+) T-cell count at baseline was 85 cells/ μ l. Mean weight was 59 kg, mean age was 32 years and 71% were women. All started non-nucleoside reverse transcriptase inhibitor-based ART (60% on efavirenz) and 75% started on stavudine (d4T). After 3 years, 75% remained in care on-site, of whom 72% remained on their initial regimen. Substitutions due to toxicity of nevirapine (8% by 3 years), efavirenz (2%) and zidovudine (8%) occurred early. Substitutions on d4T occurred in 21% of patients by 3 years, due to symptomatic hyperlactataemia (5%), lipodystrophy (9%) or peripheral neuropathy (6%), and continued to accumulate over time. Those at greatest risk of hyperlactataemia or lipodystrophy were women on ART ≥ 6 months, weighing ≥ 75 kg at baseline. Discussion: A high proportion of adult patients are able to tolerate their initial ART regimen for up to 3 years. In most instances treatment-limiting toxicities occur early, but continue to accumulate over time in patients on d4T. Whilst awaiting other treatment options, the risks of known toxicities could be minimized through early identification of patients at the highest risk.

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Boyd MA, Cooper DA. **Second-line combination antiretroviral therapy in resource-limited settings: facing the challenges through clinical research.** *AIDS* 2007; 21 Suppl. 4: S55-S63.

Abstr. Combination antiretroviral therapy (ART) has dramatically altered the prognosis of individuals infected with HIV. In the past 5 years there has been a concerted effort to increase access to ART in the developing world. The evidence to date suggests that adherence to therapy and clinical outcomes in developing world programmes are at least the equal of those observed in developed countries. Although access to first-line therapy is reasonably well established, there is a substantial and unacceptable mortality rate in the first 6 months after initiation of ART, particularly in those with low CD4 cell counts and late-stage disease. Failure of first-line ART is inevitable in a proportion of patients. Access to second-line ART regimens in developing countries is problematic, mainly because of the expense of HIV protease inhibitors (PIs). Access to second-line ART may be facilitated by novel strategies using the existing recommended agents or by the use of new agents or classes. Refinement of programmes in the developing world must be

underpinned by the same rigorous scientific research effort that has characterized the success of the effort in the developed world. Therefore, the funding bodies responsible for the roll-out of antiretroviral access across the globe must mandate, incorporate and fund clinical research as an intrinsic aspect of combination ART rollout programmes.

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Doherty T, Chopra M, Jackson D, Goga A, Colvin M, Persson LA. **Effectiveness of the WHO/UNICEF guidelines on infant feeding for HIV-positive women: results from a prospective cohort study in South Africa.** *AIDS* 2007;21(13):1791-1797.

Abstr. Background: The World Health Organization (WHO) and UNICEF recommend that HIV-positive women should avoid all breastfeeding only if replacement feeding is acceptable, feasible, affordable, sustainable and safe. Little is known about the effectiveness of the implementation of these guidelines in developing country settings. Objective: To identify criteria to guide appropriate infant-feeding choices and to assess the effect of inappropriate choices on infant HIV-free survival. Method: Prospective cohort study of 635 HIV-positive mother-infant pairs across three sites in South Africa to assess mother to child transmission of HIV. Semistructured questionnaires were used during home visits between the antenatal period and 36 weeks after delivery to collect data concerning appropriateness of infant feeding choices based on the WHO/UNICEF recommendations. Results: Three criteria were found to be associated with improved infant HIV-free survival amongst women choosing to formula feed: piped water; electricity, gas or paraffin for fuel; and disclosing HIV status. Using these criteria as a measure of appropriateness of choice: 95 of 311 women who met the criteria (30.5%) chose to breastfeed and 195 of 289 women who did not meet the criteria (67.4%) chose to formula feed. Infants of women who chose to formula feed without fulfilling these three criteria had the highest risk of HIV transmission/death (hazard ratio, 3.63; 95% confidence interval, 1.48-8.89). Conclusions: Within operational settings, the WHO/UNICEF guidelines were not being implemented effectively, leading to inappropriate infant-feeding choices and consequent lower infant HIV-free survival. Counselling of mothers should include an assessment of individual and environmental criteria to support appropriate infant feeding choices.

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Grinszten B, Veloso VG, Pilotto JH, Campos DP, Keruly JC, Moore RD. **Comparison of clinical response to initial highly active antiretroviral therapy in the patients in clinical care in the United States and Brazil.** *Journal of Acquired Immune Deficiency Syndromes* 2007;45(5):515-520.

Abstr. Background: US and Brazilian Studies indicate that highly active antiretroviral therapy (HAART) has been effective in reducing morbidity and mortality from HIV/AIDS. Differences exist in the adoption and patterns of antiretroviral drug use and in the incidence of AIDS-defining illness (ADI) between the 2 countries, however, and there has not been a direct comparison of clinical response between Brazil and the United States. We sought to determine if there have been differences in the clinical response to HAART from HIV clinical practices in the United States and Brazil. Methods: We compared 2 similarly designed clinical cohorts from Baltimore, Maryland and Rio de Janeiro, Brazil. Patients who started HAART from 1997 to 2004 were compared for HIV-1 RNA suppression and CD4- T-lymphocyte count change by 1 year of therapy and for development of an ADI up to 6 years of follow-up. A total of 1368 patients from Baltimore and 1045 patients from Rio de Janeiro were studied. Results: There was no difference by location in achieving an HIV-1 RNA level <400 copies/mL (46.9% in Rio de Janeiro, 50.8% in Baltimore), in the log change in HIV-1 RNA level (- 1.65 log in Rio de Janeiro, - 1.63 log in Baltimore), or in the change in CD4 count (116 cells/mm³ in Rio de Janeiro, 122 cells/mm³ in Baltimore) by 12 months after starting HAART. By Kaplan-Meier analysis and Cox regression adjusted for demographic and clinical prognostic factors, there was no difference by location in development of the first ADI

after starting HAART (relative hazard = 1.02; 95% confidence interval: 0.82 to 1.25 for Rio de Janeiro vs. Baltimore). The most commonly occurring ADI in Rio de Janeiro was tuberculosis (27.7% of patients), and the most commonly occurring ADI in Baltimore was esophageal candidiasis (36.8% of patients). Conclusions: There were only minor differences in clinical response to the use of HAART comparing Rio de Janeiro with Baltimore, despite differences in patterns of antiretroviral drug use and ADI incidence. This analysis indicates that HAART can be similarly effective in treating HIV/AIDS in countries with different economics.

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Kamya MR, Gasasira AF, Achan J, Mebrahtu T, Ruel T, Kekitiinwa A, Charlebois ED. **Effects of trimethoprim-sulfamethoxazole and insecticide-treated bednets on malaria among HIV-infected Ugandan children.** *AIDS* 2007;21(15):2059-2066.

Abstr. Background: Trimethoprim-sulfamethoxazole (TMP/SMX) prophylaxis and insecticide-treated bednets reduce malaria risk among HIV-infected adults. The efficacy of TMP/SMX may be diminished where antifolate resistance to malaria is high. We evaluated the efficacy of these interventions for malaria prevention among Ugandan children. Methods: We concurrently followed 300 HIV-infected children aged 1-10 years and a community-based cohort of 561 healthy children aged 1-11 years over 11 months in Kampala, Uganda. The HIV-infected children received TMP/SMX prophylaxis and insecticide treated bednets. In the community cohort, insecticide-treated bednets were introduced during the observation period. Children from both cohorts were followed using a standardized protocol to measure the incidence of malaria. Results: Only nine episodes of malaria were diagnosed among HIV-infected children (incidence= 0.07/person-year) in comparison with 440 episodes among children from the community (incidence = 0.90/person-year; $P < 0.0001$). The use of insecticide-treated bednets was associated with a 43% reduction in malaria incidence ($P < 0.001$), and a combination of TMP/SMX and use of insecticide-treated bednets with a 97% reduction in malaria incidence ($P < 0.001$). The prevalence of five mutations associated with antifolate resistance was high among malaria cases detected in both the HIV (100%) and community cohorts (75%). Malaria accounted for only 4% of febrile episodes in the HIV cohort in comparison with 33% in the community-based cohort ($P < 0.0001$). Conclusion: In a malaria endemic area with a high level of molecular markers of antifolate resistance, the combined use of TMP/SMX prophylaxis and insecticide-treated bednets was associated with a dramatic reduction in malaria incidence among HIV-infected children.

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Kamya MR, Mayanja Kizza H, Kambugu A, Bakeera Kitaka S, Semitala F, Mwebaze Songa P, Castelnuovo B, Schaefer P, Spacek LA, Gasasira AF, Katabira E, Colebunders R, Quinn TC, Ronald A, Thomas DL, Kekitiinwa A. **Predictors of long-term viral failure among Ugandan children and adults treated with antiretroviral therapy.** *Journal of Acquired Immune Deficiency Syndromes* 2007;46(2):187-193.

Abstr. Background: HIV RNA viral load testing is costly and is generally unavailable in resource-limited settings. We identified predictors of viral failure and documented genotypic mutations in a subset of patients with viral failure after 12 months on antiretroviral therapy (ART). Methods: From April 2004 to June 2005, consecutive treatment-naïve patients beginning ART at a university clinic in Uganda were enrolled. Clinical information, CD4 cell count, and HIV RNA level were collected at baseline and every 3 to 6 months. Independent predictors of viral failure were identified using multivariate logistic regression. Genotypic drug resistance for 8 patients with viral failure at 12 months was measured at baseline and at 6 and 12 months. Results: Five hundred twenty-six adults and 250 children (0 to 18 years of age) were started on first-line ART regimens and followed for 12 months. Outcomes could not be assessed in 13% of patients (79 died and 21 were withdrawn). Children were almost twice as likely to have viral failure compared with adults (26% vs. 14%; $P = 0.0001$). In adults, the sole

independent predictor of viral failure was treatment with stavudine (d4T)/lamivudine (3TC)/nevirapine (NVP) versus zidovudine (ZDV)/3TC/efavirenz (EFV) (odds ratio [OR] = 2.59, 95% confidence interval [CI]: 1.20 to 5.59). In children, independent predictors of viral failure included male gender (OR = 2.44, 95% CI: 1.20 to 4.93), baseline CD4% < 5 (OR = 2.69, 95% CI: 1.28 to 5.63), and treatment with d4T/3TC/NVP versus ZDV/3TC/EFV (OR = 2.46, 95% CI: 1.23 to 4.90). All 8 patients with viral breakthrough and genotypic drug resistance results had nonnucleoside reverse transcriptase inhibitor (NNRTI)- and 3TC-associated mutations. Conclusions: These data demonstrate the effectiveness of ART in a low-resource setting. Children and patients of all ages taking the d4T/3TC/NVP regimen were more likely to have viral failure. Our data suggest that viral failure occurring 6 months or more after the start of ART regimens commonly used in Uganda is likely to be associated with NNRTI- and 3TC-resistant virus.

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Lewden C, Chene G, Morlat P, Raffi F, Dupon M, Dellamonica P, Pellegrin JL, Katlama C, Dabis F, Leport C. **HIV-infected adults with a CD4 cell count greater than 500 cells/mm(3) on long-term combination antiretroviral therapy reach same mortality rates as the general population.** Journal of Acquired Immune Deficiency Syndromes 2007;46(1):72-77.

Abstr. Objective: To compare mortality rates in combination antiretroviral therapy (cART)-treated HIV-infected adults with mortality in the general population according to the level of CD4 cell count reached and the duration of exposure to cART. Methods: HIV-infected adults initiating a protease inhibitor-containing treatment between 1997 and 1999 were selected in the Agence Nationale de Recherches sur le Sida et les hepatites virales (ANRS) APROCO and AQUITAINE cohorts. CD4 cell counts were estimated during follow-up using a 2-phase mixed linear model. Standardized mortality ratios (SMRs) were computed in reference to the 2002 French population rates, overall and for the time period spent with a CD4 count \geq 500 cells/mm(3). To identify if and when mortality rates reached values of the general population, SMRs were computed successively with truncation at each year of follow-up. Results: The 2435 adults (77% men, baseline median age = 36 years, and baseline median CD4 count = 270 cells/mm(3)) had a median follow-up of 6.8 years. The SMR was 7.0 (95% confidence interval [CI]: 6.2 to 7.8). During the 5402 person-years spent with a CD4 count \geq 500 cells/mm(3), the mortality reached the level of the general population after the sixth year after cART initiation (SMR 0.5, 95% CI: 0.1 to 1.6). Conclusion: Although overall mortality was higher in cART-treated HIV-infected adults, a subgroup with especially good prognosis can be identified, and these characteristics should be targeted for longterm treatment.

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Little K, Newell ML, Luo C, Ngongo N, Borja MC, McDermott P. **Estimating the number of vertically HIV-infected children eligible for antiretroviral treatment in resource-limited settings.** International Journal of Epidemiology 2007;36(3):679-687.

Abstr. Background With the gradual roll-out of antiretroviral therapy (ART) to delay progression of HIV disease in children in programmes across sub-Saharan Africa and resource-limited settings elsewhere, reliable information on the number of vertically infected children eligible for such treatment is urgently required. Methods We present a model to estimate the number of vertically HIV-infected children by age who have progressed to moderate to severe disease (MSD) and as such are eligible for ART on the basis of clinical disease, allowing for: antenatal HIV prevalence, use of interventions to prevent mother-to-child transmission (PMTCT), infant feeding policies and availability of co-trimoxazole to prevent opportunistic infections that may hasten the onset of serious disease. The model assumptions were informed by published evidence and expert opinion; rates of progression to serious disease were inferred from mortality of infected and uninfected children of HIV-infected mothers; and mortality among children treated with ART was based on a study of treated children in Abidjan. To allow widespread use

the model has been developed using the Excel spreadsheet software. Results With South Africa as a hypothetical example, published antenatal prevalence and demographic data, and assuming PMTCT coverage with single dose nevirapine of 11%, all exposed and infected children receive co-trimoxazole, and various infant feeding policy scenarios, estimated numbers of children eligible for ART are presented. Conclusions. This model is easy to implement and flexible and can be used in ART programmes at national and local level.

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Notes: Little *et al.* present an original model to estimate the number of vertically HIV-infected children in need of antiretroviral therapy (ART) in resource-limited settings. It is of great importance to ascertain the number of children in need of treatment in such a context and particularly in sub-Saharan Africa where 90% of the paediatric infection occurs¹. The model considers antenatal HIV prevalence, the risk of transmission before or at birth, infant feeding policies and their associated risk of transmission, use of co-trimoxazole (CTX) to prevent opportunistic infections, use of ART and mortality rates at different ages by disease stage and according to ART regimen received. Background mortality rates are inferred from the mortality rates of non-infected children of HIV-positive mothers. Built on an Excel spreadsheet, it is easy to implement and can be used in ART programmes at national or local level. Using South Africa as an illustration, the authors provide an illustration of the model for programmatic purposes to estimate the number of HIV-infected children at different ages that would become eligible for ART. They calculated that without ART and CTX prophylaxis, with the rapid disease progression and high mortality rate early in life and the difficulty of diagnosing vertically-acquired infection in young infants, the number of infected infants surviving the first year who become eligible for treatment is relatively small. When CTX is available for all children under 18 months, and for all symptomatic children, the substantially reduced mortality results in an increased proportion of infants who develop moderate to severe disease surviving long enough to be diagnosed and become eligible for treatment. On the other hand, ART when available only to children of one year or older, only impacts on numbers of surviving children known to be infected. As children who become eligible for treatment remain on treatment for the rest of their lives and the mortality rate when on ART is dramatically reduced, there is an accumulation of children in the treatment category. With both ART and CTX for all infants there is a rise in the number of children eligible for ART and the number of children alive and not on treatment. By the end of the first year the numbers of eligible children would approximately double than without early treatment. This then substantially increases the numbers on treatment across all age ranges. As May and Egger² pointed out in a commentary in the same issue of the journal, the data feeding this illustration come from a pick-and-mix of studies, and sometimes from a different geographical area than South Africa (from Côte d'Ivoire for instance). Hopefully, with the scaling-up of ART, and the monitoring and evaluation that follows these initiatives; more data to inform such valuable models will become widely available. An interesting possible use of the model will be to evaluate the success of an intervention program either at programmatic level or at disease treatment level by predicting the number of HIV-infected children born or eligible for treatment that would be expected under the new regimen and comparing these to the actual numbers observed. And the model could also be extended to include evaluation of different feeding strategies, including exclusive breastfeeding, and/or taking into account different burdens of other infectious diseases. The monitoring and evaluation of the scaling-up of treatment and prevention programmes such as those targeting PMTCT and paediatric HIV care and ART using is crucial to public health planning and the promotion of good practice and could partly rely on such models that are user-friendly.

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Lowrance D, Makombe S, Harries A, Yu J, Aberle Grasse J, Eiger O, Shiraishi R, Marston B, Ellerbrock T, Libamba E. **Lower early mortality rates among patients receiving antiretroviral treatment at clinics offering cotrimoxazole prophylaxis in Malawi.** *Journal of Acquired Immune Deficiency Syndromes* 2007;46(1):56-61.

Abstr. Objective: To determine whether Malawi antiretroviral treatment (ART) clinics providing cotrimoxazole (CTX) prophylaxis had lower early mortality rates compared with clinics not providing CTX. Methods: Retrospective cohort study of eleven ART clinics in Malawi that were or were not providing CTX. Medical record abstraction was performed for all patients (N = 1295) initiating ART between July 1 and December 15, 2005. At 5 ART sites, CTX was given to patients dosed at 960 mg daily or 480 mg twice a day (according to national guidelines). Results: When all defaults (patients lost to follow-up for >90 days) were excluded from the analysis, the 6-month mortality rate was 10.7% in patients receiving ART at CTX clinics compared with 18.0% in those not at CTX clinics (6-month mortality risk reduction = 40.7%; P = 0.0013). Kaplan-Meier survival curves for patients receiving CTX and patients not receiving CTX were significantly different; survival differences were apparent as early as 40 to 45 days after initiation of ART. Conclusions: Patients receiving ART in Malawi at clinics offering CTX prophylaxis had significantly reduced mortality during the first 6 months of ART. This additional intervention may have the potential to improve the lives of patients on ART, because CTX is readily available and relatively inexpensive and can, in principle, be easily introduced into ART delivery programs.

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Abstr. Background: Raltegravir is an HIV-1 integrase strand-transfer inhibitor with potent in vitro activity. This study explored the antiretroviral activity and safety of raltegravir in treatment-naive patients with plasma HIV 1 RNA levels \geq 5000 copies/mL and CD4(+) T -cell counts \geq 100 cells/mm³. Methods: Multicenter, double-blind, randomized, controlled study of raltegravir at doses of 100, 200, 400, and 600 mg twice daily versus efavirenz at a dose of 600 mg/d, all in combination with tenofovir at a dose of 300 mg/d and lamivudine at a dose of 300 mg/d (clinicaltrials.gov identifier: NCT00100048). Results: In the 198 patients treated (160 on raltegravir and 38 on efavirenz), the mean HIV-1 RNA level ranged from 4.6 to 4.8 log₁₀ copies/mL at baseline. At weeks 2, 4, and 8, the proportion of patients achieving an HIV-1 RNA level < 50 copies/mL was greater in each of the raltegravir treatment groups than in the efavirenz group. By week 24, all treatment groups appeared similar, with plasma HIV-1 RNA levels < 400 copies/mL in 85% to 98% of patients and < 50 copies/mL in 85% to 95% of patients. These reductions were maintained through week 48 in 85% to 98% of patients and in 83% to 88% of patients, respectively. Five (3%) patients on raltegravir and 1 (3%) on efavirenz experienced virologic failure before week 48. Drug-related clinical adverse events were less common with raltegravir than with efavirenz. After 24 and 48 weeks of treatment, raltegravir did not result in increased serum levels of total cholesterol, low-density lipoprotein cholesterol, or triglycerides. Conclusions: Raltegravir at all doses studied was generally well tolerated in combination with tenofovir and lamivudine. Raltegravir exhibited potent and durable antiretroviral activity similar to that of efavirenz at 24 and 48 weeks but achieved HIV-1 RNA levels below detection at a more rapid rate.

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Martinson NA, Karstaedt A, Venter WDF, Omar T, King P, Mbengo T, Marais E, McIntyre J, Chaisson RE, Hale M. **Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study.** AIDS 2007;21(15):2043-2050.

Abstr. Objective: To ascertain the immediate and underlying causes of death in adults who died in hospital with a premortem diagnosis of tuberculosis. Design: Causes of death were assessed independently by internists and pathologists in 50 adults admitted to two Soweto hospitals who died 24 h or more after admission. Detailed record reviews and complete autopsies including HIV tests when not performed premortem were performed. In addition, a variety of postmortem microbiological tests were performed. Results: Forty-seven patients had HIV infection; all were antiretroviral naive. Their median age was 34.5 years, median CD4 cell count was 48 cells/ μ l and median length of hospitalization before death was 6 days. Autopsy confirmed the premortem diagnosis of tuberculosis in 37 HIV-infected patients (79%), whereas 10 (21%) did not demonstrate tuberculosis. Bronchopneumonia and cytomegalovirus pneumonitis were the leading pathologies in these 10 patients. In 47 HIV-infected cadavers immediate or contributory causes of death were: extensive pulmonary tuberculosis, 32 (68%); disseminated tuberculosis, 28 (60%); bacterial pneumonia, 13 (26%); cytomegalovirus pneumonitis in seven (15%); cytomegalovirus DNA was found in 31 (66%) and Pneumocystis pneumonia was found in five cadavers (11%). The lung, followed by lymph nodes, liver and kidney, were the commonest sites of tuberculosis. Mycobacterium tuberculosis was cultured from 19 spleens, one of which was multidrug resistant, and Salmonella spp. was cultured from 11 splenic specimens. Conclusion: We demonstrated disseminated, extensive tuberculosis associated with advanced HIV disease. Severe bacterial infections, including salmonellosis, were the leading co-morbidity, suggesting that hospitalized HIV-infected adults in whom tuberculosis is suspected may benefit from broad-spectrum antibiotic therapy.

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May M, Egger M. **Commentary: State of the ART modelling for HIV-infected children?** International Journal of Epidemiology 2007;36(3):687-689.

Abstr. NA

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Palombi L, Marazzi MC, Voetberg A, Magid NA. **Treatment acceleration program a experience of the DREAM program in prevention of mother-to-child transmission of HIV.** AIDS 2007;21 Suppl. 4:S65-S71.

Abstr. Background: The Drug Resource Enhancement against AIDS and Malnutrition (DREAM) program is a large antiretroviral therapy treatment program financed by the Treatment Acceleration Program (TAP) of the World Bank. In addition to provision of antiretroviral treatment to individuals infected with human immunodeficiency virus (HIV) in sub-Saharan Africa, one major aspect of the DREAM program is nutritional supplementation and prevention of mother-to-child transmission (PMTCT) of HIV. Methods: HIV-positive pregnant women enrolled in the DREAM program receive highly active antiretroviral therapy (HAART) free of charge from the 25th week of gestation, irrespective of clinical stage, CD4 count, and viral load. Their infants receive post-exposure prophylaxis. From 2004 to 2006, women enrolled in the DREAM program in Mozambique, Tanzania, and Malawi received water filters and formula for the first 6 months of lactation. In a second cohort starting in 2005 until 2006 in Mozambique, women received HAART for up to 6 months after delivery and were given the option to breastfeed. We conducted a comparative analysis of the two cohorts of HIV-positive pregnant women followed prospectively and evaluated HIV-1 mother-to-child transmission rates, infant morbidity, and mortality in both cohorts. Results: In the first cohort, 879 live-born children were delivered, with 809 evaluable infants at 1 and 6 months. In the second cohort, 341 infants were delivered and evaluable at 1 month, and 251 infants were evaluable at 6 months. At age 1 month, HIV-1 transmission rates were 4/341

(1.2%) among breastfed infants and 7/809 (0.8%) among formula-fed infants. At age 6 months, HIV-1 mother-to-child transmission rates were 2/251 (0.8%) among breastfed infants of women receiving HAART and 15/809 (1.8%) among formula-fed infants ($X-2 = 0.77$, $P=0.38$ [NS]). The cumulative incidence rate at 6 months of age was 2.7% for formula-fed infants and 2.2% for breastfed infants ($X-2 = 0.27$, $P=0.60$ [NS]). There was a trend for HIV-1 infection rates to be slightly greater among formula-fed infants, but overall mother-to-child transmission rates in both cohorts were extremely low. Most infants did relatively well on both feeding regimens. Observed Z scores were greater than among the general infant population in the community. Z scores ≤ 2.0 for weight by age occurred in 92/809 formula-fed infants (11.4%) and in 28/251 breastfed infants (11.1%). The rates of anemia in the study infant population were also lower than that of the general population. A hemoglobin value < 8 g/dl was found in 40/809 formula-fed infants (4.9%) and in 17/251 breastfed infants (6.8%) ($X-2 = 0.92$, $P=0.33$). The mortality rate at 6 months of age was 27 per 1000 person-years among formula-fed infants and 28.5 per 1000 person-years in breastfed infants - both considerably lower than the rates of 101 per 1000 person-years observed in Mozambique. Conclusions: The DREAM HIV-1 PMTCT protocol was safe and efficacious in reducing transmission in infants of 1 and 6 months of age. Results were comparable to those from developed countries. Breastfeeding among HIV-1 infected mothers receiving HAART posed no additional risk of late postnatal HIV-1 transmission to the infant by 6 months of age.

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Pearson CR, Micek MA, Simoni JM, Hoff PD, Matediana E, Martin DP, Gloyd SS. **Randomized control trial of peer-delivered, modified directly observed therapy for HAART in Mozambique.** Journal of Acquired Immune Deficiency Syndromes 2007; 46(2): 238-244.

Abstr. Objective: To assess the efficacy of a peer-delivered intervention to promote short-term (6-month) and long-term (12-month) adherence to HAART in a Mozambican clinic population. Design: A 2-arm randomized controlled trial was conducted between October 2004 and June 2006. Participants: Of 350 men and women (≥ 18 years) initiating HAART, 53.7% were female, and 97% were on 1 fixed-dose combination pill twice a day. Intervention: Participants were randomly assigned to receive 6 weeks (Monday through Friday; 30 daily visits) of peer-delivered, modified directly observed therapy (mDOT) or standard care. Peers provided education about treatment and adherence and sought to identify and mitigate adherence barriers. Outcome: Participants' self-reported medication adherence was assessed 6 months and 12 months after starting HAART. Adherence was defined as the proportion of prescribed doses taken over the previous 7 days. Statistical analyses were performed using intention-to-treat (missing = failure). Results: Intervention participants, compared to those in standard care, showed significantly higher mean medication adherence at 6 months (92.7% vs. 84.9%, difference 7.8, 95% confidence interval [CI]: 0.0, 13.0) and 12 months (94.4% vs. 87.7%, difference 6.8, 95% CI: 0.9, 12.9). There were no between-arm differences in chartabstracted CD4 counts.

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Rajasekaran S, Jeyaseelan L, Vijila S, Gomathi C, Raja K. **Predictors of failure of first-line antiretroviral therapy in HIV-infected adults: Indian experience.** AIDS 2007; 21 Suppl. 4: S47-S53.

Abstr. objectives: To study the incidence and risk factors for failure of treatment with antiretroviral therapy among adults in the national treatment program in India, and to estimate the possible number of persons living with human immunodeficiency virus (HIV) who will need a second-line treatment regimen in the next 3 and 3.5 years. Design and setting: Data of a cohort of HIV-positive adult patients, who were enrolled in the government-sponsored antiretroviral therapy program, were obtained from the electronic medical record system of the largest HIV care center in India and subjected to

analysis. Main outcomes: Treatment failure defined by the World Health Organization criteria, assessed immunologically on the basis of CD4 T cell count, with a minimum period of 12 months of follow-up and with a minimum of two CD4 T cell follow-up measures. Results: The cumulative incidence of treatment failure in the 1370 adult patients included in the study was 3.9% (95% confidence interval [CI] 2.9 to 4.9). Men had a 3.5 (1.6 to 7.4) times significantly greater risk of treatment failure. Patients who had negative changes in absolute lymphocyte count, hemoglobin concentration and body weight had 3.1 (1.6 to 6.2), 3.2 (1.6 to 6.2), and 3.5 (1.9 to 6.4) times significantly greater risk of treatment failure. In India, after 2007, by 2, 3, and 3.5 years, respectively, an estimated 16000, 35000, and 51 000 patients receiving antiretroviral therapy are likely to require second-line treatment. Conclusion: Monitoring of hemoglobin concentration, absolute lymphocyte count, and body weight during follow-up emerged as inexpensive predictors of treatment failure in a resource-poor setting. A significant number of patients will need second-line therapy as a result of failure of their first-line antiretroviral therapy regimen in 3 and 3.5 years in India, and therefore the development of an appropriate policy for second-line drugs is urgently needed.

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Stringer EM, Kaseba C, Levy J, Sinkala M, Goldenberg RL, Chi BH, Matongo I, Vermund SH, Mwanahamuntu M, Stringer JA. **A randomized trial of the intrauterine contraceptive device vs hormonal contraception in women who are infected with the human immunodeficiency virus - art. no. e8.** American Journal of Obstetrics and Gynecology 2007;197(2):NIL_35-NIL_42.

Abstr. OBJECTIVE: The purpose of this study was to determine whether the intrauterine contraceptive device (IUD) is effective and safe among women who are infected with the human immunodeficiency virus (HIV). STUDY DESIGN: We randomly assigned 599 postpartum, HIV-infected women in Zambia to receive either a copper IUD or hormonal contraception and followed them for at least 2 years. RESULTS: Women who were assigned randomly to hormonal contraception were more likely to become pregnant than those who were assigned randomly to receive an IUD (rate, 4.6/ 100 vs 2.0/ 100 woman-years; hazards ratio, 2.4; 95% CI, 1.3- 4.7). One woman who was assigned to the IUD experienced pelvic inflammatory disease (crude rate, 0.16/100 woman- years; 95% CI, 0.004- 868); there was no pelvic in- flammatory disease among those women who were assigned to hormonal contraception. Clinical disease progression (death or CD4+ lymphocyte count dropping below 200 cells/ mu L) was more common in women who were allocated to hormonal contraception (13.2/ 100 woman-years) than in women who were allocated to the IUD (8.6/ 100 woman-years; hazard ratio, 1.5; 95% CI, 1.04- 2.1). CONCLUSION: The IUD is effective and safe in HIV- infected women. The unexpected observation that hormonal contraception was associated with more rapid HIV disease progression requires urgent further study.

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Subbaraman R, Chaguturu SK, Mayer KH, Flanigan TP, Kumarasamy N. **Adverse effects of highly active antiretroviral therapy in developing countries.** Clinical Infectious Diseases 2007;45(8):1093-1101.

Abstr. Recent increases in access to highly active antiretroviral therapy (HAART) have made the management of drug toxicities an increasingly crucial component of human immunodeficiency virus (HIV) care in developing countries. The spectrum of adverse effects related to HAART in developing countries may differ from that in developed countries because of the high prevalence of conditions such as anemia, malnutrition, and tuberculosis and frequent initial presentation with advanced HIV disease. The severity of adverse effects may vary as a result of host genetics and diagnostic delays attributable to inadequate laboratory monitoring. This article reviews current knowledge about toxicities related to HAART in resource-limited regions, which are in the process of rapid treatment scale-up. We conclude that initiating HAART before advanced

immunosuppression, titrating doses in single-pill drug combinations to differences in patients' body weights, providing more intensive laboratory monitoring during the initial months of therapy, and providing access to less-toxic nucleoside reverse-transcriptase inhibitors may decrease the incidence of toxicities related to HAART in resource-limited regions.

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Tonwe Gold B, Ekouevi DK, Viho I, Amani Bosse C, Toure S, Coffie PA, Rouet F, Becquet R, Leroy V, El Sadr WM, Abrams EJ, Dabis F. **Antiretroviral treatment and prevention of peripartum and postnatal HIV transmission in west africa: Evaluation of a two-tiered approach - art. no. e257.** Plos Medicine 2007;4(8):1362-1373.

Abstr. Background Highly active antiretroviral treatment (HAART) has only been recently recommended for HIV-infected pregnant women requiring treatment for their own health in resource-limited settings. However, there are few documented experiences from African countries. We evaluated the short-term (4 wk) and long-term (12 mo) effectiveness of a two-tiered strategy of prevention of mother-to-child transmission of HIV (PMTCT) in Africa: women meeting the eligibility criteria of the World Health Organization (WHO) received HAART, and women with less advanced HIV disease received short-course antiretroviral (scARV) PMTCT regimens. Methods and Findings The MTCT-Plus Initiative is a multi-country, family-centred HIV care and treatment program for pregnant and postpartum women and their families. Pregnant women enrolled in Abidjan, Cote d'Ivoire received either HAART for their own health or short-course antiretroviral (scARV) PMTCT regimens according to their clinical and immunological status. Plasma HIV-RNA viral load (VL) was measured to diagnose peripartum infection when infants were 4 wk of age, and HIV final status was documented either by rapid antibody testing when infants were aged \geq 12 mo or by plasma VL earlier. The Kaplan-Meier method was used to estimate the rate of HIV transmission and HIV-free survival. Between August 2003 and June 2005, 107 women began HAART at a median of 30 wk of gestation, 102 of them with zidovudine (ZDV), lamivudine (3TC), and nevirapine (NVP) and they continued treatment postpartum; 143 other women received scARV for PMTCT, 103 of them with sc(ZDV+3TC) with single-dose NVP during labour. Most (75%) of the infants were breast-fed for a median of 5 mo. Overall, the rate of peripartum HIV transmission was 2.2% (95% confidence interval [CI] 0.3%-4.2%) and the cumulative rate at 12 mo was 5.7% (95% CI 2.5%-9.0%). The overall probability of infant death or infection with HIV was 4.3% (95% CI 1.7%-7.0%) at age week 4 wk and 11.7% (95% CI 7.5%-15.9%) at 12 mo. Conclusions This two-tiered strategy appears to be safe and highly effective for short-and long-term PMTCT in resource-constrained settings. These results indicate a further benefit of access to HAART for pregnant women who need treatment for their own health.

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Women Deliver Conference, London, October 18-20 2007.

Twenty years since the Safe Motherhood initiative was launched, little progress has been reported. Of the estimated total 536 000 maternal deaths worldwide in 2005, developing countries accounted for 99% of these deaths. In this context, the Safe Motherhood 20th anniversary conference "Women Deliver" took place on October 18-20, in London, UK. The meeting covered topics on the health of women and newborn; maternal health as a human rights imperative; financing, advocacy and political will; and the role of women in the world. A clear consensus that came out of the meeting was on the three pillars for saving the lives of women and newborns: comprehensive reproductive health services;

skilled care during and immediately after pregnancy and childbirth; and emergency care when life-threatening complications develop. For this, more funds with greater accountability are needed as well as closer synergies with HIV programs, women education, and human rights, so as to think and act globally. The conference was the opportunity to recognise the link between maternal and newborn health in the context of the continuum of maternal, newborn and child health as well as to emphasise maternal health as a development issue. A complete agenda of the meeting is found on the conference web-site: <http://www.womendeliver.org/agenda/index.htm>

Due to this event, three journals published topics related to the theme of the meeting, content which informed discussion and action in the conference. The Lancet, 370 (9595), 2007 include research and policy articles ([http://www.thelancet.com/journals/lancet/issue?issue_key=S0140-6736\(07\)X6043-4](http://www.thelancet.com/journals/lancet/issue?issue_key=S0140-6736(07)X6043-4)). New estimates of maternal mortality for 2005 are described by Hill et al; Chowdhury and colleagues show, that access to safe abortion is among the factors that have led to a substantial decrease in maternal mortality in Bangladesh and the constraints that have plagued the Safe Motherhood Initiative are discussed by Shiffman and Smith. The Bulletin of the World Health Organization, 85 (10), 2007 (<http://www.who.int/bulletin/volumes/85/10/en/index.html>) contains, among others, papers that describe the challenges to reduce child and maternal mortality in the developing world (Islam, 2007); the role of community health workers in the provision of contraceptive injections (Stanback, et al; 2007); Hatt et al. (2007) conclude that the poorest women still find it hard to access emergency obstetric care and Harvey et al, (2007) who raise the following question: Are skilled birth attendants really skilled? Finally, the overall low coverage of PMTCT worldwide and the need to strengthen maternal and child services as well as to integrate HIV and safe motherhood to achieve UNGASS targets (Lou et al., 2007; Freedman et al, 2007)) are among the papers included in the issue of the journal Reproductive Health Matters, 15 (30), 2007 (<http://www.rhmjournal.org.uk>) entitled "Maternal mortality and morbidity: is pregnancy getting safer for women?"

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