



HIV Care & PMTCT in Resource-Limited Settings

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Number of citations selected for this issue: **34**

Citation format (by alphabetical order of the authors): Author(s). **Title**. Source. **Abstr.** (Authors' abstract) or **Notes** (prepared by the Bordeaux Working Group) **Author address**, if available, **Subject Headings**

Subject headings / Subheadings indexing the selected references (by alphabetical order)

Adults / Women	Eastern Europe	Infant feeding / Breastfeeding	Prevention of Mother-To- Child Transmission (PMTCT) / AntiRetroViral (ARV)	Treatment impact and response
Children	Gynæcology	Infections (Others) / Prophylaxis	Prevention of sexual transmission	Treatment monitoring
Clinical manifestations (Others)	Hepatitis B infection (HBV)	Low Income Countries (LICs) / Africa, Asia, Caribbean, South America	Randomized Controlled Trial (RCT)	Treatment programme
Comprehensive care	Hepatitis C infection (HCV)	Mother-To-Child Transmission (MTCT)	Termination of pregnancy / Abortion	Tuberculosis (TB) / Prophylaxis
Conference summary	Highly Active AntiRetroviral Treatment (HAART)	Natural history	Treatment adherence	Viral resistance
Contraception	Industrialized countries	Obstetrics	Treatment complications	Voluntary Counselling and Testing (VCT)

Akileswaran C, Lurie MN, Flanigan TP, Mayer KH. **Lessons learned from use of highly active antiretroviral therapy in Africa.** *Clinical Infectious Diseases* 2005;41(3):376-385.

Abstr. Background. Because antiretrovirals are becoming increasingly available in developing countries, we reviewed the findings of studies that have documented highly active antiretroviral therapy (HAART) use in Africa to identify lessons learned. With the World Health Organization (WHO) guidelines used as a frame of reference, we assessed the feasibility of implementing such programs in Africa. Moreover, clinical and laboratory outcomes were compiled to determine the effectiveness of HAART programs. Methods. We searched academic databases and recent conference abstracts for studies, and we included all studies that documented patients receiving HAART in Africa. In particular, we examined studies for such program features as type of regimen and frequency of monitoring, in addition to evaluations of patient outcomes. Results. Twenty-eight articles and abstracts involving studies from 14 African countries were reviewed. Overall, 6052 patients (96.4%) were receiving HAART, mainly consisting of 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and 1 nonnucleoside reverse-transcriptase inhibitor. All studies reported an increase in mean and median CD4 cell counts, and a median of 73% of patients achieved undetectable viral loads by the end of the study period. Monitoring of CD4 cell count and viral load at 6-month intervals was completed by all studies. The median weight gained was 5.0 kg, and the median mortality rate was 7.4% (range, 0% - 27%). Six studies reported that 68% - 99% of patients took > 95% of medications. Five studies measured drug resistance; most cases of resistance involved NRTIs. Conclusions. Many studies reported positive health outcomes, including high levels of treatment adherence that were comparable to those of industrialized countries. Regimens and monitoring means based on WHO guidelines were implemented - and at times, exceeded - in all studies reviewed. We found compelling evidence that HAART can be feasibly administered in resource-limited settings.

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LICs / Africa, HAART

Allavena C, Ferre V, Brunet Francois C, Delfraissy JF, Lafeuillade A, Valantin MA, Bentata M, Michelet C, Poizot Martin I, Dailly E, Launay O, Raffi F. **Efficacy and tolerability of a nucleoside reverse transcriptase inhibitor-sparing combination of lopinavir/ritonavir and efavirenz in HIV-1-infected patients.** *Journal of Acquired Immune Deficiency Syndromes* 2005;39(3):300-306.

Abstr. Background: Recommended antiretroviral regimens include a nucleoside reverse transcriptase inhibitor (NRTI) component. Class cross-resistance and mitochondrial toxicity are recognized as problems with this class of antiretrovirals. Methods: In a pilot open-label study, 65 antiretroviral-naïve and 21 experienced but nonnucleoside reverse transcriptase inhibitor-naïve HIV-1-infected adults were given a combination of lopinavir/ritonavir (533.3/133.3 mg twice daily) and efavirenz (600 mg once daily) for 48 weeks. Results: At baseline, the mean viral load was 4.84 log₁₀ copies/mL and the mean CD4 count was 311 cells/mm³. At week 24, the proportions of patients with a viral load < 400 copies/mL were 78% and 93% using an intent-to-treat and on-treatment analysis, respectively. At week 48, proportions were 73% and 97%, respectively. Treatment discontinuation occurred in 21 patients during the 48-week period, with 33% of those attributable to drug-related adverse effects. A viral load > 400 copies/mL at week 24 or 48 was associated with non-adherence in 3 patients and virologic failure in 1 patient. After an increase during the first 8 weeks, fasting lipid levels remained stable up to 48 weeks. Conclusion: The lopinavir/ritonavir-efavirenz combination is associated with a high rate of virologic response and should be compared with more classic NRTI-containing regimens in randomized and controlled clinical trials.

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Adult, HAART, Industrialized countries, Treatment impact and response

Antunes JLF, Waldman EA, Borrell C. **Is it possible to reduce AIDS deaths without reinforcing socioeconomic inequalities in health?** *International Journal of Epidemiology* 2005;34(3):586-592.

Abstr. Background The wide use of highly active antiretroviral therapy has led to an impressive improvement in AIDS survival after the mid-1990s in cities and countries with a high access to these medications. Notwithstanding its beneficial overall effect, antiretroviral therapy was also reported as a factor for the increase in socioeconomic inequalities in health, because AIDS patients have unequal access and adherence to these medications. Methods We assessed trends AIDS mortality in districts of S (a) over capo Paulo, Brazil, from 1995 to 2002, in order to test their association with area-level socioeconomic indices in a city with a large-scale and cost-free distribution of highly active antiretroviral therapy. We gathered information on yearly death rates due to AIDS, adjusted for gender, age group, income, instruction, living standards, and the human development index. Trend estimation used the autoregression procedure of exact maximum-likelihood estimation for time-series analysis. Regression analysis was used to study the association between the annual percentage decrease in AIDS deaths and socioeconomic indices. Results AIDS mortality decreased in S (a) over capo Paulo from 32.1

deaths (per 100 000 inhabitants) in 1995 to 11.2 deaths (per 100 000 inhabitants) in 2002. District-level figures of social development did not show an association with the annual percentage decrease in AIDS mortality, with all correlation coefficients corresponding to P-values > 0.27. Conclusions This observation indicates that the perspective of public policies addressed to the entire population contribute to reducing inequalities in health, while attaining an overall reduction in AIDS deaths, may have been feasible in the Brazilian context.

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LICs / South America, Treatment programme

Blumberg HM, Leonard MK, Jasmer RM. **Update on the treatment of tuberculosis and latent tuberculosis infection.** JAMA 2005;293(22):2776-2784.

Abstr. Tuberculosis (TB) has emerged as a global public health epidemic. Despite decreasing numbers of cases in the United States since 1992, TB remains a serious public health problem among certain patient populations and is highly prevalent in many urban areas. The responsibility for prescribing an appropriate drug regimen and ensuring that treatment is completed is assigned to the public health program or the clinician not to the patient. The initial prescribed regimen for the treatment of TB usually consists of 4 drugs: isoniazid, rifampin, pyrazinamide, and ethambutol. The minimum length for the treatment of drug-susceptible TB with a rifampin-based regimen is 6 to 9 months. Providing medications directly to the patient and watching him/ her swallow the anti-TB drugs, which is termed directly observed therapy, is recommended for all patients diagnosed with TB and can help ensure higher completion rates, prevent the emergence of drug resistant TB, and enhance TB control. There has been renewed interest in the treatment of those with latent TB infection as a TB-control strategy in the United States for eliminating the large reservoir of individuals at risk for progression to TB. The 2 broad categories of persons who should be tested for latent TB infection are those who are likely to have been recently infected (such as contacts to infectious TB cases) and persons who are at increased risk of progression to TB disease following infection with Mycobacterium tuberculosis (eg, human immunodeficiency virus infection and selected medical conditions; recent immigrants to the United States from high TB-burden countries). The preferred regimen for the treatment of latent TB infection is 9 months of isoniazid. There is now renewed interest in and great need for the development of new drugs to treat TB and latent TB infection.

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Industrialized countries, Tuberculosis / Prophylaxis

Bunders M, Thorne C, Newell ML. **Maternal and infant factors and lymphocyte, CD4 and CD8 cell counts in uninfected children of HIV-1-infected mothers.** AIDS 2005;19(10):1071-1079.

Abstr. Objective: To evaluate the effects of antiretroviral treatment (ART) for mother-to-child transmission of HIV and infant/maternal characteristics on total lymphocytes (TLC) and lymphocyte subsets in uninfected children of HIV-1-infected mothers. Design: The European Collaborative Study followed 1663 uninfected children from birth until at least 8 years of age using a standard protocol. Methods: Smoothers (running medians) illustrated patterns of immune markers over age by ART exposure and race. Associations between lymphocyte parameters and maternal/infant characteristics were quantified in linear regression analyses using z-scores obtained after modelling log(10)-transformed TLC, CD4 and CD8 cell counts using the LMS method. Cox proportional hazard models assessed time to TLC, CD4 and CD8 cell counts below the defined cut-off. Covariates included prematurity, gender, race, drug withdrawal and ART exposure. Results: Overall, black children had lower TLC, CD4 and CD8 cell counts than white children, and an increased risk of TLC, CD4 and CD8 cell counts below the cut-off. ART exposure was associated with TLC levels (but not with TLC below the cut-off for lymphopenia), with reduced CD4 cell counts in the first year of life, and with reduced CD8 cell counts until at least 8 years of age. Duration and intensity of ART exposure was associated with TLC levels. Conclusion: The effect of ART exposure in fetal and early life on TLC and CD8 cell counts was prolonged until at least 8 years. These results add to the growing list of adverse effects associated with ART used as prevention of mother-to-child transmission of HIV.

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Adults / Women, Children, PMTCT, Treatment complications

Coetzee D, Hilderbrand K, Boule A, Draper B, Abdullah F, Goemaere E. **Effectiveness of the first district-wide programme for the prevention of mother-to-child transmission of HIV in South Africa.** Bulletin of the World Health Organization 2005;83(7):489-494.

Abstr. Objective The aim of this study was to estimate the field efficacy of the first routine programme for the prevention of mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) initiated in South Africa, in the subdistrict of Khayelitsha. Methods A consecutive sample of 658 mother-infant pairs, identified

from the PMTCT register from 1 March to 30 November 2003, were identified for enrolment in this study. Details of the regimen received were established and HIV status of the infants at between 6 and 10 weeks of age was determined by qualitative DNA polymerase chain reaction. Zidovudine (AZT) was provided antenatally from week 34 of gestation and during labour. Infant-formula milk was offered to mothers who chose not to breastfeed. The protocol was amended in July 2003 such that women who had received < 2 weeks of treatment with AZT were given a single dose of nevirapine (NVP) at the onset of labour, and the infant received a weight-adjusted dose of NVP within 72 h of delivery. Results Of the 535 mother-infant pairs (81%) eventually included in the study, 410 (77%) received an effective PMTCT intervention according to the protocol. The rate of transmission of HIV from mother to child was 8.8% (95% confidence interval (CI), 6.2-10.9). A maternal age of > 25 years was the only significant independent risk factor for transmission (odds ratio, 2.12; 95% CI, 1.1-4.07). Conclusion The results of this study demonstrate the feasibility and effectiveness of a large-scale PMTCT programme in an urban public-sector setting.

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LICs / Africa, PMTCT, Treatment programme

Colebunders R, Ronald A, Katabira E, Sande M. **Rolling out antiretrovirals in Africa: There are still challenges ahead** [Editorial Commentary]. *Clinical Infectious Diseases* 2005;41(3):386-389.

Introduction: In their article "Lessons Learned from Highly Active Antiretroviral Therapy in Africa," Akileswaran et al review the effectiveness of HAART programs in Africa. They report positive health outcomes, including high levels of treatment adherence and virological suppression that are comparable to those of industrialized countries. Most of these studies, however, were performed in settings with significant external financial support, and the duration of patient follow-up was relatively short. Also, many of the studies are only currently available as abstracts, and as a result, a critical analysis of the strengths and weaknesses of the various programs is not possible. There is no doubt that the availability of antiretroviral drugs in Africa from the President's Emergency Plan for AIDS Relief; the Global Fund for AIDS, Tuberculosis, and Malaria; and other donor programs is an extremely important life-saving initiative, especially when it is strategically linked to well-organized, community-based HIV-prevention programs. However, the challenge to roll out antiretrovirals in Africa to all those who need them and to obtain achievable long-term results is daunting. In this commentary, we detail some of these challenges.

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HAART, LICs / Africa

Cressey TR, Leenasirimakul P, Jourdain G, Tod M, Sukrakanchana P, Kunkeaw S, Puttimit C, Lallemand M. **Low-doses of indinavir boosted with ritonavir in HIV-infected Thai patients: pharmacokinetics, efficacy and tolerability.** *Journal of Antimicrobial Chemotherapy* 2005;55(6):1041-1044.

Abstr. Objectives: To assess the steady-state pharmacokinetics of two reduced doses of indinavir boosted with ritonavir (indinavir/ritonavir) in HIV-infected Thai patients. Patients and methods: Thirteen immunocompromised antiretroviral-naive patients (6 males, 7 females) initiated 600/100 mg indinavir/ritonavir, zidovudine and lamivudine, every 12 h. After 1 month, blood samples were taken at pre-dose, and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8 and 12 h after drug intake. Indinavir dosing was then reduced to 400 mg (twice daily) and 1 week later an identical series of samples were drawn. Patients then resumed 600 mg of indinavir. HIV-1 RNA viral load was determined at 8, 24 and 48 weeks. Indinavir plasma levels were determined by HPLC and pharmacokinetic parameters by non-compartmental analysis. Results: Median (range) weight was 58 kg (51-73) for men and 53 kg (46-59) for women. On 600 mg of indinavir, median indinavir AUC, C-max and C-min were 39.3 mg(.).h/L (20.6-50.5), 6.2 mg/L (3.7-9.0) and 0.41 mg/L (0.12-0.77), respectively, and on indinavir 400 mg, 18.3 mg(.).h/L (11.1-33.0), 3.8 mg/L (2.2-7.8) and 0.17 mg/L (0.10-0.39), respectively. No renal complications were observed. At 48 weeks, 6/13 (46%) patients had stopped 600 mg of indinavir due to intolerance (gastrointestinal and cutaneous), and 5/7 (71%) patients had a HIV-1 viral load < 50 copies/mL. Conclusions: Reduced doses of indinavir/ritonavir maintained adequate indinavir plasma levels compared to current guidelines suggesting that these doses are efficacious in this setting. Considering the poor tolerability of 600 mg of indinavir, the 400 mg of indinavir may be preferred due to its lower exposure indices but long-term efficacy data are needed.

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HAART, LICs / Asia, Treatment complications, Treatment impact and response

De Cock KM, Marston B. **The sound of one hand clapping - Tuberculosis and antiretroviral therapy in Africa** [Editorial]. American Journal of Respiratory and Critical Care Medicine 2005;172(1):3-4.

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HAART, LICs / Africa, TB

del Rio C, Priddy F. **Outcomes for patients receiving antiretroviral therapy in the developing world appear to be not much different from those in the developed world** [Editorial Commentary]. Clinical Infectious Diseases 2005;41(2):225-226.

Introduction: During the first decade of the AIDS epidemic, the outcome for nearly every person infected with HIV around the world was virtually the same: most of those who became infected with HIV eventually died as a result of AIDS. However, this began to change in 1996, with the advent of protease inhibitors and HAART. In a very short time, we saw dramatic decreases in the morbidity and mortality associated with HIV infection throughout the developed world, and, as a result, the gap between outcomes for HIV-infected persons in the developed world and outcomes for those in the developing world began to widen. This unacceptable inequity between the countries that bear the greatest burden of disease and those that benefit the most from therapy is now beginning to change, thanks largely to the efforts of nongovernmental organizations, such as Médecines Sans Frontières (MSF), and initiatives such as the President's Emergency Plan For AIDS Relief and the "3 by 5" strategy of the World Health Organization (WHO). The WHO estimates that, as a result of such programs, the estimated number of people receiving antiretroviral therapy in the developing world increased from 400,000 to 700,000 during the second half of 2004. However, this number still represents only 12% of the nearly 6 million people who are in dire need of antiretroviral treatment

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HAART, LICs / Africa, Treatment impact and response

Duerr A, Hurst S, Kourtis AP, Rutenberg N, Jamieson DJ. **Integrating family planning and prevention of mother-to-child HIV transmission in resource-limited settings.** Lancet 2005;366(9481):261-263.

Notes: This paper explores integration strategies of family planning services into existing PMTCT programmes, in settings where HIV sero-prevalence and rates of unintended pregnancy are high, mainly in sub-Saharan Africa. The risks of unwanted pregnancies and the adverse consequences of pregnancy for HIV-infected women are exposed, the contraceptive options for HIV-infected women are mentioned, and operational political and programmatic service integration strategies are suggested. The authors conclude that promotion of modern contraception for HIV-infected women could be as effective at decreasing HIV infection in infants as strategies that provide antiretroviral drugs for PMTCT to HIV-infected pregnant women.

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Comprehensive care, LICs, PMTCT

Dye C, Watt CJ, Bleed DM, Hosseini SM, Raviglione MC. **Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally.** JAMA 2005;293(22):2767-2775.

Abstr. Context The United Nations Millennium Development Goals (MDGs) are stimulating more rigorous evaluations of the impact of DOTS (the WHO-recommended approach to tuberculosis control based on 5 essential elements) and other possible strategies for tuberculosis (TB) control. Objective To evaluate the prospects for detecting 70% of new sputum smear-positive cases and successfully treating 85% of these by the end of 2005, for reducing TB incidence, and for halving TB prevalence and deaths globally between 1990 and 2015, as specified by the MDGs. Data Sources TB case notifications (1980-2003) from DOTS and non-DOTS programs and cohort treatment outcomes (1994-2002) reported annually to the World Health Organization (WHO) by up to 200 countries, TB death registrations, and prevalence surveys of infection and disease. Study Selection Case notification series that reflect trends in incidence, treatment outcomes from DOTS cohorts, death statistics from countries with WHO-validated vital registration systems, and national prevalence surveys of infection and disease. Data Extraction Case reports, treatment outcomes, prevalence surveys - and death registrations from WHO's global TB database covering 1990-2003 to estimate TB incidence, prevalence, and death rates through 2015 for 9 epidemiologically different world regions. Data Synthesis TB incidence increased globally in 2003, but incidence, prevalence, and death rates were approximately stable or decreased in 7 of 9 regions. The exceptions were regions of Africa with low (<4% in adults 15-49 years) and high rates (>4% of HIV infection). The global detection rate of new smear-positive cases by DOTS programs increased from 11% in 1995 to 45% in 2003 (with the lowest case-detection rates in Eastern Europe and the highest rates in the Western Pacific) and could reach 60% by 2005. More than 17 million patients were treated in DOTS programs between 1994 and 2003, with overall treatment success rates more than 80% since 1998. In 2003, overall reported treatment success was 82%, with much variation among regions. The highest rates were reported in the Western Pacific region (89%) and lowest rates in African countries with high and low HIV infection rates (71%

and 74%, respectively), in established market economies (77%), and in Eastern Europe (75%). To halve the prevalence rate by 2015, TB control programs must reach global targets for detection (70%) and treatment success (85%) and also reduce the incidence rate by at least 2% annually. To halve the death rate, incidence must decrease more steeply, by at least 5% to 6% annually. Conclusion Reduction of TB incidence, prevalence, and deaths by 2015 could be achieved in most of the world, but the challenge will be greatest in Africa and Eastern Europe.

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Industrialized countries, LICs, TB

Egger M, Boule A, Schechter M, Miotti P. **Antiretroviral therapy in resource-poor settings: scaling up inequalities?** International Journal of Epidemiology 2005;34(3):509-512.

Introduction: Since 1996, the increasingly widespread use of potent antiretroviral therapy (ART), a combination of at least three drugs from different classes, has transformed a fatal infection into a chronic disease that is manageable in most patients. However, in resource-poor settings in Africa, Asia, and Latin America, where 90% of people with HIV/AIDS live, access to ART has so far been limited to a minority of patients, owing to the high cost of drugs and the lack of an infrastructure capable of delivering ART on a large scale. In recent years, costs of proprietary drugs have fallen and low-cost generic preparations have increasingly become available. Many African countries have qualified for grants from the 'Global Fund to fight AIDS, Tuberculosis, and Malaria'. Worldwide, the Fund has approved over 1 billion US dollars for programmes against HIV/AIDS.

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HAART, LICs / South America, Treatment programme

Ekpini RE, Gilks C. **Antiretroviral regimens for preventing HIV infection in infants** [Editorial]. Bulletin of the World Health Organization 2005;83(7):483.

Introduction: Several initiatives have been launched to reinforce countries' efforts to scale up programmes for the prevention of mother-to-child transmission (PMTCT) of human immunodeficiency virus (HIV) infection, though the shift from donor-funded projects and limited initiatives towards nationwide programmes is very slow. Coverage of PMTCT programmes and uptake of services provided through them are still very low worldwide. Provision of antiretroviral (ARV) drugs to mothers and infants is one of the key interventions for the prevention of HIV infection in infants. Various short-course ARV regimens have been shown to reduce significantly HIV peripartum transmission in both breastfeeding and non-breastfeeding populations in resource-constrained settings. Pilot programmes have been implemented to offer these interventions to a large number of women and infants, with varying degrees of success. Concerns have been raised, however, about their mid-term and long-term effectiveness at population level. In sub-Saharan Africa where breastfeeding is the norm, their overall efficacy is diminished, but not outweighed, over time by postnatal transmission through breastfeeding. So far, single-dose nevirapine (NVP) has been considered to be the most cost-effective regimen in settings where antenatal care coverage is low and where pregnant women do not present until late in pregnancy. Recent evidence strongly supports the use of combination regimens, especially shortcourse zidovudine (AZT) and singledose NVP, to achieve a more dramatic reduction in perinatal transmission of HIV. That combination regimen is now recommended as one of the simplest, highly efficacious regimens, but its large-scale introduction has been problematic.

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PMTCT / ARV

Eshleman SH, Hoover DR, Chen S, Hudelson SE, Guay LA, Mwatha A, Fiscus SA, Mmiro F, Musoke P, Jackson JB, Kumwenda N, Taha T. **Nevirapine (NVP) resistance in women with HIV-1 subtype C, compared with subtypes A and D, after the administration of single-dose NVP.** Journal of Infectious Diseases 2005;192(1):30-36.

Abstr. Objective. In the Human Immunodeficiency Virus (HIV) Network for Prevention Trials (HIVNET) 012 trial in Uganda, 6-8 weeks after single-dose nevirapine (SD-NVP), NVP resistance mutations were detected at a higher rate in women with HIV-1 subtype D than in women with subtype A. Here, we evaluate the rate of NVP resistance mutations in women with subtype C. Methods. NVP resistance mutations were detected using the ViroSeq HIV-1 Genotyping System. Results. The portion of women with any NVP resistance mutation was higher in those with subtype C (45/65 [69.2%]) in the NVP and zidovudine trial, Malawi) than in those in the HIVNET 012 trial with either subtype A (28/144 [19.4%]; $P < .0001$) or subtype D (35/97 [36.1%]; $P < .0001$). In a multivariate model, subtype (C vs. A: odds ratio [OR], 8.73 [95% confidence interval {CI}, 4.29-17.76]; C vs. D: OR, 3.38 [95% CI, 1.65-6.93]) and viral load at delivery (OR, 2.35 [95% CI, 1.62-3.40]) independently predicted NVP resistance mutations, but maternal age, parity, and time between SD-NVP and the 6-8-week visit did not. Conclusions. The rate of NVP resistance mutations after SD-NVP was significantly higher in women

with HIV-1 subtype C than in women with subtype A or D. Studies are needed to assess the clinical significance of this finding.

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LICs / Africa, PMTCT / ARV, Viral resistance

Flys T, Nissley DV, Claasen CW, Jones D, Shi CJ, Guay LA, Musoke P, Mmiro F, Strathern JN, Jackson JB, Eshleman JR, Eshleman SH. **Sensitive drug-resistance assays reveal long-term persistence of HIV-1 variants with the K103N Nevirapine (NVP) resistance mutation in some women and infants after the administration of single-dose NVP: HIVNET 012.** Journal of Infectious Diseases 2005;192(1):24-29.

Abstr. Background. The HIV Network for Prevention Trials (HIVNET) 012 trial showed that NVP resistance (NVPR) emerged in some women and children after the administration of single-dose nevirapine (SD-NVP). We tested whether K103N-containing human immunodeficiency virus (HIV)-1 variants persisted in women and infants 1 year or more after the administration of SD-NVP. Methods. We analyzed samples from 9 women and 5 infants in HIVNET 012 who had NVPR 6-8 weeks after the administration of SD-NVP. Samples were analyzed with the ViroSeq system and with 2 sensitive resistance assays, LigAmp and TyHRT. Results. ViroSeq detected the K103N mutation in 8 of 9 women and in 2 of 5 infants. LigAmp detected the K103N mutation at low levels in 8 of 9 women and in 4 of 5 infants. K103N was not detected by ViroSeq 12-24 months after the administration of SD-NVP but was detected by LigAmp in 3 of 9 women and in 1 of 5 infants. K103N was also detected in those samples by use of the TyHRT assay. Conclusions. K103N-containing variants persist in some women and infants for 1 year or more after the administration of SD-NVP. Sensitive resistance assays may provide new insight into the impact of antiretroviral drug exposure on HIV-1 evolution.

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LICs / Africa, PMTCT / ARV, Viral resistance

Gish RG, Trinh H, Leung N, Chan FKL, Fried MW, Wright TL, Wang C, Anderson J, Mondou E, Snow A, Sorbel J, Rousseau F, Corey L. **Safety and antiviral activity of emtricitabine (FTC) for the treatment of chronic hepatitis B infection: A two-year study.** Journal of Hepatology 2005;43(1):60-66.

Abstr. Background/Aims: The aim of this study was to evaluate long term safety and antiviral activity of different doses of emtricitabine given once daily to patients chronically infected with hepatitis B. Methods: Eligible patients were randomized in a double-blind, parallel study to evaluate 25, 100 or 200 mg once daily doses of emtricitabine for 48 weeks. Patients were then followed for an additional 48 weeks on open-label 200 mg emtricitabine. Serum HBV DNA, ALT, and hepatitis B serology were measured at regular intervals over the 2 years. Resistance surveillance was performed after 1 and 2 years on viremic samples, i.e. > 4700 copies/mL. Results: Emtricitabine was well tolerated and produced a dose proportional antiviral response. After 2 years, 53 % of the patients had serum HBV DNA ≤ 4700 copies/mL, 33% seroconverted to anti-HBe and 85% had normal ALT. Eighteen percent of the patients who had received 200 mg emtricitabine for 2 years developed resistance mutations. Conclusions: Emtricitabine was well tolerated and demonstrated a potent antiviral response for up to 2 years in patients with chronic hepatitis B infection. Based on these data, 200 mg emtricitabine once daily was chosen as the optimal dose for future hepatitis B studies.

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HBV

Grabar S, Le Moing V, Goujard C, Egger M, Leport C, Kazatchkine MD, Weiss L, Costagliola D. **Response to highly active antiretroviral therapy at 6 months and long-term disease progression in HIV-1 infection.** Journal of Acquired Immune Deficiency Syndromes 2005;39(3):284-292.

Abstr. Objective: To compare the long-term prognostic significance of different definitions of immunologic and virologic responses to highly active antiretroviral therapy (HAART) at 6 months. Methods: This was a prospective study conducted in 68 French hospitals. HAART was initiated in 2236 protease inhibitor-naïve patients included in the French Hospital Database on HIV. Multivariate Cox proportional hazard models measuring time from 6 months after starting HAART were used to compare the strength of the association between different definitions of immunologic and virologic responses at 6 months and subsequent progression to AIDS or death. The Akaike's Information Criteria were used to identify the most appropriate model. Results: During a median follow-up of 58 months, 325 patients experienced an AIDS-defining event or died. The model that fitted best was the model in which the CD4 cell count and plasma HIV-1 RNA values attained at 6 months were considered. The risk of clinical progression at 5 years ranged from 7% (95% confidence interval [CI]: 4-10) in patients whose CD4 cell count at 6 months was ≥ 350 cells/μL and whose HIV-1 RNA concentration was < 3 log₁₀ copies/mL to 63% (95% CI: 52-75) in patients whose CD4 cell count at 6 months was < 100 cells/μL and whose HIV-1 RNA concentration was ≥ 5 log₁₀. Conclusions: Plasma HIV-1 RNA

concentration and CD4 cell count should be taken into account independently when evaluating early response to treatment. The persistent impact of early response on clinical progression at 5 years emphasizes the major importance of the success of first-line HAART.

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HAART, Industrialized countries, Treatment impact and response

Grant AD, Charalambous S, Fielding KL, Day JH, Corbett EL, Chaisson RE, De Cock KM, Hayes RJ, Churchyard GJ. **Effect of routine isoniazid preventive therapy on tuberculosis incidence among HIV-infected men in South Africa - A novel randomized incremental recruitment study.** JAMA 2005;293(22):2719-2725.

Abstr. Context Tuberculosis preventive therapy reduces tuberculosis incidence among human immunodeficiency virus (HIV)-infected individuals in clinical trials, but implementation has been limited and there are no data on effectiveness under routine conditions. Objective To determine the effect on tuberculosis incidence of a clinic providing isoniazid preventive therapy to HIV-infected adults under routine conditions., Design, Setting, and Participants Randomized intervention study with a novel incremental recruitment design. Between 1999 and 2001 (before antiretroviral therapy was available), 1655 HIV-infected male employees of a South African gold-mining company (median age, 37 years) were enrolled in the study. Median follow-up was 22.1 months. Intervention Employees were invited in random sequence to attend a workplace HIV clinic. Isoniazid, 300 mg/d, was self-administered for 6 months among attendees with no evidence of active tuberculosis. Main Outcome Measure Incidence of tuberculosis (including both first and recurrent episodes) during the periods before and after clinic enrollment. Results A total of 1016 of 1655 men included in the analysis attended the clinic at least once. Six hundred seventy-nine (97%) of 702 men eligible to start primary isoniazid preventive therapy did so. The tuberculosis incidence rate before vs after clinic enrollment was 11.9 vs 9.0 per 100 person-years, respectively (incidence rate ratio [IRR] after adjustment for calendar period, 0.68; 95% confidence interval [CI], 0.48-0.96). In a multivariable analysis adjusting for calendar period, age, and silicosis grade, the tuberculosis IRR for clinic enrollment was 0.62 (95% CI, 0.43-0.89). In a further analysis excluding individuals with a history of tuberculosis (and, hence, ineligible for isoniazid preventive therapy), the adjusted IRR for clinic enrollment was 0.54 (95% CI, 0.35-0.83). Conclusions Enrollment in a clinic offering primary isoniazid preventive therapy to HIV-infected adults reduced tuberculosis incidence by 38% overall and by 46% among individuals with no history of tuberculosis prior to the study. Tuberculosis incidence remained high despite isoniazid preventive therapy, and further work is needed to determine how to use additional interventions most effectively to reduce morbidity and mortality due to tuberculosis in HIV-infected persons.

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LICs / Africa, TB / Prophylaxis

Hammer SM. **Single-dose nevirapine and drug resistance: The more you look, the more you find** [Editorial Commentary]. Journal of Infectious Diseases 2005;192(1):1-3.

Introduction: Within the context of the historic development of drugs to treat HIV infection, there is perhaps no subject that has created more controversy than the use of these agents to interrupt the mother-to-child transmission (MTCT) of HIV-1. No one now takes issue with the fact that the AIDS Clinical Trials Group Protocol 076 in which zidovudine (ZDV), given to the mother pre- and intrapartum and to the infant for the first 6 weeks of life, reduced MTCT of HIV-1 by 70% has been one of the most noteworthy advances in treatment of the past 20 years. However, the development phase of that protocol was fraught with intense debate, particularly with respect to the ethics of the trial. The reduction in MTCT of HIV-1 from 25% to 8% immediately led to changes in public health policy in the developed world and, with the subsequent application of potent combinations of antiretroviral drugs for the mother and judicious use of caesarean section, neonatal HIV-1 infection is now a rare event in resource-unconstrained settings. During the past 2 years, a revolutionary commitment to bring the life-saving benefits of antiretroviral treatment to the developing world has been evident. The President's Emergency Plan for AIDS Relief, the World Health Organization's 3 × 5 Initiative, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria are the most publicized aspects of this effort. However, well before these recent actions to provide treatment to millions of persons with HIV, clinical researchers around the world were attempting to develop more cost-effective strategies than the relatively complex 076 regimen to reduce MTCT of HIV-1. A number of strategies have been tested, but the one that has had the greatest impact and has created the greatest stir is the use of single-dose nevirapine (SD-NVP). In 1999, the HIV Network for Prevention Trials (HIVNET) 012 trial, performed in Uganda, reported that a single 200-mg dose of NVP given to the mother at the time of delivery followed by a single 2-mg/kg dose given to the infant within 72 h of birth resulted in a reduction in MTCT of 50% at 1416 weeks after treatment, compared with a short course of ZDV, and its persistent benefit extended to 18 months after treatment. This result was hailed as a

dramatic breakthrough, because it was an easy regimen to administer, was inexpensive, required no additional health care infrastructure, and could potentially be deployed widely and rapidly in even the most rural of settings. In recent months, the HIVNET 012 trial has come under renewed scrutiny, prompting an Institute of Medicine review.

Free full text: http://www.journals.uchicago.edu/JID/journal/issues/v192n1/34683/34683_web.pdf

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PMTCT / ARV, Viral resistance

Ivers LC, Kendrick D, Doucette K. **Efficacy of antiretroviral therapy programs in resource-poor settings: A meta-analysis of the published literature.** *Clinical Infectious Diseases* 2005;41(2):217-224.

Abstr. Background. Despite the advent of effective combination antiretroviral drug therapy (ART) for the treatment of human immunodeficiency virus (HIV) infection, many doubt the feasibility of ART treatment programs in resource-poor settings. We performed a meta-analysis of the efficacy of ART programs in the developing world. We searched the Medline database with the index terms "HIV," "antiretroviral therapy," "CD4 count," "viral load," "experience," and "outcomes." A total of 201 abstracts were reviewed, and 25 articles were selected for detailed review. Ten observational studies with details on patient outcomes were ultimately included in the analysis. Methods. Three readers independently extracted data from the articles. The details recorded included patient demographic characteristics, baseline CD4 cell counts, baseline HIV RNA viral loads, ART histories, outcomes, and timing of the outcome measure. Results. The proportion of subjects with an undetectable HIV viral load provided the measure of treatment efficacy. A random-effects model weighted the proportion of patients with undetectable viral load at various time points during ART. The proportion was 0.697 (95% CI, 0.582 - 0.812) at month 6 and 0.573 (95% CI, 0.432 - 0.715) at month 12 of ART. The provision of medications free of charge to the patient was associated with a 29% - 31% higher probability of having an undetectable viral load at months 6 and 12 than was the requirement that patients pay part or all of the cost of therapy. Conclusions. ART treatment programs in resource-poor settings have efficacy rates similar to those reported for developed countries. The provision of medications free of charge to the patient is associated with a significantly increased probability of virologic suppression at months 6 and 12 of ART.

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HAART, LICs, Treatment impact and response, Treatment programme

Johnson JA, Li JF, Morris L, Martinson N, Gray G, McIntyre J, Heneine W. **Emergence of drug-resistant HIV-1 after intrapartum administration of single-dose nevirapine is substantially underestimated.** *Journal of Infectious Diseases* 2005;192(1):16-23.

Abstr. Conventional sequence analysis detects human immunodeficiency virus (HIV)-1 drug resistance mutations in similar to 40% of women shortly after they receive intrapartum single-dose nevirapine (SD-NVP). Using sensitive real-time polymerase chain reaction assays for the K103N and Y181C resistance mutations, we tested genotyped virus before and after SD-NVP in 50 South African women infected with HIV-1 subtype C. By sequence analysis, 40 women had no detectable resistance mutations, and an additional 6 women were negative for Y181C after SD-NVP. We found K103N in 16 (40%) of 40 women and Y181C in 5 (11%) of 46 women at 6-36 weeks postpartum. Clonal sequencing confirmed K103N in 5 of 5 representative samples and Y181C in 4 of 4 samples. Four of the 5 women with newly identified Y181C also had K103N. These findings indicate that resistance mutations emerged in at least 65% of the women after SD-NVP and emphasize the importance of further research to determine the clinical implications.

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LICS / Africa, PMTCT / ARV, Viral resistance

Khoo S, Back D, Winstanley P. **The potential for interactions between antimalarial and antiretroviral drugs** [Editorial Review]. *AIDS* 2005;19(10):995-1005.

Introduction: The rapid increase in access to antiretroviral therapy in developing countries has brought with it new challenges. These include the unprecedented need for lifelong treatment for an infectious disease, and the pressure this will place on health services. The use of fixed dose combinations from generic manufacturers does not easily allow for individualization of dosage (e.g. with coadministered drugs for tuberculosis). Gaps in current knowledge that urgently need to be addressed are the effect of ethnicity, gender and body weight upon antiretroviral drug disposition, and defining interactions with other drugs, including antimalarial and antituberculosis drugs and traditional medicines. Malaria is widespread across areas of the world where resources are limited, and most of these areas also bear the brunt of the HIV pandemic. There are potentially many different ways in which both diseases interact, at political, social and public health levels, as well as emerging evidence for how one disease may affect the pathogenesis and outcome of the other. At a time when

access to antiretroviral drugs is increasing, and new combinations of antimalarial drugs are being evaluated, it is important that potential interactions between therapies for these two infections are also reviewed.

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Infections (Others) / Prophylaxis, LICs

Kovacs A, Montepiedra G, Carey V, Pahwa S, Weinberg A, Frenkel L, Capparelli E, Mofenson L, Smith E, McIntosh K, Burchett SK. **Immune reconstitution after receipt of highly active antiretroviral therapy in children with advanced or progressive HIV disease and complete or partial viral load response.** *Journal of Infectious Diseases* 2005;192(2):296-302.

Abstr. We assessed CD4 cell recovery in 175 children with advanced human immunodeficiency virus disease who had received a 4-drug antiretroviral regimen and were categorized as viral load (VL) responders (VLRs), partial VLRs, or non-VLRs. Median CD4 cell counts increased from baseline to week 48, and, among children with maximal follow-up, increases in CD4 cell counts were sustained to week 96 among VLRs and partial VLRs but not among non-VLRs. For VL rebounders still in the study, CD4 cell counts remained increased for 32 weeks after VL rebound. Sustained immunologic benefits can be achieved even with partial VL response in children with advanced disease.

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Children, HAART, Industrialized countries, Treatment impact and response

Lacombe K, Gozlan J, Boelle PY, Serfaty L, Zoulim F, Valleron AJ, Girard PM. **Long-term hepatitis B virus dynamics in HIV-hepatitis B virus-co-infected patients treated with tenofovir disoproxil fumarate.** *AIDS* 2005;19(9):907-915.

Abstr. Background: The long-term impact of tenofovir disoproxil fumarate (TDF) on hepatitis B virus (HBV) replication has not yet been studied in HIV-HBV-co-infected patients. Methods: We conducted a prospective study of HBV-DNA decay kinetics in 28 HIV-HBV-co-infected patients treated by TDF. HBV dynamics were studied using mixed linear models, and baseline factors affecting them were analysed using Cox models. Results: The HBV-DNA load declined by a mean of 4.6 log copies/ml during follow-up (mean 71 weeks), and fell below the detection limit (200 copies/ml) in 21 patients. Inhibition of viral replication by TDF was associated with a decrease in alanine aminotransferase levels (125 versus 68 IU, $P < 0.05$). HBV-DNA decay was biphasic, with an rapid fall followed by a gradual decline. Baseline factors associated with a steeper first slope in the HBV-DNA decrease were high HBV load, positive hepatitis B e antigen (HBeAg) and YMDD mutations. Baseline factors increasing the time to reach an HBV-DNA level less than 200 copies/ml were high HBV load (150 days when HBV-DNA $< 10(8)$ log, 316 days when HBV-DNA $> 10(8)$ log) and positive HBeAg. Previous exposure to lamivudine or TDF-lamivudine did not modify HBV-DNA decrease under therapy in this population with a high prevalence of YMDD mutations. Conclusion: The long-term decline in HBV DNA under TDF is biphasic and is primarily influenced by the initial HBV load. However, the clinical significance of such an association remains moderate, and TDF can be efficiently included in the highly active antiretroviral therapy regimen of HIV-HBV-co-infected patients, regardless of HBV strains and their degree of replication.

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HAART, HBV, Treatment impact and response

Laurent C, Meilo H, Guiard Schmid JB, Mapoure Y, Noel JM, M MB, Joko A, Rozenbaum W, Ntone FN, Delaporte E. **Antiretroviral therapy in public and private routine health care clinics in Cameroon: Lessons from the Douala antiretroviral (DARVIR) initiative.** *Clinical Infectious Diseases* 2005;41(1):108-111.

Abstr. A review of the hospital charts for 788 patients treated in 19 public and private clinics in Cameroon showed that clinical follow-up visits, biologic follow-up visits, and drug supply were irregular and that many patients interrupted treatment. Virological and immunologic effectiveness of therapy was as expected in patients for whom results were available.

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HAART, LICs / Africa, Treatment programme

Mermin J, Lule J, Ekwaru JP, Downing R, Hughes P, Bunnell R, Malamba S, Ransom R, Kaharuzza F, Coutinho A, Kigozi A, Quick R. **Cotrimoxazole prophylaxis by HIV-infected persons in Uganda reduces morbidity and mortality among HIV-uninfected family members.** *AIDS* 2005;19(10):1035-1042.

Abstr. Background: The effect of cotrimoxazole prophylaxis taken by persons with HIV on community health and antimicrobial resistance is unknown. Objective: To assess the effect of cotrimoxazole prophylaxis taken by persons with HIV on morbidity, mortality, and antimicrobial resistance of diarrheal pathogens infecting their HIV-negative family members. Design: Prospective cohort in rural Uganda. Methods: A total of 879 persons with HIV and 2771 HIV-negative family members received weekly home-visits. After 5 months, persons with HIV received daily cotrimoxazole prophylaxis and households were followed for an average of 17 additional months. Findings: During the study, 224 participants with HIV (25%) and 29 household members (1%) died. Mortality among HIV-negative family members < 10 years old was 63% less during the cotrimoxazole period than before [hazard ratio, 0.37; 95% confidence interval (0), 0.14-0.95; P = 0.04]. Malaria among family members was less common during cotrimoxazole treatment [incidence rate ratio (IRR), 0.62; CI, 0.53-0.74; P < 0.0001], as were diarrhea (IRR, 0.59; CI, 0.45-0.76; P = 0.0001), and hospitalizations (IRR, 0.57; CI, 0.36-0.92; P = 0.02). Death of a parent with HIV was associated with a threefold increase in mortality among HIV-negative children < 10years old (hazard ratio, 2.9; CI, 1.1-8.1; P=0.04). Of 134 bacterial isolates from family members before cotrimoxazole treatment, 89 (66%) were resistant to cotrimoxazole; of 75 recovered during cotrimoxazole treatment, 54 (72%) were resistant (P = 0.41). Interpretation: Cotrimoxazole prophylaxis taken by persons with HIV was associated with decreased morbidity and mortality among family members. Antimicrobial resistance among diarrheal pathogens infecting family members did not increase. Concerns regarding the spread of bacterial resistance should not impede implementation of cotrimoxazole programs.

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Infections (Others) / prophylaxis, LICs / Africa

Mohlala BKF, Tucker TJ, Besser MJ, Williamson C, Yeats J, Smit L, Anthony J, Puren A. **Investigation of HIV in amniotic fluid from HIV-infected pregnant women at full term.** *Journal of Infectious Diseases* 2005;192(3):488-491.

Abstr. Background. In the absence of interventions and breastfeeding, the in utero transmission rate of human immunodeficiency virus (HIV) is estimated to be 10%-15%, and the role that amniotic fluid (AF) plays in this is unclear. Objectives. Levels of cytomegalovirus (CMV) in AF and levels of HIV-1 in AF, maternal blood, and fetal cord blood were assessed. Study design. We enrolled 23 HIV-1-positive women with healthy, singleton pregnancies who underwent elective cesarean section (CS) at full term. The Roche Amplicor HIV-1 Monitor test (version 1.5) was used for determination of maternal plasma VLs. The NASBA Nuclisens assay was used for determination of VLs in other samples. To determine the feasibility of detecting viral infections in AF, CMV polymerase chain reaction DNA extraction was performed on the AF samples by use of the QIAamp DNA kit. Results. HIV-1 RNA was not detected in either AF or fetal cord blood. CMV was detected in 4 AF samples. Maternal CD4(+) T cell counts were 158-654 cells/mL (mean, 405 cells/mL). The maternal plasma VLs ranged from below detectable limits to 169,990 copies/mL (mean, 33,700 copies/mL). Conclusions. In the absence of medical complications and before labor, AF collected during elective CS from women who had received either zidovudine or nevirapine during late-stage pregnancy was free of HIV.

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Adults / Women, MTCT, Obstetrics

Ponnet M, Frederix K, Petdachai W, Wilson D, Eksaengsri A, Zachariah R. **A drug dosage table is a useful tool to facilitate prescriptions of antiretroviral drugs for children in Thailand.** *International Journal of Std and Aids* 2005;16(6):420-426.

Abstr. Scaling up of antiretroviral treatment (ART) for children in countries like Thailand will require decentralization and management by non-specialist doctors. We describe (a) the formulation of a standardized drug dosage table to facilitate antiretroviral drug (ARV) prescriptions for children, (b) the acceptability of such a table among doctors and (c) the safety and efficacy of drug doses in the table. Acceptability was assessed using a questionnaire. Safety and efficacy were assessed on the basis of incidence of adverse effects and virological response to treatment, respectively. Of all doctors (n = 18), 17 (94%) found that the table was practical to use, avoided miscalculations and made them more confident with prescriptions. Of 49 children prescribed ARVs, less than 5% had adverse side-effects. All ARV-naive children achieved undetectable viral loads within six months of ART. In our setting, a standardized drug dosage table provided a simple and reliable tool that facilitated ARV prescriptions for children.

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Children, HAART, LICs / Asia, Treatment monitoring

Puthanakit T, Oberdorfer A, Akarathum N, Kanjanavanit S, Wannarit P, Sirisanthana T, Sirisanthana V. **Efficacy of highly active antiretroviral therapy in HIV-infected children participating in Thailand's National Access to Antiretroviral Program.** *Clinical Infectious Diseases* 2005;41(1):100-107.

Abstr. Background. Programs for access to antiretroviral treatment were only recently implemented in developing countries. This study aimed to describe the effect of highly active antiretroviral therapy (HAART) in treating human immunodeficiency virus (HIV)-infected children in Thailand's National Access to Antiretroviral Program for People Living with HIV/AIDS. Methods. From August 2002 to July 2003, a total of 107 children were enrolled in the study. They received HAART consisting of either nevirapine or efavirenz, together with lamivudine and stavudine. Generic drugs and/or adult formulations were used. CD4 lymphocyte count, plasma HIV RNA level, and weight-for-age and height-for-age z scores were measured before, 2 months after, and every 6 months after initiation of HAART. A genotypic resistance assay was performed for patients with poor virological response. Results. The mean age of the patients was 7.7 years (range, 2.1-13.8 years). At baseline, the median CD4 cell percentage was 3%, and the plasma HIV RNA level was 5.4 log₁₀ copies/mL. Four patients died from HIV-related illness. After 72 weeks of HAART, the median CD4 cell percentage was 21%, and 76% of patients had HIV RNA levels of ≤ 50 copies/mL. The mean weight-for-age and height-for-age z scores increased from -1.9 to -1.3 ($P<0.0001$) and from -2.3 to -2.0 ($P<0.0001$), respectively. The percentage of patients who took >math>\geq 95\%</math> of prescribed medications during the interval between every follow-up visit was 86%. For patients with suboptimal virological response, the most common resistance mutations among HIV isolates were associated with lamivudine and with nonnucleoside reverse-transcriptase inhibitors. Conclusion. In this resource-limited setting, HAART is safe and effective for HIV-infected children despite initiation of treatment during the advanced stage of disease. The use of generic and nonpediatric drug formulations is feasible.

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Children / HAART, LICs / Asia, Treatment impact and response, Treatment programme

Rouet F, Ekouevi DK, Chaix ML, Burgard M, Inwoley A, Tony TD, Danel C, Anglaret X, Leroy V, Msellati P, Dabis F, Rouzioux C. **Transfer and evaluation of an automated, low-cost real-time reverse transcription-PCR test for diagnosis and monitoring of human immunodeficiency virus type 1 infection in a west African resource-limited setting.** *Journal of Clinical Microbiology* 2005;43(6):2709-2717.

Abstr. There is an urgent need for low-cost human immunodeficiency virus type 1 (HIV-1) viral load (VL) monitoring technologies in resource-limited settings. An automated TaqMan real-time reverse transcription-PCR (RT-PCR) assay was transferred to the laboratory of the Centre de Diagnostic et de Recherches sur le SIDA, Abidjan, Cote d'Ivoire, and assessed for HIV-1 RNA VL testing in 806 plasma samples collected within four ANRS research programs. The detection threshold and reproducibility of the assay were first determined. The quantitative results obtained with this assay were compared with two commercial HIV-1 RNA kits (the Versant version 3.0 and Monitor version 1.5 assays) in specimens harboring mainly the circulating recombinant form 02 strain (CRF02). The clinical evaluation of this test was done in different situations including the early diagnosis of pediatric infection and the monitoring of antiretroviral-treated patients. The quantification limit of our method was 300 copies/ml. The HIV-1 RNA values obtained by real-time PCR assay were highly correlated with those obtained by the Versant kit ($r = 0.901$; $P < 0.001$) and the Monitor test ($r = 0.856$; $P < 0.001$) and homogeneously distributed according to HIV-1 genotypes. For the early diagnosis of pediatric HIV-1 infection, the sensitivity and specificity of the real-time PCR assay were both 100% (95% confidence intervals of 93.7 to 100.0 and 98.3 to 100.0, respectively), compared to the Versant results. Following initiation of antiretroviral treatment, the kinetics of HIV-1 RNA levels were very comparable, with a similar proportion of adults and children below the detection limit during follow-up with our technique and the Versant assay. The TaqMan real-time PCR (\$12 per test) is now routinely used to monitor HIV-1 infection in our laboratory. This technology should be further evaluated in limited-resource countries where strains other than CRF02 are prevalent.

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Childre, Comprehensive care, LICs / Africa, PMTCT, Treatment monitoring

Rouzioux C, Hubert JB, Burgard M, Deveau C, Goujard C, Bary M, Sereni D, Viard JP, Delfraissy JF, Meyer L. **Early levels of HIV-1 DNA in peripheral blood mononuclear cells are predictive of disease progression independently of HIV-1 RNA levels and CD4(+) T cell counts.** *Journal of Infectious Diseases* 2005;192(1):46-55.

Abstr. Background. The objective of this work was to assess the role of human immunodeficiency virus (HIV) reservoirs in the risk of disease progression, by studying the relationship between HIV DNA level in peripheral blood mononuclear cells (PBMCs) and progression toward acquired immunodeficiency syndrome (AIDS). Methods. HIV-1 DNA levels in PBMCs were determined by quantitative polymerase chain reaction for 383

patients enrolled in the SEROCO Cohort Study who had experienced seroconversion and had been followed up for > 8 years. We compared the predictive values of HIV DNA level, HIV RNA level, and CD4(+) cell count. Results. Between 6 and 24 months after seroconversion, HIV DNA level was a major predictor of progression to AIDS independently of HIV RNA level and CD4(+) T cell count (adjusted relative risk [RR] for a 1-log(10) increase, 3.20 [95% confidence interval {CI}, 1.70-6.00]). HIV DNA level was also a major predictor of disease progression during the first 6 months after seroconversion (adjusted RR, 4.16 [95% CI, 1.70-10.21]), when HIV RNA level and CD4(+) T cell count were less predictive. Thus, a combination of these 3 markers provides the best estimate of the risk of disease progression for each patient. Conclusions. Our results suggest that HIV DNA level could be a useful additional marker in clinical practice and could aid in helping to define the best time to initiate treatment for each patient.

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Industrialized countries, Treatment monitoring

Seyler C, Toure S, Messou E, Bonard D, Gabillard D, Anglaret X. **Risk factors for active tuberculosis after antiretroviral treatment initiation in Abidjan.** American Journal of Respiratory and Critical Care Medicine 2005;172(1):123-127.

Abstr. Rationale: In sub-Saharan Africa: (1) tuberculosis is the first cause of HIV-related mortality; (2) the incidence of tuberculosis in adults receiving highly active antiretroviral therapy (HAART) is lower than in untreated HIV-infected adults but higher than in HIV-negative adults; and (3) factors associated with the occurrence of tuberculosis in patients receiving HAART have never been described. Objective. To look for the risk factors for active tuberculosis in HIV-infected adults receiving HAART in Abidjan. Methods: Seven-year prospective cohort of HIV-infected adults, with standardized procedures for documenting morbidity. We analyzed the incidence of active tuberculosis in patients who started HAART and the association between the occurrence of tuberculosis and the characteristics of these patients at HAART initiation. Main Results: A total of 129 adults (median baseline CD4 count 125/mm³) started HAART and were then followed for 270 person-years (P-Y). At HAART initiation, 31 had a history of tuberculosis and none had current active tuberculosis. During follow-up, the incidence of active tuberculosis was 4.8/100 P-Y (95% confidence interval [CI], 2.5-8.3) overall, 3.0/100 P-Y (95% CI, 1.1-6.6) in patients with no tuberculosis history, and 11.3/100 P-Y (95% CI, 4.1-24.5) in patients with a history of tuberculosis (adjusted hazard ratio, 4.64; 95% CI, 1.29-16.62, p = 0.02). Conclusion: The risk of tuberculosis after HAART initiation was significantly higher in patients with a history of tuberculosis than in those with no tuberculosis history. If confirmed by others, this finding could lead to assessment of new patterns of time-limited tuberculosis secondary chemoprophylaxis during the period of initiation of HAART in sub-Saharan African adults.

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HAART, LICs / Africa, TB, Treatment impact and response

Timmermans S, Tempelman C, Godfried MH, Nellen J, Dieleman J, Sprenger H, Schneider MEE, de Wolf F, Boer K, van der Ende ME. **Nelfinavir and nevirapine side effects during pregnancy.** AIDS 2005;19(8):795-9.

Abstr. Background: The risk of vertical transmission of HIV has been substantially reduced since the introduction of highly active antiretroviral therapy (HAART); however, the impact of taking HAART during pregnancy on the woman, the fetus and the infant is not yet understood. Objective: To assess and compare tolerability, safety and efficacy of nelfinavir- or nevirapine-containing HAART in a cohort of pregnant and non-pregnant HIV-infected women in the Netherlands. Design: Retrospective comparative study. Methods: In 15 centres specializing in HIV in the Netherlands, data on patient characteristics, HAART, adverse events, viral load response, mode of delivery and HIV status of the neonate were obtained from medical records of HIV-infected pregnant women who received HAART during pregnancy between January 1997 and June 2003. These data were compared with a control group of HIV-infected non-pregnant women that was obtained from the Dutch HIV-monitoring foundation database. Results: Data from 186 pregnant and 186 non-pregnant HIV-infected women using a nelfinavir- or nevirapine-containing regimen were analysed. The pregnant women were younger, used a nelfinavir containing regimen more often, had higher CD4 cell counts and lower HIV RNA levels. Nelfinavir-related gastrointestinal symptoms (P < 0.001), hyperglycaemia (P < 0.001) and nevirapine-related hepatotoxicity (P = 0.003) occurred more often during pregnancy. The risk of nevirapine-induced rash was not increased. No major adverse events occurred. Conclusion: Nelfinavir- or nevirapine-containing HAART regimens during pregnancy are well tolerated. Side effects of antiretroviral therapy are more frequent in pregnant than in non-pregnant women. (c) 2005 Lippincott Williams and Wilkins.

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HAART, Industrialized countries, PMTCT / ARV, Treatment complications