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## HIV Care & PMTCT in Resource-Limited Settings

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prepared by the Bordeaux Working Group

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Bolhaar MG, Karstaedt AS. **A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa.** *Clinical Infectious Diseases* 2007;45(2):254-260.

**Abstr.** Background. Lactic acidosis and symptomatic hyperlactatemia may complicate nucleoside reverse-transcriptase inhibitor use. Females may be at increased risk for such complications. Our study evaluated the incidence of lactic acidosis and symptomatic hyperlactatemia by sex, analyzed clinical features, and described the safety of reintroducing highly active antiretroviral therapy (HAART) with zidovudine replacing stavudine. Methods. A retrospective cohort analysis was performed for 1735 adults (63% of whom were female) who initiated HAART from April 2004 through August 2005 in Soweto, South Africa, with follow-up until February 2006. Patients with lactate levels  $\geq$  4.5 mmol/L and no potential cause of elevated lactic acidosis other than receipt of HAART were included in the study. Results. A total of 23 patients (22 of whom were female) experienced lactic acidosis. The overall incidence was 10.6 cases per 1000 patient-years; the incidence was 16.1 cases per 1000 patient-years in female patients and 1.2 cases per 1000 patient-years in male patients. Seven (30.4%) of the patients died. Eight (34.8%) of the patients were obese (body mass index [calculated as weight in kilograms divided by the square of height in meters],  $\geq$  30) at HAART initiation. Forty-four patients (37 of whom were female) had symptomatic hyperlactatemia. The overall incidence was 20.2 cases per 1000 patient-years, with an incidence of 27.0 cases per 1000 patient-years in female patients and 8.7 cases per 1000 patient-years in male patients. None of the patients died. Nine (20.4%) of the patients were obese at HAART initiation. Sixty-six of 67 patients were receiving stavudine, and 5 patients were receiving didanosine. Among 56 patients who restarted HAART with zidovudine for a cumulative nucleoside reverse-transcriptase inhibitor reexposure of 44.6 patient-years-including 41 patients who received treatment for  $\geq$  9 months-there were no relapses. Conclusion. Women in Soweto, South Africa, have a higher frequency of symptomatic hyperlactatemia and lactic acidosis than has been reported for patients in other study groups. In cases associated with stavudine use, restarting HAART with zidovudine seemed to be safe and effective for patients with limited nucleoside reverse-transcriptase inhibitor alternatives.

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Currier JS. **Sex differences in antiretroviral therapy toxicity: Lactic acidosis, stavudine, and women.** *Clinical Infectious Diseases* 2007;45(2):261-262.

**Abstr. NA**

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Gupta A, Nayak U, Ram M, Bhosale R, Patil S, Basavraj A, Kakrani A, Philip S, Desai D, Sastry J, Bollinger RC. **Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in Pune, India, 2002-2005.** *Clinical Infectious Diseases* 2007;45(2):241-249.

**Abstr.** Background. In contrast with many other countries, isoniazid preventative therapy is not recommended in clinical care guidelines for human immunodeficiency virus (HIV)-infected persons with latent tuberculosis (TB) in India. Methods. Seven hundred fifteen HIV-infected mothers and their infants were prospectively followed up for 1 year after delivery at a public hospital in Pune, India. Women were evaluated for active TB during regular clinic visits, and tuberculin skin tests were performed. World Health Organization definitions for confirmed, probable, and presumed TB were used. Poisson regression was performed to determine correlates of incident TB, and adjusted probabilities of mortality were calculated. Results. Twenty-four of 715 HIV-infected women who were followed up for 480 postpartum person-years developed TB, yielding a TB incidence of 5.0 cases per 100 person-years (95% confidence interval [CI], 3.2-7.4 cases per 100 person-years). Predictors of incident TB included a baseline CD4 cell count  $<$  200 cells/mm<sup>3</sup> (adjusted incident rate ratio [IRR], 7.58; 95% CI, 3.07-18.71), an HIV load  $\geq$  150,000 copies/mL (adjusted IRR, 3.92; 95% CI, 1.69-9.11), and a positive

tuberculin skin test result ( adjusted IRR, 3.08; 95% CI, 1.27-7.47). Three ( 12.5%) of 24 women with TB died, compared with 7 ( 1.0%) of 691 women without TB ( IRR, 12.2; 95% CI, 2.03-53.33). Among 23 viable infants with mothers with TB, 2 received a diagnosis of TB. Four infants with mothers with TB died, compared with 28 infants with mothers without TB ( IRR, 4.71; 95% CI, 1.19-13.57). Women with incident TB and their infants had a 2.2- and 3.4-fold increased probability of death, respectively, compared with women without active TB and their infants, controlling for factors independently associated with mortality ( adjusted IRR, 2.2 [ 95% CI, 0.6-3.8] and 3.4 [ 95% CI, 1.22-10.59], respectively). Conclusions. Among Indian HIV-infected women, we found a high incidence of postpartum TB and associated postpartum maternal and infant death. Active screening and targeted use of isoniazid preventative therapy among HIV-infected women in India should be considered to prevent postpartum maternal TB and associated mother-to-child morbidity and mortality.

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John Stewart GC. **Breast-feeding and HIV-1 transmission - How risky for how long?** Journal of Infectious Diseases 2007;196(1):1-3.

**Abstr. NA**

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Kiguba R, Byakika Tusiime J, Karamagi C, Ssali F, Mugenyi P, Katabira E. **Discontinuation and modification of highly active antiretroviral therapy in HIV-infected Ugandans - Prevalence and associated factors.** Journal of Acquired Immune Deficiency Syndromes 2007;45(2):218-223.

**Abstr.** Background: Data on discontinuation and modification of highly active antiretroviral therapy (HAART) are scarce among sub-Saharan African populations. We sought to estimate the prevalence and to identify factors associated with these phenomena in our resource-limited setting. Methods: Patients were recruited into this cross-sectional study from 2 treatment centers in Kampala, Uganda. Discontinuation and modification were assessed by self-report using semistructured quantitative and unstructured qualitative interviews. Discontinuation was defined as the simultaneous stopping of all antiretrovirals for at least 1 month, and modification as the changing of at least 1 antiretroviral used in an initial HAART regimen. Factors independently associated with each outcome were assessed using multivariate logistic regression. Results: Of 686 subjects evaluated, 94 (13.7%) had ever discontinued therapy, whereas 175 (25.5%) had ever modified their regimen. The median CD4 count was 175 (interquartile range: 66-297) cells/ $\mu$  L. Factors associated with discontinuation were HAART experience before starting the current regimen (odds ratio [OR] = 3.70, 95% confidence interval [CI]: 2.13 to 6.25), use of alternative medicines (OR = 2.18, 95% CI: 1.06 to 4.47), hospitalization (OR = 2.36, 95% CI: 1.32 to 4.20), and 1 year or less on HAART (OR = 11.11, 95% CI: 5.00 to 25.00). Modification was associated with more than 3 months' duration on HAART (OR = 3.13, 95% CI: 1.16 to 8.33) and being unmarried (OR = 1.64, 95% CI: 1.02 to 2.70). Conclusions: The proportions of discontinuation and modification of antiretroviral therapy (ART) observed in our resource-poor setting pose a challenge to the limited treatment options presently available. Drug cost as a major reason for discontinuation of HAART has major implications for ART programs that charge fees in resource-limited settings.

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Martinson NA, Ekouevi DK, Dabis F, Morris L, Lupodwana P, Tonwe Gold B, Dhlamini P, Becquet R, Steyn JG, Leroy V, Viho I, Gray GE, McIntyre JA. **Transmission rates in consecutive pregnancies exposed to single-dose Nevirapine in Soweto, South Africa and Abidjan, Cote d'Ivoire.** Journal of Acquired Immune Deficiency Syndromes 2007; 45(2):206-209.

**Abstr.** Background: Large numbers of women receive single-dose nevirapine (sdNVP) to prevent mother-to-child transmission (MTCT) of HIV; over time, an increasing proportion will return to prevention of MTCT programs for a second pregnancy. Because sdNVP selects resistance in a high percentage of women, we compared the effectiveness of sdNVP in preventing peripartum MTCT in successive pregnancies. Methods: Prospective cohorts were recruited from MTCT programs in South Africa and Cote d'Ivoire. HIV-1-infected women and their infants exposed to sdNVP in 2 consecutive pregnancies-used alone or with zidovudine (ZDV) or ZDV plus lamivudine-were included. Results: The median age of women at their initial exposure to sdNVP in Soweto (n = 120) and Abidjan (n = 41) was 26 (interquartile range [IQR]: 22-29) years and 28 (IQR: 24-31) years, respectively, and their median delivery interval was 21 (IQR: 15-29) months and 26 (IQR: 20-32) months, respectively. Transmission rates in Soweto and in Abidjan were 11.1% and 13.2% for the first pregnancy and 11.1% and 5.4% for the second pregnancy (P = 1.000 and P = 0.449 for Soweto and Abidjan, respectively, in impaired analysis). Conclusion: This analysis suggests that the effectiveness of sdNVP when used in successive pregnancies is probably not impaired, possibly because viral resistance selected by prior exposure to sdNVP may wane with time.

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May M. **Prognosis of HIV-1-infected patients up to 5 years after initiation of HAART: collaborative analysis of prospective studies.** AIDS 2007; 21(9):1185-1197.

**Abstr.** Objective: To estimate the prognosis over 5 years of HIV-1-infected, treatment-naive patients starting HAART, taking into account the immunological and virological response to therapy. Design: A collaborative analysis of data from 12 cohorts in Europe and north America on 20379 adults who started HAART between 1995 and 2003. Methods: Parametric survival models were used to predict the cumulative incidence at 5 years of a new AIDS-defining event or death, and death alone, first from the start of HAART and second from 6 months after the start of HAART. Data were analysed by intention-to-continue-treatment, ignoring treatment changes and interruptions. Results: During 61 798 person-years of follow-up, 1005 patients died and an additional 1303 developed AIDS. A total of 10046 (49%) patients started HAART either with a CD4 cell count of less than 200 cells/ $\mu$ l or with a diagnosis of AIDS. The 5-year risk of AIDS or death (death alone) from the start of HAART ranged from 5.6 to 77% (1.8-65%), depending on age, CD4 cell count, HIV-1-RNA level, clinical stage, and history of injection drug use. From 6 months the corresponding figures were 4.1-99% for AIDS or death and 1.3-96% for death alone. Conclusion: On the basis of data collected routinely in HIV care, prognostic models with high discriminatory power over 5 years were developed for patients starting HAART in industrialized countries. A risk calculator that produces estimates for progression rates at years 1 to 5 after starting HAART is available from [www.artcohort-collaboration.org](http://www.artcohort-collaboration.org).

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Mocroft A, Phillips A, Gatell J, Ledergerber B, Fisher M, Clumeck N, Losso M, Lazzarin A, Fatkenheuer G, Lundgren JD. **Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study.** *Lancet* 2007;370(9585):407-413.

**Abstr.** Background Combination antiretroviral therapy (cART) has been shown to reduce mortality and morbidity in patients with HIV. As viral replication falls, the CD4 count increases, but whether the CD4 count returns to the level seen in HIV-negative people is unknown. We aimed to assess whether the CD4 count for patients with maximum virological suppression (viral load <50 copies per mL) continues to increase with long-term CART to reach levels seen in HIV-negative populations. Methods We compared increases in CD4 counts in 1835 antiretroviral-naive patients who started CART from EuroSIDA, a pan-European observational cohort study. Rate of increase in CD4 count (per year) occurring between pairs of consecutive viral loads below 50 copies per mL was estimated using generalised linear models, accounting for multiple measurements for individual patients. Findings The median CD4 count at starting CART was 204 cells per mu L (IQR 85-330). The greatest mean yearly increase in CD4 count of 100 cells per mu L was seen in the year after starting CART. Significant, but lower, yearly increases in CD4 count, around 50 cells per mu L, were seen even at 5 years after starting CART in patients whose current CD4 count was less than 500 cells per mu L. The only groups without significant increases in CD4 count were those where CART had been taken for more than 5 years with a current CD4 count of more than 500 cells per mu L, (current mean CD4 count 774 cells per mu L; 95% CI 764-783). Patients starting CART with low CD4 counts (<200 cells per mu L) had significant rises in CD4 counts even after 5 years of CART. Interpretation Normalisation of CD4 counts in HIV-infected patients for all infected individuals might be achievable if viral suppression with cART can be maintained for a sufficiently long period of time.

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Mocroft A, Staszewski S, Weber R, Gatell J, Rockstroh J, Gasiorowski J, Panos G, Monforte AD, Rakhmanova A, Phillips AN, Lundgren JD. **Risk of discontinuation of nevirapine due to toxicities in antiretroviral-naive and -experienced HIV-infected patients with high and low CD4(+) T-cell counts.** *Antiviral Therapy* 2007;12 (3):325-333.

**Abstr.** Introduction: It is unknown whether the increased risk of toxicities in antiretroviral-naive HIV-infected patients initiating nevirapine-based (NVPc) combination antiretroviral therapy (cART) with high CD4(+) T-cell counts is also observed when NVPc is initiated in cART-experienced patients. Patients and methods: 1,571 EuroSIDA patients started NVPc after 1/1/1999, with CD4(+) T-cell counts and viral load measured in the 6 months before starting treatment, and were stratified into four groups based on CD4+ T-cell counts at initiation of NVPc (high [H], >400/mm<sup>3</sup> or >250/mm<sup>3</sup> for male or female, respectively, or low [L], ≤ 400/mm<sup>3</sup> or ≤ 250/mm<sup>3</sup> for male or female) and prior antiretroviral experience (antiretroviral-naive [N] or -experienced [E]). Cox proportional hazards models compared the risks of discontinuation of nevirapine due to toxicities or patient/physician choice (TOXPC). Results: After adjustment, there was a significantly lower risk of discontinuation of nevirapine due to TOXPC in the HE group (n=588; proportion discontinued by 3/12 months: 10/17%, respectively) than in HN (n=62; 21/32% respectively; overall relative hazard [RH]: 0.56; 95% confidence interval [CI]: 0.34-0.94; P=0.027). This difference was most pronounced during the first 3 months of NVPc [RH: 0.44; 95% CI: 0.23-0.87; P=0.017]. There were no deaths in the 6 months after starting NVPc resulting from exposure to <3 months of NVPc exposure within the HE group (incidence: 0; per 1,000 person-years follow up; 95% CI: 0-6.9). After adjustment, there were no differences between the HE and HN groups in discontinuation due to TOXPC in patients starting efavirenz-based cART (RH: 0.91; 95% CI: 0.60-1.38; P=0.66) or protease-inhibitor-based cART (RH: 1.13; 95% CI: 0.77-1.66; P=0.52). Conclusions: Results from this non-randomized study suggest that NVPc might

be safer to initiate in antiretroviral-experienced than in anti retroviral-naive patients with high CD4(+) T-cell counts.

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Mofenson LM, Laughon BE. **Human immunodeficiency virus, Mycobacterium tuberculosis, and pregnancy: A deadly combination.** Clinical Infectious Diseases 2007; 45(2):250-253.

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Myer L, Denny L, Wright TC, Kuhn L. **Prospective study of hormonal contraception and women's risk of HIV infection in South Africa.** International Journal of Epidemiology 2007; 36(1):166-174.

**Abstr.** Background Many women using hormonal contraceptives are also at risk of sexually transmitted HIV infection, but data are mixed on whether hormonal contraception increases women's risk of HIV. We investigated associations between HIV incidence and use of combined oral contraceptives (COC), norethindrone enanthate (NET-EN) or depot medroxyprogesterone acetate (DMPA) in a cohort of South African women. Methods Participants were 4200 HIV-negative women aged 35-49 years enrolled into a cervical cancer screening trial. At enrollment, women were tested for sexually transmitted infections and reported on their sexual behaviour and contraceptive use. During the 24 months of follow-up, women reported on their sexual behaviours and contraceptive use and underwent repeat HIV testing. Results During the 5010 person-years of follow-up, 111 incident HIV infections were observed (HIV incidence, 2.2 infections/100 person-years). At enrollment, 21% of women reported using hormonal contraception, primarily DMPA (14% of all women) or NET-EN (5%). After adjusting for sexual risk behaviours and sexually transmitted infections, the incidence of HIV was similar among women using COC, NET-EN or DMPA compared with women not using any hormonal method [incidence rate ratios and 95% confidence intervals, 0.65, 0.16-2.66; 0.79, 0.31-2.02 and 0.96, 0.58-1.59, respectively]. There was also no association between increased duration of DMPA use and HIV incidence (P-value for trend, 0.51). Conclusions These findings contribute to the evidence from general population cohorts of women that hormonal contraceptive use is not associated with increased risk of HIV acquisition. Nonetheless, family planning services are an important venue for HIV prevention activities.

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Orrell C, Harling G, Lawn SD, Kaplan R, McNally M, Bekker LG, Wood R. **Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited.** Antiviral Therapy 2007; 12 (1):83-88.

**Abstr.** Objectives: To determine rates and causes of switching from first- to second-line antiretroviral treatment (ART) regimens in a large treatment-naive cohort (a South African community-based ART service) where a targeted adherence intervention was used to manage initial virological breakthrough. Methods: ART-naive adults (n=929) commencing first-line non-nucleoside-based ART [according to WHO (2002) guidelines] between September 2002 and August 2005 were studied prospectively. Viral load (VL) and CD4(+) T-cell counts were monitored every 4 months. All drug switches were recorded. Counsellor-driven adherence interventions were targeted to patients with a VL > 1,000 copies/ml at any visit (virological breakthrough) and the VL measurement was repeated within 8 weeks. Two consecutive VL measurements > 1,000 copies/ml was considered virological failure, triggering change to a second-line regimen. Results: During 760 person-years of observation [median (IQR) 189 (85-441) days], 823 (89%) patients were retained on ART, 2% transferred elsewhere, 7% died and 3% were lost to follow-up. A total of 893 (96%) patients remained on first-line therapy and 16 (1.7%) switched

to second-line due to hypersensitivity reactions (n=9) or lactic acidosis (n=7). A Kaplan-Meier estimate for switching to second-line due to toxicity was 3.0% at 32 months. Virological breakthrough occurred in 67 (7.2%) patients, but, following use of a targeted adherence intervention, virological failure was confirmed in just 20 (2.2%). Kaplan-Meier estimates at 32 months were 20% for virological breakthrough but only 5.6% for confirmed virological failure. Conclusion: Regimen switches were due to virological failure or toxicity. Although follow-up time was limited, over 95% of individuals remained on first-line ART using a combination of viral monitoring and a targeted adherence intervention.

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Padian NS, van der Straten A, Ramjee G, Chipato T, de Bruyn G, Blanchard K, Shiboski S, Montgomery ET, Fancher H, Cheng H, Rosenblum M, van der Laan M, Jewell N, McIntyre J. **Diaphragm and lubricant gel for prevention of HIV acquisition in southern African women: a randomised controlled trial.** *Lancet* 2007;370(9583):251-261.

**Abstr.** Background Female-controlled methods of HIV prevention are urgently needed. We assessed the effect of provision of latex diaphragm, lubricant gel, and condoms (intervention), compared with condoms alone (control) on HIV seroincidence in women in South Africa and Zimbabwe. Methods We did an open-label, randomised controlled trial in HIV-negative, sexually active women recruited from clinics and community-based organisations, who were followed up quarterly for 12-24 months (median 21 months). All participants received an HIV prevention package consisting of pre-test and post-test counselling about HIV and sexually transmitted infections, testing, treatment of curable sexually transmitted infections, and intensive risk-reduction counselling. The primary outcome was incident HIV infection. This study is registered with ClinicalTrials.gov, number NCT00121459. Findings Overall HIV incidence was 4.0% per 100 woman-years: 4.1% in the intervention group (n=2472) and 3.9% in the control group (n=2476), corresponding to a relative hazard of 1.05 (95% CI 0.84-1.32, intention-to-treat analysis). The proportion of women using condoms was significantly lower in the intervention than in the control group (54% vs 85% of visits,  $p < 0.0001$ ). The proportions of participants who reported adverse events (60% [1523] vs 61% [1529]) and serious adverse events (5% [130] vs 4% [101]) were similar between the two groups. Interpretation We observed no added protective benefit against HIV infection when the diaphragm and lubricant gel were provided in addition to condoms and a comprehensive HIV prevention package. Our observation that lower condom use in women provided with diaphragms did not result in increased infection merits further research. Although the intervention seemed safe, our findings do not support addition of the diaphragm to current HIV prevention strategies.

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Schackman BR, Neukermans CP, Fontain SNN, Nolte C, Joseph P, Pape JW, Fitzgerald DW. **Cost-effectiveness of rapid syphilis screening in prenatal HIV testing programs in Haiti - art. no. e183.** *Plos Medicine* 2007;4(5):937-947.

**Abstr.** Background New rapid syphilis tests permit simple and immediate diagnosis and treatment at a single clinic visit. We compared the cost- effectiveness, projected health outcomes, and annual cost of screening pregnant women using a rapid syphilis test as part of scaled- up prenatal testing to prevent mother- to- child HIV transmission in Haiti. Methods and Findings A decision analytic model simulated health outcomes and costs separately for pregnant women in rural and urban areas. We compared syphilis syndromic surveillance ( rural standard of care), rapid plasma reagin test with results and treatment at 1- wk follow- up ( urban standard of care), and a new rapid test with immediate results and treatment. Test performance data were from a World Health Organization - Special Programme for Research and Training in Tropical Diseases field trial conducted at the GHESKIO Center Groupe Haitien d'Etude du Sarcome de Kaposi et

des Infections Opportunistes in Port- au- Prince. Health outcomes were projected using historical data on prenatal syphilis treatment efficacy and included disability-adjusted life years ( DALYs) of newborns, congenital syphilis cases, neonatal deaths, and stillbirths. Cost- effectiveness ratios are in US dollars/ DALY from a societal perspective; annual costs are in US dollars from a payer perspective. Rapid testing with immediate treatment has a cost- effectiveness ratio of \$ 6.83/ DALY in rural settings and \$ 9.95/ DALY in urban settings. Results are sensitive to regional syphilis prevalence, rapid test sensitivity, and the return rate for follow- up visits. Integrating rapid syphilis testing into a scaled- up national HIV testing and prenatal care program would prevent 1,125 congenital syphilis cases and 1,223 stillbirths or neonatal deaths annually at a cost of \$ 525,000. Conclusions In Haiti, integrating a new rapid syphilis test into prenatal care and HIV testing would prevent congenital syphilis cases and stillbirths, and is cost- effective. A similar approach may be beneficial in other resource- poor countries that are scaling up prenatal HIV testing.

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Seyler C, Adje Toure C, Messou E, Dakoury Dogbo N, Rouet F, Gabillard D, Nolan M, Toure S, Anglaret X. **Impact of genotypic drug resistance mutations on clinical and immunological outcomes in HIV-infected adults on HAART in West Africa.** AIDS 2007; 21(9):1157-1164.

**Abstr.** Objectives: To analyse the association between the presence of resistance mutations and treatment outcomes. The impact of HIV-1 drug resistance mutations in African adults on HAART has so far never been reported. Methods: In 2004 in Abidjan, Cote d'Ivoire, 106 adults on HAART had plasma viral load measurements. Patients with detectable viral loads had resistance genotypic tests. Patients were followed until 2006. Main outcomes were serious morbidity and immunological failure (CD4 cell count < 200 cells/ $\mu$ l). Results: At study entry, the median previous time on HAART was 37 months and the median CD4 cell count was 266 cells/ $\mu$ l; 58% of patients had undetectable viral loads, 20% had detectable viral loads with no major resistance mutations, and 22% had detectable viral loads with one or more major mutations. The median change in CD4 cell count between study entry and study termination was +129 cells/ $\mu$ l in patients with undetectable viral loads, +51 cells/ $\mu$ l in those with detectable viral loads with no mutations and +3 cells/ $\mu$ l in those with detectable viral loads with resistance mutations. Compared with patients with undetectable viral loads, those with detectable viral loads with resistance mutations had adjusted hazard ratios of immunological failure of 4.32 (95%CI 1.38-13.57, P = 0.01). One patient died. The 18-month probability of remaining free of morbidity was 0.79 in patients with undetectable viral loads and 0.69 in those with resistance mutations (P=0.19). Conclusion: In this setting with restricted access to second-line HAART, patients with major resistance mutations had higher rates of immunological failure, but most maintained stable CD4 cell counts and stayed alive for at least 20 months.

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Taha TE, Hoover DR, Kumwenda NI, Fiscus SA, Kafulafula G, Nkhoma C, Chen S, Piwovar E, Broadhead RL, Jackson JB, Miotti PG. **Late postnatal transmission of HIV-1 and associated factors.** Journal of Infectious Diseases 2007; 196(1):10-14.

**Abstr.** Background. The present study was undertaken to determine the risk and timing of late postnatal transmission ( LPT) of human immunodeficiency virus type 1 ( HIV-1). Methods. Breast-fed infants previously enrolled in 2 trials of antiretroviral prophylaxis were monitored in Malawi. Kaplan-Meier and proportional hazard models assessed cumulative incidence and association of factors with LPT. Results. Overall, 98 infants were HIV infected, and 1158 were uninfected. The cumulative risk of LPT at age 24 months was 9.68% ( 95% confidence interval, 7.80%-11.56%). The interval hazards at 1.5-6, 6-12, 12-18, and 18-24 months were 1.22%, 4.05%, 3.48%, and 1.27%,

respectively. Conclusions. The risk of LPT beyond 6 months is substantial. Weaning at 6 months could prevent >85% of LPT.

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van Griensven J, De Naeyer L, Mushi T, Ubarijoro S, Gashumba D, Gazille C, Zachariah R. **High prevalence of lipoatrophy among patients on stavudine-containing first-line antiretroviral therapy regimens in Rwanda.** Transactions of the Royal Society of Tropical Medicine and Hygiene 2007;101(8):793-798.

**Abstr.** This study was conducted among individuals placed on WHO-recommended first-line antiretroviral therapy (ART) at two urban health centres in Kigali, Rwanda, in order to determine (a) the overall prevalence of lipodystrophy and (b) the risk factors for lipoatrophy. Consecutive individuals on ART for > 1 year were systematically subjected to a standardised case definition-based questionnaire and clinical assessment. Of a total of 409 individuals, 370 (90%) were on an ART regimen containing stavudine (d4T), whilst the rest were receiving a zidovudine (AZT)-containing regimen. Lipodystrophy was apparent in 140 individuals (34%), of whom 40 (9.8%) had isolated lipoatrophy, 20 (4.9%) had isolated lipohypertrophy and 80 (19.6%) had mixed patterns. Fifty-six percent of patients reported the effects as disturbing. The prevalence of lipoatrophy was more than three times higher when taking d4T compared with AZT-containing regimens (31.4% vs. 10.3%). Being female, d4T-based ART, baseline body mass index  $\geq 25$  kg/m<sup>2</sup> or baseline CD4 count  $\geq 150$  cells/ $\mu$ l and increasing duration of ART were all significantly associated with lipoatrophy. Lipoatrophy appears to be an important long-term complication of WHO-recommended first-line ART regimens. These data highlight the urgent need for access to more affordable and less toxic ART regimens in resource-limited settings.

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Vekemans M, John L, Colebunders R. **When to switch for antiretroviral treatment failure in resource-limited settings?** AIDS 2007;21(9):1205-1206.

**Abstr. NA**

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Violari A, Cotton M, Gibb D, Babiker A, Steyn J, Jean-Philippe P, McIntyre J. **ART initiated before 12 weeks reduces early mortality in young HIV-infected infants: evidence from the Children with HIV Early Antiretroviral Therapy (CHER) Study.** Late breaker IAS Conference, Sidney (abstract WESS103) 2007.

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**Note** on a ground-breaking study in which investigators at the Sidney IAS conference last July reported critical interim results from the CHER phase III randomized trial of immediate versus deferred antiretroviral therapy (ART) for 6- to 12-week-old HIV infected infants in South Africa. Though this study has not yet been published, we have chosen to highlight its importance as it may have an immediate or at least rapid impact upon paediatric treatment guidelines in resource-limited settings and is likely to affect practice as well as encourage further research. The premises for this research study were that ART in infants is known to be complex but probably worth to initiate due to the early and high risk of death and disease progression in infancy<sup>1, 2</sup> as well as the poor predictive value of CD4 count and plasma viral load as indicators of disease progression. Comparative prospective data were thus needed to inform on ART guidelines in vertically HIV-infected infants.

At present, the World Health Organization (WHO) guidelines encourage the treatment of infants <18 months when CD4 percentage is <25% or according to clinical criteria (stage III and IV). The hypothesis of this study was that early limited ART until the 1st or 2nd

birthday will have a long term benefit by delaying disease progression and delay time when long-term continuous ART needs to be started.

In this randomized trial, the investigators reported that 375 infants diagnosed HIV-infected before 12 weeks, ART naïve except for prevention of mother-to-child transmission [PMTCT]) and with CD4 % >25% were enrolled into three arms: 1/ the differed arm (n=125), 2/ the short-course arm to 1st birthday (n =125) and lastly a long-course arm up to the second birthday. Infants were started or restarted on ART if CD4 % < 20% (<25% from August 2006) or in case of clinical events and follow-up is scheduled for a minimum of 3.5 years. Primary endpoints were death or failure of first-line regimen, which in this trial was a regimen of zidovudine, lamivudine and ritonavir-boosted lopinavir.

An independent review panel closed the differed arm in June 07 when the risk of death proved 75% lower in the 252 early-treated children compared to the 125 children randomized to the differed arm. After a median follow-up of 32 weeks (inter-quartile range: 20-48), 10 children (4%) had died in the early-treated arm versus 20 (16%) in the late-treated arm (Hazard ratio: 0.24; [95% CI/ 0.11-0.52], p=0002).

These provocative although interim results have shown directly for the first time that early treatment in infants might be the way forward to avoid the high mortality seen in vertically HIV-infected children. A move toward earlier treatment in infants will require timely review of current international guidelines. Also as the authors point out, these results support the need for enhanced effectiveness of PMTCT programmes and the promotion of early infant diagnosis leading to effective transition to care. Finally, whether pediatric ART can be interrupted later on after such early initiation is the last scientific question the CHER trial should answer within the next two years.

#### **Références**

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