



ICAP
International Center for AIDS
Care and Treatment Programs
MAILMAN SCHOOL OF PUBLIC HEALTH
Columbia University



WHO. Dpt of HIV/AIDS

HIV Care & PMTCT in Resource-Limited Settings

Monthly Intelligence Report
2008, Vol 4, Issue 2

[Back Issues on Line](#)

prepared by the Bordeaux Working Group

Members: Elise Arrivé, Renaud Becquet, François Dabis (Chair), Valériane Leroy, Charlotte Lewden, Evelyne Mouillet (Coordinator), Joanna Orne-Gliemann (Coordinator), Freddy Perez, Besigin Tonwe-Gold; Hapsatou Touré.

Number of citations selected for this issue: 23

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

Arribas JR, Pozniak AL, Gallant JE, DeJesus E, Gazzard B, Campo RE, Chen SS, McColl D, Holmes CB, Enejosa J, Toole JJ, Cheng AK. **Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients - 144-week analysis.** Journal of Acquired Immune Deficiency Syndromes 2008;47(1):74-78.

Abstr. Background: As antiretroviral regimens for the treatment of HIV infection improve, trials providing data on long-term follow-up are increasingly important. Methods: A regimen of tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), and efavirenz (EFV) demonstrated superior virologic, immunologic and morphologic effects compared with a regimen of fixed-dose zidovudine/lamivudine (ZDV/3TC) and EFV through 96 weeks in a randomized open-label trial. After 96 weeks, patients on TDF + FTC transitioned to fixed-dose combination TDF/FTC. Results: Through 144 weeks, significantly more patients in the TDF/FTC arm reached and maintained an HIV RNA level <400 copies/mL (71% receiving TDF/FTC and EFV vs. 58% receiving ZDV/3TC and EFV; P = 0.004), with a trend toward greater CD4 cell increase in the TDF/FTC arm (312 vs. 271 cells/mm³; P = 0.09). Over 144 weeks of follow-up, more patients in the ZDV/3TC arm discontinued therapy because of adverse events (11% vs. 5%; P = 0.01) and no patients discontinued because of renal events. Patients in the ZDV/3TC arm had significantly less limb fat than patients in the TDF/FTC arm (5.4 vs. 7.9 kg; P < 0.001) at 144 weeks. Conclusions: Cumulative results from 3 years of follow-up suggest that a regimen of TDF/FTC and EFV demonstrates superior durability of viral load suppression and an improved safety and morphologic profile compared with ZDV/3TC and EFV.

Address: Holmes, CB; Gilead Sci Inc; 300 Lakeside Dr; Foster City; CA 94404; USA. charles.holmes@gilead.com

Aurpibul L, Puthanakit T, Lee B, Mangklabruks A, Sirisanthana T, Sirisanthana V. **Lipodystrophy and metabolic changes in HIV-infected children on non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy.** Antiviral Therapy 2007;12 (8):1247-1254.

Abstr. Background: Highly active antiretroviral therapy (HAART) has recently been implemented in Thailand. Its long-term effects have not been clearly evaluated. The objective of this study was to estimate the prevalence of lipodystrophy (LD) and other metabolic changes in HIV-infected children receiving HAART. Methods: Ninety children who began HAART (either nevi-rapine or efavirenz, together with lamivudine and stavudine) were prospectively followed. LD was assessed by waist-to-hip ratio and LD checklist. Hypercholesterolaemia was defined as total cholesterol >200 mg/dl and low-density lipoprotein cholesterol >130 mg/dl. Low levels of high-density lipoprotein cholesterol (HDL-c), hypertriglyceridaemia and hyperglycaemia were defined as HDL-c <40 mg/dl, triglyceride >200 mg/dl and plasma glucose >110 mg/dl, respectively. Results: The mean age at entry was 7.6 (SD 2.9) years. Fifty-three children received nevirapine- and 37 received efavirenz-based HAART. The prevalence of LD was 9%, 47% and 65% at 48, 96 and 144 weeks after HAART initiation, respectively. Patterns of LID at week 144 were central lipohypertrophy (46%), peripheral lipoatrophy (20%), and combined type (34%). A higher prevalence of LD was found among females (61% versus 39%; P=0.04) and those with more advanced disease (CDC category B or C) at baseline (73% versus 51%; P=0.04). There was no difference in prevalence of LID between the two regimens. At 144 weeks, fasting hypertriglyceridaemia was detected in 12%, hypercholesterolaemia in 11%, and increased plasma glucose in 4% of children. Low HDL-cholesterolaemia decreased from 94% at baseline to 12% at week 144 (P<0.01). Conclusions: More than half of the children developed LID at 144 weeks after HAART. Dyslipidaemia occurred in 11-12% of children.

Address: Sirisanthana, V; Chiang Mai Univ; Dept Pediat; Chiang Mai 50000; Thailand. vsirisan@mail.med.cmu.ac.th

Brou H, Djohan G, Becquet R, Allou G, Ekouevi DK, Viho I, Leroy V, Desgrees du Lou A. **When do HIV-Infected women disclose their HIV status to their male partner and why? A study in a PMTCT programme, Abidjan - art. no. e342.** Plos Medicine 2007; 4(12):1912-1920.

Abstr. Background In Africa, women tested for HIV during antenatal care are counselled to share with their partner their HIV test result and to encourage partners to undertake HIV testing. We investigate, among women tested for HIV within a prevention of mother-to-child transmission of HIV (PMTCT) programme, the key moments for disclosure of their own HIV status to their partner and the impact on partner HIV testing. Methods and Findings Within the Ditrane Plus PMTCT project in Abidjan, 546 HIV-positive and 393 HIV-negative women were tested during pregnancy and followed-up for two years after delivery. Circumstances, frequency, and determinants of disclosure to the male partner were estimated according to HIV status. The determinants of partner HIV testing were identified according to women's HIV status. During the two-year follow-up, disclosure to the partner was reported by 96.7% of the HIV-negative women, compared to 46.2% of HIV-positive women ($\chi^2=265.2$, degrees of freedom [df] 1, $p < 0.001$). Among HIV-infected women, privileged circumstances for disclosure were just before delivery, during early weaning (at 4 mo to prevent HIV postnatal transmission), or upon resumption of sexual activity. Formula feeding by HIV-infected women increased the probability of disclosure (adjusted odds ratio 1.54, 95% confidence interval 1.04-2.27, Wald test=4.649, df=1, $p=0.031$), whereas household factors such as having a spouse or living with family reduced the probability of disclosure. The proportion of male partners tested for HIV was 23.1% among HIV-positive women and 14.8% among HIV-negative women ($\chi^2=10.04$, df=1, $p=0.002$). Partners of HIV-positive women who were informed of their wife's HIV status were more likely to undertake HIV testing than those not informed (37.7% versus 10.5%, $\chi^2=56.36$, df=1, $p < 0.001$). Conclusions In PMTCT programmes, specific psychosocial counselling and support should be provided to women during the key moments of disclosure of HIV status to their partners (end of pregnancy, weaning, and resumption of sexual activity). This support could contribute to improving women's adherence to the advice given to prevent postnatal and sexual HIV transmission.

Address: Desgrees-du-Lou, A; Inst Rech Dev; Lab Populat Environm Dev; Nogent Sur Marne; France. annabel.desgrees@ird.fr

Free Full Text: <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2100145&blobtype=pdf>

Dalal RP, MacPhail C, Mqhayi M, Wing J, Feldman C, Chersich MF, Venter WDF. **Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in Johannesburg, South Africa.** Journal of Acquired Immune Deficiency Syndromes 2008; 47(1):101-107.

Abstr. Background: A significant proportion of those initiating antiretroviral treatment (ART) for HIV infection are lost to follow-up. Causes for discontinuing ART follow-up in resource-limited settings are not well understood. Methods: A retrospective analysis was conducted of all, adult patients receiving ART at an urban public clinic in Johannesburg, South Africa between April 2004 and June 2005. Patients discontinuing follow-up for at least 6 weeks were identified and further studied, and causes for treatment default were tabulated. Results: Of 1631 adult patients studied, 267 (16.4%) discontinued follow-up during the study period. Gender, ethnicity, and age were not predictive of loss to follow-up. Of those discontinuing follow-up, 173 (64.8%) were successfully traced. Death accounted for 48% ($n = 83$) of those traced. Characteristics associated with death were older age at ART initiation ($P = 0.022$), lower baseline CD4 cell count ($P = 0.0073$), higher initial HIV RNA load ($P = 0.024$), and loss of weight on ART ($P = 0.033$). Date of death was known for 71% ($n = 59$) of patients traced deceased, of whom 83% ($n = 49$)

had died within 30 days of active ART. Common nonmortality losses included relocation or clinic transfer (25.4%) and hospitalization or illness not resulting in death (10.4%). Few cited financial difficulty or medication toxicity as reasons for discontinuing follow-up. Conclusions: Nearly 1 in 6 patients receiving ART in a resource-constrained setting had discontinued follow-up over a 15-month period. Early mortality was high, especially in those with profound immunosuppression. Improving access to care and streamlining patient tracking may improve ART outcomes.

Address: Dalal, RP; 7 Maryland Plaza, Apartment 601; St Louis; MO 63108; USA.
dalal@msnotes.wustl.edu

Diabate S, Alary M, Koffi CK. **Short-term increase in unsafe sexual behaviour after initiation of HAART in Cote d'Ivoire.** AIDS 2008;22(1):154-156.

Abstr. A study of 312 untreated and 303 HAART-initiating patients to determine whether HAART is related to sexual risk taking in Cote d'Ivoire. At enrolment, unprotected sex was higher among untreated patients ($P = 0.014$). During follow-up, risk taking was similar ($P = 0.484$) as a result of an increase in unprotected sex among treated patients (from 20.4 to 30.1%, $P < 0.0001$) and stability among untreated patients (from 27.0 to 28.8%, $P = 0.301$). HAART appeared to be associated with sexual risk taking.

Address: Diabate, S; Univ Laval; Unite Soins Ambulatoires Conseils; Quebec City; PQ G1K 7P4; Canada

Dieterich DT. **Special considerations and treatment of patients with HBV-HIV coinfection.** Antiviral Therapy 2007;12 Suppl. 3:H43-H51.

Abstr. Coinfection with HIV and hepatitis B virus (HBV) substantially alters the natural course of HBV infection as well as its management. Therapy for HBV infection in HIV-coinfected patients requires several factors to be taken into consideration, such as whether the antiviral activity of a particular agent is specific for HBV (that is, adefovir, entecavir, telbivudine and pegylated interferon) or for both viruses (that is, lamivudine, emtricitabine and tenofovir), whether the chosen drug has the potential for inducing drug resistance and cross-resistance, and whether use of the agent is associated with hepatotoxicity. For coinfecting patients who do not require therapy for their HIV infection, clinicians should avoid prescribing monotherapy with agents that have activity against HIV (that is, tenofovir, entecavir, emtricitabine or lamivudine) so as not to compromise future HIV care. This review discusses the current status of treatment of hepatitis B in the setting of HIV infection. It describes emerging therapeutic strategies and addresses challenges in the treatment of coinfection.

Address: Dieterich, DT; Mt Sinai Sch Med; Dept Med; New York; NY 10029; USA.
douglas.dieterich@mountsinai.org

Foster C, Lyall H. **HIV and mitochondrial toxicity in children.** Journal of Antimicrobial Chemotherapy 2008;61(1):8-12.

Abstr. In the last 10 years, the enormous impact of combination antiretroviral (ARV) therapy on paediatric HIV-associated mortality and morbidity in well-resourced settings and its role in the prevention of mother-to-child transmission (MTCT) of HIV cannot be underestimated. However, it is thus inevitable that children with HIV-1 infection will be exposed to ARVs for an ever-increasing length of time throughout post-natal growth and development, and the cumulative toxicities are becoming progressively apparent. Evidence for nucleoside reverse transcriptase inhibitor (NRTI)-associated mitochondrial

toxicity is seen in vitro, in animal models and in NRTI-exposed adults and children. Proposed mechanisms of NRTI mitochondrial toxicity include, among others, impairment of mitochondrial DNA (mtDNA) replication and acquisition of mtDNA point mutations. Alterations in the mtDNA synthesis potentially reduce the production of mtDNA-encoded respiratory chain subunits, resulting in impaired oxidative phosphorylation and mitochondrial dysfunction. NRTI-associated mitochondrial toxicity in children has varied presentations including lactic acidosis, pancreatitis, cardiomyopathy and neuropathy, which are comparable to NRTI-exposed adults and children with congenital mitochondrial disorders. In the prevention of MTCT, uninfected infants are exposed to an ever-widening range of ARVs, often from conception and throughout fetal life. Animal models demonstrate evidence of mitochondrial toxicity from perinatal NRTI exposure, but controversy continues as to the extent of mitochondrial effects in NRTI-exposed children. Paediatric studies assessing the impact of reduced exposure to NRTIs or the use of NRTIs with lower mitochondrial toxicity are urgently required. In an era of expanding treatment options, minimizing toxicities becomes an increasing possibility, indeed a necessity.

Address: Lyall, H; St Marys Hosp; Family Clin; Praed St; London W2 1NY; England.
hermione.lyall@st-marys.nhs.uk

Ghys PD, Zaba B, Prins M. **Survival and mortality of people infected with HIV in low and middle income countries: results from the extended ALPHA network.** AIDS 2007; 21 Suppl. 6:S1-S4.

Selection

This supplement brings together analyses and papers from the ALPHA network, a collaboration aimed at maximizing the usefulness of data generated in community-based longitudinal HIV studies in sub-Saharan Africa. The network organized a workshop in Entebbe, Uganda, in November 2006, to which additional cohort study sites from low and middle income countries in different regions of the world were invited. At this workshop, study sites presented their preliminary findings on survival and mortality, and discussed appropriate definitions and methods.

Published at a time when antiretroviral treatment (ART) is rapidly being scaled up in most low and middle income countries, this collection of papers represents a major collaborative effort to quantify and analyse the survival from HIV seroconversion to death in the absence of ART. The advent of effective treatment means it will not be possible to conduct any further studies of this nature in the future, so the results from these analyses together with a small number of previously published survival studies will serve as a baseline against which to assess the impact of ART in low and middle income countries. In addition, this new information is important for deriving parameters to model HIV epidemics.

Address: Ghys, PD; Joint United Nations Programme AIDS; 20 Ave Appia; CH-1211 Geneva; Switzerland. ghysp@unaids.org

See contents of AIDS special issue (Suppl 6):

<http://www.aidsonline.com/pt/re/aids/toc.00002030-200711006-00000.htm;jsessionid=H9JCJ1K23byRrbwvfvfJkrJJSLyJw2qyB86YmlPh1QdDkKyDhsk4tI-383192544!181195628!80911-1>

Gibb DM, Duong T, Dunn D, Chintu C, Mulenga V, Cotton M, Eley B, Zar H, Ellis J, Graham S, Giaquinto C, Nanyonga M, Msellati P, Meyers T, Moultrie H, Hani C, Pinto J, Roux P, Weigel R, Araujo C, Carvalho A, Carvalho I, Diniz A, Ferreira F, Lobato V, Sanchez T, Morelli E, Atai B, Duff C. **Markers for predicting mortality in untreated HIV-infected children in resource-limited settings: a meta-analysis.** AIDS 2008;22(1):97-105.

Abstr. Objectives: To evaluate the prognostic value of selected laboratory and growth markers on the short-term risk of mortality in untreated HIV-infected children in resource-limited settings. Design: A meta-analysis of individual longitudinal data on children aged 12 months onwards from 10 studies (nine African, one Brazilian in the 3Cs4kids collaboration). Methods: The risk of death within 12 months based on age and the most recent measurements of laboratory and growth markers was estimated using Poisson regression models, adjusted for cotrimoxazole prophylaxis use and study effects. Results: A total of 2510 children contributed 357 deaths during 3769 child-years-at-risk, with 81% follow-up occurring after start of cotrimoxazole. At first measurement, median age was 4.0 years (interquartile range, 2.2-7.0 years), median CD4% was 15% and weight-for-age z-score -1.9. CD4% and CD4 cell count were the strongest predictors of mortality, followed by weight-for-age and haemoglobin. After adjusting for these markers, the effects of total lymphocyte count and BMI-for-age were relatively small. Young children who were both severely malnourished and anaemic had high mortality regardless of CD4 values, particularly those aged 1-2 years. By contrast, high CD4% or CD4 cell count values predicted low mortality level amongst either children older than 5 years or those younger with neither severe malnutrition nor anaemia. Conclusions: CD4 measurements are the most important indicator of mortality and wider access to affordable tests is needed in resource-limited settings. Evaluation of antiretroviral initiation in children also needs to consider weight-for-age and haemoglobin. Prevention and treatment of malnutrition and anaemia is integral to HIV paediatric care and could improve survival. (c) 2008 Wolters Kluwer Health.

Address: Gibb, DM; MRC; Clin Trials Unit; 222 Euston Rd; London NW1 2DA; England

Gillespie S, Greener R, Whiteside A, Whitworth J. **Investigating the empirical evidence for understanding vulnerability and the associations between poverty, HIV infection and AIDS impact.** AIDS 2007;21 Suppl. 7:S1-S4.

Selection

It is just over 25 years since the first cases of AIDS were reported. Over this quarter-century, AIDS has become one of most highly studied diseases in history. There have been significant medical advances in understanding the consequences of HIV infection and treating AIDS, as is well documented in many journals, including AIDS. The complex and place-specific social, economic, behavioural and psychological drivers of the spread of HIV remain less well delineated. The consequences of increased illness and death in poor countries and communities are still unfolding. This supplement, written by social scientists, looks at how socioeconomic determinants drive HIV spread and how AIDS illness and mortality is impacting on communities. .

Address: Whiteside, A; Univ KwaZulu Natal; Hlth Econ HIV AIDS Res Div; Block 1418 Westville,Univ Rd Westville,PB XS4001; ZA-4000 Durban; South Africa.
whitesid@ukzn.ac.za

See contents of AIDS special issue (Suppl 7):

<http://www.aidsonline.com/pt/re/aids/toc.00002030-200711007-00000.htm;jsessionid=H9VBGsPdZ6PV01dydHTZfnsD2T1hB03XOrNblFQQqSt1PLvjFGcXI-1428189930!181195629!8091!-1>

Ginsburg AS, Hoblitzelle CW, Sripipatana TL, Wilfert CM. **Provision of care following prevention of mother-to-child HIV transmission services in resource-limited settings.** AIDS 2007;21(18):2529-2532.

Abstr. Objective: To evaluate the provision of care for mother and child after institution of prevention of mother-to-child transmission (PMTCT) of HIV services. Design: As part of an effort to improve services, we undertook a review of our multicountry PMTCT program. Methods: Review of key indicators from our PMTCT database and reporting practices from January 2005 to June 2006 throughout 18 resource-limited countries. Results: 1066 606 pregnant women were counseled and tested, and 102 336 tested HIV-positive. Antiretroviral prophylaxis was dispensed to 81 384 mothers and 52342 HIV-exposed infants. From available reporting, 1388 pregnant women were dispensed antiretroviral drugs for treatment and 9060 children received cotrimoxazole prophylaxis at 6 weeks. Conclusions: PMTCT services are integrated into maternal-child health services but adult and pediatric care and treatment programs often function independently, without coordination or linkages. Integrating care into maternal-child health services and linking mother's HIV status to child are necessary for HIV-infected mothers and HIV-exposed children to receive appropriate follow-up and treatment. (C) 2007 Wolters Kluwer Health vertical bar Lippincott Williams and Wilkins.

Address: Ginsburg, AS; Elizabeth Glaser Pediat AIDS Fdn; 2950 31st St,Suite 125; Santa Monica; CA 90405; USA. messageforamy@gmail.com

Hirsch JS, Parker RG, Aggleton P. **Social aspects of antiretroviral therapy scale-up: introduction and overview.** AIDS 2007;21 Suppl. 5:S1-S4.

Selection

Whereas policymakers, clinicians and advocates have struggled to address the formidable technical, economic, and policy challenges that ART scale-up involves, many of the broader social dimensions of this remarkable mobilization have barely been explored. In this special issue of AIDS, we have gathered social science voices to begin to articulate, across geographies and disciplines, what scale-up is doing other than improving the quality of and adding longevity to individual lives, to articulate a range of potential social outcomes of this global intervention. The social impacts of scaling up access, however, will be both outcomes of scale-up and mediators of the process, and so the papers collected in this special supplement argue that attending more closely to the multiple social impacts of scale-up will not just provide interesting case studies for social scientists, but will also increase our ability to achieve our clinical and public health goals successfully.

Address: Hirsch, JS; Columbia Univ; Mailman Sch Publ Hlth; 722 W 168th St,9th Floor; New York; NY 10032; USA. jsh2124@columbia.edu

See contents of AIDS special issue (Suppl 5):

<http://www.aidsonline.com/pt/re/aids/toc.00002030-200710005-00000.htm;jsessionid=H9JCJ1K23byRrbwvfvfJkrJJSLyJw2qyB86YmiPh1QdDkKyDhsk4t!-383192544!181195628!80911-1>

Homsanit M, Nelson KE, Sonjai A, AnekthanAnon T, Suwanagool S, Cofrancesco J. **Body shape and metabolic abnormalities in Thai HIV-infected patients.** AIDS Research and Human Retroviruses 2007;23(11):1314-1321.

Abstr. Fat and metabolic abnormalities and their associated factors in HIV-infected patients in Thailand were examined. Body fat and fasting lipids (total cholesterol, TC; triglyceride, TG; and HDL-cholesterol, HDL-c) were evaluated in 247 HIV-infected Thais. Body fat was evaluated by subjects and blinded observers, and measured using dual-

energy X-ray absorptiometry. Descriptive statistics and logistic regression were used for analyses. Antiretroviral (ARV)-treated Thais were significantly older, more likely to be male, and had higher education and income compared to untreated subjects. The prevalence of lipoatrophy was 10.3% in ARV-naive patients, 36.7% in patients receiving non-protease inhibitor (PI)-based ARV, and 78.7% in PI-based ARV-treated patients ($p < 0.001$). Excess abdominal or neck fat was found in 0.8%, 6.7%, and 24.6% of the naive, non-PI-treated, and PI-treated, respectively ($p < 0.001$). Hypercholesterolemia (TC \geq 240 mg/dl) was found in 4.8%, 26.6%, and 42.6%; hypertriglyceridemia (TG \geq 150 mg/dl) in 8.2%, 48.3%, and 75.4%; and low HDL-c (HDL-c $<$ 40 mg/dl) in 42.9%, 20.0%, and 31.2% of the naive, non-PI treated, and PI-treated, respectively ($p < 0.05$ for all). Central to peripheral fat ratios were 1.11 \pm 0.03, 1.45 \pm 0.06, and 1.93 \pm 0.08 for the naive, non-PI, and PI-treated, respectively ($p < 0.001$). Treatment was associated with abnormal fat. The adjusted ORs (95% CI) of lipoatrophy for excess fat were 4.6 (2.0-10.7); 6.3 (0.6-71.1) for ARV-naive vs. non-PI; 5.6 (3.4-9.1); 10.7 (3.4-33.8) for ARV-naive vs. PI, and 5.7 (2.4-13.9); 5.3 (1.2-11.4-13.9) for ARV-naive vs. PI. ARV-associated metabolic abnormalities are common in this non-Western population. Appropriate selection and monitoring of ARV treatment are critical to minimize the risk of long-term complications.

Address: Homsanit, M; Siriraj Hosp; Dept Prevent & Social Med; Bangkok 10700; Thailand. mhomsanit@yahoo.com

Keiser O, Fellay J, Opravil M, Hirsch HH, Hirschel B, Bernasconi E, Vernazza PL, Rickenbach M, Telenti A, Furrer H. **Adverse events to antiretrovirals in the Swiss HIV Cohort Study: Effect on mortality and treatment modification.** Antiviral Therapy 2007;12 (8):1157-1164.

Abstr. Background: Antiretroviral therapy (ART) decreases morbidity and mortality in HIV-infected patients but is associated with considerable adverse events (AEs). Methods: We examined the effect of AEs to ART on mortality, treatment modifications and drop-out in the Swiss HIV Cohort Study. A cross-sectional evaluation of prevalence of 13 clinical and 11 laboratory parameters was performed in 1999 in 1,078 patients on ART. AEs were defined as abnormalities probably or certainly related to ART. A score including the number and severity of AEs was defined. The subsequent progression to death, drop-out and treatment modification due to intolerance were evaluated according to the baseline AE score and characteristics of individual AEs. Results: Of the 1,078 patients, laboratory AEs were reported in 23% and clinical AEs in 45%. During a median follow up of 5.9 years, laboratory AEs were associated with higher mortality with an adjusted hazard ratio (HR) of 1.3 (95% confidence interval [CI] 1.2-1.5; $P < 0.001$) per score point. For clinical AEs no significant association with increased mortality was found. In contrast, an increasing score for clinical AEs (HR 1.11, 95% CI 1.04-1.18; $P = 0.002$), but not for laboratory AEs [HR 1.07, 95% CI 0.97-1.17; $P = 0.17$], was associated with antiretroviral treatment modification. AEs were not associated with a higher drop-out rate. Conclusions: The burden of laboratory AEs to antiretroviral drugs is associated with a higher mortality. Physicians seem to change treatments to relieve clinical symptoms, while accepting laboratory AEs. Minimizing laboratory drug toxicity seems warranted and its influence on survival should be further evaluated.

Address: Furrer, H; Univ Bern; Univ Hosp Bern; CH-3012 Bern; Switzerland. hansjakob.furrer@insel.ch

Lichtenstein KA, Armon C, Buchacz K, Chmiel JS, Moorman AC, Wood KC, Holmberg SD, Brooks JT. **Initiation of antiretroviral therapy at CD4 cell counts \geq 350 cells/mm³ does not increase incidence or risk of peripheral neuropathy, anemia, or renal insufficiency.** Journal of Acquired Immune Deficiency Syndromes 2008;47(1):27-35.

Abstr. Background: US guidelines recommend deferring initiation of highly active antiretroviral therapy (HAART) for most patients with CD4 counts >350 cells/mm³ in part because of concerns about antiretroviral toxicity. Methods: Incidence rates of peripheral neuropathy, anemia, and renal insufficiency in a cohort of 2165 patients followed more than 3 years (mean) were analyzed in multivariate Cox proportional hazards models by CD4 cell counts at initiation of HAART. A nested cohort of 895 patients restricted to study participants who did or did not start HAART within a CD4 cell count stratum were also compared. Results: Incidence and risks of all 3 comorbidities decreased with initiation of HAART at CD4 counts >200 cells/mm³ versus <200 cells/mm³. Incidence and risks of renal insufficiency were similar with HAART initiation at CD4 counts ≥ 350 cells/mm³ versus 200 to 349 cells/mm³, but risk of peripheral neuropathy and anemia were further decreased in persons starting HAART at a CD4 count ≥ 350 cells/mm³. The incidence of these conditions was highest during the first 6 months of treatment at any CD4 cell count and declined up to 19-fold with further therapy. Discussion: Initiating HAART at CD4 cell counts ≥ 200 cells/mm³ reduced the incidence and risk of the 3, comorbid conditions and for anemia and peripheral neuropathy as well by starting at CD4 counts ≥ 350 cells/mm³. The incidence of each condition decreased rapidly and remained low with increasing time on HAART.

Address: Brooks, JT; Ctr Dis Control & Prevent; Div HIV AIDS Prevent; 1600 Clifton Rd NE, Mailstop E-45; Atlanta; GA 30333; USA. zud4@cdc.gov

Maartens G, Wilkinson RJ. **Tuberculosis** [Review]. Lancet 2007;370(9604):2030-2043.

Abstr. Tuberculosis is still a leading cause of death in low-income and middle-income countries, especially those of sub-Saharan Africa where tuberculosis is an epidemic because of the increased susceptibility conferred by HIV infection. The effectiveness of the Bacille Calmette Guerin (BCG) vaccine is partial, and that of treatment of latent tuberculosis is unclear in high-incidence settings. The routine diagnostic methods that are used in many parts of the world are still very similar to those used 100 years ago. Multidrug treatment, within the context of structured, directly observed therapy, is a cost-effective control strategy. Nevertheless, the duration of treatment needed reduces its effectiveness, as does the emergence of multidrug-resistant and extensively drug-resistant disease; the latter has recently become widespread. The rapid expansion of basic, clinical, and operational research, in addition to increasing knowledge of tuberculosis, is providing new diagnostic, treatment, and preventive measures. The challenge is to apply these advances to the populations most at risk. The development of a comprehensive worldwide plan to stop tuberculosis might facilitate this process by coordinating the work of health agencies. However, massive effort, political will, and resources are needed for this plan to succeed.

Address: Maartens, G; Univ Cape Town; Sch Med; K45, Old Main Bldg; ZA-7925 Observatory; South Africa. gary.maartens@uct.ac.za

Moh R, Danel C, Messou E, Cluassa T, Gabillard D, Anzian A, Abo Y, Salamon R, Bissagnene E, Seyler C, Eholie S, Anglaret X. **Incidence and determinants of mortality and morbidity following early antiretroviral therapy initiation in HIV-infected adults in West Africa.** AIDS 2007;21(18):2483-2491.

Abstr. Objective: To estimate the incidence and risk factors of mortality and severe morbidity during the first months following antiretroviral therapy (ART) initiation in West African adults. Methods: A cohort study in Abidjan in which 792 adults started ART with a median CD4 cell count of 252 cells/ μ l and were followed for a median of 8 months. Severe morbidity was defined as all World Health Organization stage 3 or 4-defining morbidity events other than oral candidiasis. Results: In patients with pre-ART CD4 cell count < 200, at 200-350 and > 350 cells/ μ l, incidence of mortality was 5.0 [95% confidence interval (CI), 2.6-8.7], 1.7 (95% CI, 0.6-3.8) and 0.0 (95% CI, 0.0-3.4)/100 person-years, and incidence of severe morbidity was 13.3 (95% CI, 9.0-19.1), 9.5 (95% CI, 6.2-12.9) and 7.9 (95% CI, 3.4-15.5)/100 person-years, respectively. The most frequent diseases were invasive bacterial diseases (32/65 episodes, 49%) and tuberculosis (25/65 episodes, 38%). Both diseases followed the same curve of decreasing incidence over time. Patients who experienced severe morbidity had higher risks of mortality, virological failure and immunological failure. Other independent risk factors for mortality and/or severe morbidity were: at baseline, high viral load, advanced clinical stage, past history of tuberculosis, low BMI, low haemoglobin and low CD4 cell count; during follow-up: low CD4 cell count and persistently detectable viral load. Conclusion: These data give new arguments to reinforce the hypothesis that, in this region, ART should be started before the CD4 cell count drops below 350 cells/ μ l. Further studies should assess whether patients with low BMI, low haemoglobin, high viral load or past history of tuberculosis should start ART earlier. (C) 2007 Wolters Kluwer Health vertical bar Lippincott Williams and Wilkins.

Address: Anglaret, X; Univ Bordeaux 2; INSERM; 146 rue Leo Saignat; Bordeaux 33076; France. Xavier.Anglaret@isped.u-bordeaux2.fr

Ojikutu B. **The realities of antiretroviral therapy rollout: Overcoming challenges to successful programmatic implementation.** Journal of Infectious Diseases 2007;196 Suppl. 3:S445-S448.

Selection In 2006, 2 million human immunodeficiency virus (HIV)-infected people living in low- to middle-income countries were receiving antiretroviral therapy (ART). Although this is an improvement over previous years, significant operational challenges have inhibited progress toward universal access to HIV care and treatment. Despite these challenges, the intense efforts focused on addressing the HIV epidemic present an opportunity for overall health systems improvement in developing nations. In October 2006, Harvard University's Centers for AIDS Research, the Nelson Mandela School of Medicine, the Department of Health of KwaZulu-Natal, and the Medical Research Council of South Africa held a conference entitled "The Realities of Antiretroviral Therapy Rollout: Challenges to Successful Programmatic Implementation" in Durban, South Africa. The goal of the meeting was to bring together international and local leadership,, including policy makers, health care workers, and funders, to propose an agenda that would address the challenges to more expeditious provision of HIV care and treatment in resource-limited settings.

Address: Ojikutu, B; Harvard Univ; Sch Med; 401 Pk Dr,2nd Fl E; Boston; MA 02215; USA. bojikutu@partners.org

See contents of JID special issue (Suppl 3):
<http://www.journals.uchicago.edu/toc/jid/196/s3>

Potter D, Goldenberg RL, Chao A, Sinkala M, Degroot A, Stringer JSA, Bulterys M, Vermund SH. **Do targeted HIV programs improve overall care for pregnant women? Antenatal syphilis management in Zambia before and after implementation of prevention of mother-to-child HIV transmission programs.** *Journal of Acquired Immune Deficiency Syndromes* 2008;47(1):79-85.

Abstr. Background: The implementation of disease-specific research or service programs may have an ancillary beneficial or harmful impact on routine clinical services. Methods: We reviewed the records of 5801 first visits to 22 antenatal clinics from 1997 to 2004 in Lusaka, Zambia and examined documented syphilis rapid plasma reagin (RPR) screening and syphilis treatment before and after implementation of research and/or service programs in prevention of mother-to-child (PMTCT) HIV transmission. Findings: Compared with before PMTCT program implementation, the prevalence odds ratios (PORs) and 95% confidence intervals (CIs) for documented RPR screening were 0.9 (0.7 to 1.1) after implementation of research, 0.7 (0.6 to 0.8) after service, and 2.5 (2.1 to 3.0) after research and service programs. Conclusions: Documented RPR screening was improved after implementation of PMTCT research and service were operating simultaneously and not with research or service alone. Health policy makers and researchers should plan explicitly for how the targeted HIV programs, service, and/or research can have a broader primary care impact.

Address: Potter, D; Ctr Infect Dis Res Zambia; 5977 Benekale & Mwembeshi Northmead; Lusaka; Zambia. dara.potter@cidrz.org

Rosen S, Fox MP, Gill CJ. **Patient retention in antiretroviral therapy programs in sub-Saharan Africa: A systematic review** *Plos Medicine* 2007;4(10):1691-1701.

Abstr. Background Long-term retention of patients in Africa's rapidly expanding antiretroviral therapy (ART) programs for HIV/AIDS is essential for these programs' success but has received relatively little attention. In this paper we present a systematic review of patient retention in ART programs in sub-Saharan Africa. Methods and Findings We searched Medline, other literature databases, conference abstracts, publications archives, and the "gray literature" (project reports available online) between 2000 and 2007 for reports on the proportion of adult patients retained (i.e., remaining in care and on ART) after 6 mo or longer in sub-Saharan African, non-research ART programs, with and without donor support. Estimated retention rates at 6, 12, and 24 mo were calculated and plotted for each program. Retention was also estimated using Kaplan-Meier curves. In sensitivity analyses we considered best-case, worst-case, and midpoint scenarios for retention at 2 y; the best-case scenario assumed no further attrition beyond that reported, while the worst-case scenario assumed that attrition would continue in a linear fashion. We reviewed 32 publications reporting on 33 patient cohorts (74,192 patients, 13 countries). For all studies, the weighted average follow-up period reported was 9.9 mo, after which 77.5% of patients were retained. Loss to follow-up and death accounted for 56% and 40% of attrition, respectively. Weighted mean retention rates as reported were 79.1%, 75.0% and 61.6 % at 6, 12, and 24 mo, respectively. Of those reporting 24 mo of follow-up, the best program retained 85% of patients and the worst retained 46%. Attrition was higher in studies with shorter reporting periods, leading to monthly weighted mean attrition rates of 3.3%/mo, 1.9%/mo, and 1.6%/month for studies reporting to 6, 12, and 24 months, respectively, and suggesting that overall patient retention may be overestimated in the published reports. In sensitivity analyses, estimated retention rates ranged from 24% in the worse case to 77% in the best case at the end of 2 y, with a plausible midpoint scenario of 50%. Conclusions Since the inception of large-scale ART access early in this decade, ART programs in Africa have retained about 60% of their patients at the end of 2 y. Loss to follow-up is the major cause of attrition, followed by death. Better patient tracing procedures, better understanding of loss to follow-up, and earlier initiation of ART to reduce mortality are needed if retention is to be improved. Retention varies widely across programs, and

programs that have achieved higher retention rates can serve as models for future improvements.

Address: Rosen, S; Boston Univ; Sch Publ Hlth; Boston; MA 02215; USA.
sbrosen@bu.edu

Free Full Text:

http://medicine.plosjournals.org/archive/1549-1676/4/10/pdf/10.1371_journal.pmed.0040298-L.pdf

Saitoh A, Fenton T, Alvero C, Fletcher CV, Spector SA. **Impact of nucleoside reverse transcriptase inhibitors on mitochondria in human immunodeficiency virus type 1-infected children receiving highly active antiretroviral therapy.** *Antimicrobial Agents and Chemotherapy* 2007;51(12):4236-4242.

Abstr. Mitochondrial toxicity induced by nucleoside reverse transcriptase inhibitors (NRTIs) has been reported to be responsible for various adverse effects. The relative impact of NRTIs on the mitochondria of human immunodeficiency virus (HIV) type 1 (HIV-1)-infected children receiving highly active antiretroviral therapy (HAART) is unknown. Mitochondrial DNA (mtDNA) levels were quantified longitudinally from peripheral blood mononuclear cells (PBMCs) in 31 HIV-1-infected children from Pediatric AIDS Clinical Trial Group Study 382 who were receiving HAART, including nelfinavir, efavirenz, and different NRTIs, and who had had undetectable plasma HIV-1 RNA levels for > 2 years. The median mtDNA levels in PBMCs increased from 137 copies/cell at the baseline to 179 copies/cell at week 48 ($P = 0.01$) and 198 copies/cell at week 104 ($P < 0.001$). Before the initiation of HAART, children who received regimens containing didanosine had mtDNA levels persistently lower than those in children not receiving didanosine (106 versus 140 copies/cell; $P = 0.008$). During HAART, the median increase in the mtDNA level from the baseline to week 104 was the lowest in children who received regimens containing didanosine (+26 copies/cell) compared to those in children who received other regimens (+79 copies/cell) ($P = 0.02$). A multivariate analysis also demonstrated that didanosine, as part of HAART, was the only NRTI associated with the change in mtDNA levels ($P = 0.007$). Children receiving didanosine-containing antiretroviral regimens have the lowest mtDNA levels in PBMCs and may be at greater risk for long-term adverse effects due to mitochondrial toxicity. This may be of particular importance in resource-limited countries where didanosine is widely used for the treatment of HIV-infected children.

Address: Saitoh, A; Univ Calif San Diego; Dept Pediat; 9500 Gilman Dr; La Jolla; CA 92093; USA. asaitoh@ucsd.edu

Sterne JAC, May M, Sabin C, Phillips A, Costagliola D, Chene G, Justice AC, de Wolf F, Hogg R, Battegay M, Monforte AD, Faetkenheuer G, Staszewski S, Gill J, Egger M. **Importance of baseline prognostic factors with increasing time since initiation of highly active antiretroviral therapy - Collaborative analysis of cohorts of HIV-1-Infected patients.** *Journal of Acquired Immune Deficiency Syndromes* 2007;46(5):607-615.

Abstr. Background: The extent to which the prognosis for AIDS and death of patients initiating highly active antiretroviral therapy (HAART) continues to be affected by their characteristics at the time of initiation (baseline) is unclear. Methods: We analyzed data on 20,379 treatment-naive HIV-1-infected adults who started HAART in 1 of 12 cohort studies in Europe and North America (61,798 person-years of follow-up, 1844 AIDS events, and 1005 deaths). Results: Although baseline CD4 cell count became less prognostic with time, individuals with a baseline CD4 count < 25 cells/ μ L had persistently higher progression rates than individuals with a baseline CD4 count > 350

cells/ μ L (hazard ratio for AIDS = 2.3, 95% confidence interval [CI]: 1.0 to 2.3; mortality hazard ratio = 2.5, 95% CI: 1.2 to 5.5, 4 to 6 years after starting HAART). Rates of AIDS were persistently higher in individuals who had experienced an AIDS event before starting HAART. Individuals with presumed transmission by means of injection drug use experienced substantially higher rates of AIDS and death than other individuals throughout follow-up (AIDS hazard ratio = 1.6, 95% CI: 0.8 to 3.0; mortality hazard ratio = 3.5, 95% CI: 2.2 to 5.5, 4 to 6 years after starting HAART). Conclusions: Compared with other patient groups, injection drug users and patients with advanced immunodeficiency at baseline experience substantially increased rates of AIDS and death up to 6 years after starting HAART.

Address: Sterne, JAC; Univ Bristol; Dept Social Med; Cagnynge Hall, Whiteadies Rd; Bristol BS8 2PR; Avon; England. jonathan.steme@bristol.ac.uk

Wagner G, Ryan G, Taylor S. **Formative evaluation of antiretroviral therapy scale-up efficiency in sub-Saharan Africa.** AIDS Patient Care and Stds 2007;21(11):871-887.

Abstr. With millions in need of HIV antiretroviral therapy (ART) in the developing world, and scarce human and fiscal resources available, we conducted a formative evaluation of scale-up operations at clinics associated with AIDS Healthcare Foundation in Africa to identify lessons learned for improving scale-up efficiency. Site visits were made to six selected clinics in Uganda, Zambia, and South Africa, during which semistructured interviews with key stakeholders and observation of client flows and clinic operations were performed. This evaluation revealed the following lessons related to factors that are critical to efficient ART scaleup: (1) to ensure steady ART uptake, it is important to involve the community and community leaders in outreach, HIV education, and program decision-making; (2) minimizing bottlenecks to smooth patient flow requires efficient staff allocation to appropriate clinical duties, streamlined clinic visit schedule protocols, and tapping clients and the HIV community as a key source of labor; (3) to minimize clients dropping out of care, structures should be developed that enable clients to provide support and a "safety net" for helping each other remain in care; (4) computerized record management systems are essential for accurate antiretroviral inventory and dispensing records, quality assurance monitoring, and client enrollment records and visit scheduling; (5) effective organizational management and human resource policies are essential to maintain high job performance and satisfaction and limit burnout; (6) to maximize impact on social and economic health, it is important for ART programs to develop effective mechanisms for coordinating and referring clients to support service organizations.

Address: Wagner, G; RAND Corp; 1776 Main St; Santa Monica; CA 90407; USA. gwagner@rand.org