HIV Update in Africa

January 2014

Dear Colleagues

Welcome to the fifth edition of the HIV Update in Africa bulletin, an educational resource for healthcare professionals that focuses on HIV treatment and management in Sub-Saharan Africa. The regularly updated bulletin reports the key data from international congresses and peer-reviewed journals.

This issue includes important findings with African (or global) relevance presented at the recent 17th International Conference on AIDS and Sexually Transmitted Infections in Africa (ICASA) held in Cape Town (December 2013), the 14th European AIDS Conference held in Brussels (October 2013) and data from key publications during the past three months.

We hope you will find this newsletter an informative and useful resource, and we look forward to receiving your feedback regarding the content of this issue.

Sincerely,

Dr Mark Nelson
UK

Dr David Spencer
South Africa

Prof Elly Katabira
Uganda

SSAT
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Steering Committee

Dr Mark Nelson, UK

Dr Mark Nelson is a Consultant Physician in HIV at Chelsea & Westminster Hospital and an Honorary Senior Lecturer at Imperial College, London. His major interests are the treatment of HIV co-infection with Hepatitis B/C, antiretroviral (ARV) treatments and AIDS-related lymphoma. He is the Head of International Development for the St Stephen's AIDS Trust (SSAT), and he leads HIV educational programmes throughout Africa and Asia. He is a member of the British HIV Association Executive Committee where he is the lead for science and education, having previously been the lead for hepatitis infection.

Dr David Spencer, South Africa

Dr David Spencer is the Head of the Adult ARV Programme at Right to Care, Johannesburg, a not-for-profit organisation that supports initiatives for the clinical care and treatment of individuals living with HIV and its complications. His major interests are drug resistance and the development of 'third-line' ARV regimens. Through his work at Right to Care, he is committed to helping HIV physicians across Africa to meet the challenges of clinical HIV management.

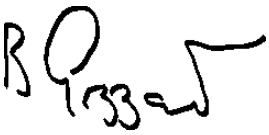
Prof Elly Katabira, Uganda

Prof Elly Katabira is the Clinical Advisor at the AIDS Clinic in Mulago Hospital, Kampala and at the Infectious Diseases Unit of Makerere University College of Health Sciences, Kampala. His major interests are clinical research on ARV treatments and operational research issues on various aspects of HIV/AIDS care and support, and the development of treatment and management guidelines for HIV/AIDS. Following his election in 2010, he completed his term in July 2012 as the President of the International AIDS Society, the world's leading independent association of HIV professionals.

Foreword by the SSAT

The St Stephen's AIDS Trust (SSAT) was founded in 1991, and is based at St Stephen's Centre, Chelsea and Westminster Hospital, London, UK. The charity's mission statement is "To promote clinical research into the treatment of HIV and those infections and malignancies associated with the acquired immunodeficiency syndrome (AIDS), in particular the research undertaken at the Chelsea and Westminster Hospital, and to publish such research. It also promotes education regarding all aspects and matters relating to HIV by providing information, training and advice throughout the world". The Research Unit at SSAT conducts clinical research on HIV, hepatitis and sexually transmitted diseases, from 'first-in-man' phase I trials to post-approval phase IV studies.

SSAT runs several educational programmes in Sub-Saharan Africa and Asia, with the aim of improving the standard of patient care and ensuring that national treatment guidelines reflect the best possible treatment options with the treatment resources available. SSAT is dedicated to improving the quality of life for people living with HIV all over the world.



Prof Brian Gazzard, CBE
Founding Chair of the SSAT, and Director of HIV/GUM Clinical Research & Education

The development of the **HIV Update in Africa** bulletin by the SSAT is conducted in collaboration with an international steering committee; all the articles cited are based on the recommendations of this expert committee.* It is funded by an independent educational grant from Janssen Pharmaceutica.†

In developing the content for this newsletter, the following sources were used to identify the latest key publications relating to HIV/AIDS treatment and management:

- The 17th International Conference on AIDS and Sexually Transmitted Infections in Africa (ICASA)
- The 14th European AIDS Conference (EACS)
- Pubmed – publications were identified using the search terms HIV and antiretroviral therapy, with date limits from mid-September 2013 to December 2013.

The publications were selected on the basis of their relevance to Sub-Saharan Africa or, such as in the case of important new data on treatments, their global importance. Topics covered in this issue include adult and paediatric antiretroviral treatment, tuberculosis, opportunistic infections, prevention of mother-to-child transmission and retention in care.

*All editorial content reflects the personal views of the steering committee and is provided independently from the sponsoring company.

†Aspen Pharmacare is the market authorisation holder in Africa for ARV treatments developed by Janssen Pharmaceutica.

CONTENTS

TUBERCULOSIS

1. The effects of tuberculosis treatment at combination antiretroviral therapy initiation on subsequent mortality: a systematic review and meta-analysis.

H.M. Soeters, C. Poole, M. R. Patel, A. van Rie.

Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA.

The aim of this systematic review and meta-analysis was to assess the impact of tuberculosis (TB) treatment at the time of antiretroviral treatment (ART) initiation on the risk of subsequent mortality. Studies were eligible for inclusion is they reported adult mortality among adult patients taking ART according to TB treatment status at ART initiation. Database searches identified 22 eligible studies, reporting outcomes for 98,350 patients (range 74-15,225). Overall, 14,779 (15%) of patients were receiving TB therapy at ART initiation. Eight studies reported on outcomes 1-3 months after ART initiation. Patients receiving TB therapy, compared to individuals not receiving this treatment, had a non-significant increase in mortality risk (1.10 [CI: 0.87-1.40]). Outcomes after 6-12 months were reported by 11 studies, these also showing no significant difference in mortality risk between patients receiving TB treatment compared to individuals not taking TB therapy (1.15 [CI: 0.94-1.41]). Outcomes between months 18-98 were reported in 10 studies. These showed that patients receiving TB treatment at ART initiation had a significant increase in their risk of death (1.33 [CI: 1.02-1.75).

However, the results of studies conducted at later time points were more heterogeneous. Factors associated with increased mortality risk included lower median baseline CD4 T-cell counts; baseline haemoglobin; longer follow-up; and not adjusting for body weight at months 18-98.

CONCLUSION: This study shows that patients receiving TB treatment at ART initiation did not have an increase in their short-term mortality risk compared to patients not receiving TB treatment. However, after 18 months of follow-up, TB treatment at ART initiation was associated with increased mortality. This finding suggests that patients taking TB treatment at ART initiation may require continued support after the completion of TB therapy.

Source: PLoS One 2013; 8(10): e78073.
Free full text article available: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0078073

2. Tuberculosis in antiretroviral treatment programs in lower income countries: availability and use of diagnostics and screening.

L. Fenner[1,2,3], M. Ballif[1], C. Graber[1], V. Nhandu[4], J. C. Dusingize[5], C. P. Cortes[6], G. Carriquiry[7], K. Anastos[8], D. Garone[9], E. Jong[10], J. C. Gnokoro[11], O. Sued[12], S. Ajayi[13], L. Diero[14], K. Wools-Kaloustian[14,15], S. Kiertiburanakul[16], B. Castelnuovo[17], C. Lewden[18], N. Durier[19], T. R. Sterling[20], M. Egger[1], for the International epidemiological Databases to Evaluate AIDS (IeDEA).

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Tuberculosis (TB) is a leading cause of morbidity and mortality among HIV-positive patients in resource-constrained settings. TB is often present in patients initiating antiretroviral treatment (ART), but is undetected in a large number of patients. This study therefore analyzed approaches to TB diagnosis and screening in ART programmes in sub-Saharan Africa, Asia and Latin America. In 2012, online questionnaires were distributed to care providers to collect progamme-level and patient-level data on TB detection rates and diagnostic tests. A total of 47 sites in 26 countries participated, and patient-level data were collected on 987 adult patients at 40 sites. Analysis of the programme-level data indicated sputum smear microscopy and chest x-ray were available at all 47 sites; TB culture at 44 (94%) and Xpert MTB/RIF (automated test to diagnose TB and resistance to rifampicin) at 23 (47%). Xpert MTB/RIF was only rarely available in Latin America and Central Africa. At sites with access to these tests, microscopy was used for 745 (76%) of patients diagnosed with TB, culture in 220 (24%) and chest x-ray in 688 (70%). The availability of some diagnostics was related to cost: when free, culture was performed for 27% of patients, compared to 21% when the test was charged for (p = 0.033); similarly, Xpert MTB/RIF was undertaken for 26% of patients when free compared to 15% when there was a charge (p = 0.001). Diagnostic tests for active TB before the initiation of ART included symptom screening at 46 sites (98%), chest x-ray at 38 (81%), sputum microscopy at 37 (79%), culture at 16 (34%) and Xpert MTB/RIF at 5 (11%).

CONCLUSION: This study shows that mycobacterial culture was available at most sites but was used in only 24% of patients diagnosed with TB. Sputum culture testing was significantly more likely to be carried out where it was free of charge. Xpert MTB/RIF was not generally available, and its use was related to cost.

Source: PLoS One 2013; 8(10): e77697.
Free full text article available: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0077697

3. Tuberculosis immune reconstitution inflammatory syndrome in A5221 STRIDE: timing, severity and implications for HIV-TB programs.

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Tuberculosis (TB) is a leading cause of death among HIV-positive patients, especially in resource-limited settings. Antiretroviral treatment (ART) reduces the risk of mortality. However, early initiation of ART among patients taking TB therapy has been associated with an increased risk of immune reconstitution inflammatory syndrome (IRIS). The aim of this study was to assess the severity, frequency and complications of TB IRIS among 806 HIV-positive TB patients enrolled in a study comparing early ART (initiated within 2 weeks of TB therapy commencing) versus delayed ART (started 8-12 weeks after TB therapy). IRIS was defined as severe if it resulted in death or required hospitalisation; moderate if it was managed using an invasive procedure or with corticosteroids; or mild in cases without hospitalisation/procedures/steroids. TB IRIS occurred in 61 (7.6%) patients. The rate was non-significantly higher among patients in the early vs. delayed ART arm (10.4% vs. 4.7%). TB IRIS occurred in 11.5% of patients with CD4 T-cell counts below 50 cells/mm^3 compared to 5.4% of individuals with CD4 T-cell counts above this level. TB IRIS occurred in 44.3% of patients with low CD4 T-cell counts who received early ART, and there was a significant interaction between early ART and a CD4 T-cell count below 50 cells/mm^3 and an increased TB IRIS risk ($p = 0.014$). TB IRIS occurred sooner with early vs. delayed ART (median 29 vs. 82 days; $p < 0.001$). The common manifestations of IRIS included lymphadenopathy (59%), constitutional symptoms (54.1%) and changes detected by x-ray (41%). TB IRIS with central nervous system involvement was rare (6.6%). As regards severity, TB IRIS was severe in 31.1% of cases, moderate in 41% and mild in 27.9%. There were no deaths associated with TB IRIS, but its management involved 1 or more invasive procedure in 34.4% of individuals, 31.1% were hospitalised and 54.1% received therapy with corticosteroids.

CONCLUSION: The researchers concluded that TB IRIS is more frequent with early ART initiation, but only when CD4 T-cell counts are below 50 cells/mm^3. These findings have implications for ART/TB programmes, which will require the appropriate diagnostic capabilities, clinical resources and skills necessary to manage TB IRIS.

Source: J Acquir Immune Defic Syndr, November 2013; Epub ahead of print.

ANTIRETROVIRAL TREATMENT

4. Extraordinary heterogeneity of virological outcomes in patients receiving highly active antiretroviral therapy and monitored with the World Health Organization public health approach in Sub-Saharan Africa and Southeast Asia.

A. F. Aghokeng,[1,2] M. Monleau,[2] S. Eymard-Duvernay,[2] A. Dagnra,[3] D. Kania,[4] N. Ngo-Giang-Huong,[5] T. D. Toni,[6] C. Touré-Kane,[7] L. X. T. Truong,[8] E. Delaporte,[2] M-L. Chaix,[9] M. Peeters,[2] and A. Ayouba;[2] for the ANRS 12186 Study Group.

[1]Virology-Laboratory, CREMER/IMPM/IRD, Yaoundé, Cameroon; [2]UMI 33 TransVIHMI, IRD and Université de Montpellier 1, Montpellier; [3]Centre National de Référence VIH-IST/PNLS, BIOLIM, FMMP/UL, Lomé, Togo; [4]Laboratoire de Virologie, Centre Muraz, Bobo-Dioulasso, Burkina Faso; [5]IRD UMI 174-PHPT and Chiang Mai University, Chiang Mai, Thailand; [6]Programme PAC-CI, Abidjan, Cote d'Ivoire; [7]Laboratoire de Bactériologie-Virologie, Dakar, Senegal; [8]Laboratoire de VIH/SIDA, Institut Pasteur, Ho Chi Minh City, Vietnam; and [9]Université Paris Descartes, EA 3620, AP-HP, Laboratoire de Virologie, CHU Necker-Enfants Malades, Paris, France.

A major limitation of antiretroviral treatment (ART) programmes in resource-limited settings is limited access to viral load monitoring. This cross-sectional study assessed rates of virological failure and antiretroviral drug resistance 12 and 24 months after initiating ART among 3935 patients in Burkina Faso, Cameroon, Cote d'Ivoire, Senegal, Togo, Thailand and Vietnam between 2009-2011. Virologic failure was defined as a HIV-1 RNA above 3.0 log10 copies/ml. Data on 12-month outcomes were available for 2060 patients and 24-month outcome data for 1875 individuals. Median CD4 T-cell counts at ART initiation were low (99-172 cells/mm^3). The principal ART regimens were d4T/AZT plus 3TC in combination with efavirenz/nevirapine. Overall failure rates were 11.1% among month-12 patients and 12.4% for month-24 patients and 71% and 86.1% of these patients, respectively, had drug-resistant virus. Rates of virological failure varied across study sites from 2.9% to 20.6% for month-12 patients and from 3.7% to 26% for month-24 patients. The detected drug resistance mutations were predominantly associated with drugs included in the ART regimens. However, a small number of patients had mutations associated with drugs that were not used, including abacavir, ddI, tenofovir, etravirine and rilpivirine, therefore potentially limiting future treatment options.

CONCLUSION: This study shows heterogeneity in virological outcomes among patients taking ART in resource-limited settings. Viral load monitoring and appropriate management of ART are required to improve outcomes in these settings.

Source: Clin Infect Dis 2014 Jan;58(1):99-109.

5. Effect of once-daily dosing and lower pill burden antiretroviral regimens for HIV infection: a meta-analysis of randomised controlled trials.

J.B. Nachega[1,2], J.-J. Parienti[3], O.A. Uthman[4,5], R. Gross[6], D.W. Dowdy[7], P.E. Sax[8], J.E. Gallant[9], M.J. Mugavero[10], E.J. Mills[11], T.P. Giordano.[12]

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In recent years efforts to improve antiretroviral therapy have focused on the optimization of therapy through once-daily dosing and development of fixed-dose combinations with low pill burden. Randomised studies have produced conflicting findings regarding the relative contribution of each parameter to virologic outcomes.

The aim of this meta-analysis was to assess the impact of once-daily dosing and pill burden on adherence and virologic suppression among HIV-positive patients taking antiretroviral treatment (ART). A database search in March 2013 identified 19 randomised-controlled trials comparing adherence and virologic suppression between patients taking once-daily ART compared to twice-daily ART, and also according to pill burden. A total of 6312 adult patients were enrolled in these studies. The average adherence percentage was modestly - but significantly – higher among patients taking once daily ART (weighted mean difference = 2.51% [1.20-3.83]; p = 0.0002). However, once-daily treatment did not increase the odds of achieving virologic suppression (RR = 1.01 [0.98-1.03]). However, higher pill burden was associated with poorer adherence and lower odds of virologic suppression for patients taking once- or twice-daily treatment. The association with adherence was non-significant for patients taking once-daily regimens.

CONCLUSION: This study shows that adherence, but not virological suppression, was improved with once-daily ART. Lower pill burden improved both adherence and the odds of achieving virologic suppression.

Source: Presented at the 14th European AIDS Conference (EACS), oral abstract PS4/5.

6. Dynamic logistic regression model and population attributable fraction to investigate the association between adherence, missed visits and mortality: a study of HIV-infected adults surviving the first year of ART.

S. Kiwuwa-Muyingo[1,2], H. Oja3, A. S. Walker[4], P. Ilmonen[5], J. Levin[2], I. Mambule[6], A. Reid[7], P. Mugyenyi[8], J. Todd[9] and DART Trial team.

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It is well established that adherence is an important factor affecting the chances of viral suppression and drug resistance in HIV-positive patients taking antiretroviral treatment (ART). The aim of this study was to determine if adherence was associated with mortality risk after the first year of ART. The study population comprised patients in Uganda and Zimbabwe enrolled in the DART study who had completed 12 months of ART. The patients were randomized to receive HIV care based upon laboratory and clinical monitoring or clinical monitoring alone. Adherence was assessed at 4-week intervals using pill count and questionnaire. The impact of non-adherence on mortality risk was assessed at an individual level and a population level. 2960 patients were eligible for inclusion. Outcomes differed between study arms. In the clinically-driven monitoring arm, patients with poor adherence in the previous 3-9 months had a significantly higher risk of death compared to patients with good adherence (OR = 2.18 [CI:1.47-3.22]). Poor adherence did not significantly increases mortality risk for patients in the laboratory and clinical monitoring arm (OR = 1.30 [0.78-2.10). Adherence had a significant impact on mortality risk at the population level. It was estimated that, over 5 years, optimal adherence would prevent 16% (0.7%-31.6%) of deaths among patients receiving laboratory and clinical monitoring and 33.1% (20.5%-44.8%) of deaths among patients with clinically driven monitoring.

CONCLUSION: This study showed that simple tools to measure adherence can be used to reduce the mortality risk of patients taking established ART. Poor adherence was associated with high mortality at both individual and population levels. Implementation of effective interventions to improve adherence could save a substantial number of lives.

Source: BMC Infectious Diseases, 2013; 13: 395.
Free full text article available: http://www.biomedcentral.com/1471-2334/13/395

7. Advanced HIV disease at entry into HIV care and initiation of antiretroviral therapy during 2006- 2011: findings from four sub-Saharan African countries.

M. Lahuerta[1,2], Y. Wu[1], S. Hoffman[2,3], B. Elul[1,2], S. Gorrell Kulkarni[1], R. H. Remien[3], H. Nuwagaba-Biribonwoha[1], W. El Sadr[1,2], and D. Nash[2,3,5], for the LSTART Team and the Identifying Optimal Models of HIV Care Collaboration.

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Prevention of HIV-related morbidity and onward transmission of HIV are reliant upon timely diagnosis, enrolment and retention in care, and prompt ART initiation. Challenges exist at each step in this matrix in sub-Saharan Africa. In this study, investigators examined data for 334,557 adults who enrolled in HIV care at 132 facilities in Kenya, Mozambique, Rwanda and Tanzania, between 2006-211. ART was initiated by 149,032 individuals. Data were gathered on the proportion of patients initiating ART with advanced disease (CD4 T-cell counts below 100 cells/mm^3 or WHO stage IV disease) and the factors associated with advanced disease. During the period of analysis, median CD4 T-cell counts at the time of enrollment increased from 238 to 286 cells/mm^3. Median CD4 T-cell counts at ART initiation increased only modestly, from 125 to 186 cells/mm^3. However, the proportion of patients starting ART with advanced disease fell from 42% to 29%. The odds of advanced disease at ART initiation were higher among men (AOR = 1.6 [CI: 1.3-1.5]); patients on tuberculosis therapy (AOR = 1.6 [CI: 1.3-2.0]); and individuals who dropped out of care for 12 or more months before ART initiation (AOR = 2.0 [CI: 1.6-2.6]). Enrollment in a programme to prevent mother-to-child HIV transmission was associated with lower odds of starting ART with advanced disease (AOR = 0.66 [CI: 0.55-0.80]).

CONCLUSION: This study shows that the proportion of patients initiating ART with advanced disease has fallen. However, median CD4 T-cell counts at the initiation of therapy have increased only modestly. Enhanced effort is required to identify patients and link them to care and to ensure retention in care so that ART can be initiated according to guidelines.

Source: Clin Infect Dis. 2013 Dec 4. (Epub ahead of print).

8. Gaps in adult HIV viral load monitoring and management: observations from baseline assessment of 56 primary healthcare facilities in two provinces of South Africa.

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Where viral load monitoring is available for detection of antiretroviral treatment failure, optimal use of this technology depends on consistent implementation of viral monitoring protocols. South African national antiretroviral treatment guidelines recommend initial viral load monitoring six months following initiation of therapy and 12 months thereafter. Recently revised recommendations require viral load follow-up within 2 months and increased adherence counselling for individuals with a VL > 1000 copies/mL.

Baseline assessments of compliance with viral load monitoring protocols were conducted at 56 public healthcare facilities in two sub-districts in two provinces of South Africa. 151 patient records were audited. Of the files audited, 107 of 151 (71%) were eligible for viral load monitoring, 39 (25%) were ineligible and in 5 cases (3%) eligibility could not be determined. Of those eligible for viral load monitoring, 49 (46%) had HIV-1 RNA measurements obtained according to current guidelines. Twenty four (22%) had HIV-1 RNA measurements drawn at intervals greater than every 12 months, and 34 (32%) files included no documentation of viral load monitoring despite eligibility by ART start greater than six months previously. Of the 74 individuals for whom VLs were obtained at least six months after ART initiation, the results were as follows: 35 (48%) VLs were less than 40 copies/mL, 20 (27%) VL results were between 40-1000 copies/mL, 15 (19%) VL results were greater than 1000 copies/mL, and four (5%) results were either pending or not documented.

CONCLUSION: The researchers identified substantial non-compliance with viral load monitoring protocols in an audit of patient records drawn from a cross-section of public health facilities. Failure to carry out testing at the prescribed intervals, or failure to test despite at least 6 months of antiretroviral treatment, occurred in the majority of patients on ART. Furthermore, of those tested, 52% did not have HIV-1 RNA<40 copies/ml, indicating the need for interventions to support adherence and follow-up monitoring in order to determine successful virologic suppression. Strengthened routine viral load monitoring is essential in order to optimise and sustain the benefits of antiretroviral therapy in the world's largest ART programme, and to avoid drug resistance and switches to more costly second-line regimens. Routine audit of compliance with monitoring protocols has the potential to improve staff awareness and compliance.

Source: Presented at 17th ICASA, abstract ADS039, 2013.

9. Accumulation of protease mutations among patients failing second-line antiretroviral therapy and response to salvage therapy in Nigeria.

H E. Rawizza[1,2], B Chaplin[2], Seema T. Meloni[2], K M. Darin[3], O Olaitan[4], K K. Scars[i3], C K. Onwuamah[5], R A. Audu[5], P R. Chebu[6], G E. Imade[6], P Okonkwo[4], P J. Kanki[2]

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Antiretroviral treatment (ART) guidelines and programmes in resource-limited settings have focused on first- and second-line therapy. An increasing number of patients now have extensive experience of ART and have experienced the failure of first- and second-line regimens. Guidelines are now required for third-line treatment. The purpose of this study was to inform third-line treatment strategies by examining the consequences of maintaining patients on failing second-line combinations, specifically the accumulation of protease inhibitor (PI) resistance mutations. Failure was defined as two consecutive viral load measurements ≥ 3 $\log_{10}$ copies/ml 6 months after starting second-line treatment. The study population consisted of 673 patients who received PI-based second-line ART between 2004-2011 through the Harvard/APIN PEPFAR programme. Genotypic resistance tests were performed on 61 samples and 38% of patients had no PI-associated mutations. Duration of non-suppressive second-line therapy was associated with the accumulation of PI-associated resistance mutations. Patients taking failing therapy for < 12 months had a median of 2 mutations (0-5), compared to a median of 5 mutations (0-6) among patients taking failing treatment for > 24 months. Patients developed a median of 0.6 (0-1.4) mutations per 6 months on failing therapy. Analysis of patients who remained on failing regimens for > 24 months indicated that high-or intermediate-level resistance to lopinavir and atazanavir was present in 63%, with 5% having this level of resistance darunavir.

CONCLUSION: This study shows that failure to switch from a non-suppressive second-line regimen is associated with the accumulation of PI-associated resistance mutations that compromise response to lopinavir/ritonavir or atazanavir. Mutations associated with high-level resistance to darunavir/ritonavir were infrequent, emphasising the importance of access to this drug for viable third-line treatment regimens in resource-limited settings.

Source: PLoS One 2013; 8(9): e73582.
Free full text article available: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0073582

10. HIV lipodystrophy in participants randomised to lopinavir/ritonavir (LPV/r) +2–3 nucleoside/nucleotide reverse transcriptase inhibitors (N(t)RTI) or LPV/r + raltegravir as second-line antiretroviral therapy.

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An association between inclusion of a nucleoside reverse transcriptase inhibitor (NRTI) treatment and greater fat redistribution has been observed in protease inhibitor-treated patients receiving first-line antiretroviral therapy in the ACTG 5142 study (Haubrich, 2009). Conversely the ACTG 5142 study found greater elevation of cholesterol in the NRTI-sparing arm.

NRTI-sparing treatment has been proposed as a means of limiting the incidence of lipoatrophy. The association between NRTI exposure during second-line protease inhibitor-based therapy and fat redistribution and metabolic abnormalities is less well characterized.

The aim of this study was to compare 48-week changes in body fat, lipids, and Metabolic Syndrome and cardiovascular disease (CVD) risk among patients taking second-line antiretroviral treatment (ART)who were randomised on a 1:1 basis to receive lopinavir/ritonavir (LPV/r) plus raltegravir (RAL) compared or LPV/r plus 2-3 nucleoside/nucleotide reverse transcriptase inhibitors (N[t]RTIs). Whole body dual x-ray absorptiometry (DEXA) was performed at baseline and week 48. Metabolic Syndrome and CVD risk were calculated and differences in lipids and body fat parameters were compared. Results were adjusted for gender body mass index and smoking status. The study population consisted of 210 patients. Both regimens were associated with gains in limb fat over 48 weeks. The mean increase was 15.7% (5.3-25.9) among patients receiving LPV/r plus N(t)RTI and 21.1% (11.1-31.1) among patients randomised to LPV/r plus RAL. This difference was not significant. Increases in total body fat mass and trunk mass fat were also similar for the two regimens. The total:HDL cholesterol ratio was significantly higher in the RAL arm ($p = 0.03$), but other lipid parameters were similar between the two regimens. No significant differences were observed in CVD risk or the incidence of Metabolic Syndrome between the two arms. Baseline factors associated with increased levels of limb fat gain were high HIV-1 viral load, high insulin and not taking lipid-lowering therapy.

CONCLUSION: This study shows switching to second-line ART regimens consisting of LPV/r plus N(t)RTIs or LPV/r plus RAL was associated with similar improvements in limb fat. However, the RAL-containing combination was associated with a more favourable total:HDL cholesterol ratio.

Source: PLOS One 2013; 8(10): e77138.
Free full text article available: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0077138

11. Increases in regimen durability associated with the introduction of tenofovir at a large public-sector clinic in Johannesburg, South Africa.

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South Africa's national treatment guidelines recommend a total of seven antiretroviral drugs for use in first- and second-line regimens. Limited treatment options necessitate an increase in regimen durability (minimising the rates of substituting individual drugs and of treatment failure in first-line treatment).

In April 2010 the South African government following WHO's recommendation replaced stavudine with tenofovir in public-sector first-line ART. Tenofovir is associated with fewer side effects and toxicities; its use should result in increased regimen durability. Prior to 2010 first-line regimens comprised stavudine or zidovudine with lamivudine and either efavirenz or nevirapine.

This cohort analysis of prospectively collected data of ART naïve, non-pregnant adults aged ≥ 18 who initiated a standard public-sector first-line regimen between April 2004 and December 2011 at the Themba Lethu Clinic, Johannesburg, South Africa evaluated the frequency and type of single-drug substitution. Cox models were used to evaluate the association of single-drug substitution during the first twelve months on ART with year of ART initiation and type of ARV.

Among the 19,699 patients the overall frequency of single-drug substitution in the first twelve months on ART was 10% (1,964). From 2005 to 2010 the frequency ranged from 10.1% (95% CI: 8.9-11.4%) to 13.1 % (95% CI: (11.9-14.5%).I In 2011, when over 85% of patients were initiated on tenofovir, the rate of single drug substitution decreased substantially to 5.6% (95%CI: 4.8-6.5%).

Single-drug substitution was lowest among those on tenofovir (5.1%) compared to zidovudine (11.3%), 30 mg stavudine (10.5%) or 40 mg stavudine (14.4%).

Adjusted Cox model analysis showed that those initiating ART between 2005 and 2010 vs 2011 had a two-fold increased risk of single-drug substitution while those on stavudine or zidovudine had a two or three-fold increased risk compared to those on tenofovir.

CONCLUSION: This study shows use of tenofovir, associated with a decline in single-drug substitution in the first 12 months on ART, could improve regimen durability and treatment outcomes in resource-poor settings.

Source: Journal of the International AIDS Society 2013; 16:18794.
Free full text article available: http://www.jiasociety.org/index.php/jias/article/view/18794

12. Rates of intolerance to efavirenz, in the context of the imminent mass switch to TDF/3TC/EFV: the experience at the Lighthouse Clinic, Lilongwe, Malawi.

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The non-nucleoside reverse transcriptase inhibitor efavirenz is recommended as the preferred third agent for first-line therapy in many national and international antiretroviral treatment guidelines, and is widely available as part of fixed-dose ARV combinations also containing tenofovir and FTC or 3TC. Efavirenz treatment is associated with mild-to-moderate neuropsychiatric adverse effects including dizziness, abnormal or vivid dreams and impaired sleep quality in the majority of patients, but these adverse effects resolve or greatly diminish beyond the first few months of therapy. Clinical trials and cohort studies indicate a lower incidence (1 – 2%) of more serious treatment-limiting neuropsychiatric adverse effects, such as psychosis, depression and disabling dizziness in developed world settings. The incidence of treatment-limiting SAEs associated with efavirenz treatment in less well-resourced settings, and their operational implications, have been less well explored.

In order to evaluate the potential burden of treatment-limiting neuropsychiatriac SAEs associated with efavirenz after a planned switch of all patients to efavirenz-containing regimens in Malawi, researchers examined the records of 4808 patients alive and in care and receiving antiretroviral treatment with TDF/3TC/EFV at the Lighthouse clinic, Lilongwe. A case-control study compared age, weight and gender in the 106 patients who had switched from efavirenz to nevirapine as a result of intolerance.

The imputed intolerance rate was 2%, but a clear reason for the switch was documented only in 45 cases. The most frequent reasons were disabling dizziness (58%), rash (16%), psychosis (13%), memory loss (9%) and confusion (7%). Switching due to intolerance occurred after a median of 47 days (IQR 28-105). Age, gender and weight had no significant predictive value.

CONCLUSION: The rate of efavirenz intolerance identified in this clinic population implies a rate higher than previous national estimates, indicating a higher-than-predicted need for alternative first-line regimens. This may present particular challenges in settings where a limited number of regimens are available, and where clinician experience in the prescription of alternative regimens is limited. The researchers estimate that the imminent switch of 350,000 patients to efavirenz in Malawi may result in up to 2,000 cases of severe and potentially hazardous psychiatric disturbances. The researchers conclude that it is vital that all clinicians be aware of the risk for severe neuropsychiatric adverse events in patients initiating efavirenz, and patients with a previous history of psychiatric problems should initiate an alternative regimen.

Source: Presented at 17th ICASA, abstract ADS032, 2013.

13. Impact of antiretroviral therapy on Kaposi's Sarcoma incidence among HIV-infected adults in East Africa.

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Kaposi's sarcoma is the most commonly diagnosed malignancy in HIV-infected persons in much of sub-Saharan Africa and is associated with a high prevalence of HHV-8 in the general population, especially in eastern and central Africa. Comprehensive epidemiologic information on the impact of ART on Kaposi's Sarcoma prevalence has been lacking due to lack of infrastructure.

The International epidemiologic Databases to Evaluate AIDS (IeDEA) collaboration conducted an analysis of cohorts participating in the East Africa International Epidemiologic Databases to Evaluate AIDS (IeDEA) consortium (Mbarara & Kampala, Uganda, and AMPATH, Kenya). All cohort participants without KS at baseline were followed from January 2004 until July 2012, for a median of 5.4 years (IQR 3.6-6.9). 159,063 participants were available for evaluation (67% female), with baseline median age of 36 years (IQR: 30-43) and median CD4+ T-cell count of 226 cells/mm^3 (IQR: 90-415). 1326 incident cases of KS were diagnosed (32% biopsy-proven) (260 cases per 100,000 person-years) and incidence declined over time, from 781/100,000 p-y (95% CI: 669 to 912) in 2005 to 225/100,000 p-y (95% CI: 173 to 293) in 2012. Adjusted analysis showed that persons receiving antiretroviral therapy had an 80% (95% CI: 70% to 90%; p<0.001) reduction in incident KS compared to those not on ART. The reduction in incidence was greatest in those with baseline CD4+ T-cell counts <100 cells/mm^3 (p<0.01). Despite the reduction in risk, KS incidence was 75 per 100,000 cases in those who achieved CD4+ cell counts above 500 cells/mm^3 on antiretroviral therapy.

CONCLUSION: Antiretroviral therapy greatly reduces the risk of KS, especially at low CD4+ T-cell counts, but does not eliminate risk despite immune restoration.

Source: Presented at 17th ICASA, abstract ADS063, 2013.

14. Dual therapy with lopinavir/ritonavir (LPV/r) and lamivudine (3TC) is non-inferior to standard triple drug therapy in naïve HIV-1 infected subjects: 48-week results of the GARDEL Study.

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Antiretroviral monotherapy using a ritonavir-boosted protease inhibitor has been proposed as a means of minimising toxicity and cost of first-line antiretroviral therapy. Various ritonavir-boosted protease-inhibitors including lopinavir, atazanavir and darunavir have been evaluated in randomized clinical trials as monotherapy. A previous systematic review (Bierman et al, 2009) concluded that the use of the boosted protease inhibitor lopinavir/ritonavir as monotherapy in first-line therapy in antiretroviral-naïve HIV-positive subjects was inferior to triple therapy containing two nucleosides.

The GARDEL study was designed to evaluate the safety and effectiveness of lopinavir/ritonavir combined with the well-tolerated and inexpensive nucleoside reverse transcriptase inhibitor lamivudine (3TC). 426 antiretroviral-naïve subjects with no IAS-USA-defined baseline protease or reverse transcriptase resistance mutations were randomly assigned to receive 400/100mg lopinavir/ritonavir plus 150mg 3TC (bid) (dual therapy, DT), or lopinavir/ritonavir plus two NRTIs (triple therapy, TT) assigned according to national treatment guidelines in participating countries (9% abacavir/3TC (*Kivexa*), 37% tenofovir/emtricitabine (*Truvada*), 54% AZT/3TC (*Combivir*)).

The median baseline CD4+ T-cell cell count of subjects was 325 cells/mm^3, 43% had HIV RNA >100,000 copies/ml and 3% had a prior AIDS diagnosis.

The primary study endpoint was virologic response rate, defined as the proportion of patients with HIV-1 RNA< 50 copies/mL in an ITT-exposed analysis at 48 weeks (FDA-snapshot algorithm). 416 of 426 subjects were dosed; at week 48 88.3% of subjects receiving DT and 83.7% of subjects receiving TT were responders (p= 0.171, difference +4.6% [95% CI:-2.2% to +11.8%]). By observed analysis 96% (DT) and 97% (TT) were responders, respectively. There was no significant difference in virologic response between study arms in the proportion of subjects with baseline HIV RNA > 100,000 copies/ml (87% vs 78%). There was no significant difference in virologic failure between study arms (5% vs 6%), nor in CD4+ cell count increases (DT +227 cells/mm^3, TT+217 cells/mm^3, p=0.625). Treatment discontinuations due to toxicity were more frequent in the TT arm (DT=1[0.4%], TT=10[4.9%, p=0.01; CI95%:-8,1% to + 0,9%%]). One SAE was considered possibly associated with study drug (DT).

CONCLUSION: Dual therapy with lopinavir/ritonavir and lamivudine was non-inferior to triple therapy and resulted in fewer treatment discontinuations due to toxicity. The researchers concluded that the dual regimen merits further evaluation, and note its potential attractions for resource-poor settings. As well as its low cost, the regimen requires no monitoring for renal, hepatic or haematologic toxicities, unlike regimens containing d4T or AZT.

Source: Presented at 14th European AIDS Conference, oral abstract LBPS7/6

RETENTION IN CARE

15. Are they really lost? "true" status and reasons for treatment discontinuation among HIV infected patients on antiretroviral therapy considered lost to follow up in urban Malawi.

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The high rate of loss to follow-up (LTFU) is a challenge to the long-term success of ART programmes in sub-Saharan Africa. Among those LTFU an estimated 40% of those traced had been reported dead but the status of the remaining patients may not be accurately recorded, thus over-estimating the proportion of patients who are no longer retained in care.

This retrospective cohort study of routine data from a patient-tracing programme at Lighthouse Trust's two high-volume public urban ART clinics in Malawi identified adult patients on ART who missed scheduled clinic appointments by at least 21 days, considered LTFU, between January 2006 and December 2010. Patients who had consented at ART registration were traced by phone or home visit and true ART status documented and reasons for ART discontinuation among those who stopped ART reported.

Among the 21,382 adults accessing ART at the clinics 4,580 (21%) were suspected LTFU. Of these 30% (1,384) could not be traced due to incorrect/incomplete information or change of residence. Among the 3,176 traced 30% (952) were dead. Of the 2,195 patients (99%) who agreed to be interviewed 2,183 had started ART according to phone-based self-reports or in-person interviews.

Of those who had started ART 58% (1,226) were still taking ART at interview of which 61% were receiving ARVs from another clinic, 121 self-transferred and 623 officially transferred but records were inaccurate. The remaining 39% were still in care at the clinics of which 189 reported uninterrupted treatment in spite of missed appointments, having acquired drugs from alternate sources, and 293 reported treatment gaps.

Of the 957 who stopped treatment 940 gave reasons: 159 (17%) failed to remember; 110 (12%) felt too ill/weak to collect ARVs; 431 (46%) due to difficulties in travelling to the clinic and 152 (16%) due lack of money for transport. Men were more likely than women to stop due to travel 54% vs 41% (p=0.001) and conversely women were more likely to stop due to lack of money 22% vs 14% (p=0.013).

CONCLUSION: This study shows a considerable proportion (25%) of those considered LTFU were still taking ART, potentially underestimating ART retention rates at clinic and national levels. The researchers conclude that

increased decentralisation of ARV distribution, expanded clinic hours, increased ARV supplies for stable patients and improved communication between clinics will enhance adherence, retention and management.

Source: PLoS One, 2013 Sept 26; 8(9).
Free full text article available: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0075761

16. Differences between HIV-Infected men and women in antiretroviral therapy outcomes – six African countries, 2004-2012.

US Department of Health and Human Services Centers for Disease Control and Prevention (CDC).

Proportionally more HIV-infected women than men access ART services in sub-Saharan Africa. Evaluating the differences in ART enrolment characteristics and treatment outcomes may help identify reasons for those differences, providing opportunities for improved programme management.

This analysis of retrospective cohort studies from representative samples of adult men and women (aged ≥ 15 and ≥ 18) who initiated ART during 2004 -2010 in six countries in western (Côte d'Ivoire), southern (Swaziland, Mozambique and Zambia) and eastern (Uganda and Tanzania) Africa estimated enrolee attrition from death, stopping ART or loss to follow-up at six-monthly intervals after ART initiation.

A representative sample of facilities was selected in each country. At each facility a sample frame of study eligible patients was created and simple random sampling used to select the desired sample size of patient medical records. The primary outcome was enrolee attrition. Cox proportional hazards regression models were used to estimate the effect of sex on attrition.

In the six countries sample sizes ranged from 1,457 to 3,682. Analysis from a total of 13,175 records showed women represented 61-67% of enrolees in each country; median age at ART initiation was 37-40 years and 32-35 years for men and women, respectively. Median CD4 + T cell count ranged from 119-141 cells/mm^3 for men and 137-161 cells/mm^3 for women.

A higher proportion of men than women initiated ART at WHO stage IV: in Côte d'Ivoire (26% vs. 21%), Swaziland (18% vs. 10%), Mozambique (20% vs. 13%), Zambia (11% vs. 9%), Uganda (16% vs. 10%) and Tanzania (30%v vs. 27%). Men had a higher attrition risk in each country. Multivariate analysis after adjusting for baseline predictors of ART outcomes showed women had a 15-26% statistically significant lower risk for attrition in western and southern Africa. In eastern Africa, while women had an 11-12% adjusted lower risk for attrition, the association between sex and attrition was not statistically significant.

CONCLUSION: The study authors propose further research on country-specific causes for increased attrition and delayed initiation of care among men that may identify strategies to improve male enrolment, retention and programme outcomes.

Source: Morb Mortal Wkly Rep. 2013 Nov 29;62(47):946-52.
Free full text article available: http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6247a2.htm

ANTIRETROVIRAL TREATMENT IN PREGNANT WOMEN: MATERNAL AND INFANT OUTCOMES

17. Reduction of maternal mortality with highly active antiretroviral therapy in a large cohort of HIV-infected pregnant women in Malawi and Mozambique.

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HIV contributes significantly to maternal mortality in resource-poor settings. ART scale-up for HIV-infected pregnant women in recent years has helped reverse the trend of increased maternal mortality due to HIV.

Since 2000 the Drug Resource Enhancement Against AIDS and Malnutrition (DREAM) Programme has been providing comprehensive HIV care in sub-Saharan Africa; triple ART is routinely provided to all HIV-infected pregnant women, regardless of CD4+ T-cell count, during prenatal care and breastfeeding.

Data from HIV-infected pregnant women attending any of the 16 DREAM centres for prenatal care in Malawi (2006-2009) and Mozambique (2002-2010) were analysed according to maternal mortality, ART uptake, laboratory parameters and loss to follow-up in two distinct populations: group 1: women initiating triple ART during prenatal care (n=8172) and group 2: women initiating ART for their own health who became pregnant while on treatment (n=1978).

Over an eight-year period 10,150 pregnancies were followed. Median age was 26 years (IQR: 23-30) with a baseline median CD4+ T-cell count of 392 cells/mm^3 (IQR: 258-563). All had detectable viral loads at baseline before ART initiation 3.9 $\log_{10}$ copies/mL (IQR: 3.2-4.4), a mean body mass index of 23.4 (IQR: 21.5-25.7) and median haemoglobin value of 10.0 g/dL (IQR: 9.0-11.0).

101 (0.99%) maternal deaths occurred within 42 days post-delivery; 87 (1.1%) in group 1 and 14 (0.7%) in group 2. Mortality risk among women with CD4+ T-cell count <350 cells/mm^3 vs >350 cells/mm^3, was 1.3% and 0.7%, respectively. Mortality risk among women on antenatal ART for < one month compared to women on antenatal

ART for 31 days or more was 2.2% (22/991) and 0.9% (79/9159), respectively, OR: 2.6, 95% CI:1.6-4.2, p<0.001. Multivariate analysis showed maternal mortality was associated with shorter pre-delivery ART exposure (RR: 3.035, p<0.001), at baseline lower BMI (RR:.602, p=<0.001), haemoglobin values (RR .660, p=0.005): viral load (RR: 1.134, p=0.440) and CD4+ T-cell counts (RR: .884, p=0.021).

Survival at 4 years was 92% for women on shorter antenatal ART vs. 98%, p=0.001 for women on ART for >270 days before pregnancy.

CONCLUSION: The researchers conclude that these findings support universal access to ART during pregnancy given the impact on maternal (and infant) mortality, with a particular emphasis on ensuring early initiation of ART after diagnosis in pregnant women.

Source: PLoS One. 2013 Aug 19; 8(8)e71653.
Free full text article available: http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0071653

18. Efficacy and safety of an extended nevirapine regimen in infants of breastfeeding mothers with HIV-1 infection for prevention of HIV-1 transmission (HPTN 046): 18-month results of a randomized, double-blind placebo-controlled trial.

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Breastfeeding is critical to infant survival but presents a risk of HIV transmission to HIV-exposed infants in high-prevalence resource-poor settings. Strategies optimising the benefits of breastfeeding while minimising the risk of transmission during breastfeeding are crucial.

HPTN, 046 a phase 3, randomised double-blind placebo-controlled trial assessed the efficacy and safety of extending once-daily infant nevirapine (NVP) prophylaxis to six months of age or until cessation of breastfeeding to prevent post-natal transmission in HIV-exposed breastfeeding infants who had received NVP until six weeks of age. Primary analyses showed a statistically significant reduction in transmission risk among infants receiving daily NVP

from 6 weeks to six months of age [1.1 % (95% CI:0.2-1.8%) vs placebo 2.4% (95% CI: 1.3-2.6%) p=0.049]. This study reports the final 18-month outcomes of the trial conducted among HIV-infected pregnant women in South Africa, Tanzania, Uganda and Zimbabwe. Infant diagnostic testing was carried out regularly from birth until 18 months of age. Kaplan-Meier analysis assessed 18-month cumulative infant HIV infection, HIV infection/death and mortality rates.

The analyses included 1522 infants (759 and 763 in the NVP and placebo arms respectively. At randomisation maternal and infant demographics and clinical status were similar with 29% of women in both arms (total =439) receiving ART for their own health.

There were no statistically significant differences from six months to 18 months between arms in post-natal transmission.

Cumulative 18-month follow-up rates of transmission between 6 weeks and 18 months were low, 2.2% (95% CI:1.1-3.3%) and 3.1% (95% CI:1.9-4.4%) , in the NVP and placebo arms, respectively, p=0.28. The HIV-free survival and infant survival rates did not differ significantly between arms.

Women receiving ART for their own health had the lowest 18-month infection rates (0.5%, 95% CI:0.01-1.1%). Yet for infants of mothers on ART HIV infection/death rates at 18 months (3.7% 95% CI:1.9-5.5%) did not differ significantly from infants of mothers not on ART but with CD4+ T-cell counts >350 (4.8%, 95% CI:2.7-6.8%, p=0.46). Adverse events did not differ between arms.

CONCLUSION: These findings add to the body of literature supporting the effectiveness of extended infant prophylaxis throughout the breastfeeding period in reducing the risk of transmission through breast milk.

Source: J Acquir Immun Defic Syndr 2013; [epub ahead of print].

19. Increasing proportion of HIV-infected women entering PMTCT already on antiretroviral therapy: implications for PMTCT programmes.

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Programmes for the prevention of mother-to-child HIV transmission (PMTCT) in South Africa and other high-prevalence countries are designed to identify HIV-infected pregnant women and initiate antiretroviral treatment. In recent years expansion of antiretroviral therapy and changes in treatment guidelines have increased the likelihood that women will conceive after beginning antiretroviral treatment, while under care in an adult antiretroviral clinic. Services may not be tailored to the needs of women already taking antiretroviral treatment.

This study examined the proportion of HIV-infected women entering antenatal care who were already on ART at the time of conception in Cape Town, South Africa between January 2010 and December 2012.

16,172 women made their first antenatal visit during the study period, of which 4302 (27%) tested HIV-positive. The HIV prevalence and median age among HIV-positive women (28 years) was constant over this period. The proportion of women entering antenatal care already on ART increased from 4.8% in the first quarter of 2010, to 8.5% in the first quarter of 2011, to 23.8% in the first quarter of 2012, to 33.2% in the fourth quarter of 2012 ($p<0.001$). Among women on ART at the time of starting antenatal care, the median CD4+ T-cell count increased from 340 cells/mm^3 in the first quarter of 2010 to 437 cells/mm^3 in the last quarter of 2012 ($p<0.001$).

CONCLUSION: Whereas PMTCT services have traditionally focussed on identifying HIV-positive women and initiation of antiretroviral therapy, the rapid increase in the proportion of women already on treatment attending PMTCT services in Cape Town after January 2010 indicates the importance of identifying non-adherence and treatment failure among PMTCT service attendees.

Source: Presented at 17th ICASA, abstract ADS068, 2013.

CHILDHOOD DEVELOPMENT AND ART

20. Long-term follow-up of children in the HIVNET 012 perinatal HIV prevention trial: five-year growth and survival.

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HIVNET 012, a phase IIB trial, was conducted to evaluate the safety and efficacy of peripartum nevirapine (NVP) or zidovudine (ZDV) in HIV-infected Ugandan women for PMTCT. This prospective, long-term study examined the growth patterns, long-term safety of peripartum ART prophylaxis (NVP or ZDV), morbidity and 5-year survival among HIV-infected and uninfected children born to mothers enrolled in HIVNET 012.

Study children alive at 18 months of age were eligible. Following consent children were enrolled and evaluated every six months from 24 to 60 months. Evaluation comprised history, serious adverse events, physical examination, growth measures according to WHO Z-scores and neurological assessment and development. HIV-infected children had complete blood counts, CD4+ T-cell count and HIV-RNA measured.

Of the 651 total births 528 (84%) were alive at 18 months of which 491 (93%) (426 HIV-uninfected and 65 infected) were consented and enrolled in the 5-year follow-up; 91% (447) were retained. Over the five years in both uninfected but HIV-exposed and HIV-infected children lower height and weight compared to WHO growth standards were sustained. On average an HIV-infected infant weighed 0.15 standard deviation (SDs) less than an uninfected infant in the first year after being infected ($p < 0.0001$), and was 0.2 SD shorter, ($p<0.0001$). Among uninfected infants normal brain growth as measured by head circumference was preserved over the 5-year period.

The five-year survival in HIV-exposed uninfected infants was 93% (95% CI: 90-95%) vs. 43% (95% CI: 35-53%), $p<0.0001$ in HIV-infected infants. Safety and growth outcomes were similar in both arms.

CONCLUSION: These findings showing long-term stunting and impaired weight growth outcomes among all children of HIV-positive mothers, both HIV-infected and HIV-exposed, and low five-year survival among HIV-infected children. The researchers conclude that initiation of ART, provision of nutritional interventions in all children born to HIV-infected mothers and overall strengthening of the maternal child health infrastructure in resource-poor settings should be prioritised in order to improve growth outcomes.

Source: J Acquir Immune Defic Syndr 2013; 64:464-471.

21. Effect of age at antiretroviral treatment initiation on growth reconstitution within the first 24 months among HIV-infected children in the IeDEA West African Pediatric Cohort.

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The impact of ART on improved survival among children and adolescents in sub-Saharan Africa is well established. Its impact on growth constitution for malnourished children is less well characterized. In particular, the contribution of age at ART initiation to catch-up growth requires further study.

The International epidemiologic Databases to Evaluate AIDS (IeDEA) collaboration assessed paediatric growth outcomes in all children < 10 years of age at 11 clinical sites across West Africa (n=2004) who initiated ART between 2001 and 2012. All subjects who had received at least 24 months of ART and at least two anthropometric measurements during follow-up, including one at ART initiation, were evaluable.

Malnutrition (Z-score <-2SD) was defined by three anthropometric parameters: weight-for-age for underweight (WAZ), height-for-age for stunting (HAZ) and body mass index for age (WHZ/BAZ) for wasting. At ART initiation, 51% of study participants were underweight, 48% were stunted, and 33% were wasted.

At 24 months on ART, the probability rate for catch-up was 72% for those underweight (95% CI: 69-76), 57% for those stunted (95% CI: 53-61), and 91% for those wasted (95% CI: 89-94). Those who were severely malnourished, and those who were under five years of age, were more likely to catch up. Children who experienced acute malnutrition, rather than chronic malnutrition, were more likely to catch up. Age-related differences in WHZ/BAZ were non-significant.

Parameter	aHR relative to age > 5yrs at ART initiation			
	<2 yrs (95% CI)	2 years of age	3 years	4 years
WAZ	1.93 (1.55 – 2.44)	2.14 (1.67 – 2.73)	1.48 (1.10-1.99)	1.45 (1.07–1.95)
HAZ	1.89 (1.46-2.44)	1.93 (1.48-2.53)	1.79 (1.32-2.40)	1.45 (1.05-2.01)

CONCLUSION: The authors suggest that ART be initiated as early as possible in children, before growth failure, and that nutritional supplements be given to encourage growth and clinical response to ART in HIV-infected children.

Source: Presented at 17th ICASA, abstract ADS044, 2013.

22. Prospective study assessing neurodevelopmental benefits of anti-retroviral therapy in Ugandan children 0-6 years of age with HIV.

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HIV infection is associated with a high burden of neurodevelopmental deficits in children. HIV-positive children can experience a wide range of disabilities such as generalized cognitive defects, motor defects, and visual, language, and learning disorders. Knowledge regarding the frequency of these deficits, and the impact of antiretroviral therapy on neurodevelopment in young children receiving treatment in sub-Saharan Africa, remains limited.

A study conducted in Rakai, Uganda, sought to quantify the extent of neurodevelopmental deficits in children born with HIV in comparison to HIV-negative children exposed or unexposed to HIV. The study also sought to assess the impact of duration of antiretroviral therapy on neurodevelopment. Subjects were recruited from mother-infant pairs in two cohorts, the Rakai Community Cohort Study and the Nevirapine PMTCT study, and from ART clinics in Rakai.

Gross motor, visual reception, fine motor receptive and expressive language scores were assessed using Mullen Scales of Early Learning in children aged 0 to 6 years. Composite scores were calculated from the sum of the four scores and compared with age-averaged scores. Generalized linear models were fitted to estimate prevalence rate ratios (PRR) of disability by HIV status and antiretrioviral usage.

329 mothers and children were included in the study, stratified into three groups: mother and child HV negative (group A); mother HIV positive and child HIV negative (group B), and both the mother and baby HIV positive (group C) (n=116). Researchers found that compared to children in group A, children exposed to HIV were more likely to have a language impairment despite being HIV negative (PRR=2.86, 95% CI 1.23-6.65), whereas children who were HIV positive (group C) had a wide range of cognitive disabilities, including problems with language and motor skills.

For those HIV positive, 44% had initiated ART. Those who were initiated later (>60 months) were more likely to exhibit neurodevelopmental disability, and those on treatment for longer than 24 months exhibited significantly improved neurologic scores for fine motor (adjusted PRR=0.15, CI 0 01-0.5), receptive language (adj PRR=0.38, CI0.2 – 0.8), expressive language (adj PRR=0.09, CI 0.01-0.3) and early language composite scores (PRR=0.45, CI 0.1-0.15).

CONCLUSION: This study reports a greater frequency of neurodevelopmental disorders in children with HIV, and also a higher frequency of language impairment in HIV-exposed, HIV negative children. Earlier initiation of ART and greater duration of ART was associated with substantial mitigation of all defects. These findings underline the importance of early diagnosis and treatment of HIV in children.

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