HIV Update in Africa

November 2013

Dear Colleagues

Welcome to the fourth 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 7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention and data from key publications during the past six months.

This edition also includes a guest article by Dr Andrew Revell of the HIV Resistance Response Database Initiative on the use of computational models to optimise antiretroviral therapy in low- and middle-income countries. This innovative approach draws on data from over 110,000 patients to predict responses to second- and third-line antiretrovirals in the absence of genotypic resistance data.

This guest article is particularly relevant in the light of the first two abstracts featured in this edition, which examine the prevelance of resistance mutations in individuals after failure of first-line regimens in South Africa.

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

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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.

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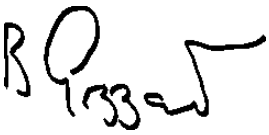
Prof Elly Katabira, Uganda

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
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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 7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Kuala Lumpur, 30 June – 3 July 2013.
- Pubmed – publications were identified using the search terms HIV and antiretroviral therapy, with date limits from March 2013 to mid-September 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, opportunistic infections, prevention of mother-to-child transmission and task shifting.

*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

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Learning from others' experience: Computational models to optimise therapy in low- and middle-income countries

"Only the foolish learn from experience — the wise learn from the experience of others."
Romanian Proverb

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Since the launch of AZT, the first antiretroviral drug to be approved for the treatment of HIV infection in 1987, physicians and patients in high-income countries have amassed millions of patient-years of experience of using antiretrovirals. These days antiretroviral therapy in such settings has truly 'come of age': there are more than 20 drugs from 6 classes in use; long-term viral suppression is common; changes to therapy are mostly due to tolerability issues. If treatment does fail, it is detected quickly as a result of regular viral load testing and viral suppression is usually restored quickly through the introduction of a new, highly active regimen, often guided by genotypic resistance testing[1,2].

It is easy to forget that it was not always so. Today's success story is the result of a quarter of a century of experience, of success and failure. A journey from monotherapy to triple therapy, from debilitating toxicities to the benign, from dozens of pills on a complex schedule to just one pill once a day.

The picture is different in low- to middle-income countries. While the situation has improved dramatically, with around 10 million people in such settings treated with antiretrovirals in 2012 and a dramatic reduction in mortality and morbidity in those populations with access to treatment, there are a number of potential threats to the long-term success of antiretroviral treatment.[3] Typically only around half of the licensed drugs are available or affordable and genotyping is generally unaffordable so can't be used to help individualise drugs following failure. Therapy failure is often detected late because of the infrequence or absence of viral load testing, which facilitates the development of resistance that can compromise future treatment responses.[4-8]

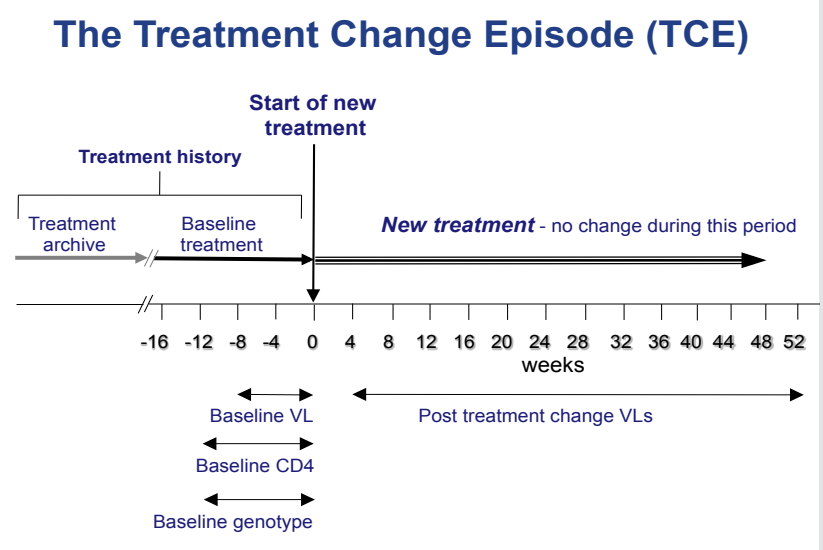
The recent access to antiretrovirals in these settings and the lack of monitoring and diagnostic tools to finesse their application means that many physicians do not have the technical means or experience to optimise

therapy on an individual basis. Faced with these considerable challenges, the WHO has promulgated a public health approach to therapy, including simple protocols for first- and second-line therapy and guidance for third.[3] This is in stark contrast to the individualised approach to HIV management in high income countries.[1,2]

This article asks whether we can learn from the accumulated experience of thousands of doctors treating millions of patients for decades in high-income countries to obtain the most benefit from the available drugs and resources for individual patients in low to middle income settings. How can those millions of patient-years of experience be distilled and made available to physicians around the world?
The solution may be computational modelling. The HIV Resistance Response Database Initiative (RDI) is a global not-for-profit research collaboration established in 2002 to collect data from clinical practice and use those data to train computational models to predict virological response to combination antiretroviral therapy.[9] The aim from the outset was to make these models freely available over the Internet as an experimental tool to help optimise therapy.

As of October 2013, data from approximately 110,000 patients have been collected and significant progress has been made in the development of accurate models to predict the response to a new antiretroviral therapy. Information is collected immediately before the treatment was changed and these data, plus the identity of the drugs in the new regimen and the viral load at follow-up, which we term a treatment change episode (TCE), are used to train the models to predict the virological response (Figure 1).

Figure 1: The Treatment Change Episode (TCE)

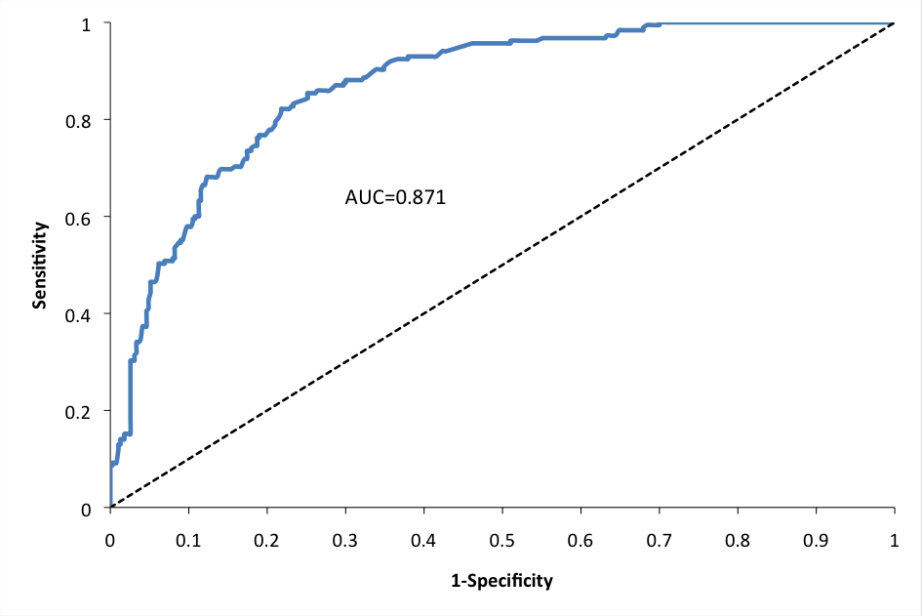


The modelling techniques investigated include artificial neural networks, support vector machines, logistical regression and, most successfully, random forest (RF) models.[10] The early models made their predictions using the viral genotype (mutations in reverse transcriptase and protease) and the viral load, while on the failing therapy. Since then, additional input variables including CD4 count on failing therapy and details of

treatment history have been studied, found to contribute to improved accuracy of prediction and added to the methodology.[11-14] Other potential variables have been found not to contribute, notably historical or cumulative genotypes.[15]

The models have achieved predictive accuracy (measured primarily as the area under the receiver operator characteristic curve) of 80% or more (Figure 2) and have proved more accurate predictors of response than genotyping (genotypic sensitivity scores from common rules-based interpretation systems).[16-18] In open prospective clinical studies of the models used as a treatment decision-making tool, highly experienced HIV clinicians evaluated the system as being a useful clinical tool and changed around one-third of their treatment decisions following use of the system.[19]

Figure 1: ROC curve from the best-performing model during cross validation[16-18]



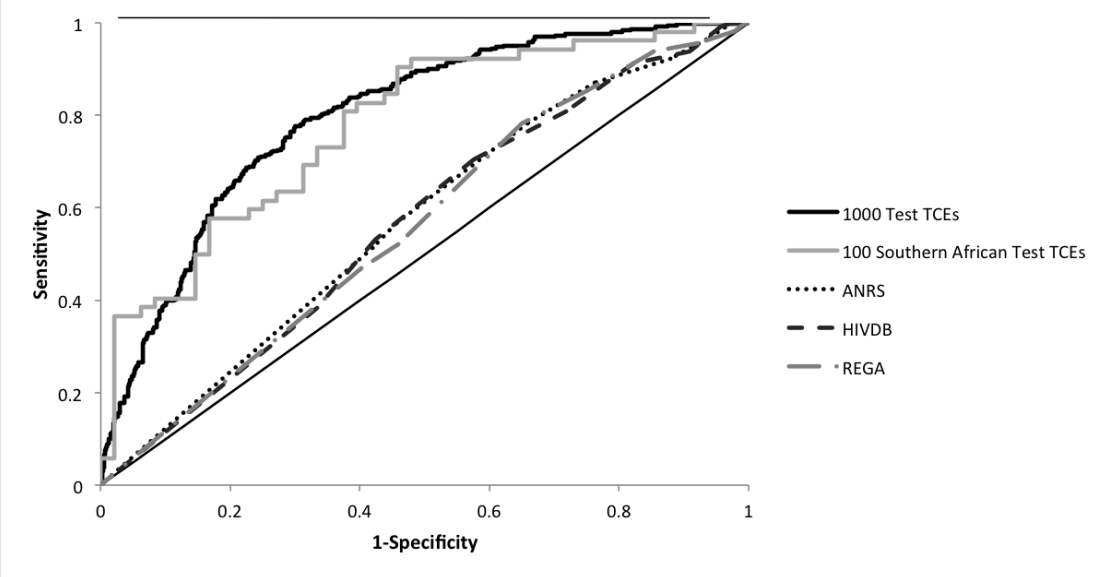
Having established the accuracy and potential clinical utility of the approach, the models were made freely available over the Internet in 2010. It was clear that the system could have most utility in those settings where only a limited range of drugs was available and the salvage of a patient on a failing regimen presents the greatest challenge. However, the conundrum we faced was that genotyping is almost never available in such settings and even viral load monitoring is still the exception rather than the rule.

To begin to address this, models were developed without the genotype, which at the time represented around two-thirds of the input information from which the models were making their predictions. The positive trade off, however, was that there were many more treatment-change episodes available to use to train the models if we didn't require a genotype. Early attempts to develop these models were promising.[20] In 2011-12 the models predicted response without a genotype with an accuracy comparable to the genotype

models when tested with independent cases from the high-income countries that provided the data used in their development, but reduced accuracy for cases from a low to middle income setting (sub-Saharan Africa).[21-24] This was consistent with previous studies we had undertaken showing that, despite the data used to develop our models coming from around 40 sources in more than 30 countries, there remains a tendency for them to be more accurate for cases from familiar settings (those that provided the training data) rather than unfamiliar settings.[25] The challenge was to collect sufficient data from the low- and middle-income settings where the system could be of most use to contribute to the development of the models.

In 2013 we trained a new set of models that do not require a genotype using our largest training data set so far (22,500 TCEs), including more than 1,000 from southern Africa. The results were extremely encouraging in that the models achieved approximately 80% accuracy in independent testing with little diminution of accuracy when tested with cases from southern Africa.[26] The models were also significantly more accurate than using the genotype to predict therapy response (Figure 3). For most of the therapy failures, the models were able to identify alternative simple regimens, comprising only those drugs that were available in each clinic at the time, that were predicted to be more likely to result in virological response than the regimen that was used in the clinic.

Figure 3: ROC curves for RF models tested with a global test set (n=1000), southern African cases (n=100) and GSS using three common interpretation systems (ANRS, Stanford HIVDB and REGA)[26]



Our previous studies have shown that inclusion of baseline viral load makes a significant contribution to the accuracy with which the models estimate the probability of a virological response (data on file). However, because of its cost, viral load monitoring remains the exception rather than the rule in many resource-limited settings. The 'public health' approach to guide therapy in such settings has been shown to be associated with deferred treatment switching, accumulation of resistance and increased morbidity and mortality.[4-8] The results of our modelling and the potential utility of their use to help optimise treatment are another argument for the use of viral load monitoring in these settings.

In recognition of the mounting evidence in its favour, viral load is now recommended as the preferred approach to monitoring antiretroviral therapy success and diagnosing treatment failure in the latest WHO guidelines.[3] Simpler technology being developed requires less infrastructure, maintenance and technical expertise and reduces test costs.[27-28] New funding mechanisms, such as UNITAID and the Load Zero Foundation, and the campaigning efforts of some NGOs such as Médicins sans Frontières, are also beginning to have an impact.

The RDI's models are available for use, free of charge, as part of the HIV Treatment Response Prediction System (HIV-TRePS). The system has been designed to provide the maximum clinical utility to the healthcare professional user. The user can obtain predictions of the probability of virological response (follow-up viral load <50 copies/ml), for any regimen that they define, or for more than a hundred alternative regimens in clinical use around the world, or both. A report is presented to the user in a matter of a minute or less, which lists the five alternative regimens with the highest probability of response, plus any user-defined regimens, with the estimated probability of response ranked in order of the probability of response (Figure 4 overleaf). The system can be instructed to make the predictions for any follow-up time from 4-52 weeks. Unavailable or poorly tolerated drugs can be ruled out on an individual or default basis. Local therapy costs can be added and the system used to identify potentially effective regimens within a certain budget. A recent retrospective study using data from a cohort in India found the system was able to identify regimens that were more likely to work than those used in the clinic at substantially less cost, for the majority of cases.[29]

This approach, which has been pursued and refined for over ten years, involving dozens of studies and hundreds of thousands of TCEs, has produced a system that has enormous potential for supporting the effective salvage treatment of HIV infection, particularly in settings with limited resources. The level of accuracy achieved means many cases of failure could potentially be avoided, with substantial personal, financial and public health benefits.

The system, made possible by the sheer power of computing, does indeed learn from the mistakes, and the successes, of others: the experience of hundreds of physicians treating thousands of patients made available at the click of a mouse. Wise indeed.

Acknowledgements
The RDI thanks all the individuals and institutions which have provided the data used in training and testing its models.

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Register to use the HIV Treatment Response Prediction System at: **https://www.hivrdi.org/treps**

Figure 4: example of HIV-TRePS report

HIV TRePS HIV Treatment Response Prediction System

rdi hiv resistance response database initiative

Case summary for RDI case 1292, patient ID TestCase

Baseline Data Completed: 27/09/2013

Patient Details

DATE OF BIRTH	SEX	PREGNANT
22/01/1970	M	N

Viral Load

SAMPLE DATE	VIRAL LOAD VALUE
16/09/2013	25,400

CD4

SAMPLE DATE	CD4 VALUE
09/09/2013	342

Genotype

GENOTYPE SAMPLE DATE	PROTEASE MUTATIONS	RT NRTI MUTATIONS	RT NNRTI MUTATIONS
No genotype provided			

Treatment History and Drug Exclusions

PREVIOUS DRUG EXPOSURE	UNAVAILABLE DRUGS	EXCLUDED DRUGS
3TC,AZT,D4T,DDI,IDV/rtv LPV/rtv,NFV,NVP,SQV/rtv	ENF,MVC	D4T,ENF,MVC,TPV/rtv

Predictions*

HIV-TRePS (v5.3.2.0) was instructed to model responses at 24 weeks to user-defined antiretroviral regimens plus alternatives comprising no more than 4 drugs.

The table below lists the regimen(s) you selected plus the top five alternatives, ranked by the predicted probability of virological response (viral load <50 copies).
Those regimens that the system predicts will produce a response (using the cut-off value for the probability of response that produces optimal accuracy) are highlighted in green and those predicted to fail in red.

Predictions of responses at 24 weeks for the regimens you selected plus the top five alternatives (up to 4 drugs)

RANK	DRUGS USED TO TREAT PATIENT	NO. DRUGS	PROBABILITY VL <50	RANGE OF MODELS PREDICTION	RESPONSE CATEGORY
1	DRV/rtv, ETV, RAL	3	83%	75 - 96%	Response
2	3TC, DRV/rtv, ETV, RAL	4	82%	73 - 96%	Response
3	AZT, DRV/rtv, ETV, RAL	4	81%	76 - 93%	Response
4	3TC, DRV/rtv, RAL	3	80%	71 - 96%	Response
5	DRV/rtv, EFV, RAL	3	79%	71 - 96%	Response
User	ABC, ETV, RAL, TDF	4	55%	45 - 70%	Response
User	DRV/rtv, EFV, FTC, TDF	4	51%	43 - 63%	Response

These predictions were requested without genotype information being provided and were made by models specially developed for that purpose. Their predictions may be less accurate than those made by models that use the genotype.

*** TRePS Predictions Disclaimer**

Use of the HIV-TRePS is subject to the following conditions, to which you have agreed:

1. HIV-TRePS is an on-line software programme ("Programme") which enables physicians to input specific user-defined information in order to obtain predictions concerning the use of combinations of antiretroviral drugs ("Predictions").
2. The RDI does not accept any responsibility for the accuracy of the data entered by the user or the consequences of any inaccuracies in those data.
3. The Predictions provided by the Programme are produced by an experimental system that is unproven and intended for research use only.
4. Responses to HIV treatment are complex and affected by a number of factors not taken into account by the Programme.
5. The selection of drugs for the treatment of HIV infection is the responsibility of the physician in consultation with the patient and reliance should not be placed on the Predictions for such purposes.
6. The Predictions are not intended to replace professional medical care and attention by a qualified medical practitioner and consequently the RDI does not accept any responsibility for the selection of drugs, the patient's response to treatment or differences between the Predictions and patients' responses.

27th September 2013

References

1. Thompson MA, Aberg JA, Hoy JF *et al*. Antiretroviral treatment of adult HIV infection 2012 recommendations of the International Antiviral Society–USA Panel. *JAMA* 2012;308(4): 387-402.
2. Williams I, Churchill D, Anderson J *et al*. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2012, *HIV Med* 2012;13 Suppl 2: 1-85.
3. World Health Organisation. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. WHO; Geneva: 2013.
4. Hosseinipour MC, van Oosterhout JJ, Weigel R *et al*. The public health approach to identify antiretroviral therapy failure: high-level nucleoside reverse transcriptase inhibitor resistance among Malawians failing first-line antiretroviral therapy. *AIDS* 2009; 23(9): 1127-34.
5. Sigaloff KCE, Hamers RL, Wallis CL *et al*. Unnecessary antiretroviral treatment switches and accumulation of HIV resistance mutations; two arguments for viral load monitoring in Africa. *J Acquir Immune Defic Syndr* 2011; 58(1): 23-31.
6. Zhou J, Li P, Kumarasamy N, Boyd M *et al*. Deferred modification of antiretroviral regimen following documented treatment failure in Asia: results from the TREAT Asia HIV Observational Database (TAHOD). *HIV Medicine* 2010; 11(1): 31-9.
7. Keiser O, Chi BH, Gsponer T *et al*. Outcomes of antiretroviral treatment in programmes with and without routine viral load monitoring in southern Africa. *AIDS* 2011; 25(14): 1761-1769.
8. Barth RE, Aitken SC, Tempelman H *et al.* Accumulation of drug resistance and loss of therapeutic options precede commonly used criteria for treatment failure in HIV-1 subtype C infected patients. *Antivir Ther* 2012; 17: 377-386.
9. Larder BA, DeGruttola V, Hammer S *et al*. The international HIV resistance response database initiative: a new global collaborative approach to relating viral genotype treatment to clinical outcome. *Antivir Ther* 2002; 7: S111.
10. Wang D, Larder BA, Revell AD *et al*. A comparison of three computational modelling methods for the prediction of virological response to combination HIV therapy. *Artificial Intelligence in Medicine* 2009; 47: 63-74.
11. Revell AD, Wang D, Boyd MA *et al*. The development of an expert system to predict virological response to HIV therapy as part of an online treatment support tool. *AIDS* 2011;25: 1855-1863.
12. Larder BA, Wang D, Revell A. Previous drug exposure data significantly increase the accuracy of artificial neural networks in predicting virological response to combination therapy [abstract 109]. 13th International Drug Resistance Workshop; Tenerife Sur, Canary Islands, Spain; June 8-12, 2004.
13. Larder BA, Wang D, Revell A. Treatment history and adherence information significantly improves prediction of virological response by neural networks [abstract 52]. *Antivir Ther* 2005; 10:S57.
14. Larder BA, Wang D, Revell A. Treatment history data significantly increase the accuracy of neural networks in predicting virological response to combination therapy [abstract WePe12.6C05]. 3rd IAS Conference on HIV Pathogenesis and Treatment; 24-27 July 2005, Rio de Janeiro, Brazil.
15. Larder BA, Wang D, Revell A. Treatment history but not previous genotype improves the accuracy of predicting virologic response to HIV therapy [abstract H1051]. 45th ICAAC. Washington DC, USA.
16. Larder BA, Revell A, Wang D. Neural networks are more accurate predictors of virological response to Antiretroviral therapy than rules-based genotype interpretation systems [abstract 653]. 13th Conference on Retroviruses and Opportunistic Infections, February 5-8, 2006.
17. Revell AD, Wang D, Boyd MA *et al*. The development of an expert system to predict virological response to HIV therapy as part of an online treatment support tool. *AIDS* 2011;25: 1855-1863.
18. Frentz D, Boucher CA, Assel M, *et al*. Comparison of HIV-1 genotypic resistance test interpretation systems in predicting virological outcomes over time. PLoS One. 2010; 5(7): e11505.
19. Larder, BA, Revell, AD, Mican J, *et al*. Clinical evaluation of the potential utility of computational modeling as an HIV treatment selection tool by physicians with considerable HIV experience. *AIDS Patient Care and STDs* 2011; 25(1): 29-36.

20. Revell AD, Wang D, Harrigan R, *et al*. Modelling response to HIV therapy without a genotype – an argument for viral load monitoring in resource-limited settings. *J Antimicrob Chemother* 2010; 65(4): 605-607.

21. Larder BA, Revell AD, Wang D *et al*. Predicting response to antiretroviral therapy without a genotype: a clinical tool for resource-limited settings [abstract MOPE744]. XIX International AIDS Conference 2012; Washington DC, USA

22. Larder BA, Revell AD, Wang D, Ene L, Tempelman H, Barth *et al*. Predicting response to antiretroviral therapy without a genotype: a treatment tool for resource-limited settings. [abstract MOPE146] 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, 17-20 July 2011; Rome, Italy.

23. Larder BA, Revell AD, Wang D *et al*. Modelling response to antiretroviral therapy without a genotype as a clinical tool for resource-limited settings [abstract 34]. *Antivir Ther* 2011; 16(1)A42.

24. Revell AD, Wang D, Wood R, Morrow C, Tempelman, Hamers R, *et al*. Computational models can predict response to HIV therapy without a genotype and may reduce treatment failure in different resource-limited settings. *J Antimicrob Chemother* 2013; 68(6): 1406-14.

25. Larder BA, Wang D, Revell A *et al*. The development of artificial neural networks to predict virological response to combination HIV therapy. *Antivir Ther* 2007; 12:15-24.

26. Revell AD, Wang D, Wood R *et al*. An update to the HIV-TRePS system: The development of new computational models that do not require a genotype to predict HIV treatment outcomes. *J Antimicrob Chemother* 2013 (in press).

27. Stevens WS, Scott LM and Crowe SM. Quantifying HIV for monitoring antiretroviral therapy in resource-poor settings. *J Infect Dis* 2010 201 (S1): S16-S26.

28. Stevens W, Crowe S & Rinke de Wit T. Affordable laboratory monitoring and antiretroviral therapy in resource-poor settings. In book: *Sande's HIV/AIDS Medicine – Global Care*, Edition: second, Chapter: 43, Publisher: Elsevier Saunders, Editors: PA Volberding, WC Greene, JMA Lange, JE Gallant, N Sewankambo, (2012) pp.577-589.

29. Revell AD, Alvarez-Uria G, Wang D, Pozniak A, Montaner JS, Lane HC *et al*. Potential impact of a free online HIV treatment response prediction system for reducing virological failures and drug costs after antiretroviral therapy failure in a resource-limited setting. *Biomed Res Int* 2013: 579741.

DRUG RESISTANCE

1. High-levels of acquired drug resistance in adult patients failing first-line antiretroviral therapy in a rural HIV treatment programme in KwaZulu-Natal, South Africa.

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This cross-sectional study investigated the frequency and patterns of acquired antiretroviral (ARV) drug resistance among patients taking first-line antiretroviral therapy (ART) at 17 rural primary health care clinics. A total of 222 adult patients (≥ 18 years) treated with d4T- or AZT-containing first-line ART regimens and evidence of virological failure (at least one HIV-1 RNA measurement > 3.0 $\log_{10}$ copies/mL) were included in the study. Genotypic resistance testing was undertaken and genotypic susceptibility scores (GSS) for standard second-line regimens were calculated. Approximately three-quarters of patients were women and the median age was 37 years (32-44). The most commonly used first-line regimens were d4T/3TC/efavirenz (51%) and d4T/3TC/nevirapine (24%). Overall, 40% of patients at sometime had HIV-RNA < 1.7 $\log_{10}$ copies/mL. The median duration of ART before sequencing was 42 months (32-53), and the median period under therapy with a virologically-failing regimen was 27 months (17-40). Median HIV-RNA at the time of sequencing was 4.25 $\log_{10}$ copies/mL (3.68–4.83). At least one drug resistance mutation was detected in 191 (86%) of individuals; 181 (82%) had NNRTI resistance mutations and 179 (81%) had NRTI resistance mutations. The most common NRTI mutation was M184V, detected in 173 (78%) of patients, whereas K103N/S was the most common NNRTI mutation, present in 101 (45%) of individuals. Thirty-four patients (15%) had a calculated GSS < 2 for the standard, guideline-recommended second-line ART regimen, thus suggesting that the virological efficacy of this regimen would be compromised. Five individuals had a GSS of 1, indicating that the only fully active drug in their second-line combination would be the protease inhibitor. Patients who substituted a NRTI had an almost six-fold increase in the risk of a GSS < 2 compared to patients who remained on the same NRTIs throughout [OR: 5.90; CI: 2.60-12.49].

CONCLUSION: This study demonstrates that there are high levels of acquired resistance to antiretrovirals among patients taking first-line ART with virological failure. A significant proportion of patients also have resistance mutations that compromise the efficacy of standard, guideline-recommended second-line ART regimens.

Source: *PLoS One* 2013; 8(8): e72152.

2. Trends in genotypic HIV-1 antiretroviral resistance between 2006 and 2012 in South African patients receiving first- and second-line antiretroviral treatment regimens.

G. U. Van Zyl[1,2], T. F. Liu[3], M. Claassen[1,2], S. Engelbrecht[1,2], T. de Oliveira[4], W. Preiser[1,2], N. T. Wood[5], S. Travers[5], R. W. Shafer[3].

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This study investigated changes in antiretroviral (ARV) drug resistance patterns between 2006 and 2012 among South African patients experiencing virological failure on first- and second-line antiretroviral treatment (ART). The investigators wished to determine the extent to which resistance patterns had changed as a result of the expansion in 2010 of South African ART programmes to include tenofovir for adults and abacavir for children. Protease inhibitor resistance patterns were also analysed among patients who received regimens containing ritonavir-boosted lopinavir (LPV/r). The study population comprised 569 adults receiving first-line regimens; 508 children treated with first-line therapy; and 290 adults taking second-line treatment. Overall, the patients provided 1667 samples for genotypic analysis. A total of 720 patients received therapy based on d4T or AZT and 153 were treated with a tenofovir-containing regimen. Patients treated with tenofovir were significantly more likely than patients taking d4T or AZT to have the reverse transcriptase mutations K65R (46 vs. 4%; $p < 0.001$), Y115F (10 vs. 0.6%; $p < 0.001$), L74VI (8.5 vs. 1.8%; $p < 0.001$) and K70EGQ (7.8 vs. 0.4%). Among patients taking abacavir-containing first-line therapy, there was a higher prevalence of the K65R mutation (17 vs. 4%; $p < 0.001$), along with Y115F (30 vs. 0.6%; $p < 0.001$) and L74VI (56 vs. 1.8%; $p < 0.001$). Analysis of the 490 patients treated with LPV/r showed that 55 (11%) had one or more LPV-resistance mutation, including 45 (9.6%) with intermediate to high-levels of resistance. Cross-resistance to darunavir was present in 23 (4.6%) of the LPV/r-treated patients. This was rated as intermediate-level in 20 patients and low-level in 3 individuals.

CONCLUSION: This study shows that first-line therapy with tenofovir in adults and abacavir in children is associated with an increased prevalence of four major non-thymidine analogue mutations. Resistance to LPV/r was also common, often at intermediate or high levels. However this was associated with low levels of cross-resistance to darunavir.

Source: *PLoS One* 2013; 8(6): e67188.

ADULT ANTIRETROVIRAL TREATMENT

3. A pragmatic randomised controlled strategy trial of three second-line treatment options for use in public health rollout programme settings: the Europe-Africa Research Network for Evaluation of Second-line Therapy (EARNEST) Trial.

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The choice of second-line antiretroviral therapy in low- and middle-income settings may be complicated by lack of access to viral load testing to facilitate early switching, and resistance testing to select the optimal regimen. A limited range of affordable antiretroviral agents also limits the options for assembling viable second- and third-line regimens in many settings. World Health Organization antiretroviral treatment guidelines (2013) recommend the use of two nucleoside reverse-transcriptase inhibitors (NRTIs) + a ritonavir-boosted protease inhibitor (PI). After failure on a TDF + 3TC (or FTC)–based first-line regimen, AZT + 3TC are recommended as the NRTI backbone in second-line regimens. After failure on an AZT or d4T + 3TC–based first-line regimen, TDF + 3TC (or FTC) are recommended as the NRTI backbone in second-line regimens.

The Europe-Africa Research Network for Evaluation of Second-Line Therapy (EARNEST) trial was designed to compare three strategies for second-line antiretroviral therapy: switching to a ritonavir-boosted protease inhibitor combined with new or recycled nucleoside reverse transcriptase inhibitors (NRTIs); switching to a ritonavir-boosted protease inhibitor combined with an integrase inhibitor (raltegravir) or switching to a ritonavir-boosted protease inhibitor accompanied by a 12-week induction regimen of raltegravir.

The Europe-Africa Research Network for Evaluation of Second-Line Therapy (EARNEST) trial was a randomised, open-label, non-inferiority trial conducted at 14 sites in sub-Saharan Africa. All participants were assigned to receive lopinavir/ritonavir 400mg/100mg bid for 96 weeks, and randomised to receive either 96 weeks of therapy with 2 or 3 NRTIs selected by the treating physician (group A), raltegravir 400mg bid for 96 weeks (group B) or 12 weeks of induction therapy consisting of raltegravir 400mg bid (group C).

The primary outcome of the study was good disease control, defined as no new WHO stage 4 events or death after randomisation, and CD4+ T-cell count of >250 cells/ mm3 and HIV-1 RNA < 10,000 $\log_{10}$ copies/mL at week 96. On-treatment monitoring consisted of open-label clinical and CD4 cell count monitoring at all study visits, and annual blinded resistance testing.

Study participants had a median baseline CD4 cell count of 71 cells/mm3, HIV-1 RNA of 69,782 $\log_{10}$ copies/mL, and 58% were female. 70% of participants in the NRTI group received tenofovir/emtricitabine, 12% received

didanosine/abacavir and 9% received tenofovir, emtricitabine and zidovudine. 1.3% of randomised participants were lost to follow-up prior to week 96.

There was no significant difference in primary outcome between the three arms. The proportions with good disease control were: (A) 60%; (B) 65% (absolute risk difference vs group A +4.2% (95% CI 0.9%, - 2.4%, +10.8%, p = 0.21); (C) 57% (absolute risk difference vs A: - 4.1% (95% CI -10.8, +2.6%, p=0.23). Lopinavir/ritonavir monotherapy (group C) was associated with a significantly lower frequency of HIV-1 RNA <10,000 $\log_{10}$ copies/mL, or HIV-1 RNA >10,000 $\log_{10}$ copies/mL without primary protease inhibitor mutations, when compared to group A (89% vs 98%, p <0.001). This difference was consistent at all viral load strata (<10,000, <1,000, <400 and <50 $\log_{10}$ copies/mL). There was no significant difference in rates of viral suppression between groups A and B in any viral load strata.

CONCLUSION: Selection of a second-line antiretroviral regimen containing NRTIs in the absence of resistance testing resulted in non-inferior viral suppression when compared to switching to a regimen composed of new drug classes. In this study the use of boosted protease inhibitor monotherapy was associated with inferior virological outcomes and a higher frequency of protease inhibitor resistance mutations in subjects with HIV-1 RNA >10,000 $\log_{10}$ copies/mL, potentially compromising the efficacy of a third-line protease inhibitor-containing regimen. These findings lend support to WHO guidance on selection of second-line antiretroviral regimens.

Source: Presented at IAS 2013, abstract WELBB02.

4. A daily dose of 400mg efavirenz (EFV) is non-inferior to the standard 600mg dose: week 48 data from the ENCORE1 study, a randomised, double-blind, placebo-controlled, non-inferiority trial.

R, Puls[1], ENCORE Study Group.

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Efavirenz is recommended in World Health Organization, United States Department of Health and Human Services and European AIDS Clinical Society guidelines as a preferred option for first-line adult antiretroviral therapy. A reduced dose could result in substantial cost savings in all settings.

ENCORE1 is an ongoing randomised, double-blind comparison of efavirenz 400mg (reduced dose) or 600mg (standard dose) in HIV-infected adults with HIV-1 RNA > 1000 $\log_{10}$ copies/mL and CD4+ T-cell counts of 50-500 cells/mm^3. All subjects receive tenofovir /emtricitabine. The primary study endpoint is the difference in proportions of participants with HIV-1 RNA <200 $\log_{10}$ copies/mL at week 48. The primary analysis was a modified intent-to-treat analysis (mITT) comprising 630 subjects (EFV400+321; EFV600=310) (mean baseline CD4+ cell count 273 cells/mm^3; mean baseline HIV-1 RNA 4.75 $\log_{10}$ copies/mL). The study recruited participants in Asia, Australasia, Africa, Europe and Latin America and the ethnic distribution of the study population was 37% African, 33% Asian and 30% Caucasian. 32% of participants were female.

At week 48, efavirenz 400mg was non-inferior by mITT analysis (94.1% vs 92.2% HIV-1 RNA < 200 $\log_{10}$ copies/mL, difference 1.85%, 95% CI -2.10 – 5.79, p=0.36). Virological responses did not differ significantly when stratified by

baseline viral load (<100,000 log_{10} copies/mL, 95% EFV400 vs 93% EFV600; >100,000 log_{10} copies/mL, 93% EFV 400 vs 91% EFV 600). Mean CD4 cell counts were significantly higher in the EFV400 group at week 48 (+25 cells/mm3, 95% CI 6 – 44, p=0.01). There was no significant difference in the rate of serious adverse events (EFV400=7.17%, EFV600=7.12%, difference 0.05%, 95% CI 3.9804.07, p = 0.98). The frequency of central nervous system (CNS) adverse events was significantly lower in the EFV400 group (37% vs 47%, p<0.001) and fewer subjects in the EFV400 group discontinued therapy as a consequence of CNS adverse events (2% vs 6%).

CONCLUSION: This study demonstrated that EFV400 was non-inferior to EFV600, and that implementation of this dose would reduce the cost of first-line antiretroviral therapy by one-third (approximately USD50) in low-income settings. Fewer patients in the EFV 400 arm discontinued treatment due to CNS adverse events.

Source: Presented at IAS 2013, abstract WELBB02.

5. Early initiation of antiretroviral therapy (ART) for individuals with HIV infection: a systematic review

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The World Health Organization issued new consolidated guidance on antiretroviral treatment in June 2013. The guidance recommends initiation of treatment in all adults with CD4+ T- cell counts < 500 cells/mm^3, and prioritisation of treatment for adults with CD4+ T-cell counts < 350 cells/mm^3. As part of the guidelines development process WHO commissioned a systematic review to estimate differences in disease progression in adults with baseline CD4+ T-cell counts >350 cells/mm^3 (early therapy) and adults with baseline CD4+ T-cell counts in the range 200-349 cells/mm^3 (deferred).

Evidence from randomised trials was limited. One RCT found a non-significant reduction in the risk of death associated with early treatment (RR=0.77, 95% CI 0.34-1.75). Two RCTs found a significant reduction in the risk of AIDS or death associated with early treatment (RR=0.48, 95% CI 0.26-0.91). One RCT found that early treatment was associated with a significant reduction in risk of progression to clinical AIDS (RR=0.31, 95% CI 0.10-0.96).

The systematic review identified 13 observational studies comparing early and deferred treatment. A reduced mortality risk was associated with early treatment in all 13 studies, with a pooled risk ratio of 0.66 (95% CI 0.55-0.79) (heterogeneity I^2=46%).

A significant reduction in the risk of AIDS or death was reported in nine observational studies (pooled RR=0.72, 95% CI 0.65-0.81) but no significant reduction in the risk of progression to clinical AIDS in four studies (pooled RR=0..70, 95% CI=0.40-1.24).

Sub-group analysis did not find a significantly reduced risk of mortality when comparing subjects who began treatment with CD4+ T- cell counts above or below 500 cells/mm^3 (RR = 0.94, 95% CI 0.69-1.28), but in four observational studies

which compared immediate treatment with deferral of treatment until the CD4+ T-cell count fell below 500 cells/mm^3, a pooled risk reduction of borderline significance was observed (RR=0.78, 95% CI 0.57-1.06).

Observational studies reported the risk of AIDS or death (n=9) found a pooled risk reduction of 0.72 (95% CI 0.65-0.81) (no heterogeneity).

CONCLUSION: The reviewers concluded that the risk of AIDS or death was reduced in subjects who initiated treatment at CD+ T-cell counts >350 cells/mm3 and that subgroup analyses suggest a continued if attenuated reduction in risk at higher CD4+ T-cell counts. The systematic review did not make a distinction between mortality, AIDS or morbidity risks by high-, middle- or low-income settings. More data are needed on the specific risks of AIDS, death and other morbidity at CD4+ cell counts above 350 in low- and middle-income settings to guide decisions about earlier treatment. The START study is comparing the outcomes of subjects who initiate antiretroviral therapy at CD4+ cell counts > 500 cells/mm^3 with those of subjects who defer treatment until reaching a CD4 cell count of 350 cells/mm^3. The START study is expected to report results in 2016.

Source: Presented at IAS 2013, poster exhibition abstract TUPE302.

6. Delay in antiretroviral therapy initiation is common among east African HIV-1-infected individuals in serodiscordant partnerships

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Evidence of the significant treatment and prevention benefits of ART led the World Health Organization in April 2012 to issue guidance recommending immediate ART initiation, regardless of CD4+ T-cell count, for HIV-positive partners in known serodiscordant relationships.

ART initiation among HIV-positive individuals from Kenya and Uganda with known uninfected partners was assessed in this prospective study of 4747 discordant couples (the Partners PrEP study, a randomised trial of daily PrEP to decrease HIV acquisition within serodiscordant couples). This sub-study evaluated factors associated with delayed initiation of treatment or decline of treatment offer in subjects who became eligible for ART during the Partners study.

HIV-infected partners were eligible to enter the study with CD4+ T-cell counts ≥250 cells/mm^3 at baseline and became eligible for ART during the study in accordance with national guidelines. During the four-year period (2008-2012) of data collection national guidelines for ART initiation changed: from <200 cells/mm^3 and <250 cells/mm^3 for Kenya and Uganda, respectively to <350 cells/mm^3 or for those with WHO stage 3 or 4 regardless of CD4+ T-cell count. Participants were actively counselled to start ART, referred to partnering clinics for ART, clinically monitored every three months with six-monthly CD4+ T-cell counts. 1998 of the 2184 (46%) HIV-infected partners

became ART eligible and completed one clinic visit. Median age was 34 years (IQR: 28-40) with women comprising 58% (1163). Median CD4+ T-cell count at eligibility was 273 cells/mm^3 (IQR: 221-328) with 79% at WHO stage 1 or 2; 96% were on cotrimoxazole prophylaxis.

Among the 1422 (71%) who initiated ART 60.8%, 78.8% and 91.5% did so by six, twelve and twenty-four months, respectively. The higher the CD4 T-cell count at eligibility the more likely were participants to defer treatment (see figure). Approximately 40% of HIV-infected participants had not initiated ART six months after referral in spite of close clinical monitoring, counselling and active linkage to care. Higher CD4 T-cell counts, being asymptomatic and importantly alcohol use were all significant predictors of delayed ART initiation. Lengthy pre-treatment processing and repeating CD4 counts were frequently cited as barriers to ART initiation, and 33% reported stigma as a barrier.

CONCLUSION: Barriers to treatment initiation in this study population related both to individual perceptions of their need for treatment and to experiences of the health care system, such as long waiting times and the need to return for test results. Both types of barriers need to be addressed in order to maximise the uptake of treatment in serodiscordant partnerships.

Source: Presented at IAS 2013, abstract MOAC 0202.

PMTCT AND EARLY INFANT DIAGNOSIS

7. Texting improves testing: a randomized controlled trial of text messaging to increase postpartum clinic attendance and rates of early infant diagnosis of HIV.

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Early infant diagnosis (EID) is a key step in linking children born to HIV-positive mothers to care and treatment, so reducing morbidity and mortality. Keeping mothers and their infants in care, especially after birth, is a critical issue. Studies have reported loss to follow-up from PMTCT programmes ranging from 43% to as high as 75%. This randomised controlled trial was conducted to see whether interactive text messaging improved rates of clinic attendance and EID in a PMTCT programme in Kenya.

HIV-positive pregnant women aged ≥18 were randomised to receive either SMS text messages (n=195) or the usual care (n=193). Messages were delivered according to the constructs of the Health Belief Model. Depending on gestational age those in the SMS group received up to eight messages before delivery and six after.
Overall there were outcome data for 381 (98.2%) women with a median age of 27 years. At baseline median gestational age was 34 weeks (IQR: 32-36).

While postpartum retention improved significantly in the intervention group the overall proportion of women attending remained low. Close to 20% (38/194) of those in the SMS group attended a maternal postpartum clinic compared to 11.8% (22/187) in the control. Women in the control group had a significantly higher risk of not attending clinic after giving birth, RR 1.66, 95% CI: 1.02-2.70.

Use of text messaging significantly improved the rate of EID. 92% (172/187) of infants in the SMS group were tested within eight weeks compared to 85.1% (154/181) in the control group, RR, 1.08, 95% CI: 1.00-1.16.

Source: Presented at IAS 2013, poster exhibition abstract TULBPE43.

8. Improved uptake of institutional birth and early infant HIV diagnosis following SMS reminders among PMTCT patients in Mozambique: a randomized control trial.

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In Mozambique in 2011 only two-thirds of HIV-positive pregnant women and less than half of newborns received

prophylaxis of which only 47% underwent testing for HIV. Absolute Return for Kids (ARK) undertook a randomised controlled trial to test the hypothesis that sending regular SMS reminders and educational messages to HIV-positive pregnant women would improve retention in PMTCT programmes and EID.

A structured series of SMS reminders and educational messages were sent to HIV-positive pregnant women followed for twelve months while attending five clinics in Maputo Province (one urban, two peri-urban and two rural). Data collected was entered into an electronic patient database from which the SMS platform retrieved data that included upcoming antenatal and postnatal appointments to then send the sequential reminders and messages. Groups were compared using logistic regression analysis.

Of the 1012 HIV-positive pregnant women interviewed 490 (47%) were ineligible; either they did not own a cell phone (35%) or they were illiterate (21%). Median age of those enrolled (522 with 261 in each arm) was 27 years and over two-thirds had some primary level education.

Of the 468 births (90%) only 315 infants were followed up until eight weeks with no difference between arms. Infants in the SMS group, however, had a significant uptake in EID at eight weeks, 77.1% compared to 70.9%, p=0.026.

Institutional births in peri-urban sites also increased significantly compared to the control group, at 97% and 88%, p=0.018, respectively. Mothers getting SMS reminders whose child was born anywhere other than at the study centres were more likely to bring their infants for EID; 75% compared to 38%, p=0.034.

The study authors concluded that while SMS had a significant impact on EID and institutional births at peri-urban sites more research is needed to effectively reach rural, illiterate women with these tools.

CONCLUSION: As these two studies illustrate, the expanding ownership of mobile phones in sub-Saharan Africa offers new opportunities for follow-up of patients, especially in urban areas where ownership is most prevalent. These studies illustrate ways in which messaging software designed to support clinical services can promote patient retention and improve clinic attendance for early infant diagnosis.

Source: Presented at IAC 2013, poster exhibition abstract TULBPE42.

9. Home visits during antenatal care enhances male partner HIV-1 counseling and testing during pregnancy in Kenya: a randomized controlled trial.

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This randomised controlled trial tested the hypothesis that male partner HIV counselling and testing could be increased by offering home-based couples HIV counselling and testing (CHCT), when compared to an invitation

for a clinic-based CHCT visit to women seeking prenatal care male partner. The hypothesis is based on research showing male involvement is associated with improved uptake of PMTCT interventions and HIV-free child survival. Women attending Ahero Hospital, in Nyanza, Kenya on their first antenatal visit, unaccompanied by their partners and unaware of their HIV status or negative at the last test, were enrolled. Nyanza province has an HIV prevalence of 14% compared to the national one of 6.3%. Following smartphone audio-computer assisted self-interviews (ACASI) participants were randomly assigned to the home-based or clinic-based arm. Those in the home-based arm were immediately accompanied home for CBCT while those in the clinic arm were given an invitation for the male partner to accompany them for clinic-based counselling and testing.

Of the 495 women screened 312 were eligible with 300 (96%) randomised to either the home-based or clinic-based arm. The women had a median age of 22, 70% had primary education or lower and close to 90% were monogamous. While 75% were below the poverty line daily cell phone use was high (71%).

Men were significantly more likely to be reached and tested at home (85%) than at the clinic (36%). There was a more than two-fold increase in male partner access and CHCT in the home-based arm compared to the clinic arm (RR 2.37, 95% CI: 1.90-2.96, p<0.001).

Women in the home-based arm were more than twice as likely to report improved or stable relationships (RR 2.36, 95% CI: 1.79-3.13,p<0.001).

Discordance was 16%; more men tested at home were discordant than at the clinic, 22 (14.7%) and 7 (4.7%), respectively. Overall prevalence among both men and women tested was 16%.

CONCLUSION: Home visits for male partners were acceptable, safe, had no adverse effect on relationship status in the short-term and identified a high prevalence of HIV among male partners. Where human resources permit, this strategy is easy to implement and generalisable to low-resource settings with high prevalence.

Source: Presented at IAS 2013, abstract TUAC0103.

10. Roll-out of universal antiretroviral therapy for HIV-infected pregnant and breastfeeding women ("Option B+") in Malawi: factors influencing retention in care.

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Malawi was the first country to implement "Option B+" for PMTCT with all HIV-infected pregnant and breastfeeding women starting lifelong ART. The strategy was adopted in Malawi in response to local variations in the availability and reliability of CD4+ cell counting machines, and in order to simplify operational guidance regarding antiretroviral prophylaxis during pregnancy and breastfeeding in the context of task-shifting of ART initiation to nurses and clinical officers.

Meta-analysis, logistic regression and competing risk survival models were used in this short-term cohort study to explore facility- and patient-level factors influencing retention in care among Option B+ women six months after starting ART.

Overall aggregated country-wide data (21939 women data from 540 facility sites and 28428 individual patient-level data from 19 sites with electronic medical record systems EMRS) showed 17% of women were lost to follow-up (LTFU) six months after starting ART. There was substantial variation between sites in LTFU. Whereas 37% of sites reported LTFU rates < 10%, 33% of sites reported LTFU > 20%. LTFU was higher in sites operated by the Ministry of Health and in urban areas. EMRS sites had a higher proportion of LTFU compared to non-electronic sites, 22% and 16%, respectively.

Cumulative incidence of LTFU was highest among Option B+ pregnant women, followed by women starting ART while breastfeeding and lowest among those starting ART for their own health (low CD4 T-cell counts or WHO stage 3/4).

Women starting ART during pregnancy were almost five times more likely to be LTFU after the first visit (OR, 4.8, 95% CI: 4.0-5.7) and twice as likely after the second visit (OR: 2.0, 95% CI: 1.5-2.7) compared to those with low CD4 T-cell counts. Women starting ART during breastfeeding were twice as likely to be LTFU after their first visit (OR: 2.1 (1.7-2.6) than those with low CD4 T-cell counts. 36% of pregnant women started ART on the day they were tested and were almost twice as likely not to return compared to those who started later (OR1.7, 95% CI: 1.4-2.2).

CONCLUSION: Compared to those starting ART for their own health, women starting ART during pregnancy or breastfeeding were at greater risk for LTFU with pregnant women at greatest risk. Most of those LTFU started ART on the same day they tested, highlighting the critical need for ART preparation at first visit. Rates of retention varied widely between sites; many had a low rate of LTFU, showing good retention in care is possible.

Source: Presented at IAS 2013, abstract WELBD01.

11. Greater suppression of nevirapine resistance with 21- vs 7-day antiretroviral regimens after intrapartum single-dose nevirapine for prevention of mother-to-child transmission of HIV

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This study investigated the emergence of nevirapine (NVP) resistance in HIV+ women during a randomised study of three short-term postpartum antiretroviral treatment (ART) strategies based on single-dose intrapartum nevirapine (sdNVP) for the prevention of mother-to-child transmission (MTCT) of HIV. The study population comprised 484 patients who were randomised to receive sdNVP in combination with either AZT/3TC, or tenofovir/FTC or lopinavir/ritonavir for either 7 or 21 days postpartum. The primary end-point was the emergence of new NVP resistance mutations 2 and 6 weeks after the completion of treatment as detected by standard genotyping. Allele-specific polymerase chain reaction (ASP) testing was used to detect low-frequency NVP or 3TC resistance in a subset of patients. 422 women (87%) received treatment and primary endpoint results were available for 412 (98%) of these patients. New NVP resistance was detected in 5 patients (1.2%). This included 4 women in the 7-day arms (1.9%); the K103N mutation was detected in all 4 patients, with 3 also having the Y181C, Y188C or G190A mutations. Only 1 patient (0.5%) in the 21-day arms developed NVP resistance (V1081). The emergence of new NVP resistance did not differ significantly between the 7- and 21-day arms ($p = 0.37$). ASP results were available for 150 women, showing that new NVP mutations developed more frequently in the 7-day arms than in the 21-day arms (18 vs 5%; $p = 0.19$). New M184V/I mutations, conferring resistance to 3TC/FTC, were rare (0 – 9%) and their frequency did not differ by arm.

CONCLUSION: These results show that three ART treatment strategies based on sdNVP resulted in a low rate of new NVP-resistance mutations after the completion of treatment when assessed by standard genotyping. ASP showed that a 21-day course of therapy was significantly better than 7-day regimens at preventing the minor NVP mutations.

Source: *Clin Infect Dis* 2013; 56(7): 1044-51.

PAEDIATRIC TREATMENT

12. Plasma efavirenz concentrations in HIV-infected children in Thailand: comparison between FDA and WHO 2010 dosing guidelines.

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Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI) together with a backbone of two nucleoside reverse transcriptase inhibitors (NRTIs) is the preferred ART regimen for children with HIV aged three and over weighing over 10kg. Efavirenz absorption and pharmacokinetics in children are inadequately characterised, particularly in respect of their relationship to toxicity. The lack of data has led to differing recommendations regarding paediatric dosing of EFV. A concentration target of 1 to 4 mg/L 12 hours after efavirenz dosing has been recommended to ensure efficacy and minimise the risk of toxicities.

To evaluate current Food and Drug Administration (FDA) and World Health Organization (WHO) 2010 efavirenz dosing guidelines a population pharmacokinetic model was developed to describe efavirenz absorption over time in Thai children with HIV.

This retrospective analysis evaluated 623 blood samples from 190 Thai children with HIV, of which 40 had 24-hour pharmacokinetic sampling data available. With a median age of 7.2 years (IQR: 0.1-5.2), bodyweight of 16 kg (IQR:5-42) and efavirenz dose given according to FDA bodyweight band recommendations, 8% (16) had an efavirenz level below 1mg/L twelve hours after a dose (C_{12}) 6% (12) had a level above 4mg/L. No serious adverse events were reported.

Bodyweight affected efavirenz clearance. The estimated median area under the concentration-time curve (AUC 0-24) was 49 (IQR: 8-296) mg/L.hr. A predicted efavirenz C_{12} was 2.3(0.07-11.9) mg/L.

Model simulations showed that the percentage of children with a drug concentration C_{24} between 1mg/L and 4mg/L using FDA dosing guidelines was similar to 2010 WHO recommendations. While the percentage with sub-optimal levels was lower using WHO guidelines the percentage of children with potentially toxic levels about 4mg/L increased by 11%. These differences persisted across all weight-bands.

Genotyping for CYP2B6 polymorphisms was not done. An estimated11% prevalence of CYP2B6 TT (associated with high EFV exposure) in this population may explain higher levels in this group.

CONCLUSION: This study shows that while 2010 WHO dosing recommendations ensure that a higher proportion of children with HIV have EFV drug levels above the recommended therapeutic level (1mg/L) compared to FDA guidelines, they also result in a higher proportion with potentially toxic levels (above 4mg/L) in a Thai population.

Source: Presented at IAS 2013, abstract MOAB0104.

13. A randomized study comparing low dose versus standard dose lopinavir/ritonavir among HIV-infected children with virological suppression.

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This multi-centre, randomised open-label trial at eleven sites in Thailand tested the hypothesis that viral load suppression would be maintained with adequate drug levels and less dyslipidemia using a reduced dose of lopinavir/ritonavir (*Kaletra*/*Aluvia*) (LPV/r-70% standard dose) as maintenance therapy compared to standard dose in children with HIV.

Children <18 years of age, weighing 25-50 kg, already on a LPV/r-based regimen and virally suppressed (HIV-1 RNA < 1.7 $\log_{10}$copies/mL) were randomly assigned by minimisation scheme to the Food and Drug Administration-recommended standard dose of LPV/r heat stable tablet or low-dose.

Twice daily dosages for children weighing between 25 and 35 kg were 300/75mg or 200/50mg for standard and low-dose LPV/r, respectively; and for children over 35 to 50kg 400/100mg and 300/75mg, respectively.

The primary endpoint was the proportion of children virally suppressed at week 48. Secondary endpoints included the lowest concentration of drug in the blood at 12 hours (C_{min}) and dyslipidemia.

The trial comprised 199 children with a mean age of 13.4 years and mean CD4 T-cell count of 786 cells/mm^3. The most commonly used nucleoside reverse transcriptase inhibitor (NRTI) backbones were zidovudine/lamivudine (47%), zidovudine/didanosine (17%) and tenofovir/lamivudine (16%). Mean time on ART was 8.8 years and a mean of 3.5 years on a LPV/r-based regimen.

Intention-to-treat analysis at week 48 showed the proportion of children with suppressed viral load was 91.8% and 88.1%, p=0.38 in the standard- and low-dose arms, respectively, While the per-protocol analysis showed the proportions to be 93.7% and 91.8%, respectively.

Multivariate analysis showed both adherence <95% and weighing between 35 and 50 kg had over a threefold increased risk of virological failure. At 48 weeks median lopinavir C_{min} was 6.9 (0.3-20.4) and 5.2 (0.2-11.8) mg/dl in the standard- and low-dose arms, respectively. Of the 14 children with a C_{min} <1mg/dl, ten were in the low-dose arm.

A significant proportion of children in the low-dose arm had a greater reduction in both cholesterol and trygliceride levels compared to the standard arm.

CONCLUSION: Low-dose LPV/r worked as well as standard dose in maintaining viral suppression, with less dyslipidemia and reduced costs. Only generalisable to children with controlled, undetectable viral load, not to children with high viral loads starting ART, these findings are not applicable to liquid LPV/r therapy since tablets have a higher bioavailability.

Source: Presented at IAS 2013, abstract MOAB0101.

14. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial.

Arrow Trial team.

This study investigated outcomes over 5 years in HIV+ children and adolescents (3 months to 17 years) taking first-line ART in Uganda and Zimbabwe, who were randomised to receive clinically driven monitoring or routine monitoring for treatment toxicity and efficacy. They were simultaneously randomised to receive standard triple drug therapy (NNRTI, 3TC, abacavir) or induction therapy with four drugs (NNRTI, 3TC, abacavir and AZT). After 36 weeks, patients receiving 4-drug therapy decreased their therapy to 3 drugs; either a NNRTI, with 3TC and abacavir or triple NRTI therapy consisting of abacavir, 3TC and AZT. The primary efficacy end-points for monitoring were death or new WHO stage 4 events. For ART strategy, the end-points were change in CD4+ T-cells percentage at weeks 72 and 144. The toxicity end-point was grade 3 or 4 adverse events.

Overall, 47 (8%) children receiving clinically driven monitoring died or developed a new WHO stage 4 event compared to 39 (7%) in the routine monitoring arm. Between years 2-5, event rates were slightly higher among patients receiving clinically driven monitoring (1.3 vs 0.4 per 100 patient years; difference 0.99, 0.37-1.60, p = 0.002). Grade 3 or 4 adverse events occurred in identical proportions of patients on clinically driven and routine monitoring (n = 283, 47% vs 47% n = 282). Mean increases in CD4+ T-cell percentage at week 36 were superior for

patients on 4-drug ART (12.4 vs 14.1 vs 14.6%). However, these differences had disappeared by week 72 (16.5 vs 17.1 vs 17.3%). Grade 3/4 adverse events occurred in 40% of children on standard 3-drug ART and in 47% (NNRTI, plus 2 NRTIs) and 54% (triple NRTI) of patients in the 4-drug induction arms. These were largely asymptomatic cases of neutropenia among patients receiving AZT therapy, and only 4 subjects changed therapy as a result.

CONCLUSION: The results of this study show that first-line ART can be safely administered in children without routine monitoring. Regardless of monitoring strategy, there were few deaths or stage 4 events and long-term survival was high, emphasising the degree to which antiretroviral therapy for children can be delivered successfully in resource-limited settings. Immunological benefits from 4-drug induction ART were of short duration and long-term 3-drug ART consisting of NNRTI plus 2 NRTIs or triple NRTI therapy had similar immunological and clinical efficacy.

Source: *Lancet* 2013; 381: 1391-403.

OPPORTUNISTIC INFECTIONS

15. Burden of HIV-related cytomegalovirus retinitis in resource-limited settings: a systematic review.

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Cytomegalovirus (CMV) retinitis occurs in HIV+ patients with advanced immune suppression, typically in the context of CD4+ T-cell counts below 100 cells/mm^3 and is responsible for 90% of cases of blindness in HIV+ patients. Antiretroviral therapy (ART) roll-out programmes have led to the assumption that CMV retinitis is no longer a problem in resource-limited settings. However, appropriate diagnostic skills and oral therapies for CMV are often lacking in middle- and low-income countries, and the burden of CMV retinitis in these settings is uncertain. This study was a systematic review and meta-analysis of published and unpublished studies conducted between 1996 and 2013 examining the prevalence of cytomegalovirus (CMV) retinitis in middle- and low-income settings. To be included, studies were required to have a sample of $\geq$ 10 patients and to have examined the occurrence of CMV retinitis by fundoscopic examination. A total of 65 studies involving 20,280 patients were identified. The majority were conducted in Asia (39 studies, 12,931 patients), followed by Africa (18 studies, 4325 patients) and Latin America (5 studies, 2836 patients). The quality of the studies was rated as low to moderate: 52 were prospective and reported using indirect ophthalmoscopy with dilation of the pupils; in 30 studies an ophthalmologist conducted the screening. Prevalence of CMV retinitis ranged from 0.2% in a Nigerian study to 72% in a study conducted in Thailand. Prevalence above 5% was reported in 4 countries (Thailand, 24%; Myanmar, 25%; China, 15%; India, 7%). By region, the highest prevalence was in Asia (14%) and the lowest in Arica (2%). Only 19 studies reported the extent of ocular involvement; their findings showed that 43% of patients had CMV retinitis in both eyes and 32% of patients had lost vision in one or both eyes. Approximately three-quarters of cases (73%) involved patients with CD4+ T-cell counts below 50 cells/mm^3; a further 16% were in patients with CD4+ T-cell counts between 50-100 cells/mm^3. Prevalence of CMV retinitis did not vary over time, and was 12% for studies conducted between 1993-2002 compared to 17% for research undertaken between 2009-2013. Prevalence did not differ according to whether screening was undertaken by an ophthalmologist or an HIV clinician trained in retinal examination.

CONCLUSION: These findings show that CMV retinitis frequently occurs among HIV+ patients in low- and middle-income settings, especially in Asian countries. Routine retinal screening by indirect ophthalmoscopy for all patients presenting with CD4+ T-cell counts below 100 cells/mm^3 should be considered and oral CMV prophylaxis with ganciclovir or valganciclovir may be beneficial for some patients where available. The developers of PEEK (www.peekvision.org), a smart-phone imaging technology, are seeking research collaborators for the validation of PEEK in retinal screening where other diagnostics are not available. A recent agreement between Roche and the Medicines Patent Pool may eventually lead to wider availability of generic versions of valganciclovir. The high prevalence of CMV retinitis reported in these studies emphasises the critical importance of early diagnosis of HIV infection and initiation of antiretroviral therapy prior to the onset of severe immunodeficiency.

Source: *Clin Infect Dis* 2013; 57 (9): 1351-61.

16. Cytomegalovirus viremia in Thai HIV-infected patients on antiretroviral therapy: prevalence and associated mortality.

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Little is known about the prevalence, risk factors and clinical consequences of cytomegalovirus (CMV) viraemia among HIV+ patients starting antiretroviral therapy (ART) in resource-limited settings. This study assessed the baseline and six-month prevalence of CMV DNA in stored plasma samples of 293 Thai patients who initiated ART with CD4++ T-cell counts < 200 cells/mm^3. The association between CMV viraemia and 24-month mortality and the development of new AIDS-defining illnesses was investigated. The majority of patients (n = 159, 54.3%) were male and the median age at baseline was 33 years. The patients had advanced immune suppression at baseline: median CD4+ T-cell count was 82 cells/mm^3 and median HIV-1 RNA was 4.9 $\log_{10}$ copies/mL. A total of 77 patients (26.3%) were CMV viraemic at baseline. The prevalence of CMV viraemia was related to immune suppression (<50 cells/mm^3 = 46% vs. 101-200 cells/mm^3 = 10%; p < 0.001). Almost all the patients (n = 293, 93.2%) initiated triple-drug ART. The remaining 20 individuals (6.8%) were treated with a dual NRTI regimen. After 6 months of ART, median CD4+ T-cell counts had increased to198 cells/mm^3 and 48% had CD T-cells counts above 200 cells/mm^3. CMV DNA prevalence after 6 months of treatment had fallen to 4.5%. Median CMV DNA was 114 copies/mL. A total of 8 deaths and 28 new AIDS-defining events were observed over 24 months. Baseline factors associated with mortality in in univariate analysis were CDC stage C disease, CMV viraemia (p < 0.001), haemoglobin < 10g/dL (p = 0.011) and lower CD4+ T-cell count (p =0.022). In multivariate analysis, baseline CMV DNA > 500 copies/mL was associated with a 7-fold increase in mortality risk [CI: 1.32-40.29](p = 0.023%). Each 50 cell/mm^3 increase in CD4+ cell count decreased the risk of developing a new AIDS-defining event by 30% [CI: 0.49-0.997] (p = 0.048).

CONCLUSION: These findings show that there is a high prevalence of CMV viraemia among patients starting ART in resource-limited settings and that CMV DNA > 500 copies/mL is associated with an increased risk of death despite ART. Patients starting ART with low CD4+ T-cell counts should therefore be screened for CMV viraemia wherever possible. A large-scale prospective study is needed to determine if pre-emptive anti-CMV therapy reduces mortality risk in severely immunosuppressed patients starting ART.

Source: *Clin Infect Dis* 2013; 57 (1): 147-55.

17. Immune reconstitution inflammatory syndrome associated with Kaposi sarcoma: higher incidence and mortality in Africa than in the UK.

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This study assessed the incidence, risk factors and outcomes of Kaposi sarcoma-associated paradoxical immune reconstitution inflammatory syndrome (KS-IRIS) among patients starting antiretroviral therapy (ART) with Kaposi sarcoma (KS) in sub-Saharan Africa and the UK. Investigators pooled the results of 4 prospective, observational cohorts involving 463 patients. Three of the cohorts were in Africa and contributed 49% of participants; the remaining 51% of patients were enrolled in a UK cohort. Common criteria were used to diagnose KS-IRIS across all four cohorts and two investigators had to agree the diagnosis, with a separate investigator reviewing all cases. Patients in the UK cohort were more likely to be male than patients in the Africa cohorts (95 vs. 45%; $p < 0.001$) and were older at the time of KS diagnosis (39 vs. 35 years, $p < 0.001$). Patients in the UK were also less likely to have T1 disease (62 vs. 87%; $p = 0.001$) and to have a detectable KS-associated viraemia (58 vs. 76%; $p = 0.004$) than individuals in Africa. All the patients enrolled in the sub-Saharan African cohorts were of African ethnicity, as were 16% of patients who received care in the UK. Median CD4+ T-cell counts at the time ART was started were 196 cells/mm^3 for patients in the UK compared to 138 cells/mm^3 for patients in Africa ($p < 0.001$). All individuals in the African cohorts were treated with ART alone, whereas 34% of patients in the UK received ART in conjunction with chemotherapy. Overall, 58 patients (13.9%) experienced a KS-IRIS, however, incidence was significantly higher in Africa (20%; 7 cases per 100 person-months of follow-up) than the UK (9%; 3 cases per 100 person-months of follow-up). Risk factors for KS-IRIS were initial treatment with ART alone ($p = 0.047$), stage T1 disease ($p = 0.013$), HIV-1 RNA ≥ 5 $\log_{10}$ copies/mL ($p = 0.005$) and detectable KS-associated viraemia ($p = 0.015$). After the occurrence of KS-IRIS 55% of patients were treated with ART in combination with chemotherapy and 45% with ART alone.

A complete response to therapy was observed in 7%; 40% had a partial response; KS disease remained stable in 12%; disease progression occurred in 36% of individuals, including 33% who died. All the patients in the UK had a complete or partial response; this compared to 23% of patients in Africa. KS-related mortality was 3.3 fold higher in Africa. Mortality risk factors were treatment with ART alone [HR: 2.35; CI:1.09-5.05] (p= 0.029); baseline CD4+ T-cell counts below 200 cells/mm^3 [HR: 2.04; CI: 0.99-4.2] and detectable KS-associated viraemia at baseline [HR: 2.12; CI 0.94-4.77].

CONCLUSION: These findings show the KS-IRIS incidence and mortality are higher in Africa than the UK; this is principally due to more advanced disease in African settings and restricted availability of chemotherapy. Education regarding KS-IRIS is needed in resource-limited settings and there is an urgent need for global guidance on the appropriate management of KS and KS-IRIS.

Source: *AIDS* 2013; 27(10): 1603-13.

18. Treatment response and mortality among patients starting antiretroviral therapy with and without Kaposi sarcoma: a cohort study

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This study evaluated the impact of Kaposi sarcoma (KS) on survival and immunological and virological responses among individuals starting antiretroviral therapy (ART) in South Africa between January 2001- January 2008. Differences in mortality between patients with KS and without KS at the initiation of ART (6 months before or 6 months starting therapy) were compared during the first 12 months of ART and also after a year of ART. Immunological and virological responses between the 2 groups were compared after 6 and 12 months of ART. A total of 13,847 patients initiated ART during the study period. Patients with KS (n = 247, 1.8%) were similar to non-KS patients (13,600, 98.2%) in terms of age (35 vs. 35 years), baseline CD4+ T-cells count (74 vs. 85 cells/m^3) and the proportion taking tuberculosis (TB) therapy (37 vs. 30%). Patients with KS were followed for a median of 12 .3months (2.3-29.8) and non-KS patients for a median of 19.1 months (7.8-32). Overall, 10% of patients died. However a greater proportion of patients with KS died after commencing ART than patients without KS (27 vs. 10%). Patients with KS were over 3 times more likely to die at any time after initiating ART than non-KS patients (HR: 3.62; CI: 2.71-4.84). The risk was highest in the first year of ART (HR: 4.05; CI: 2.95-5.55) but also persisted thereafter (HR: 2.30; CI: 1.08-4.89). Patients with KS also had a poorer immunological response to ART during the

first 6 months of therapy. Their median gain in CD4+ T-cells was 29 cells/mm^3 lower than non-KS patients (98 vs. 121 cells/mm^3). KS patients were also less likely than non-KS patients to achieve a 50 cell/mm^3 increase in CD4+ T-cells after 6 months of ART (24.4 vs. 18.3%) and 100 cell/mm^3 increase 12 months after treatment initiation (29.9 vs. 23.3%). Virological outcomes were similar between the two patient groups at the 6- and 12-month follow-up intervals, with a trend slightly in favour of the KS patients.

CONCLUSION: This study shows that patients with KS have an increased mortality risk after starting ART, despite similar CD4 cell count at treatment initiation. KS patients also have a poorer immunological response to ART. These findings emphasise the need for chemotherapy with specialist advice on management wherever available, in addition to antiretroviral therapy in patients with advanced HIV disease and KS.

Source: *PLoS One* 2013; 8(6): e64392.

19. High prevalence of pulmonary tuberculosis but low sensitivity of symptom screening among HIV-infected pregnant women in South Africa.

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The World Health Organization (WHO) recommends a 4-part symptom screen – any cough, fever, night sweats and any weight loss - for identifying patients with possible TB. A meta-analysis of studies involving HIV+ patients showed that the four-part symptom screening had 90.1% sensitivity for identifying possible TB patients and was therefore an effective tool for identifying most HIV+ patients with TB. However, HIV+ pregnant women were not included in the meta-analysis. This cross-sectional study therefore investigated the use of the 4-part symptom screening for the identification of possible TB cases among 1415 HIV+ pregnant women in South Africa. Results of the symptom screen and sputum smear microscopy and mycobacterial culture were reviewed for all patients. 226 (16%) of women had a positive symptom screen. 35 (2.5%) were newly diagnosed with culture-positive TB and 12 patients with were already on TB therapy at the time of screening, therefore 47 patients (3.3%) with TB were identified. The majority of women with prevalent TB were asymptomatic (cough = 23%; fever = 2.8%; weight loss = 8.6%; night sweats = 11%). For patients without known TB, symptom screening had an overall sensitivity of 28% [CI: 15-46] and specificity of 84% [CI: 82-86].

CONCLUSION: Women with HIV have an elevated risk of TB during pregnancy. These results show that there is a high prevalence of TB among HIV+ pregnant women in South Africa and the 4-part WHO symptom screen was ineffective at identifying new TB cases.

Source: *PLos One* 2013; 8(4): e62211.

TASK SHIFTING

20. Noninferiority of a task-shifting HIV care and treatment model using peer counselors and nurses among Ugandan women initiated on ART: evidence from a randomized trial.

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This study investigated the non-inferiority of task-shifting of HIV treatment from HIV physicians to peer counsellors and nurses for HIV+ pregnant women starting antiretroviral therapy (ART) for the prevention of mother-to-child transmission (MTCT). The randomised study was conducted at the Mulago Hospital, Kampala, Uganda. The primary outcome was the proportion of patients attaining virological suppression, defined as HIV-1 RNA below 2.6 $\log_{10}$ copies/ml, 6 and 12 months after ART initiation. CD4+ T-cells count and adherence were also compared. Non-inferiority was defined as the lower 95% confidence limit, with a difference in the proportion of patients achieving virologic suppression of less than 10%. The study population consisted of 85 patients: 45 were randomised to receive care from peer-counsellors/nurses; 40 from HIV physicians. Virologic success was achieved by 91% of patients cared for by peer-counsellors/nurses compared to 89% of individuals who received care from a physician. The +3% [CI: - 11% to +12%] difference in success rates showed the non-inferiority of the intervention. Mean CD4++ T-cell increases were similar between patients in the peer-counsellor/nurse arm and the physician care arm (217 vs. 206 cells/mm^3; difference +11 cells/mm^3 [CI: - 60 to +82 cells/mm^3]). A similar proportion of patients in both study arms took $\geq$ 95% of their ART doses (99.8% vs. 99.7%; difference, 0.0% [CI: - 5 to +5%]).

CONCLUSION: These results show that care for women taking ART for the prevention of MTCT provided by peer-counsellors/nurses is non-inferior to care provided by an HIV physician. This approach may facilitate the provision of HIV care to more people in resource-limited settings.

Source: *J Acquir Immune Defic Syndr* 2013; 63, e125-e132.

PREVENTION

21. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial.

Bangkok Tenofovir Study Group, Bangkok, Thailand.

The IPrEX study has demonstrated efficacy of tenofovir/emtricitabine (*Truvada*) as pre-exposure prophylaxis against HIV infection in HIV-negative men who have sex with men and transgender women. The Botswana TDF2 study and the Partners study have demonstrated efficacy of tenofovir and emtrictabine, and of tenofovir (62% reduction incidence) or tenofovir/emtricitabine (73% reduction in incidence), in serodiscordant heterosexual partnerships. The efficacy of pre-exposure prophylaxis in populations of people who inject drugs has now been evaluated in a clinical trial conducted in Bangkok, Thailand.

The Bangkok Tenofovir Study evaluated the use of tenofovir as pre-exposure prophylaxis in HIV-negative persons aged 20 to 60 years who had reported injecting drugs in the previous year. The randomised, placebo-controlled, double-blind study enrolled 2413 participants, assigned to tenofovir (n= 1204) or placebo (n=1209). Participants elected to receive daily directly-observed dosing (86.9% of all study drug exposure) or monthly visits and were able to switch between dosing modalities at monthly visits. Participants received monthly HIV antibody testing, risk reduction and adherence counselling, and were offered condoms and methadone opioid substitution therapy. Clean injecting equipment and needle exchange were not available in this study. 63% of participants reported injecting drugs in the 12 weeks preceding enrolment and 25% reported sharing injecting equipment.

50 HIV infections occurred during a mean of 4 years of follow-up (9665 person years). 17 infections occurred in the TDF group (0.35 per 100 person-years) and 33 in the placebo group (0.68 per 100 person-years), a 48.9% reduction in HIV incidence (95% CI 9.6 – 72.2; p= 0.01). In a case control analysis detectable plasma concentrations of tenofovir were associated with 70% reduction in the risk of infection (95% CI 2·3—90·6; p=0·04). Medication was well tolerated with no significant difference in the incidence of adverse events between study arms nor evidence of significant creatinine elevations in the TDF group. Injecting drug use declined to 23% after one year. HIV incidence did not differ significantly between the two groups until year three, due in part to slow recruitment.

CONCLUSION: Pre-exposure prophylaxis with daily oral tenofovir significantly reduced the risk of HIV infection in people who injected drugs on entry to the study. As in studies of the use of pre-exposure prophylaxis to prevent sexual transmission, protection was associated with a high level of adherence.

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