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HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care. We also thank them for permission to distribute their excellent work and we encourage HTB readers to visit the source websites for further access to their coverage of HIV treatment.

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EDITORIAL

Welcome to the October/December issue of HTB South that includes selected reports from four conferences.

One cause for concern that is coming up time and again is that there seems to be no antiretroviral combination that does not cause fat accumulation.

This was highlighted at the 11th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV. Additionally it appears that there is greater prevalence among women and among Black women.

Richard Jeffreys from TAG provides an excellent analysis of the controversial results from the RV144 Thai Vaccine Trial in a report from the 9th AIDS Vaccine Conference. Jeffreys has provided a consistent voice of reason as the trial data was released amid a maelstrom of hyperbole.

Other articles include, When to start guidelines in resource poor settings and an overview of ART programme data, and our final reports from IAS2009.

As this is the last HTB South of the year we would also like to take the opportunity to thank our medical board and everyone who has provided invaluable comments and feedback.

And to all our readers Happy New Year!

Southern African HIV Clinician's Society

Since its inception in 1997, with a membership of approximately 250 members, the Southern African HIV Clinician's Society has grown to a membership of over 15 000 in the Sub Saharan region and internationally - a clear recognition of the services and support provided.

The Southern African HIV Clinician's Society is the largest special interest group within the South African Medical Association (SAMA). It is also the largest HIV interest group in the world.

The Society is thrilled to be part of the HIV Treatment Bulletin South initiative. This is a valuable publication for all Health Care Practitioners. This publication has essential, current and scientific information about research and HIV treatment updates with particular implications for clinical practice.

For more information about the Society or on how to become a member please visit:

http://www.sahivsoc.org

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CONFERENCE REPORTS

11th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV (IWADR)

26-28 October 2009, Philadelphia, USA

Introduction

The newly named 11th International Workshop on Adverse Drug Reactions and Co-morbidities in HIV was held this year from 26–28 October 2009 in Philadelphia. The workshop has expanded its earlier focus on lipodystrophy to include coinfection, particularly hepatitis and age-related morbidities including bone, cardiovascular, oncology and neurocognitive complications.

The format for the workshop continues to provide a focused forum for the range of metabolic complications but also recognises that these symptoms are becoming more difficult to view in isolation.

Reports form the meeting this year include:

- Intermuscular tissue is decreased in HIV infection
- High incidence and risk factors for diabetes in French cohort
- Gender and race differences in lipodystrophy symptoms
- Lipodystrophy is common in children from three European cohorts
- Reduced levels of vitamin D in patients taking efavirenz
- Association between inflammation and sleep apnea in the MACS cohort

Webcasts from the meeting are due to be posted to the conference website shortly.

https://lipo09.events-register.com/lipodystrophy/

Intermuscular tissue is decreased in HIV infection

Simon Collins, HIV i-Base

The first study in the main conference looked at a intermuscular adipose tissue (IMAT) - the distribution of fat that is beneath the muscle facia and muscle tissue – as a new parameter of metabolic disturbances. Led by Carl Grunfeld with the FRAM study, this group has provided important insight into the association of HIV to metabolic changes by using full body MRI to identify changes and including an HIV-negative control group. Results from the study concluded that fat loss and fat gain are separate unrelated dysfunctions and that fat loss rather than fat accumulation is the driving mechanism behind HIV-related changes.

This year the group hypothesised that IMAT, which has been reported as increasing in obese HIV-negative women and having a strong relationship to insulin sensitivity, would behave similarly to visceral adipose tissue (VAT) and would be increased in HIV-positive patients. IMAT is preserved in familial and decreased in generalised congenital lipodystrophy.

In fact, they reported that IMAT was 51% lower when comparing 425 HIV-positive patients to 211 HIV-negative controls, even after adjusting for demographics and lifestyle (adjusted to -48%), although somewhat attenuated after controlling for VAT, SAT and skeletal muscle volume (adjusted to -21%). All comparisons were significant ($p<0.0001$).

In HIV-positive people but less so in controls, IMAT was associated with higher levels of VAT, trunk SAT and leg SAT.

As both IMAT and sub-cutaneous adipose tissue (SAT) were decreased with exposure to d4T, the study concluded that IMAT shared similar cellular origins to SAT. Although the clinical implications are less significant in countries that have moved away from using d4T and ddI, this finding is likely to be most relevant to those where it is still widely used.

Ref: Grunfeld C et al. Intermuscular tissue is decreased in HIV infection. 11th Intl Workshop on Adverse Drug Reactions. 26-28 October 2009, Philadelphia. Oral abstract O-01. Antiviral therapy 2009; 14 Suppl 2: A3.

High incidence and risk factors for diabetes in French cohort

Simon Collins, HIV i-Base

The incidence of diabetes and related risk factors from the ANRS C08 APROCO-COPILOTE cohort was presented by Jacqueline Capeau. [1]

The cohort included 643 patients on their first protease inhibitor-based regimen, followed from 1997-8 for nine years, 40% of who were ARV-naive when the study started. Approximately 80% were male and 4,500 patient years of follow-up (PYFU) contributed to the analysis.

Diabetes was diagnosed as fasting glycaemia >7.0 mmol/L or 2-hour oral glucose tolerance test (OGTT) >11.1 mmol/L and/or treatment for diabetes. Cardiovascular risk was calculated using Framingham.

The group reported a high incidence of diabetes in both men (10.8 per 1000 PYFU; 95%CI: 7.9-14.3) and women (11.4; 9%CI: 5.7-20.3). After adjusting for family history, age, BMI and wasit:hip ratio, the following factors were associated with new onset diabetes: age > 40 years, BMI >25, WHR >0.97 in men and >0.92 in women and use of d4T or indinavir. HIV-related markers including CD4, CD4:CD8 ratio, viral load, ethnicity and HCV status were not associated.

When compared to patients with normal glycaemic function, people with diabetes were older (43 vs 35 years), had higher BMI (median 24 vs 21), had higher rates of hypertension (50% vs 18%) and family history of diabetes (37% vs 16%), all $p<0.001$. Diabetic patients also had a significantly higher 10-year cardiovascular risk (13% vs 3%).

The researchers commented that these rates were four times higher than an HIV-negative control cohort with similar adipose profile. [2]

COMMENT

The study hasn't so far found that impaired glucose tolerance has predicted development of diabetes. Over time the incidence of new cases appears to have levelled out, perhaps relating to reduced use

of d4T and ddI. Naive patients using neither of these RTIs seem to be protected, although further analysis are needed to see whether levels remain higher than in the general population.

References

1. Capeau J et al. High incidence and risk factors for diabetes over the 9-year follow-up after first generation protease inhibitors' initiation in the ANRS C08 APROCO-COPILOTE cohort. 11th Intl Workshop on Adverse Drug Reactions. 26-28 October 2009, Philadelphia. Oral abstract O-05. Antiviral therapy 2009; 14 Suppl 2: A5.
2. Meisinger C et al. Sex differences in risk factors for incident Type 2 Diabetes Mellitus: the MONICA Augsburg Cohort Study. Arch Intern Med 2002; 162: 82-89.
http://archinte.ama-assn.org/cgi/content/abstract/162/1/82

Gender and race differences in lipodystrophy symptoms

Simon Collins, HIV i-Base

The prevalence, type and severity of lipodystrophy in the Ontario Cohort Study was assessed using the ACTG body image questionnaire. Results from a cohort study of 746 Canadian patients on stable HAART confirmed previously reported side effect profiles in relation to gender and race.

This was a largely male (85%) and non-Black (85%) study. Median age was 48 years (IGR 42-55) and median duration of HIV infection was 13 years (IQR 7-18).

The overall prevalence of 58% lipodystrophy was similar by gender and race. However, men more frequently reported fat loss than women (31% vs 11%, p<0.0001), especially in the face (45% vs 30%, p=0.03) but similarly in the legs and buttocks. Women were more likely to report central fat accumulation (26% vs 15%, p<0.0001) especially in the abdomen (5% vs 46%, p<0.001) and breasts (31% vs 17%, P<0.0001). Women were almost twice as likely to report both symptoms (21% vs 12%, p<0.0001).

The study reported no differences by race (Black vs non-Black) for men, but Black women had a significantly higher rate of fat accumulation than non-Black women (57% vs 38%, p=0.05)

COMMENT

Although there are limitations in this study in terms of limited racial and gender balance, and reliance on personal perception, the overall observations are important for sensitivity of individual patient management. This is especially true as no combination has been identified that has not been associated with fat accumulation, including studies with recently approved "lipid-friendly" protease inhibitors or with raltegravir.

The associated between lipohypertrophy, gender and race deserves further study.

Ref: Loutfy M et al. Gender and ethnicity differences in body change and distress of HIV-positive individuals taking antiretroviral therapy in Ontario. 11th Intl Workshop on Adverse Drug Reactions. 26-28 October 2009, Philadelphia. Poster abstract P-08. Antiviral therapy 2009; 14 Suppl 2: A29.

Lipodystrophy is common in children from three European cohorts

Simon Collins, HIV i-Base

Researchers from 14 sites in Belgium, Poland and Italy reported on the prevalence of lipodystrophy in a cohort of 468 children and adolescents (92% infected at birth). Data collected included demographic and clinical history and standardised assessment was used to determine fat loss or accumulation in the face, limbs, buttocks, breasts, neck and trunk.

The cohort was evenly split by gender, with median age 13.5 years (IQR 9.9-17.0). Tanner puberty stage included 28% stage I and 34% stage V. 73% were white and 22% Black African. HIV treatment was used by 95% of the cohort for a median 8,8 years, with 62% having viral load suppressed <50 copies/mL. The median CD4% was 31% (IQR 24-38) and just over 300 children were currently asymptomatic.

Assessment of symptoms was by clinician completed questionnaire. Over 40% of children had at least one lipodystrophy symptom: 15% had just fat loss, 13% just fat accumulation (mostly trunk) and 13% had both symptoms. This group included 14 cases of severe fat accumulation and 11 cases of both severe fat loss and fat accumulation.

In multivariate analysis, after controlling for duration of treatment, maternal lipodystrophy, maximal CDC status, and ever use of d4T and efavirenz, significant associations were found for d4T use (AOR=4.23; 2.02, 8.85), efavirenz use (AOR=2.72; 1.36, 5.46), indinavir (AOR 3.23) and clinical stage (AOR 3.30; 1.28, 8.02) and either fat loss or fat accumulation. Even stronger associations were found for children who had both symptoms.

Maternal lipodystrophy was also associated with an adjusted OR of 3.01 (1.78, 5.57) for any symptom and 4.75 (1.60, 14.20) for both symptoms.

Ref: Alam NM et al. Risk factors for body fat redistribution in a European cohort of HIV-infected children and adolescents. 11th Intl Workshop on Adverse Drug Reactions. 26-28 October 2009, Philadelphia. Poster abstract P-06. Antiviral therapy 2009; 14 Suppl 2: A27.

Reduced levels of vitamin D in patients taking efavirenz

Simon Collins, HIV i-Base

Todd Brown and colleagues from Johns Hopkins University presented results from a retrospective analysis that supports a link between efavirenz and reduced levels of vitamin D. [1]

The study compared 25-(OH) vitamin D levels from stored samples from 87 treatment naive patients and compared this to levels 6-12 months after starting treatment containing efavirenz (n=51) or non-efavarinz (n=36; 89% PI-based).

Several studies have reported an association between NNRTIs and reduced levels of vitamin D, including a recent UK study linking low levels to the use of efavirenz. [2]

The current study reported a prevalence of mild, moderate and severe vitamin D deficiency at baseline in 84% (<32 ng/mL/<80 nmol/L), 56%% (<20 ng/mL/<50 nmol/L) and 33% (<15 ng/mL/< 37.5 nmol/L) patients respectively. Median levels were lower in

non-white compared to white patients (16 vs 30 ng/mL, p<0.0001) and in winter compared to summer (15 vs 27 ng/mL, p<0.001). Factors associated with low levels at baseline included race (Prevalence Ratio 6.7 95%CI: 1,7, 25.6; p=0.006), season (PR 4.6; 1.2, 17.8; p=0.03) and duration of HIV infection (PR 1.06; 1.02, 11.09; p=0.003).

Pre- and post-HAART levels in the efavirenz group dropped from 22.6 to 18.4 and increased from 21.2 to 22.9 in the non-efavirenz group (p=0.05 between group comparison post-HAART). After adjusting for baseline 25(OH)D, race and season, the adjusted mean difference between group was -5.1 ±1.5 ng/mL, (p=0.001). Using the <15 nmol/mL cut-off the percentage of patients with severe depletion increased form 27% to 48% in the efavirenz group and reduced from 42% to 31% in the non-efavirenz group. The adjusted prevalence ratio for efavirenz use was 1.8 (95%CI 1,2, 2,8, p=0.007).

No association was found with use of tenofovir, abacavir of AZT.

References:

1. Brown TT et al. Association between initiation of antiretroviral therapy with efavirenz and decreases in 25-hydroxyvitamin D. 11th Intl Workshop on Adverse Drug Reactions. 26-28 October 2009, Philadelphia. Oral abstract O-20. Antiviral therapy 2009; 14 Suppl 2: A15.
2. Welz et al. Efavirenz use is associated with severe Vitamin D deficiency in a large, ethnically diverse urban UK HIV cohort. Poster abstract TUPEB186. 5th IAS conference, 19-22 July 2009, Cape Town.
   http://www.ias2009.org/pag/Abstracts.aspx?AID=3402

Association between inflammation and sleep apnea in the MACS cohort

Simon Collins, HIV i-Base

Prompted by the concern that systemic inflammation may contribute to sleep apnea, Susheel Patil and colleagues from Johns Hopkins University presented an interesting analysis from the gently named SIESTA study (Study of Immune Effects on Sleep, (HIV) Treatment and Apnea).

The study looked at obstructive sleep apnea (OSA) and the relationship with inflammation markers (TNF-alpha soluble TNF-a receptors I and II and IL-6), in three groups of men from the MACS cohort: HIV-positive and not on HAART (n=41), HIV-positive and on HAART (n=58) and HIV negative (n=60). Severity of OSI was defined by the number of events per hour detected during a nocturnal sleep study: 5-15 = mild, 15-30 = moderate, and >30 = severe. Obesity is the strongest predictor of OSI, but OSI is also independently associated with hypertension, cardiovascular disease, stroke, diabetes mellitus and reduced quality of life.

OSI >15 was higher in the HIV- negative group (57%) compared to the HAART (41%) and no-HAART (44%) groups. However, the HIV-negative group had a significantly greater mean BMI (28.6 ±7.2kg/m2) and waist circumference (98.6 +16.9cms) compared to the HAART (25.5 ±4.5kg/m2 and 93.8 +11.5cm) and no-HAART (25.4 ±4.1 kg/m2 and 91.8 ±12.8) HIV-positive groups and a trend to greater trunk weight.

When looking at participants with normal BMI (<25 kg/m2) however, the relationship indicated a trend for higher prevalence in the no-HAART group: 25% HIV-negative (n=20), 24% on HAART (n=29) and 50% in the no HAART group (n=22); (p=0.1).

Median levels of all four inflammatory markers were higher in the HIV-positive men compared to the HIV-negative men, and were higher in the no-HAART group compared to the HAART group. Within the no-HAART group, men with moderate – severe OSA had higher levels of TNF-a and IL-6 compared to men with no or less severe OSI, although this difference was not observed between men in the other groups.

The study concluded that rates of OSI were high in HIV-positive men, even when BMI was normal, and that more severe symptoms was associated with systemic inflammation suggesting a different aetiology compared to men who are HIV-negative.

Ref: Patil SP et al. Association between systemic inflammation and obstructive sleep apnea in men with or at risk for HIV infection from the Multicenter AIDS Cohort Study (MACS). 11th Intl Workshop on Adverse Drug Reactions. 26-28 October 2009, Philadelphia. Oral abstract O-25. Antiviral therapy 2009; 14 Suppl 2: A19.

Sports supplements impact on serum creatinine and eGFR markers of renal function

Simon Collins, HIV i-Base

Several case studies showing the impact of creatinine supplementation on eGFR results were presented in a poster by Graeme Moyle from the Chelsea and Westminster Hospital. Estimated GFR is now routinely included in renal monitoring using the MDRD calculation, which incorporates serum creatinine, together with age, sex and ethnicity.

Six HIV-positive male patients (aged 25- 55) on stable HAART were referred to the hospital's HIV/renal clinic due to elevated serum creatinine (range 131-257 umol/L) and low eGFR. All were normal blood pressure and no history of diabetes. Proteinuria levels were normal and confirmed by urinary protein:creatinine ratio. Each patient routinely used protein and creatine supplementation as part of a muscle-building gym routine.

Three months after 5/6 patients discontinued the supplements, serum creatinine levels consistently dropped to between 98 and 118 umol/L and eGFR reported to normalise (eGFR data was not shown).

Although dietary intake of creatine is 1g/day, supplementation can increase this 20-30 fold, and intramuscular concentrations can remain elevated for several weeks. Creatine is converted to creatinine relative to its concentration, which can increase serum creatinine despite normal renal function. The poster suggested that ARV exposure may also be involved but also that the association of raised serum creatinine with creatine ingestion has not been published outside of the HIV context.

This study highlights the importance of considering this as a cause for elevated creatinine or low eGRF and taking a history of supplement use in patients with abnormal results.

Ref: Moyle G et al. The pitfalls of the estimated glomerular filtration rate – 'hitting the gym and creatine supplementation'. 11th Intl Workshop on Adverse Drug Reactions. 26-28 October 2009, Philadelphia. Poster abstract P27. Antiviral therapy 2009; 14 Suppl 2: A49.

CONFERENCE REPORTS

9th AIDS Vaccine Conference

19-22 October 2009, Paris, France

Introduction

The AIDS Vaccine conference is one of the most important scientific conferences on AIDS vaccine research and development. It was attended by more than 1,000 delegates and included over 400 scientific presentations.

Programme highlights that increased the profile of the meeting this year, included a full presentation from the Thai phase III trial that controversially reported top level results a few weeks earlier in a press release.

We report this study here, which coincided with publication in the NEJM.

- Thai HIV Vaccine Trial results presented and published

Conference programme:

http://www.hivvaccineenterprise.org/conference/2009/scientific_program.aspx

Several sessions including the press conferences, are available as webcasts, together with searchable online abstracts and PDF files of many or the posters or presentations:

http://www.hivvaccineenterprise.org/conference/2009/webcasting.html

Conference abstracts have been published as an open access online supplement in Retrovirology:

http://www.retrovirology.com/supplements/6/S3

Thai HIV Vaccine Trial results presented and published

Richard Jeffreys, TAG

In tandem with the presentation of the data that took place at the AIDS Vaccine 2009 conference in Paris, the results of the RV144 trial were published online in the New England Journal of Medicine. Access to the paper and the accompanying editorial is free of charge. Three different analyses of the results are presented in sequence: the intent-to-treat analysis (ITT), which includes everyone enrolled and randomised to receive vaccine or placebo, a per protocol (PP) analysis limited to everyone who received all immunisations on schedule, and finally a modified ITT (mITT) analysis that excludes seven individuals who reportedly turned out to be HIV-infected at the time of their first immunisation.

- ITT: Total n=16,402. Cases of HIV infection: 76 placebo, 56 vaccine. Efficacy: 26.4% (95% confidence interval [CI], –4.0 to 47.9; p=0.08)

- PP: Total n= 12,452. Cases of HIV infection: 50 placebo, 36 vaccine. Efficacy: 26.2% (95% CI, –13.3 to 51.9; p=0.16)

- mITT: Total n=16,395. Cases of HIV infection: 74 placebo, 51 vaccine. Efficacy 31.2% (95% CI, 1.1 to 51.2; p=0.04)

The data suggests the possibility of a marginal protective effect, almost entirely concentrated during the first year of the study. Kaplan-Meier plots of the infection rate over time show a divergence initially, but the rates in the vaccine and placebo groups are superimposable from week 52 onwards. Subgroup data are also reported, but the statistics are uncorrected for multiple analyses and should be interpreted with great caution. With this caveat, there is a hint that the difference between vaccine an placebo was greatest among those at lowest risk of HIV exposure. The age group breakdown also indicates the difference between vaccine and placebo groups was concentrated in the 20-25 age group; there is no difference in the number of infections between the groups among those under 20, and very little difference among those over 26. Among the 20-25 age group, there were 20 infections in the vaccine group and 40 in placebo.

In terms of the viral load outcomes in people who acquired infection, the ITT analysis shows a trend in the wrong direction; viral load was higher on average among vaccine recipients (4.36 log vs. 4.21 log, p=0.09). However this trend disappears in both the PP and mITT analyses. There were no differences in post-infection CD4 T cell counts in any of the analyses.

As to why the only statistically significant result is reported last in the published paper (in contrast to the September 24 press announcement, in which the mITT was the only result given), it appears that the RV144 protocol specified that the primary analysis would be ITT. The paper states that the mITT analysis was used as the primary analysis for the interim efficacy evaluation (which was conducted by the Data Safety Monitoring Board in July of 2007) and then, five months before the study was unblinded, a decision was made to make the mITT the primary analysis. Reading between the lines, perhaps the reviewers of the manuscript were not satisfied that this late adoption of the mITT as the primary analysis justified listing the result first in the paper. It is currently unclear why the RV144 protocol did not specify the mITT as the primary efficacy analysis from the start. As the import of the trial results are mulled by the larger community, it will be important to gain some clarity as to exactly how these events played out.

So far, in the limited time observers have had to digest the data, the main issues that are being discussed are the suggestion of a transient, time-limited effect and what might explain it (vaccines generally work by the induction of immunological memory, which is typically long-lived) and the hint that vaccine-mediated protection might be easier to achieve in individuals with less frequent HIV exposure compared to those at high risk.

Regrettably, the release of the data today does not change the fact that it was an appalling and woefully short-sighted decision to only release the mITT analysis to the press on September 24. On the conference call hosted by AVAC that took place that day with investigator Merlin Robb and Peggy Johnston from NIAID, Robb explicitly stated that only 16,395 people had been enrolled into the trial. Not only was this not true, but it turns out that vaccine/placebo distribution of the 7 people excluded from the mITT was crucial to the attainment of statistical significance: five of these individuals were in the vaccine group and two in placebo. By cherry-picking the mITT to announce, the RV144 investigators have created suspicion and uncertainty in a field that they well know is already plagued by controversy. Their decision will only serve to complicate efforts to glean useful information from the trial data.

Source: www.tagbasicscienceproject.typepad.com (20 Oct 2009)

The webcast of the press conference about the trial results is now available online (scroll down to the bottom of the page to the Tuesday, 20 October press conference link).

http://www.hivvaccineenterprise.org/conference/2009/webcasting.html

References

1. Supachai Rerks-Ngarm et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. 20 October 2009 (10.1056/NEJMoa0908492).

   http://content.nejm.org/cgi/content/full/NEJMoa0908492
2. Dolin R. HIV vaccine trial results - an opening for further research. NEJM Editorial. 20 October 2009 (10.1056/NEJMe0909972).

   http://content.nejm.org/cgi/content/full/NEJMe0909972

Additional reading:

Earlier articles detailing the unfolding controversies around this study and the early press release focusing on a positive trial result are covered in a number of articles from the TAG basic science web log.

http://tagbasicscienceproject.typepad.com

Marginal HIV Vaccine Trial Result Raises Hopes, Eyebrows (25 Sep 2009)

Thai HIV Vaccine Trial: Additional History & Links (28 Sep 2009)

Deconstructing the Thai Trial Vaccines (29 Sep 2009)

Did the World Get a "Fair Glimpse" of the Thai Vaccine Trial Data? (05 Oct 2009)

Thai HIV Vaccine Trial Update: Uncertainty Reigns (15 Oct 2009)

CONFERENCE REPORTS

49th International Conference on Antimicrobial Agents and Chemotherapy (ICAAC)

12-15 September 2009, San Francisco, USA

Introduction

The following short reports are summaries from a few of the interesting studies presented at ICAAC this year. As were not able to cover this meeting in person, all information is dependent on the online posters.

Reports in this issue of HTB South include:

- Smoking masks the long-term benefits of HAART on lung function
- Alcohol and marijuana may reduce drug levels of atazanavir and efavirenz

ICAAC unfortunately routinely removes online access shortly after the meeting and is one of the few medical meetings covering HIV care that does not support continued open access to this resource.

As we went to press these were still available online:

http://www.posters2view.com/icaac

[Username: ICAAC; Password: SanFran]

Smoking masks the long-term benefits of HAART on lung function

Simon Collins, HIV i-Base

A poster by Jan Gerstoft and colleagues from Copenhagen University Hospital looked at the interaction between changes in lung function in relation to smoking and HIV treatment.

Between October 2000 and November 2001, 63 HIV-positive patients had initial lung function assessed by a panel of tests (including forced expired volume, functional vital capacity, peak flow, residual volume [RV%] and total capacity and diffusing capacity/alveolar volume [DLCO/VA%]), with follow-up assessments a median of 4.5 years later (range 3.8-4.7 years).

Most participants (87%) were already on HAART at baseline for a median of about five years (range 16-79 months) with all but two on HAART at the follow-up visit (with 85% and 89% of these patients having viral load <100 copies/mL at each time point, respectively).

Some abnormal lung function parameters were present at baseline in both smoking (n=30) and non-smoking (n=33) participants, and some were further reduced in smokers. Specifically, DLCO/VA% was decreased in both groups, with lung function compatible with early obstructive lung disease. At follow-up these levels normalised in non-smokers and improved in smokers to the baseline levels of the non-smoking group.

However, results for residual volume, which returned to normal for non-smokers, increased further in the smoking group.

The researchers concluded that this study showed that HAART was beneficial for lung status and that HIV-related changes can reverse over time in non-smokers. However, smoking masks many of these potential benefits.

COMMENT

As most participants had already been on HAART for many several years at baseline, and results were not divided by HAART use and viral load, the study did not quantify the extent and timeline of the benefits due to antiretroviral therapy. Nevertheless, the suggested positive impact of HAART on lung function is important and the results reinforce the importance of smoking cessation.

Ref: Gerstoft J et al. Changes of lung function in an optimally treated HIV population: a 4.5 year follow up study. 49th ICAAC, 12-15 September 2009, San Francisco. Poster abstract H-1561.
http://www.posters2view.com/icaac/view.php?nu=H-1561

Alcohol and marijuana may reduce drug levels of atazanavir and efavirenz

Simon Collins, HIV i-Base

Two small studies from the same research group looked at the association between substance use, including alcohol and marijuana, and levels of HIV drugs.

The first study reported that trough concentrations of atazanavir were inversely related to use of tobacco and marijuana in 32 'substance using' (SU) patients from four US sites compared to 35 non-using (non-SU) patients. [1]

Substance use (% of SU patients) followed NIDA criteria and included alcohol (41%), cocaine (19%), marijuana (38%), opioids (22%) and tobacco (91%). 43% of these patients used multiple substances.

During the study period, patients had to complete three clinic visits, for entry, trough and directly observed therapy (DOT), and take scheduled doses of atazanavir at the same time for 4 days before each visit.

Adherence assessment and counseling prior to plasma sampling and each scheduled clinic visit were performed and recorded.

Multiple linear regression models were used to determine factors associated with atazanavir concentrations, immunological and virologic responses while adjusting for covariates. Other demographics including race, gender, ethnicity and BMI were included in the analysis.

Significant reductions in ATV trough concentrations were associated with tobacco and marijuana use ($p< 0.05$) but not with other substances. 36% and 50% of tobacco and marijuana users, respectively had ATV concentrations below the therapeutic range ($p<0.05$). However, no significant direct effects were linked to viral load or CD4 count.

Table 1. Substance use (SU) and atazanavir trough levels*

	SU	Non-SU	P
Tobacco	0.31 (0.12-0.79)	0.96 (0.32-1.20)	0.009
Marijuana	0.24 (0.05-0.80)	0.59 (0.27-1.11)	0.03
Alcohol	0.53 (0.13-0.91)	0.56 (0.22-1.08)	0.60
Cocaine	0.77 (0.05-1.39)	0.54 (0.19-1.05)	0.92
Opioids	0.32 (0.15-0.77)	0.71 (0.19-1.10)	0.22

* Median, ug/ml (IQR). For HTB rounded to two decimal points.

The researchers concluded that the underlying mechanism may include enzyme induction but that further studies were needed for this to be determined.

The second study looked at efavirenz metabolism in relation to the G516T single nucleoside polymorphisms (SNPs) in the CYP2B6 enzyme. Previous studies have demonstrated that GG > GT > TT polymorphisms inhibit efavirenz metabolism resulting in higher plasma concentrations, slower drug clearance, and sometimes increased toxicity.

Based on 516 genotypes, 37 patients (SU n=18; non-SU n=19) were categorised as extensive (GG, n=19), intermediate (GT, n=13), and slow (TT, n=5) metabolisers. These genotypes with were significantly associated with efavirenz trough concentrations (p=0.04). Significantly lower median (IQR) efavirenz concentrations were linked to tobacco use (1.76 ug/mL; (1.31-2.13) vs 2.29 ug/mL (1.88-4.01), p=0.04) and alcohol use (1.41 ug/mL (0.66-1.88) vs 2.25 ug/mL (1.76-2.48), p=0.02) in the extensive metaboliser group with lower CD4 counts and higher viral loads.

As with the atazanavir study, substance use had no significant relationship to antiviral responses.

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CONFERENCE REPORTS

5th IAS Conference on HIV Pathogenesis, Treatment and Prevention

19-23 July 2009, Cape Town, South Africa

Introduction

We conclude our reports from this important conference.

In this issue we include the following articles.

- When to start guidelines in resource poor settings
- ARV programme results reports at IAS
- Treating children previously exposed to single dose nevirapine

We have also included an overview of paediatric studies presented at IAS in the current issue number 36 of the Journal of HIV Medicine.

When to start guidelines in resource poor settings

Nathan Geffen, TAC

The appropriate CD4 count to initiate treatment is a topic of much research and discussion. In South Africa, the threshold in the public health system remains 200 cells/mm3, based on the Department of Health guidelines published in 2004.[1] In the private sector, medical schemes are generally using a threshold of 350 cells/mm3, based on the Southern African HIV Clinicians Society Guidelines. [2] Other sub-Saharan African generally use a 200 threshold as well. Meanwhile, Europe and North America also initiate at first CD4 count below 350 cells/mm3.

The 350 cells/mm3 threshold is supported with evidence from several studies:

The When to Start Consortium, in an analysis of 15 cohort studies, found a greater than two times hazard ratio for progression to AIDS or death in people with CD4 counts from 100 to 200 cells/mm3 compared to people with CD4 counts of 201 to 300 cells/mm3 (HR: 2.21; 95%CI 1.91-2.56). There was also a significant difference in progression between the CD4 count strata of 151-250 cells/mm3 and 251-350 cells/mm3 (HR:1.71; 95%CI 1.43-2.04). (See HTB South April-June 2009.) [3] Also see Kitahata et al., which found a 1.69 [95%CI: 1.26-2.25] greater risk of death in patients who started treatment with a CD4 count between 350 and 500 cells/mm3 versus patients who deferred. [4]

The CIPRA HT 001 study was started in Port-au-Prince, Haiti in 2005. The 816 volunteers with CD4 counts between 200 and 350 cells/mm3 were randomised to either start HAART immediately or defer until their CD4 counts dropped to below 200 cells/mm3, the current standard of care in Haiti. The DSMB stopped the trial in May 2009 when it found clear evidence favouring the earlier treatment group. In the immediate group six people died versus 23 in the deferred group. Twice as many people (36 vs 18) contracted TB in the deferred group. These results, according to NIAID, are statistically significant. [5]

The START trial will answer the question as to whether treatment should be initiated at CD4 counts > 500 cells/mm3 or when it drops to below 350 cells/mm3. The trial began this year, but its estimated completion date is March 2015. In the meanwhile guideline developers need to make decisions based on the best, albeit incomplete, evidence available.

Francois Venter's presentation at IAS2009

Francois Venter presented six issues affecting the discussion on when to start at a symposium at IAS2009. [6]

First, he presented the currently available evidence and ongoing trials to determine the appropriate CD4 count initiation threshold. He contrasted this with data presented by Matthias Egger at CROI 2007 that reviewed 176 sites from 2003 to 2005 in 42 countries that included 33,000 patients and showed when people actually are starting HAART.[7] In developed countries, the average patient initiates treatment with a CD4 count of 150 to 200 cells/mm3. In Sub-Saharan Africa, it has increased from 50 cells/mm3 to about 100 cells/mm3. Venter pointed out that this was despite a large increase in testing in South Africa over the same period, with only about 20% of tested patients eligible for HAART according to current guidelines.[8] In Venter's programme in the inner city of Johannesburg, the average CD4 count at initiation is 106, despite 70% coverage and a massive escalation in testing. He stressed that retaining patients who have been tested in care is the key challenge as opposed to escalating testing.

Secondly, he explained that many people die waiting for treatment. For example, of 4570 patients followed up for at least one year in a cohort in Free State Province, South Africa, 53.2% died. Of these, 87% died before receiving HAART. [9] Venter presented data from Braitstein and colleagues showing that expedited care reduced mortality by 60%.

Third, he considered whether treatment should start earlier to reduce non-AIDS morbidity and mortality. He presented data from Andrew Phillips and colleagues that examined the risk of non-AIDS events in four studies: Flexible Initial Retrovirus Suppressive Therapies (FIRST) trial, Data Collection on Adverse Events of Anti-HIV Drugs study (DAD), Concerted Action on SeroConversion to AIDS and Death in Europe collaboration (CASCADE) and the Strategies for Management of Antiretroviral Therapy (SMART) trial.

The adjusted relative hazards for the effect of CD4 cell count on the risk of liver disease was significant in DAD, CASCADE and SMART. For non-AIDS cancer, it was significant in FIRST, DAD and CASCADE. For renal disease it was significant in FIRST and DAD (not measured for CASCADE) and for cardiovascular disease it was significant in CASCADE. In all comparisons, even when the results were not significant for a particular study, higher CD4 counts were correlated with less disease. Venter demonstrated that these results are relevant to South Africa by pointing out that there are overlapping epidemics of obesity and HIV in South Africa. He noted the high prevalence of hypertension and diabetes and suggested this put HIV-positive people in South Africa at high risk of dying from non-AIDS illnesses at low CD4 counts.

Fourth, he considered the effect of earlier HAART on opportunistic infections. There are high rates of opportunistic infections above CD4 counts of 200 cells/mm3 in resource poor settings. For example, an analysis by Badri and colleagues compared the six-monthly risk of death according to CD4 count and WHO stage.

They found that the risk of death for WHO stages 1 and 2 was 3.5% (95%CI 1.4-7.1) for people with less than 200 cells/mm3, 2.8% (95%CI 1.3-5.3) for 200 to 350 cells/mm3 and 1.2% (0.5-2.3) for greater than 350 cells/mm3. For WHO stage 3 the death rates were 10.1% (95%CI 7.5-13.2) for <200 cells/mm3, 4·3% (95%CI 2.1-7.8) for 200 to 350 cells/mm3, and 4.9% (95%CI 2.3-9.1) for > 350 cells/mm3. For WHO stage 4, 22.2% (95%CI 17.9-27.1) for < 200 cells/mm3, 10.3% (95%CI 3.5-22.4) for 200 to 350 cells/mm3, and 13.8% (95%CI 4.1-32.6) for >350 cells/mm3. Interestingly, 52% of deaths took place in patients without AIDS. [10]

Venter pointed out the additional concerns in resource-poor settings about opportunistic infections. This has been well characterised for tuberculosis (see HTB South July to September 2009, pp. 22-28). But there are also concerns about greater risk of other bacterial (and fungal) infections including cryptococcal meningitis, pneumococcus, salmonella, wasting and malaria, even at higher CD4 counts. Cryptococcis is a particularly important concern. For example, a study by Olivier Lortholary and colleagues found that the mortality rate per 100 person-years was 15.3 [95%CI: 12.2-18.4] in the HAART era versus 63.8 [95%CI: 53.0-74.9] in the pre-HAART era for people diagnosed with this infection. [11] A study in Thailand by Jongwutiwes and colleagues retrospectively analysed 149 patients with cryptococcis. The cumulative 75% survival from relapse duration was over 10 months amongst those who did not receive HAART versus 42 months in those who did (p<0.01). [12]

Fifth, Venter considered maternal HAART and paediatric treatment. He examined the CHER results (discussed extensively in several issues of HTB) which led to the WHO guidelines recommendation of universal treatment for all HIV-infected infants younger than 12 months. [13,14] Although mortality on the immediate treatment arm of CHER was as low as 4%, Venter pointed out that in 2007, only 8% of HIV-exposed infants were tested in the first two months of life. Using data from Malawi, he showed that the vast majority of children entered HIV care via hospital wards, as opposed to PMTCT follow-up, VCT and child health institutions, indicating systemic problems with getting HIV-infected children onto early treatment. Venter stated that it was better to prevent paediatric infection in the first place and that it was much easier to treat mothers than babies.

Venter considered the pros and cons of universal treatment for pregnant women, summarised in Table 2. He also emphasised the need for universal treatment for pregnant women with CD4 counts <350 cells/mm3, citing data from Louise Kuhn shown in her plenary talk at IAS2009 that in the ZEBS study 84% of maternal deaths and 82% of postnatal infections occur in women with CD4 counts < 350 cells/mm3 (cf < 200 cells/mm3 at which 55% of maternal deaths and 47% of postnatal infections occur). [15]

Finally Venter considered the effect of earlier treatment on prevention. He pointed out that prevention programmes have had disappointing results and asked whether reducing viral load earlier might have a public health impact. He said there could be a convenient convergence of using HAART for both treatment and prevention purposes.

Venter concluded by pointing out that so long as stavudine is part of the standard care in Sub-Saharan Africa, earlier treatment would be harder to implement. The drug is in wide use. Venter presented data from Westreich and colleagues showing that stavudine is used by over 80% of Zambian, Mocambican and Tanzanian HAART patients and over 70% of Côte d'Ivoire ones. That study analysed a cohort of over 7,000 patients in Johannesburg. It found that for ongoing TB treatment at HAART initiation, the risk (adjusted hazard ratio) of a stavudine switch (compared to not being on TB treatment) was 3.18 (95%CI: 1.82-5.56) in the first 2 months of HAART, 2.51 (95%CI: 1.77-3.54) in months 3 to 6, and 1.19 (95%CI: 0.94-1.52) thereafter. For concurrent initiation of TB and HAART treatment, the risk was 6.60 (95% CI: 3.03-14.37) in the first 2 months, 1.88 (95%CI: 0.87-4.09) in months 3-6, and 1.07 (95%CI: 0.65-1.76) thereafter. There was no effect on the risk of stavudine substitution if patients were treated for TB after they had initiated HAART. [16]

In a study from a programme in Kigali Rwanda published by MSF researchers in September, stavudine side-effects were responsible for substantial switching. Out of 2190 adults followed up for a median of 1.5 years, stavudine was replaced in 175 patients (8.0%) for neuropathy, 69 (3.1%) for lactic acidosis and 157 (7.2%) for lipoatrophy. Lipoatrophy was the most frequent adverse event by three years of treatment. The authors concluded that stavudine is associated with significant long-term toxicity. They suggested stavudine-dose reduction, increased access to safer HAART regimens in low-income countries and close monitoring for those at risk. [17]

Table 2: Pros and cons of universal treatment for pregnant women

Pros	Cons
Women are often identified with higher CD4 counts in antenatal care, making it a good entry point for treatment.	What is the regimen? Nevirapine is contraindicated in women with CD4 counts > 250 cells/mm3. Efavirenz is contraindicated in pregnancy. Protease inhibitors are expensive. Triple-nukes may be less potent and data on them is scarce.
Pregnant women are much easier to treat than infants.	Greater risk of preterm delivery.
It is possible that universal treatment will be easier to implement as HAART programmes mature.	May not be so easy to implement.
Universal treatment partly resolves the concerns over formula milk versus breast milk.	Unresolved questions: Can HAART be stopped if used for PMTCT? Is HAART better than prophylaxis at high CD4 counts? PROMISE, PHPT-5 and other studies will resolve some of these questions.

Adapted from Francois Venter.

Data from IAS2009 on drug switching due to stavudine is presented in another article in this issue titled ARV Programme Results: Reports at IAS.

Cost-effectiveness of 350 cells/mm3 initiation

A study by Walensky and colleagues, published in the Annals of Internal Medicine, has modeled the cost-effectiveness of three options: (1) no treatment, (2) treatment initiated at CD4 count less than 250 cells/mm3 and (3) treatment initiated at CD4 count less than 350 cells/mm3. The study found that initiating HAART in South Africa at 350 cells/mm3 will reduce morbidity and mortality, improve long-term survival, and be cost-effective compared to initiation at 250 cells/mm3. The authors recommend that treatment guidelines should be changed to allow initiation when a patient's CD4 count is below 350 cells/mm3. [18]

The objective of the study was to inform the crucial decision of when to start now, ie in the period before clinical trial results are published. Based on their results, the editors write, "Earlier antiretroviral therapy will probably prove to be superior in South Africa."

In all scenarios, cotrimoxazole prophylaxis at a CD4 count < 500 cells/mm3 was modelled. The strategies were analysed over short-term (5 years) and life-time periods. Only direct HIV-associated uses of medical resources were considered.

The study used the CEPAC (Cost-Effectiveness of Preventing AIDS Complications) International model. All costs and life-expectancies were discounted at a rate of 3% per year. All monetary amounts were calculated using 2006 US dollars. The model has many input parameters, whose values were derived from clinical trials and observational studies in South Africa. Baseline at treatment parameters include mean age, ratio of men to women, mean CD4 count and distribution of the population over several HIV viral load strata. Parameters for modeling the onset of disease include monthly CD4 cell change (linked to viral load), monthly risk for severe opportunistic infection; efficacy of cotrimoxazole at reducing severe bacterial diseases, toxoplasmosis and PCP; monthly risk of HIV-related death and efficacy of HAART at viral load suppression by 48 weeks (broken down by first versus second-line treatment). In accordance with the South African treatment guidelines, the model provides for clinical assessments to occur every 3 months and CD4 and viral load testing every 6 months while receiving therapy.

The WHO considers an intervention cost-effective if it costs less than three times the per capita GDP to save one quality adjusted life-year. It considers an intervention very cost-effective if it costs less than the per capita GDP to save one quality adjusted life-year. However, the study examined years of life saved without adjusting for quality. Nevertheless, this is a minor difference and for practical purposes it is acceptable to directly compare the study's findings with the WHO measures of cost-effectiveness. The cost-effectiveness of the study's outputs was compared with the 2006 per capita GDP of $5,400 in South Africa.

The discounted per person lifetime cost for the strategies is $3,930 (no treatment), $12,730 (250 cells/mm3) and $13,620 (350 cells/mm3). Both treatment strategies would increase life-expectancy by at least 7.9 years over the no treatment strategy. Compared with no treatment, a treatment threshold CD4 count of 250 cells/mm3 would have an incremental cost-effectiveness ratio of $1,100 per life-year saved. And compared with a threshold of 250 cells/mm3, a threshold of 350 cells/mm3 would have an incremental cost-effectiveness ratio of $1,200 per life-year saved. (The incremental cost-effectiveness ratio is the additional cost of the intervention divided by the number of additional deaths prevented by the intervention.)

Table 1 summarises the clinical outcomes and costs over the next five years in the two treatment scenarios.

Table 1: Clinical outcomes and costs over the next five years in the treatment scenarios

Scenario	No. Opportunistic Diseases	No. Deaths	Discounted costs
10% HIV identification and linkage to care			
CD4 < 350	1.6m	1.66m	$9.97b
CD4 < 250	1.62m	1.69m	$9.83b
Difference	(22,110)	(25,281)	($142m)
30% HIV identification and linkage to care			
CD4 < 350	1.42m	1.35m	10.44b
CD4 < 250	1.48m	1.42m	10.01b
Difference	(66,329)	(75,843)	($426m)
100% HIV identification and linkage to care			
CD4 < 350	730,272	244,249	12.05b
CD4 < 250	951,370	497,059	10.63b
Difference	(221,097)	(252,810)	(1.42b)

Adapted from Walensky et al. (b = billion, m = million).

Using the WHO cost-effectiveness guidelines, the authors calculated that initiating treatment at a CD4 count of 350 cells/mm3 over the next five years should be used if the probability that a trial shows benefit for this threshold is 17% or greater.

The authors also conducted sensitivity analysis on the model's lifetime projections and made the following findings:

1. Fewer than 39% of second-line patients initiated using a 350 cells/mm3 threshold would have to achieve viral suppression at 48 weeks to match the projected survival rate from using a threshold of 250 cells/mm3. This is a 32% relative decrease from the base case.
2. Discontinuation of care in the 350 cells/mm3 group (eg due to treatment fatigue) would have to be more than 19% to decrease survival compared to the 250 cells/mm3 group.
3. Including a hypothetical third-line regimen increased life-expectancy in both treatment groups.

COMMENT

The cost-effectiveness study by Walensky and colleagues presents a strong economic argument for changing the HAART guidelines in South Africa to treat everyone with a CD4 count < 350 cells/mm3. Shortly before their study was published, NIAID announced the termination of the CIPRA HT 001, arguably settling the question that 350 is a better threshold than 200 cells/mm3 (although the cost-effectiveness study compared 350 to 250 and not 200 cells/mm3).

Venter's analysis provides an excellent summary of the complex issues affecting when to start. His presentation shows that systemic problems are at least as important as changing guidelines. Even in developed countries, many patients start late, ie well within

guideline recommendations, and the situation in resource-poor areas is much worse.

Interestingly when asked at IAS2009, one of the CIPRA HT 001 study trial researchers explained that the median CD4 count for the immediate group was 280 cells/mm3 (IQR: approximately 230-300) versus 170 cells/mm3 for the deferred group. It is notable that even in a trial, people did not start close to the stated threshold but the difference between early versus delayed treatment was still profound.

Changing the CD4 threshold will not by itself remedy this situation. It is a positive development that more people are getting tested earlier for HIV, but if there is then nothing to offer them until they are ill, they are likely to be lost to follow up, only to reappear with very low CD4 counts. Ensuring that patients who are tested early and then retained in care is the key challenge and probably requires system changes.

Ironically, if the START study demonstrates that immediate HAART is better than deferred, then this might prove to be a useful mechanism for retaining people who have tested HIV-positive in the health system.

This should not detract from the need for effective public communications programmes that encourage early testing, or provider-initiated testing. It is just that these programmes would be more effective at keeping patients in the system.

The move towards earlier treatment has become possible because of improved medicines. But the long-term side effects of stavudine make it much harder to determine an appropriate threshold in programmes that use this drug. Venter's concern about the widespread use of stavudine in sub-Saharan Africa can be alleviated if steps are taken to gradually replace it with tenofovir. As reported in the Treatment Update section of the previous issue of HTB South, there is at least one generic manufacturer making a low-cost 3-in-1 once-daily tenofovir containing fixed-dose combination pill that is WHO prequalified and FDA tentatively approved. Other generic manufacturers are intending to do the same. Surely these should become the standard first-line regimens in sub-Saharan Africa?

Discussions are underway, and it seems likely that 350 CD4 as a starting point and tenofovir in first line to replace d4T, will be added to South African guidelines. However, both of these come with significant extra costs. So qualifications may apply, at least initially.

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Treating children previously exposed to single dose nevirapine

Polly Clayden, HIV i-Base

Two studies presented at the 1st International Workshop on HIV Pediatrics, 17-18 July 2009, Cape Town, South Africa and IAS2009 looked at strategies for treatment of HIV-infected children with prior exposure to nevirapine (NVP) to prevent mother to child transmission.

IMPAACT P1060

In an oral presentation at the paediatric workshop, Avy Violari from the University of Witwatersrand, Johannesburg, South Africa, presented preliminary findings from the IMPAACT P1060

trial. [1] These data were also shown at the IAS conference as a late breaker poster. [2]

IMPAACT 1060 was a randomised trial conducted at 10 sites in 7 African countries. In this trial, two groups of HIV-infected children age 6 months to 3 years and eligible for treatment according to WHO criteria: Cohort 1, exposed (n=288) and Cohort 2, unexposed (n=288) to single dose NVP, were randomised to receive either lopinavir/r or NVP plus zidovudine (AZT) and lamivudine (3TC), with 144 children in each treatment group.

Children were stratified by age <12months vs. >=12 months with equal number to be enrolled in each age group.

The primary endpoint was virologic failure (defined as <1 log decrease in viral load between weeks 12 -24 or >400 copies/mL at week 24), treatment discontinuation or death by week 24.

The investigators used Kaplan-Meier curves to estimate failure rates at week 24. Differences between treatment arms were weighted by the inverse of the variance in each age group.

A similar study of mothers exposed and unexposed to single dose NVP had also been conducted (A5208). In this trial – which we reported in previous issues of HTB – the arm in which exposed mothers received NVP-containing HAART was stopped early by the Data Safety Monitoring Board (DSMB) due to superior performance of the LPV/r- containing HAART arm. [3, 4]

Dr Violari reported that following a scheduled DSMB review of IMPAACT 1060 on 20 April 2009, enrolment to Cohort 1 had also closed prematurely due to a trend towards consistency with the A5208 results. Children in Cohort 1 were evaluated and discussions with their parents or guardians were held to decide whether to switch children receiving NVP to LPV/r. Cohort 2 is to continue enrolment and study as planned.

At the time of the DSMB review, Cohort I had enrolled 153/288 children with a median follow up of 48 weeks. The median baseline age of the children was 0.7 years (75% <12 months), median CD4 percentage 19%, and median viral load >750,000 copies/mL. Results at week 24 by primary endpoints are detailed in Table 1.

Table 1: Cohort 1, week 24 primary endpoints (from Kaplan- Meier curve)

Age	NVP (n)	Failure %	LPV/r	Failure %	NVP-LPV/r
<12 mo	60	45%	63	23%	22%
≥12 mo	22	29%	19	17%	11%
All	82	39%	82	22%	18%

Difference in week 24 failure rate (NVP-LPV/r): all 18% (95% CI 2%-33%), p=0.015.

Of 115 children tested, 16 (14%) had baseline NVP resistance, mostly Y181C (n=14). The investigators found the difference in viral failure between arms was greater among the 16 children with baseline resistance (57%) compared to the 99 without resistance (17%).

The investigators suggested these data emphasise the need for better prevention of mother to child transmission strategies including post partum "tail" coverage and maternal HAART. And that prioritisation of resources for mother-infant pairs should be encouraged.

NEVEREST

Several guidelines already recommend using LPV/r-based treatment for single dose NVP-exposed infants.

Louise Kuhn from Colombia University, New York, USA and Ashraf Coovadia from the University of the Witswatersrand, Johannesburg, South Africa, presented findings from the NEVEREST study. NEVEREST is an investigation to see if NVP-exposed children, initially suppressed on LPV/r-based HAART can safely switch to a NVP based regimen.

In this study children 6 weeks to 2 years of age and eligible for treatment (n=323), were initiated on LPV/r plus 3TC and d4T. After achieving a viral load <400 copies/mL and maintaining it for >= 3months, children were randomised (n=195) to either remain on LPV/r (control, n=99) or switch to NVP (switch, n=96), and then followed to 52 weeks post randomisation.

Baseline (pre-treatment) characteristics of the randomised children were mostly similar: median age, 11 months vs. 9 months; median CD4 percentage 19.0% vs. 18.4%; and 57% vs. 54% had a viral load >750,000 copies/mL in the control and switch groups respectively. There was a larger group of younger children age 1-12 months in the switch group, 57.6% vs. 68.8%, but this difference was not significant.

At randomisation the median age of the children were 20 months vs. 19 months; median CD4 percentage 28.9% vs. 28.5% and 61% vs. 66% had a viral load <50 copies/mL in the control and switch groups respectively. The median time on LPV/r based therapy was 9 months in both groups.

Two children in each group died; 3 children in the control and 5 in the switch group were lost to follow up and 3 children in the control and 5 in the switch group started TB treatment.

The investigators reported 80% vs. 86% of children were adherent to the study medication at 36 weeks post randomisation in the control and switch groups respectively.

When the investigators looked at viral load <50 copies/mL to 52 weeks they found 42.4% children in the control group and 56.2% in the switch group sustained viral suppression, p=0.01. But allowing for one elevated result (blip) the two groups were similar, 72.8% vs. 73.4% in the control and switch groups respectively.

They suggested that poorer adherence in the control group, due to the unpleasantness in taste of LPV/r syrup, may have led to more blipping and, in turn, unsustained viral suppression to 50 copies/mL during follow up.

In contrast, when they looked at sustained suppression to <1000 copies/mL, 98% vs. 80% of children in the control and switch groups achieved this, p=0.001.

An analysis of patterns of viral suppression after the children were randomised revealed that of the children >50 copies/mL, 56% in the control group had viral load between 50-1000 copies/mL and the remaining 2% more than 1000 copies/mL. In the switch group more children had viral load more than 1000 copies/mL 20%; but fewer, 24%, were between 50-1000 copies/mL.

In the switch group, viral suppression <50 copies/mL at randomisation was predictive of sustained viral suppression <1000 copies/mL through 52 weeks: 86.1% of children with viral load <50 copies/mL at randomisation sustained viral suppression <1000 copies/mL through 52 weeks vs. 63.5% with viral load 50-400 copies/mL at randomisation, p<0.001.

Likewise, the presence of NNRTI mutations prior to treatment predicted sustained viral suppression after switch: 88% children with no mutations sustained viral load <1000 copies/mL through 52 weeks vs. 55.3% with mutations, p=0.007.

The median CD4 percentage at 24 weeks in the control group was 30.0% vs. 33.2% in the switch group, p<0.0001. In the control group 16.3% of children had a CD4 percentage decline of 10% vs. 3.2% in the switch group, p=0.004. Weight for age declined >1 z-score in 13.1% of children in the control group vs. 4.2% in the switch group, p=0.03.

The investigators wrote that this study provides proof of concept that re-use of NVP is possible under some circumstances for HIV-infected children exposed to NVP prophylaxis and should be further investigated. They note that the clinical significance of low-level viraemia in the control group needs further study. Switching may provide a promising option for children originally initiated on PI-based HAART to preserve second-line options. At this stage, switching requires close virological monitoring after the switch in order to be done safely.

COMMENT

The 1060 results are unsurprising and entirely consistent with the earlier maternal data. Baseline nevirapine resistance and younger age appear to be associated with the performance of the nevirapine arm.

NEVEREST was interesting and this strategy deserves further investigation. Another NEVEREST trial of efavirenz vs lopinavir/r is planned in nevirapine-exposed children >3 years old.

Both studies underscore the limited treatment options that are available for children, particularly in resource limited settings.

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ARV Programme results reports at IAS

Nathan Geffen, TAC

IAS2009 was distinguished by the large number of reports from operational HAART programmes across the world. A search of the conference website using the phrase "ART cohort" returns nearly 170 abstracts, the vast majority of them from resource-poor settings. At least 25 of these report cohorts with more than a 1,000 people in poor countries. And five of these include more than 10,000 people. Many report on children and several now include five-year data. Most report good or reasonable retention rates. Here is a summary of some of the research presented:

- Two Cambodian facilities treating over 1,160 children reported 91% survival at 36 months. Of 4,150 people receiving HAART in these facilities, 86%, 84% and 81% were alive and in care at 2, 3 and 5 years respectively. [1-2]
- In Khayeltisha South Africa, an analysis of 3,595 adults enrolled on HAART over five years showed that the cumulative proportion of patients remaining in care at 54 months was 78%. Early loss to follow-up was higher in women who had been exposed to PMTCT, in patients enrolled later in the programme and in patients initiated on efavirenz. Interestingly, diagnosis of AIDS and lower weight were protective. Increased risk for late loss to follow-up was associated with younger age, exposure to PMTCT and initiation on efavirenz. In a similar study, 87% of children on this programme remained in care after five years. [3-4]
- The Lesotho government's programme, with extensive support from Medecins Sans Frontieres (MSF), reported a 24 month retention rate of 80%. This programme comprises 14 clinics and one hospital. The number of people enrolled is 11,367 (5% children). Of these 4,347 initiated HAART (6.5% children). Interestingly, the programme also uses a three-in-one once-daily tenofovir based generic antiretroviral. [5]
- In a Malawian MSF-assisted programme, over 2,300 adults were followed up for over 1,500 person-years. There were 277 (12%) deaths, 206 (74%) of which occurred during the first three months of HAART. The cumulative mortality rate was 13 per 100 person years. A common theme through many of the IAS treatment cohort reports was early mortality associated with patients presenting with low CD4 counts and advanced disease. The extent to which patients are enrolling late was shown by a study of PEPFAR programmes. This study included PEPFAR cohort-level aggregate indicator data on the median CD4 count at HAART initiation from 248 sites in eight sub-Saharan African countries --Ethiopia, Kenya, Lesotho, Mozambique, Nigeria, Rwanda, South Africa and Tanzania-- where a total of 1,438 cohorts (defined as comprised of patients who initiated HAART at a given site each quarter) representing 103,124 patients initiated HAART. Median baseline CD4 count for all of the cohorts was 135 cells/mm3 (IQR: 109-175). This had increased steadily from 115 to 140 cells/mm3 over the study period. [6-7]
- Solidarmed, a church group running HAART facilities in several countries, reported over 65% retention after 24 months at its facilities in Tanzania, Zimbabwe, Lesotho and Mozambique, comprising over 4,300 patients. [8]
- Absolute Return for Kids (ARK) reported the results of 2,332 children enrolled on HAART at seven rural and 37 urban sites. Patients were divided into (1) urban, (2) rural and (3)

rural attending urban facility. There were 1,727; 228 and 377 people in groups 1, 2 and 3 respectively. After 18 months the probability of death was 3.0% (CI: 2.2-4.1%), 7.7% (CI:4.5-13.0%) and 3.1% (CI:1.7-5.6%) in the groups respectively. Loss to follow-up probabilities were 9.9% (CI: 8.3-11.8%), 5.8% (CI:2.7-12.2%) and 15.0% (CI:11.2-20.0%) respectively. [9]

- In Gugulethu, South Africa of 3,546 people eligible for HAART, 11 (6.5%) children and 442 (13.1%) adults died while waiting for treatment. Death while awaiting HAART initiation is another common theme dealt with in more detail below. An analysis of 2,906 adults and children who started HAART found that virological failure averaged 6.0% per year for children and 3.5% per year for adults. Adult on-treatment mortality was 12.9% at 5 years with 209 of 249 deaths (84%) within the first year. Kaplan-Meier estimates for loss-to-follow-up were 8.5% for children and 16.5% for adults at 3 years. Retention in care at 3 years was 89.3% for children and 74.1% for adults. [10]
- A total of 9,460 HIV-infected children from 11 different cohorts in South Africa, Malawi, Mozambique and Zimbabwe were included in one analysis. Overall, 5,228 (55.3%) were younger than five years. Mortality at one year after initiating HAART ranged from 0.7% to 17.7% in children aged < 5 years and from 0% to 8.9% in children ≥5 years. Overall mortality, including estimating mortality in children lost to follow-up, was calculated to be 8.8% [95%CI: 5.5-12.1. Loss to follow-up ranged from 1.9% to 33.7% (overall 13.3%). [11]
- Paediatric data from the Thai government's National Access to HAART for People Living with HIV/AIDS (NAPHA) programme were presented. This cohort consists of 3,409 treatment-naive children enrolled before January 2006. Median age at baseline was 7 years (IQR: 5-9). Median baseline CD4 was 5% (IQR: 2-13). Weight-for-age z-score was -2.0 (IQR: -2.6 to -1.4). At the end of the follow-up period (median of 1.7 years; IQR: 1-2.5), 9% of children had died, 10% were lost to follow-up (> 9 months since last appointment), 1% had stopped HAART and 80% were still on treatment and in the programme. Of the deaths, 90% were due to AIDS. The overall death rate was 5.2 per 100 person years (95%CI: 4.6-5.8) and the AIDS death rate in the first 90 days was 16.7 per 100 person years (95%CI: 14.0-19.7). The probability of a child surviving to one year was 92.7% (95% CI: 91.7, 93.5) and to five years it was 88% (95%CI: 85.9-89.8). Age, weight-for-age z score, HIV stage, baseline CD4 and attending a community as opposed to a district hospital were significantly associated with mortality. [12]
- In perhaps the oldest programme in the developing world, the São Paulo State STD/ AIDS Program, Brazil, patient records are available from 1985 and treatment, albeit with fewer than three drugs, began in 1991. An analysis of 4,191 people including 14,690 HAART prescriptions showed that by 2005, 70% of patients were still in the programme. There were 518 deaths and 726 people were lost to follow-up. [13]
- A study from Zambia compared a (1) rural government, a (2) rural mission facility and an (3) urban government facility, the latter two sponsored by PEPFAR. The first has more than 300, the second more than 1,100 and the third more than 1,700 patients. Medical records from each facility of the last 150 patients to initiate HAART in 2006 were compared. At 12 months, 67%, 84% and 75% of patients were still in care in facilities 1, 2 and 3 respectively. Despite having the best results, baseline CD4 count was lower in facility 2 (133 vs 117 vs 125 respectively). But the cost of care per patient of facility 2 was also substantially higher than the other two facilities. Cost per 150 patients in the sample were $24,940, $55,721, $35,877 respectively. [14]
- A study of an MSF project in Chiradzulu district Malawi showed the effectiveness of decentralised treatment. From March 2001 to December 2008, over 17,000 people initiated HAART, of whom 70% were followed in decentralised care. In 2003/4 6-month survival was about 84% in both centralised and decentralised care. This rose to about 94% in 2007/8. The percentage of patients with CD4 counts available rose from 53% in 2003/4 to 86% in 2007/8 (rising from 49% to 86% in decentralised and from 56% to 83% in centralised care). In decentralised care, the proportion of patients starting HAART with advanced disease declined over time, from 77% of adults in stage 3 or 4 in 2003/4 to 44% in 2007/8. Similarly for children this declined from 61% in 2003/4 to 42% in 2007/8. [15]
- Osler and colleagues presented consolidated results of the Western Cape HAART programme. The number of sites has risen from 35 in 2004/5 to 78 in 2008/9. The number of patients newly enrolled on HAART were 5,929 in 2004/5, 10,169 in 2005/6, 12,424 in 2006/7, 13,820 in 2007/8 and 20,035 in 2008/9. The number of patients remaining in care were 7,661 in 2004/5, 16,343 in 2005/6, 26,111 in 2006/7, 37,435 in 2007/8 and 54,703 in 2008/9. The proportion of adults starting HAART with a CD4 count < 50 cells/mm3 decreased from 52.9% in 2001 to 16.2% in 2008. Using the Actuarial Society of South Africa's model, this study estimated that coverage had risen from 47% in 2004/5 to 85% in 2008/9.

By 12 months, 9.6% of adults were lost to care. After six years on HAART, 72.4% of ARV-naive adults remained in care. With each year, retention in care continued to improve. By 12 months of treatment on HAART, 5.8% of children were lost to care. After five years, 86.0% of children remain in care. Just under 90% of adults and nearly 80% of children from 6 months to over four years in care were virally suppressed. By four years of HAART just under 10% of both adults and children are on second-line treatment.

Cost per patient dropped from an average of R7,504 in 2005/06 to R5,635 in 2007/08 . In the HAART budget, drugs comprised 40%, personnel 35% and laboratory services 11% of cost. Efavirenz, prescribed to 61% of first-line patients, was the most significant cost driver of HAART expenditure. [16]

Several studies showed problems with some aspects of HAART implementation. They are described here in more depth.

Retention in South Africa: a mixed picture

While the Western Cape data presented by Osler reports high retention, this was not the case for all large South African databases.

Morna Cornell and her colleagues presented data from the IeDEA-SA database, which contained about 10% of South African public sector adult patients from seven large sites by end of 2007. Loss-to-follow-up was defined as last contact greater than six months before the database was closed for the study. The cohort was followed up for another six months following database closure to get an accurate estimate of loss-to-follow-up. Four of the sites are in the Western Cape so many of the

patients in the Osler study above must be in this cohort. [17]

The cohort consists of over 27,000 people, of whom over 18,000 (67%) are female. Median age is 34 years (IQR: 29-40). The number of patients initiated per year were: 1,152 (4% of the cohort) in 2002 and 2003, 4,614 (17%) in 2004, 6,838 (25%) in 2005, 7,669 (28%) in 2006 and 6,936 (25%) in 2007 (for a total of 27,209 patients). The median CD4 count at HAART initiation was 96 (IQR: 39-162). Over 7,000 patients, of the nearly 24,000 who had baseline CD4 data, initiated with a CD4 count less than 50 cells/mm3. Median HIV RNA level at HAART initiation was 4.84 log (IQR: 4.3-5.4) for the approximately 10,500 patients for whom results were available. Over 4,000 (40%) had viral loads > 5 log. WHO staging data was available for over 12,500 patients at HAART initiation. Of these 1,132 (9%) were in stage I, 1,508 (12%) were in stage II, 6,060 (48%) were in stage III and 3,936 (31%) in stage IV.

In each successive year of the programme, median CD4 increased (from 68 in 2002/03 to 104 in 2007), the percentage of stage IV patients decreased (to 27% of all patients by 2007), 12-month mortality improved (until 2006) but 12-month loss to follow-up increased over the same period and 12-month overall retention decreased with time on the programme (see Table 1), so that by four years, only 56% of patients were still in care. In multivariate analysis the decreasing 12-month mortality per calendar year was partially explained by increasing baseline CD4 count. The authors conclude that the increasing loss to follow-up reflects the major challenge of patient retention in large HAART programmes.

Table 1: Mortality, loss to follow-up and overall retention in Cornell et al.

Period on	Mortality % (95% CI)	Loss to follow-up % (95% CI)	Overall retention % (95% CI)
12 months	6.9(6.6-7.1)	14.2(13.8-14.5)	79.9(79.5-80.3)
24 months	9.1(8.8-9.4)	23.9(23.4-24.4)	69.2(68.7-69.7)
36 months	10.5(10.1-10.9)	32.5(31.8-33.1)	60.4(59.8-61.1)
48 months	11.8(11.3-12.3)	37.0(36.2-37.8)	55.6(54.8-56.3)

Long waiting periods

Two disturbing studies from South Africa show the long time that patients have to wait for treatment in the Free State and Kwazulu-Natal provinces and the consequent high mortality.

Margaret May and her colleagues followed, until December 2007, 22,000 patients aged 15 years and older enrolled between May 2004 and December 2006 in the Free State HAART programme. They used the province's HAART data supplemented with National Health Laboratory System CD4 data to determine that over 13,400 (61%) were eligible for HAART (CD4 count <200 cells/mm3). Of these over 3,450 (26%) died while waiting for treatment. The median waiting time to death was 3.1 months (IQR: 1.1-6.9). For those who started treatment, the median waiting time was 3.6 months (IQR: 2.0-6.4). Waiting times varied by a factor of two across districts and were halved in combined assessment and treatment clinics as opposed to when these services were separated. Waiting times were shorter in 2006 than in 2004, also shorter for women (possibly due to HAART referral from PMTCT facilities) and decreased with decreasing CD4 count (p for trend <0.001), but as the authors explain many of the patients with the lowest CD4 counts will drop out of survival analyses because they have died before they have started treatment and this has the potential to bias results. [18]

This data is broadly consistent with a study by Fairall and colleagues published in January 2008 which found that of 4,570 patients followed up for at least one year in the Free State, 53% died. Of these, 87% died before receiving HAART. [19]

Similarly concerning was a study by Ingrid Bassett and colleagues. Their study had two objectives: to evaluate rates of HAART initiation within 12 months of a positive HIV test in Durban, South Africa and to identify baseline factors that predict failure to be on HAART at one year. They examined two pay-for-care semi-private, but government subsidised, facilities in Durban (McCords and Marianhill Hospitals). Their cohort included patients ≥ 18 years in outpatient departments who were English or Zulu speaking. They were enrolled prior to their HIV test. Pregnant women, people on stretchers and people with known HIV-positive status were excluded. Patients were enrolled from November 2006 to October 2008 and followed up through June 2009. [20]

After screening 3,401 patients, 1,467 HIV-positive people met the inclusion criteria for the study (HIV prevalence was 54%). In the final cohort, 54% were female, the median age was 34 years and median follow-up time was 11.4 months. Only 607 (41%) had CD4 counts within 90 days of testing positive. Of these, 368 (61%) were eligible for HAART (CD4 count < 200 cells/mm3). An additional 19 were clinically eligible for HAART. Only 213 (55%) were known to have initiated HAART within 12 months. Median time from CD4 count to ART initiation was 3.5 months (IQR: 2.0-5.5). There were 68 known deaths (18% of the HAART-eligible cohort) of which 52 (76%) occurred prior to starting treatment. Adjusting for age, CD4 count, having work outside home and distance from clinic, patients who did not start treatment were more likely to be male (RR: 1.5; 95%CI: 1.1-2.1) and to not have an HIV-positive family member or friend (RR: 5.1 95%CI: 1.8-14.9).

The authors point out several limitations of their work: the sites may not be representative of public sector hospitals in South Africa, 30% of pre-HAART patients were unreachable and they likely underestimated mortality and HAART initiation that occurred at non-study sites.

Stavudine

Some studies considered the stavudine side-effects on regimen switching and retention. Barbara Castelnuovo and colleagues prospectively followed 559 people who initiated HAART from April 2004 to April 2005 in Kampala, Uganda. At baseline the cohort was 70% female, median age was 38 years (IQR: 33-44), median CD4 count was 98 cells/mm3 (IQR: 21-163) and viral load was 5.4 log (IQR: 5.0-5.8). The primary endpoint was the substitution of at least one drug included in theinitial combination for any reason.

Most of the cohort (413, 74%) were prescribed stavudine, lamivudine and nevirapine as a fixed combination, while the remainder received zidovudine, lamivudine (fixed combination) and efavirenz. [21]

There were 148 (27%) patients with at least one treatment change (incidence rate 14.3 per 100 person years; 95%CI: 12.2-16.9), of

whom 91 changed because of toxicity. Stavudine accounted for 76 (84%) of the treatment changes followed by AZT (10, 11%).

In a multivariate analysis, being male, and treatment with the zidovudine/lamivudine/efavirenz regimen were associated with protection from any drug switches (RR 0.47 [95%CI: 0.30-0.74] and 0.38 [95%CI: 0.23-0.64]), respectively. The analysis was repeated to investigate risk factors for drug switches due to toxicities. Being male and on efavirenz were then found to be the only protective factors.

For the first 18 months, there was no difference between men and women, but drug switching in women increased in the second half of the observation period. There were significantly more women with lactic acidosis (25 versus 10, $p<0.05$) and lipodystrophy (26 versus 0 , $p<0.05$) due to stavudine that led to drug switching.

The authors concluded that the majority of the treatment changes were due to stavudine-related toxicity and that long-term stavudine use is less well tolerated in women. On the positive side, patients that are switched due to toxicity have a similar virologic outcome compared to patients on a stable regimen.

However, for children in a Malawian study, stavudine-containing regimens were relatively well tolerated. Kabue and colleagues from the Baylor College of Medicine reviewed patient records of 1,434 children who initiated HAART using fixed dose stavudine, lamivudine and nevirapine from November 2004 to October 2008. The mean and median ages at HAART initiation were 5 and 3 years respectively. They were followed up for a mean of 1.3 years. The first-line regimen was discontinued by 28 (2%) children due to adverse events (17 nevirapine-related of which 10 rash, 5 Steven Johnson Syndrome and two hepatitis; 11 stavudine-related of which 5 pancreatitis, 4 lactic acidosis and 2 peripheral neuropathy). The median time to an adverse event was two months (IQR: 10 days to 28 months). [22]

COMMENT

These studies show the substantial benefit of HAART in reducing AIDS mortality in developing countries. The Cambodian five-year results are particularly impressive. A number of these studies report improving CD4 counts and earlier stage of disease at initiation. This is possibly related to the decentralisation of HAART services.

However, even better results can be achieved if a number of problems are resolved. The most problematic is the long waiting time between enrollment and initiating HAART. This accounts for far more lives lost than any other shortcoming in programmes, including loss to follow-up after treatment begins, inferior drug regimens, lack of second and third-line regimens and lack of diagnostics. While the data on waiting time is from three South African areas [10, 18. 20], it is implausible that these are unusual either in South Africa or beyond. While most of the studies presented in this article present a positive view of HAART programmes, it is worth investigating if intention-to-treat analyses (ie including all patients who have enrolled in HAART programmes, not only those who have started treatment) would have much worse results.

Long-term patient retention is another challenge. While Morna Cornell's group's data is worrying, it appears to be inconsistent with the high retention of patients in Osler's Western Cape data, even though more than half of Cornell's sites are in the Western Cape. There are several plausible possibilities: the Western Cape programme is probably much better run than other provinces, patients that Cornell's group has counted as lost to follow-up might have transferred to other facilities or –least likely-- the Western Cape provincial data might be inaccurate. More research is needed to answer this.

But more critically, the data that Osler and Cornell have reported should be reported regularly as part of the National Department of Health's monitoring and evaluation of the HAART programme. May and Bassett also both report missing data. This points to the urgent need to improve the monitoring and evaluation of the South African public sector programme, which does not include patients who have died prior to commencing treatment. While the Western Cape programme appears to have sound data, this is not the case in the other provinces. Unfortunately the monitoring and evaluation of the state's programme is very poor currently, although the Department has committed, in a meeting with the newly formed Budget and Expenditure Monitoring Forum, to rectifying this soon.

The stavudine data suggests that while it is the least tolerated of the currently used ARVs, at least in adults, it still has an important role because of its pervasive use and low price. It should be phased out, but gradually and not at the expense of putting new patients onto treatment. Where substitution with tenofovir is possible, it appears that women should be prioritised. The use of 30mg instead of 40mg dosing and lactic acid testing of patients with symptoms of hyperlactatemia in some facilities appear to have made stavudine more manageable, but more data is needed on this. However, as developing country guidelines slowly change to earlier treatment, it will become increasingly important to phase out stavudine.

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TREATMENT ACCESS

Update on unmet need for HAART in South Africa

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In the April/June 2009 issue, we reported Leigh Johnson's presentation to the South African AIDS conference on unmet need for HAART. Johnson and Muhammad Adam have since published their findings in the South African Medical Journal. [1]

The authors conclude, "Significant progress has been made in expanding access to antiretroviral treatment in South Africa since 2004, but a substantial unmet need for treatment in adults remains."

By the middle of 2008, over 560,000 people were receiving HAART, 79% of them in the public sector. Using Department of Health (DOH) criteria (CD4 count < 200 cells/mm3 or WHO stage 4), the authors estimate coverage to have risen from 5% in 2004 to 40% in 2008. But using the Southern African HIV Clinicians Society (SAHCS) guidelines, which provides for treatment at a CD4 count below 350 cells/mm3, coverage is only 22%.

Table 1 provides a breakdown of the number of people on treatment by year, sector and province.

Table 2 provides a breakdown of estimated coverage by year and province according to AIDS sick, DOH initiation criteria and SAHCS initiation criteria.

COMMENT

As explained in the April/June 2009 issue, this excellent analysis must be considered the definitive estimate of coverage for South Africa. Adam and Johnson have provided data that should actually be calculated and published regularly by the DOH, at least for public sector data. There are however several reasons why the situation of having to depend on two independent academic researchers for HAART data is problematic:

(1) The data is over a year old and more current information is needed to assess the HAART rollout. The long-time taken for peer-review and the fact that up-to-date public health data is not easily available to researchers working in universities means this time lag cannot be overcome easily by university researchers.

(2) The authors explain that, "to allow for mortality and loss to follow-up after starting treatment, rates of retention are applied to [DOH] annual numbers of individuals starting therapy." The rates used are based on Western Cape data and a modeling equation is used to estimate the number of people on treatment. The authors have also checked their results against drug sales, but this approach to determining the number of people on treatment is not ideal. Instead each public health HAART facility should maintain an accurate database of the numbers of people who have initiated treatment, continue to be in treatment, lost to follow up and died. Facilities should also maintain records of waiting lists, patients lost to follow

Table 1: Number of people receiving HAART by year, sector and province (from Adam and Johnson).

Description	2001	2002	2003	2004	2005	2006	2007	2008
Cumulatively enrolled in public sector	0	0	0	11,000	66,000	180,000	327,000	539,000
Currently enrolled in:								
– public Sector	0	0	0	9,000	59,000	157,000	278,000	449,000
– NGO programmes	0	0	1,000	4,000	6,000	14,000	23,000	32,000
– disease management and workplace treatment programmes	6,000	15,000	25,000	34,000	44,000	57,000	70,000	86,000
Total currently enrolled	6,000	15,000	26,000	47,000	109,000	229,000	371,000	568,000
Total by province								
Eastern Cape	700	1,700	2,800	5,000	12,100	25,300	41,000	62,000
Free State	400	900	1,500	2,200	4,800	9,500	17,000	28,000
Gauteng	1,500	3,900	6,400	13,600	30,100	60,000	92,000	139,000
Kwazulu-Natal	2,000	5,100	8,500	12,800	29,800	65,000	107,000	167,000
Limpopo	300	700	1,200	1,900	4,600	11,500	20,000	34,000
Mpumalanga	500	1,200	2,000	3,100	5,600	11,900	23,000	37,000
Northern Cape	100	100	200	400	1,500	3,200	6,000	10,000
North West	400	1,000	1,600	2,600	8,500	20,500	33,000	46,000
Western Cape	300	800	1,600	5,700	12,000	21,600	31,000	45,000

Figures are rounded to the nearest 1 000, except in the case of the pre-2007 provincial estimates, which are rounded to the nearest 100. All estimates relate to the middle of the specified calendar year.

up or death before initiating treatment, baseline CD4 counts and six-monthly CD4 counts. Then this information should be collated nationally and published regularly. Instead the DOH occasionally makes available a report of the number of people on treatment. This reliability of this report is questionable. It contains very little detail and it is unclear that it has been properly calculated based on accurate clinic data. It mixes data from provinces that track the cumulative number of people initiating treatment with data from provinces that track number of people retained on treatment.

(3) It is difficult to track progress towards the HIV/AIDS National Strategic Plan (NSP) treatment target of initiating nearly 1.4 million adults and over 150,000 children on HAART from 2007 to 2011 without regular accurate and current data published by the DOH.

The DOH is aware of these problems and has informed members of the newly formed Budget and Expenditure Monitoring Forum that it is taking steps to obtain accurate monitoring and evaluation information.

While substantial progress providing HAART has been made, even by the most modest criterion, ie AIDS sick, only half of patients were receiving treatment by mid-2008. And by the most appropriate criteria, ie the SAHCS guidelines, not even a quarter of patients are receiving HAART. To compound matters, since mid-2008 the final date for when the data for this study was calculated, many problems with the public sector HAART implementation have

Table 2: Estimated HAART coverage (%) by year and province (from Adam and Johnson).

National	AIDS sick	DOH	SAHCS
2001	1.9	1.0	0.5
2002	3.9	2.1	1.0
2003	5.6	3.0	1.5
2004	8.8	4.9	2.4
2005	17.1	10.0	5.1
2006	30.1	19.1	10.0
2007	41.6	28.3	15.2
2008	54.2	40.2	22.2
2008 estimates by province			
Eastern Cape	46.4	32.4	17.5
Free State	38.4	25.8	14.2
Gauteng	57.6	43.5	24.0
Kwazulu-Natal	53.3	39.4	22.1
Limpopo	45.9	32.2	17.4
Mpumalanga	44.6	31.2	17.3
Northern Cape	72.5	61.1	33.3
North West	49.6	35.4	19.6
Western Cape	80.9	71.7	39.9

All estimates relate to the middle of the specified calendar year.

surfaced, the salient example being the Free State Department of Health's moratorium from late 2008 until February 2009 on initiating new patients on treatment. The SAHCS estimated that caused 30 people to die a day.

Reference

Adam MA et al. Estimation of adult antiretroviral treatment coverage in South Africa. September 2009, Vol. 99, No. 9 SAMJ.

FDA approval of generic ARVs

Since the last issue of HTB, the US Food and Drug Administration (FDA) has granted tentative approval for the following new generic ARV products.

Drug and formulation	Manufacturer, Country	Approval date
Efavirenz tablets 50, 100 and 200 mg tablets	Matrix, India	24 November 2009
Lopinavir/ritonavir tablets 200/50mg	Cipla, India	20 November 2009
3TC/tenofovir DF 300/300mg Fixed Dose Combination (FDC)	Hetero, India	05 November 2009

"Tentative Approval" means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, but because of existing patents and/or exclusivity rights, it cannot yet be marketed in the United States. Tentative approval does, however make the product eligible for consideration for purchase under the PEPFAR program for use outside the United States.

Effective patent dates are listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:
http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm

COMMENT

This brings the total of FDA approved generic drugs and formulations to 104 since the programme started. An updated list of generic tentative approvals is available on the FDA website:

http://www.fda.gov/oia/pepfar.htm

Source: FDA list serve:

http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm122951.htm

AIDS and mortality in South Africa

Nathan Geffen, aidstruth

On 2 November 2009, Statistics South Africa released the latest mortality data, which goes up to 2007 (Stats SA, 2009), detailed in Table 1. [1]

You do not need to be a statistician to be astounded by this. Recorded deaths have increased over 90% in a decade. Improved death registration and population growth can account for only a small portion of this increase. The vast majority of additional deaths are due to the HIV epidemic. A huge body of evidence shows this. For example, there has been a three-fold increase in TB deaths over the same period and TB is the leading cause of death in people with HIV. Also the age pattern of the deaths -younger instead of older adults comprise the bulk of them - and the drop in the median age of death from 51 in 1997 to 44 in 2007 are consistent with the way AIDS works. [2, 3, 4]

Table 1: Number of recorded annual deaths and people on treatment

Year	Number of recorded deaths by Stats SA [1]	No people on treatment [5]
1997	317,131	`
1998	365,852	`
1999	381,820	`
2000	415,983	`
2001	454,847	6,000
2002	502,031	15,000
2003	556,769	26,000
2004	576,700	47,000
2005	598,054	109000
2006	612,462	229,000
2007	601,033	371,000
2008	-	568,000

Also noticeable is that the number of deaths appears to have stabilised from 2005 to 2007 and perhaps has even begun to decrease slightly. This is most likely due to the state's antiretroviral (ARV) treatment programme. Unfortunately because the public sector programme has not been well monitored and there are numerous treatment providers in the private sector, there is not accurate data on the number of people on treatment. But by using several sources of data, including figures published by the Department of Health, medical aid data and public sector ARV procurement data it is possible to make reasonable estimates. Muhammad Aarif Adam of Sanlam and Leigh Johnson of the Centre for Actuarial Research have made plausible calculations of the number of people on treatment in the middle of each year up until mid-2008, shown also in Table 1. [5]

The programme began in earnest in 2004 and the stabilisation of the death rate has coincided with it. If you consider that many, perhaps most, of the people on the programme would be dead by now that would easily account for stemming rising deaths. Make no mistake; there has been a massive surge in deaths in South Africa for more than a decade and AIDS deaths continue to be very high; deaths might have stabilised but at a very high number. Life-expectancy declined to the low-50s. At least though, we are implementing the most effective known scientific medical intervention to mitigate the effects of the disease and it now appears that life-expectancy is increasing again.

But many unnecessary deaths occurred because of the delayed roll out of the ARV treatment programme. Two studies have conservatively estimated that former President Thabo Mbeki's AIDS denialist policies cost well over 300,000 lives. [6, 7]

Mbeki did not pursue this deadly policy without help though. Officials in government, civil servants and even some journalists supported his policy, tried to give it legitimacy and for a time succeeded in quashing the demand for a treatment rollout from health workers and AIDS activist organisations, like the Treatment

Action Campaign (TAC). Thankfully, we have moved beyond this awful era of South African history.

In the last two weeks have seen what I believe is the final death-knell of state-supported AIDS denialism. Both President Zuma and Minister of Health Motsoaledi have delivered important speeches showing their intention to fight the epidemic. On page 35 of his presentation Motsoaledi quoted mortality data for 2008 from Home Affairs which appears to be far too large. I am unaware of how this number was derived and it appears to be an error. In other respects Motsoaledi's speech was excellent and his mistake is of no great importance.

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Source: www.aidstruth.org (16 November 2009).
http://www.aidstruth.org/features/2009/aids-and-mortality-south-africa

Punishing success in tackling AIDS: funders' retreat could wipe out health gains in HIV affected countries

MSF press release

A retreat from international funding commitments for AIDS threatens to undermine the dramatic gains made in reducing AIDS-related illness and death in recent years, according to a new report by Médecins Sans Frontières (MSF). [1]

The report expresses concern that the international community is backing off of commitments to support universal access targets and point to a number of troubling signs including:

- The funding problems of the Global Fund to Fight AIDS, TB, and Malaria (GFATM). The funding shortfalls led to substantial cuts in Round 8 approved proposals (10% in Phase 1, and 25% in Phase 2) and may lead to additional cuts on Round 9 approved proposals. Also, we are very concerned that the Board of Directors of the GFATM may approve a resolution being tabled to delay Round 10 until 2011, again because of lack of funds.
- The flatlining of the US government's budget for PEPFAR in 2010 and 2011 and caps on new patients on ART, as well as anxiety and mixed messages leading to capping enrollment in Uganda.
- The changes in the donor landscape including Netherlands, the third largest donor through bilateral channels, is cutting its aid by 30%, and the UK which had led the campaign to support universal access to treatment at the G8 Summit 2005 providing less money to support scale-up.
- The dangerous trends in the global policy arena where detractors of AIDS funding are calling for a diversion of HIV/AIDS funds for other health issues, rather than building upon the success of the mobilisation of resources for AIDS by insisting that global health, of which HIV is a part, be adequately supported.

It also points to the progress of the last years, especially in South Africa and Malawi, of scaling-up ART and the resulting impact in reducing mortality and morbidity and warn that unless sustained and increased funding for HIV/AIDS is provided – by national governments as well as donors – we risk punishing the success of the last years.

The MSF report highlights how expanding access to HIV treatment has not only saved the lives of people with AIDS but has been central to reducing overall mortality in a number of high HIV burden countries in southern Africa in recent years. In Malawi and South Africa, MSF observed very significant decreases in overall mortality in areas where antiretroviral therapy (ART) coverage was high. Increased treatment coverage has also had an impact on the burden of other diseases, for example tuberculosis cases have been significantly reduced in Thyolo, Malawi and Western Cape province, South Africa.

International support to combat HIV/AIDS is faltering as reflected in significant funding shortfalls. The board of directors of the Global Fund, a key financer of AIDS programmes in poor countries is unable to respond to countries' needs and will next week in Addis Ababa vote whether or not to suspend all new funding proposals in 2010; and PEPFAR, the US AIDS programme is flatlining funding for two more years.

The report provides evidence that, particularly in high HIV-prevalence settings, treating AIDS has a positive impact on other important health goals, in particular maternal and child health.

At present, over four million people living with HIV/AIDS in the developing world receive antiretroviral therapy. An estimated six million people who are in need of life-saving treatment, are still waiting for access. MSF operates HIV/AIDS programmes in around 30 countries and provides antiretroviral treatment to more than 140,000 HIV-positive adults and children.

Source: MSF Press release: "Punishing success in tackling AIDS: Funders' retreat could wipe out health gains in HIV affected countries". (5 November 2009).

Download PDF report:

http://www.msf.org.za/punishing_success.pdf

RESISTANCE

Rate of accumulation of TAMS slow in patients continuing on failing AZT or d4T containing regimens

Polly Clayden, HIV i-Base

First line regimens in resource limited settings (RLS) – as currently recommended by WHO - are usually two nucleosides, 3TC plus a thymidine analogue (TA) either d4T or AZT, and one NNRTI.

Most programmes have limited access to virological monitoring and genotype resistance testing. Because of this most treatment switches are based on clinical or immunological failure.

A considerable number of patients are expected to receive failing TA containing regimens for extended periods before switching to second line. Since the nucleoside drugs in second line regimens may be compromised by presence of TA mutations (TAMS), there is concern over the consequences of accumulation of TAMS before switching.

Alessandro Cozzi-Lepri and investigators for the EuroSIDA Study Group used European cohort data to estimate the rate and predictors of accumulation of TA mutations (TAMS) in patients who continue to receive failing regimens. In an article published in the 1 September 2009 issue of the Journal of Infectious Diseases they report lower than anticipated accumulation of TAMs in patients experiencing virological failure.

The investigators analysed data from patients in the EuroSIDA study who experienced virological failure (defined as first viral load >=500 copies/mL after >=6 months), with >= 2 genotype resistance tests (GRTs) while receiving the same TA-containing regimen, with a viral load of >500 copies at both. The time of the first genotype test results in a pair was defined as t0, the date of the very first genotype used in the analysis as baseline-t0.

In this analysis, the majority (87%) of genotype results were obtained retrospectively from stored samples.

The rate of TAM accumulation was calculated as the number of TAMs detected at t1 that were not present at t0 divided by the interval between t0 and t1. The investigators used a multivariate Poisson regression model to identify independent predictors of TAM accumulation.

They also simulated a scenario in which all patients studied were switched to a WHO recommended second line nucleosides (eg AZT+ddI or ABC+ddI) after the extended period on failing TA-containing HAART. This was used to estimate the decrease in susceptibility of subsequent regimens due the accumulation of TAMs.

The study population of 339 patients provided 603 pairs of GRTs. At t0 their median age was 39 years and 14% were female. Of this group 67% had one pair of GRTs; 18% had two; 6% had 3 and 9% more than three pairs of GRTs. Their median viral load was 4.11 log copies/mL and CD4 244 cells/mm3. They were very treatment experienced, 53% had failed 1-3 drugs before baseline t-0 and the remainder 4 or more drugs; 35% had failed an NNRTI and 72% a PI.

During the interval t0-t1 (median 6 months, range 1-89 months) the investigators reported the patients having very stable viral loads (mean absolute change +0.03 log copies/mL, 95% CI -0.3 to +0.09, p=0.29) and CD4 counts (mean absolute change -5.74 cells/mm3, 95% CI -2.52 to +14, p=0.17).

Over t0-t1 all patients were receiving either AZT or d4T, which they received for a median of 9 and 15 months duration respectively from virological failure to t1. Twenty-nine percent received an AZT-containing regimen (176 pairs) and 71% a d4T-containing regimen (427 pairs). Besides the TA, the majority (70%) of patients were receiving 3TC at t0. Other frequently used nucleosides were ddI (25%) and abacavir (18%). The most common NNRTIs were NVP (34%), EFV (18%), but some patients were also receiving PIs, NFV (19%), IDV (26%) and LPV (9%). The investigators noted frequent switching in the drugs besides the TA between t0 and t1. In 478 (79%) patients, more than 1 drug used at t0 was no longer used at t1.

At t0, 90% of the study population had at least one TAM and a median of 3 (range 0-6). Of these 81% had TAM profile 1 (TAM1) – 41L, 210W and 215F mutations, and 62% TAM profile 2 (TAM2) – 67N, 70R and 219EQ; 65% had 41L and 68% 215Y TAM1 mutations and 52% 67N TAM2 mutations.

At t1 93% had at least one new TAM. The investigators noted that he rate of accumulation of TAM1 mutations was twice as fast as that of TAM2.

Between t0 and t1, 126 additional TAMs were accumulated during 548 patient years of follow up (PYFU), which the investigators estimated to give a rate of 0.23 per year (95% CI 0.20-0.27) or, in other words, 1 in 4.3 years (95% CI 3.7-5.0).

The rate was faster (0.3 per year) in the subset (330 pairs) with 0-3 TAMs at t0 and was slower, with a rate of 0.11 per year in the patients who already had 4-5 TAMs at baseline (245 pairs).

Using the Rega IS and the ANRS systems the investigators predicted the response to subsequent WHO recommended nucleoside pairs. Both systems appeared to show that regimens containing tenofovir (particularly with 3TC) were likely to have the greatest activity at t0 and the least reduction in activity t0-t1. These predictions however depend on the accuracy of current expert knowledge regarding which mutations may reduce susceptibility to tenofovir.

When they looked at predictors of TAM accumulation, they found that also greater susceptibility to non thymidine analogues in the failing regimen was associated with faster accumulation of TAMs (50% faster per additional active drug, RR 1.5 [95% CI,1.05-2.14], p=0.02).

Other predictive factors were acquisition of HIV through heterosexual contact (vs homosexual almost 2-fold difference in rate RR1.89 [95%CI 1.01-3.57] p=0.05) and TAM2 profiles at t0 (vs TAM1, 87% faster, RR 1.87 [95% CI 1.06-3.27], p=0.03). NNRTI+PI or PI based regimens at t0 were associated with slower accumulation of TAMs (RR 0.32 [95% CI, 0.12-0.84], p=0.02).

The investigators concluded that their data suggest, “In patients who continue to receive TA-based, virologically failing regimens, the rate of accumulation of TAMS is relatively slow, on average, though the higher the initial predicted activity of the regimen, the faster the rate at which TAMs accumulate. Nucleoside pairs including tenofovir, although expensive, seem more likely to be active against viruses harbouring TAMs and also to experience

the highest drop of activity in the face of TAM accumulation. Additional research in this area is needed to inform programme planning in RLS."

COMMENT

That two distinct pathways of TAMs can emerge under pressure of TA-containing HAART that is not fully suppressive is well described. TAM 1 has been associated with high-level resistance to AZT and most other NRTIs, including tenofovir and abacavir and TAM2 with lower levels of resistance to TDF and other NRTIs.

The finding that the rate of emergence of TAMs was slower than expected in this estimation by Cozzi-Lepri and colleagues is reassuring for programmes with limited access to monitoring and, alongside DART results, will make a big contribution to ongoing discussions about "What to measure?" "How often?" and "What are the consequences?"

The authors note that only 9% of their patients had non-B subtypes and that 24% were receiving WHO recommended first line regimens, which could limit the extent to which their results might be generalisable to patients in RLS. However, they suggest that the similarities between their estimation and that observed in RLS may make this bias negligible. They also were not able to establish an explanation why patients in EuroSIDA were left on failing regimens from these data, and so could not rule out selection bias.

While the average rate accumulation of TAMs is relatively slow and suggests a public health approach would be good, there still needs to be work on identifying why some patients do fail fast. Is it a function of the virus? The drug selection? Genes? What monitoring is needed to catch the small percentage of patients that don't respond?

While the average rate accumulation of TAMs is relatively slow and suggests a public health approach would be good, there still needs to be work on identifying why some patients fail more rapidly and what monitoring is needed to catch the small percentage of patients that don't respond?

One of the main predictors of faster accumulation suggested by this analysis (and others) was a function of the virus and drug selection. For example, the greater the amount of resistance already accumulated at the time of failure the slower the rate of accumulation of additional mutations.

And, as the authors stress "all possible efforts should be continued to increase the availability of drug options in RLS."

Ref: Cozzi-Lepri A et al. Rate of accumulation of thymidine analogue mutations in patients continuing to receive virologically failing regimens containing zidovudine or stavudine: implications for antiretroviral therapy programs in resource limited settings. J Infectious Dis 200: 687-97, 1 September 2009.

ANTIRETROVIRALS

GSK and Pfizer launch joint HIV collaboration

Following the initial announcement in April 2009 of a collaboration between GlaxoSmithKline and Pfizer's to create a new specialist company dedicated to HIV, called ViiV Healthcare was launched on 3 November 2009. GSK holds an 85% interest in ViiV Healthcare and Pfizer holds 15%.

ViiV Healthcare has 10 licensed medicines which generated £1.6 billion in 2008 and a pipeline of seven investigative compounds, including five in phase II development and 10 other potential molecules to develop new HIV treatments.

GSK previous Positive Action programme will be at the core of ViiV Healthcare's partnership programmes, supporting local communities impacted by HIV/AIDS globally.

The ViiV web site provides an overview of the new company and its current activities, including Positive Action and Community Partnerships, the R&D pipeline, initiatives to improve access, and corporate governance:

Source: Company Press Release: "ViiV Healthcare - a global specialist HIV company established by GlaxoSmithKline and Pfizer to deliver advances in treatment and care for people living with HIV". (3 November 2009).
http://www.viivhealthcare.com

BASIC SCIENCE

Recent basic science updates from Richard Jefferys excellent web log.

Aging, HIV infection and the immune system

Richard Jeffreys, TAG

In the November 9th issue of New York Magazine, David France reports on the emerging issue of accelerated aging in people with HIV infection. The article offers a series of disturbing vignettes about the complications some individuals are facing as they age, such as bone problems and impaired cognitive function, and raises important questions about how much attention is being paid to the issue by current research, particularly in terms of pursuing new therapeutic options. [1]

However, beyond mentioning inflammation, the piece does not really delve into the underlying immunological parallels between HIV infection and aging and consider how they might fit into the picture. This is a potentially important omission, as there is accumulating evidence that the accelerated aging of the immune system that has been documented in people with HIV is likely to be related to many of the clinical phenomena described in France's article.

Although it's not the sort of research that makes the front pages, the last decade or so has seen considerable progress in understanding the relationship between immune parameters and aging, and these studies provide a valuable frame of reference. Perhaps most importantly, an "immune risk phenotype" associated with mortality in the elderly has been described in considerable detail. [2]

The major features are an inverted CD4/CD8 T cell ratio, decreased proliferative responses and IL-2 production by T cells, increased levels of inflammatory cytokines (such as IL-6) and increased numbers of CD8 T cells lacking the CD28 co-stimulatory receptor (typically described as senescent cells). All of these immunological perturbations are also seen in HIV infection.

Studies have also found that people with the chronic viral infections cytomegalovirus (CMV) and Epstein-Barr virus (EBV) face a greater likelihood of acquiring the immune risk phenotype in old age. The clinical manifestations associated with the phenotype include bone loss and increased fracture risk, cognitive impairment, increased susceptibility to infections and an increased incidence of cancers and cardiovascular, kidney and liver disease.

The overarching theme that is emerging from this research – although it is still in its infancy - is that a lifetime of antigenic challenges (in the form of all the pathogens an individual is exposed to) gradually erodes immune system resources, and this plays a major role in aging. This erosion of immune system resources has multiple facets:

- A steady decline in naive T cell production by the thymus from a torrent in childhood to a trickle in old age.
- Activation of antigen-specific naive T cells every time a new pathogen is encountered, which depletes the naive T cell pool and leads to a subset of these pathogen-specific cells maturing into memory cells (the impact of these episodes of naive T cell activation is minor when the thymus is vigorously producing new cells to replace those lost, but increases as thymic output declines).
- Repeated stimulation of memory T cells by pathogens, which can eventually lead to memory T cell senescence.

Chronic pathogens (that are controlled rather than cleared) play a particularly important role because they place a persistent drain on immune system resources, as indicated by the way that memory T cell responses to CMV accumulate over time, such that 25-30% of CD8 T cells can be CMV-specific in an infected elderly person. Untreated HIV infection has an even greater effect; a young individual with AIDS typically will have lost almost all their naive T cells and 20-50% of their memory CD8 T cells will be HIV-specific. As shown recently in a study of the MACS cohort, a fast accumulation of senescent CD8 T cells lacking the CD28 molecule is associated with rapid progression from HIV infection to AIDS. [3]

Additional insight into how immunological aging relates to health may come from people who have had their thymus removed (a thymectomy) at birth. This procedure is sometimes performed to enable better access to the heart to correct congenital heart defects. A recent study published in the Journal of Clinical Investigation reported that thymectomised individuals show evidence of accelerated aging of the immune system similar to the immune risk phenotype, but it is not yet known whether this will lead to the same clinical manifestations seen in the elderly. [4] Continued follow-up will be crucial to gaining a better understanding of the relationship between the immunological and clinical consequences of aging.

In terms of HIV infection, the issue of accelerated aging raises many new questions and considerations for future research:

- Is immunology research in HIV adequately prioritised? The main clinical research network in the US, the AIDS Clinical Trials Group (ACTG), once had a specific immunology research committee but it was dissolved a few years ago and squished into a broader committee designated "Translational Research and Drug Development" (TRADD). There may be a case for re-establishing a specific immunology committee within the network.
- Do current research funding mechanisms offer adequate support for multidisciplinary and translational research? The spectrum of clinical manifestations associated with accelerated aging calls for collaborative research between groups specialising in many different disciplines (e.g. immunology, virology, pharmacology, toxicology, musculoskeletal system, cardiovascular, renal, liver, etc.), and support for this type of complex collaboration may call for the design of a specific funding mechanism (RFA). Exploration of novel therapies also requires support for conducting translational clinical research, which can be difficult and complicated to obtain under current grant procedures.
- Will earlier initiation of antiretroviral therapy prevent accelerated aging? Long term follow-up from studies such as ACTG 384 clearly show that earlier suppression of HIV is associated with an almost complete normalization of many potentially important immune parameters including the CD4/CD8 T cell ratio, the ratio of naive T cells to memory T cells

and levels of immune activation. [4] In contrast, among individuals initiating therapy at lower CD4 T cell counts, these parameters improve but do not come close to mirroring those of uninfected individuals even after seven or more of continuous HIV suppression. This may suggest that people who start treatment earlier will be at less risk for accelerated aging, but this has not yet been established.

- To what extent do drug toxicities contribute to accelerated aging? The fact that there are many close parallels between the immunology of HIV infection and aging argues strongly against drug toxicity being the primary cause, but there are clearly specific toxicities that can contribute to problems such as bone loss and cardiovascular disease. Research needs to parse out the role of drug toxicities so that safer treatments can be developed.
- Can novel therapies be developed to delay or reverse accelerated aging? The current data suggest a number of key targets for therapeutic research, including: enhancing thymic function to boost naive T cell production, reducing immune activation/inflammation and reducing numbers of senescent immune cells. Research is ongoing in these and other areas but greater resources, coordination and prioritization is needed.

TAG's Hepatitis Coinfection Project and Michael Palm Project are currently collaborating with several other community activists, including HIV i-Base, to produce a comprehensive report and advocacy recommendations on HIV and aging. The report will be released next year prior to the International AIDS Conference.

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New neutralising antibodies discovered

Richard Jefferys, TAG

A paper just published online by Science Express reports the discovery of two new antibodies capable of neutralising a broad array of diverse HIV strains. The antibodies interact with a novel conserved region of the virus envelope that is different from the sites targeted by previously described neutralising antibodies.

The research represents the first fruits of a major undertaking initiated by the International AIDS Vaccine Initiative (IAVI) in collaboration with the Scripps Institute, the Bill & Melinda Gates Foundation, Monogram Biosciences, Theraclone Sciences, a slew of scientists and over 1,800 HIV-positive volunteers who donated blood. Perhaps in keeping with the view of some skeptics that the design of an antibody-based HIV vaccine may be a mission impossible, the project goes by the espionage-invoking name of "Protocol G."

The first inkling of progress came in a paper published a couple of months ago in the Journal of Virology, which appeared with little fanfare (abstract link below). A group of scientists led by Melissa Simek at IAVI described the identification of several plasma samples with broad neutralising activity using a new "high throughput" neutralisation assay developed by Monogram Biosciences. The assay measures the ability of antibodies to neutralise a panel of "pseudoviruses" that are capable of just a single round of infection. The pseudoviruses consist of a clone of the HIV genome containing a firefly luciferase gene that emits light, into which different envelope genes from primary HIV isolates are inserted. The extent to which antibodies (or plasma samples containing antibodies) prevent the various pseudoviruses from infecting susceptible target cells is measured by quantifying the amount of light emitted by the cells.

A total of 1,798 samples from HIV-positive individuals in Australia, UK, Rwanda, Kenya, Uganda, Zambia, Ivory Coast, Thailand, South Africa and the US were evaluated in the initial study. Around 1% of the samples were found to have broad neutralising activity against a panel of pseudoviruses containing envelopes from multiple different HIV isolates from clades A, B, C, D and several circulating recombinant forms including CRF01-AE.

The new Science paper focuses on just one African individual whose plasma sample was among those capable of broad neutralisation. In order to find the antibodies that were responsible for the activity, the researchers had to go fishing for the B cells that were producing them. This daunting task involved the careful characterisation of 30,300 B cells, which were spread across 23,328 tiny "wells" in lab dishes such that each well had just 1-2 (average 1.3) B cells in it. The B cells were given eight days to pump their antibodies into the wells, then the antibodies were taken from each and tested to see whether they bound to immobilised HIV envelope proteins (gp120 or gp41) or were able to neutralise pseudoviruses in the Monogram Biosciences assay described previously.

When the wells containing antibodies capable of the broadest and most potent neutralisation were identified, the researchers extracted the antibody-encoding sections of DNA from the B cells. The process requires extraction of two sections of B cell DNA, one responsible for producing a part of the antibody called the light chain and the other for the part of the antibody called the heavy chain. The isolated DNA sections were inserted into a laboratory cell line (293 cells) which then started churning

out the antibodies encoded by the DNA, allowing researchers to figure out which DNA code was making the antibodies they were looking for by testing the antibodies for neutralisation in the Monogram assay. For the wells that contained more than one B cell, multiple light and heavy chain DNA sections were extracted and inserted into 293 cells in all possible combinations, facilitating the identification of the light/heavy chain DNA combination responsible for making the antibody of interest.

The ultimate result of this staggering amount of work was the identification of two antibodies, named PG9 and PG16, with broad and potent neutralising activity. PG9 neutralised 127 out of a panel of 162 pseudoviruses containing a diverse range of HIV envelopes and PG16 neutralised 119 pseudoviruses out of the same panel. The potency of neutralisation often exceeded that of the four known broadly neutralising antibodies that were used as controls (b12, 2G12, 2F5, and 4E10), meaning that lower concentrations of PG9 and PG16 could mediate equally strong neutralisation.

While PG9 and PG16 were very effective in the neutralisation assay, they did not efficiently bind to the immobilised HIV envelope proteins that were used as part of the screening process. The researchers conclude that this is because the individual proteins do not maintain the same shape or conformation that they have when present on an intact virus, where they combine in triplicate to form what is called an envelope trimer.

The discovery of PG9 and PG16 may be important for several reasons.

It offers compelling validation of the Protocol G approach to seeking effective new antibodies, and suggests that many more are likely to be discovered. The work has been described as a "tour de force," and that almost seems like an understatement.

The results indicate that although HIV's envelope is notoriously mutable, there are conserved regions of the trimer that are susceptible to antibody attack.

The potency of neutralisation suggests that if a vaccine could induce similar antibodies, they could be protective against HIV infection at concentrations known to be achievable with vaccination.

There are potential caveats however. It is unclear whether the relatively rare detection of broadly neutralising antibodies is related to specific genetic traits of the individuals they have been isolated from. If B cells from most people are not capable of making similar antibodies, then the applicability to vaccination will be limited. Researchers have also long been attempting to build mimics of HIV's native envelope trimer, and it has proven to be a considerable challenge; results to date are reminiscent of trying to bake a soufflé, only to have it collapse within moments of removing it from the oven. Nevertheless, the discovery of PG9 and PG16 is likely to send scientists working on the problem scurrying back into the kitchen.

Source: TAG Basic Science web log (04 September 09)

http://tagbasicscienceproject.typepad.com

Ref: Walker LM et al. Broad and potent neutralising antibodies from an African donor reveal a new HIV-1 vaccine target. Science, doi: 10.1126/science.1178746. Published online 3 September 2009.

http://www.sciencemag.org/cgi/content/abstract/1178746

The end of the line for IL-2

Richard Jeffreys, TAG

Results from two large randomised studies of interleukin-2 (IL-2) have been published in the New England Journal of Medicine. The data were first presented earlier this year at CROI in Montreal. The trials were SILCAAT, which enrolled 1,695 people with CD4 counts between 50 and 299, and ESPRIT, which enrolled 4,111 people with CD4 counts over 300. In neither case did the addition of IL-2 offer any clinical benefits compared to antiretroviral therapy alone, despite increasing CD4 T cell counts. The results indicate that expanding CD4 T cell numbers with IL-2 does not confer added benefit beyond the increase in CD4 T cells caused by suppression of HIV replication. The researchers note that CD4 T cells induced by signaling through the IL-2 pathway may be functionally compromised and/or have a phenotype (e.g. suppressive) or specificity that is not clinically beneficial. An alternative or overlapping explanation is that the increased rate of adverse events associated with receipt of IL-2 counterbalanced any benefit from CD4 increases.

Although the results have been seen as a blow to immune-based therapy (IBT) development in HIV, they do not necessarily mean that other approaches to increasing CD4 T cell numbers (such as IL-7 or growth hormones) will suffer the same fate. The outcomes of SILCAAT and ESPRIT do however stress the need to evaluate IBTs for clinical benefit. As there are individuals who experience poor CD4 T cell reconstitution despite HIV suppression (sometimes called discordant responders) who remain at increased risk for illness, there is still a potential need for IBTs. Trials evaluating the clinical benefit of newer IBTs in this population should be feasible and would not necessarily require the large numbers involved in SILCAAT and ESPRIT.

Source: TAG Basic Science Blog (21 Oct 2009)

http://tagbasicscienceproject.typepad.com

Ref: INSIGHT–ESPRIT Study Group and SILCAAT Scientific Committee. Interleukin-2 therapy in patients with HIV infection. New England Journal of Medicine, Volume 361:1548-1559, October 15, 2009, Number 16.

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MATERNAL HEALTH

South African 2008 antenatal survey results

Nathan Geffen, TAC

The South African Department of Health released the 2008 antenatal survey results in October 2009, later than usual. Nevertheless substantial improvements on last year's report made up for the delay. The survey found that HIV prevalence in pregnant women aged 15 to 49 using public antenatal facilities is 29.3% (95% CI: 28.5%-30.1%). This is statistically unchanged from the 2007 survey which calculated a prevalence of 29.4% (95% CI: 28.5-30.1). [1]

Just under 34,000 women at about 1,450 facilities in all 52 health districts were anonymously tested for HIV and syphilis, a sample size almost identical to the 2007 survey. The survey sample size has increased dramatically in recent years; in 2005 only 16,500 people in just under 340 clinics were sampled. About 130 samples were excluded because of missing data. Testing was unlinked and carried out using an ELISA assay (Abbot Axsym System for HIV-1 and HIV-2). Active syphilis was screened using a rapid plasma reagin test.

Incorrect estimates of 2007 antenatal survey corrected

The presentation of the survey is much improved. It provides a breakdown of prevalence at national, provincial and district levels (as it did last year). It also provides details of district prevalence for 2007 and 2006 making comparison relatively easy. Critically, it corrects a problem from last year's survey raised by Dorrington and Bourne in a letter to the South African Medical Journal (SAMJ). [2]

The problem was as follows: In 2007 survey age weights were introduced, so that the age profile of the weighted sample would match that of the general female population, not the population of pregnant women. Pregnant women have a different age profile from that of women in the general population, and since the antenatal survey is a survey of pregnant women, it is illogical to introduce age weights to match the general population. Furthermore, the Department of Health did not explain that they had changed the weights, so it was not apparent that the reduction in prevalence was actually due to the introduction of the age weights.

Consequently the 2007 provincial and national estimates were wrong. As Dorrington and Bourne pointed out, the survey stated, "South Africa may be making some real progress in its response to the HIV epidemic" and the "South African HIV epidemic is on a downward trend", even though it provided no evidence to support this because its comparison with data from previous surveys was invalidated by the incorrect calculation of the 2007 survey prevalence.

In December 2008 Dorrington and Bourne published another letter with corrected calculations of the provincial and national prevalence rates. The corrected prevalence was higher; while the survey reported a national prevalence of 28%, Dorrington and Bourne calculated that it was 29.4% up from 29.1% reported in 2006. This debunked the notion that there was evidence from the antenatal survey that HIV prevalence was "on a downward trend." [3]

The publication of the first Dorrington and Bourne letter coincided with the appointment of Barbara Hogan as health minister, replacing Manto Tshabalala-Msimang. Dorrington and Bourne's concerns were taken seriously and there was a commitment to correct the antenatal report. This was done by publishing the corrected calculations for the 2007 survey in this year's report.

Main results

Table 1 lists HIV and syphilis prevalence by province and nationally for 2008 and 2007.

Table 2 provides a breakdown by age group of HIV infection. Note that 138 people under 15 and five people over 49 were tested.

Table 1: Antenatal HIV and syphilis prevalence for 2007 and 2008 by province and nationally. [1]

	Kwazulu-Natal % [95%CI]	Mpumalanga	Free State	Gauteng	North West	Eastern Cape	Limpopo	Northern Cape	Western Cape	National
2008										
HIV	38.7 [37.2-40.1]	35.5 [33.1-37.8]	32.9 [30.5-35.3]	29.9 [28.4-31.2]	31.0 [28.8-33.3]	27.6 [25.6-29.6]	20.7 [19.1-22.4]	16.2 [13.7-18.9]	16.1 [12.6-20.2]	29.3 [28.5-30.1]
Syphilis	0.6 [0.4-0.8]	0.7 [0.4-1.2]	2.3 [1.7-3.1]	2.7 [2.3-3.1]	1.5 [1.1-2.2]	1.9 [1.5-2.4]	0.4 [0.3-0.7]	6.8 [5.2-8.7]	3.8 [3.1-4.6]	1.9 [1.7-2.0]
2007										
HIV	38.7 [37.2-40.2]	34.6 [32.1-37.1]	31.5 [29.1-34.1]	30.5 [29.2-31.9]	30.6 [28.6-32.8]	28.8 [26.9-30.7]	20.4 [18.9-21.9]	16.5 [13.9-19.6]	15.3 [12.2-18.9]	29.4 [28.5-30.1]
Syphilis	0.8 [0.6-1.1]	1.8 [1.3-2.4]	2.5 [1.9-3.0]	3.8 [3.3-4.3]	2.7 [2.1-3.5]	3.0 [2.5-3.6]	1.4 [1.1-1.9]	5.4 [4.2-6.9]	5.6 [4.9-6.3]	2.8 [2.6-3.0]

Table 2. Antenatal HIV prevalence for 2007 and 2008 by age. [1]

Age group	2007	2008
15-19	13.1 [12.2-14.0]	14.1 [13.1-15.0]
20-24	28.0 [26.9-29.1]	26.9 [25.9-27.9]
25-29	37.5 [36.2-38.8]	37.9 [36.4-39.3]
30-34	39.6 [38.0-41.2]	40.4 [38.7- 42.0]
35-39	33.0 [31.1-34.9]	32.4 [30.5-34.3]
40-44	22.2 [19.1-25.7]	23.3 [20.3-26.6]
45-49	20.6 [13.2-30.7]	17.6 [10.7-27.7]

The survey includes a discussion on estimating population prevalence. It presents estimates from UNAIDS models, the Actuarial Society of South Africa's ASSA2003 model and the Human Sciences Research Council (HSRC; see our review of this survey in HTB-South April-June 2009).

The Department of Health uses the UNAIDS model to calculate prevalence for the total population. This actually consists of two models, the Estimation and Projection Package (EPP) and Spectrum. EPP estimates prevalence based on antenatal and national population survey data. Spectrum uses the output of EPP (ie the population HIV prevalence) and other demographic data to estimate incidence, AIDS deaths, orphans due to AIDS and HAART and PMTCT needs. Some key outputs from all three sources are presented in Table 3.

Table 3: HIV demographic data for 2008 from three sources. Values in square brackets are 95%CI. [1]

	UNAIDS	ASSA	HSRC
HIV-positive adults and children	5.3m [4.7m-5.7m]	5.6m	5.2m [4.6m-5.7m]
HIV-positive adults older than 15 yrs	5m [4.5m-5.4m]	5.3m	4.7m [4.2m-5.3m]
HIV-positive children	220,000 [130,000-300,000]	330,000	340,000 [230,000-450,000]
Prevalence in adults older than 15 yrs	17.5% [15.9-18.7]	18.8%	16.9% [15.5-18.4]

COMMENT

The correction of the 2007 results is welcome and emphasises the change in health politics since the appointment of Hogan and subsequently Aaron Motsoaledi. Interestingly there has been no explicit acknowledgement of the correction; the new report simply used the corrected data and last year's report appears to have been removed from the Department of Health's website.

The close correspondence in prevalence estimates between UNAIDS, ASSA and HSRC is notable, though this has been the case for several years. This raises confidence that the estimates of HIV prevalence in South Africa are accurate.

Until 2001, the antenatal survey was the only large population sample of HIV prevalence in South Africa. Consequently it was the main data source for estimating HIV indicators including prevalence and incidence for the whole population. Since then three HSRC household surveys have been published in 2002, 2005 and 2008. Despite some problems, they have added considerably to our understanding of the South African epidemic.

While prevalence is an important measure, incidence is at least as important. For one thing the HIV/AIDS National Strategic Plan (NSP) commits to reducing incidence by 50% between 2007 and 2011. Unfortunately incidence is extremely difficult to calculate (see our review of the HSRC survey in HTB South April-June 2009). The relationship between population incidence, population prevalence and antenatal prevalence is complex, even more so since the wide-scale introduction of HAART in 2004. These factors mean that the antenatal surveys are not quite as critical as they once were. Furthermore, the doubling of the antenatal survey sample size in 2006 and the consequent change of methodology means we have to treat comparisons between surveys pre-2006 and since 2006 with caution. Nevertheless, they continue to be a useful source of data.

The one group in the antenatal survey that can be used to gauge incidence, at least partially, is 15-19 year-olds. Since they are likely to be pregnant for the first time the women constituting this part of the sample are unlikely to overlap significantly with a previous survey. HIV-positive women in this age group generally constitute a group of recent sero-converters. Here the news is not promising. There is no statistical change in prevalence in this group between 2002 and 2008. There is also no change in the proportion of their contribution to the sample (19.4% in 2002, 19.4% in 2008). Again, comparisons between surveys before 2006 with those since must be treated cautiously.

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Thanks to Leigh Johnson for reviewing this article.

PAEDIATRIC CARE

HIV, the brain and children

Polly Clayden, HIV i-Base

The developing brain is known to be a target for HIV, and there is concern about the long-term effect on the cognitive and behavioural development of HIV-positive children. Additionally before the introduction of HAART, the prevalence of HIV encephalopathy in HIV-positive children was up to 50%.

Two studies published in the September 10 2009 edition of AIDS, examine long-term neurocognitive and psychiatric outcomes of vertically infected adolescents and the impact of HAART on HIV encephalopathy among children and adolescents in two American cohorts.

Impact of AIDS diagnoses on neurocognitive and psychiatric outcomes of vertically infected adolescents

Sarah Woods and colleagues conducted a retrospective cohort study at the Children's Hospital of Philadelphia, USA, to examine the association between previous AIDS and neurocognitive and psychiatric outcomes in vertically infected adolescent long-term survivors. [1]

Adolescents attending the HIV clinic, born before 1 September 1995 and above 11 years of age were enrolled this study in which those with previous CDC Class C diagnosis (AIDS defining) were compared to those with non-Class C diagnosis.

Of the 172 meeting these criteria 39 (23%) patients had died, 45 (26%) transferred and 7 (4%) were lost to follow up. The remaining 81 adolescents were eligible for evaluation of whom 38 (46.9%) were girls and 58 (71.6%) were African-American. Their median age was 15.2 years (range 11.1-23.8, IQR 13.2-17.2 years). Almost half (47%) the participants were Class C and there were no significant differences in sex, race or current age between the class C and non-Class C groups.

HIV diagnosis was at a median of 9 months and Class C diagnosis was at a median of 3.1 years of age. Of the Class C group, 51% had at least one additional Class C diagnosis.

Most recent viral load, CD4 percentage and CDC immunological category were similar in both groups. By the end of the study period 93% of the cohort were receiving HAART. There was no difference between the groups in those achieving and not achieving an undetectable viral load when on HAART. The cohort was heavily treatment experienced and patients with Class C diagnosis had received a greater number of regimens p=0.002. Of this group 68.4% had initiated HAART before their AIDS diagnosis.

The median full scale intelligence quotient (FSIQ) of the cohort, measured on the Weschler Intelligence Scale for Children-IV (WISC-IV) or the Weschler Abbreviated Scale of Intelligence, was 87 (IQR 78-99), which falls within the "average" category. However, Class C patients had significantly lower median FSIQ than non-class C, 82 (IQR 73-90) vs 93.5 (IQR 84-100) respectively, p=0.0003. Learning disabilities had been diagnosed in 42% of the cohort and 17% had a lifetime history of HIV-related progressive encephalopathy (HPE).

Almost half the cohort (47%) had a diagnosed psychiatric illness and18.5% had multiple psychiatric illnesses. Treatment with psychotropic medications had been prescribed to 32% of the cohort, and 16% had a history of mental health hospitalisation.

The investigators performed a multivariate logistic regression analysis, adjusted for age at ART initiation, to look at the association between Class C diagnosis and neurocognitive and psychiatric status.

They found a significant association between previous Class C diagnosis and neurocognitive impairment: learning disabilities, adjusted OR 4.1 (95% CI 1.5-11.1), p=0.014 and lower FSIQ (median), -12.1 (-18.7 to 5.5), p=0.002. There was also significant association with psychiatric diagnosis AOR 3 (95% CI, 1.1-8.1), p=0.027, in particular multiple psychiatric diagnosis AOR 19.3 (95% CI, 2.3-162.6), p=0.001; mood disorder AOR 3.3 (95% CI, 1.1-10), p=0.023 and receiving mental health treatment AOR 4 (95% CI, 1.3-13), p=0.042.

The investigators found no difference in FSIQ or rates of learning or psychiatric disorders between Class C patients starting HAART before and after their AIDS diagnosis. But they noted that the number of patients with Class C disease was small and they were underpowered to detect even modest associations in this sub-analysis.

Impact of HAART on encephalopathy

Kunjal Patel and colleagues from The PACTG 219 study team looked at the effects of HAART and CNS penetrating regimens on the incidence of HIV encephalopathy in perinatally infected children and adolescents. [2] This study was conducted between 1994 and 2006 in a large American multicentre paediatric cohort.

The study followed 2398 perinatally infected children with at least one neurological examination.

The investigators used Cox regression models to estimate the effects of time varying HAART vs non HAART and time varying medium and high CNS penetrating regimens vs low CNS penetrating regimens on the incidence of HIV encephalopathy. They also looked at overall survival and survival following encephalopathy diagnosis. Covariates included baseline age and CD4 percentage, sex, ethnicity and birth weight. Secondary analyses used Cox models to estimate the effects of HAART and CNS penetrating regimens on HIV encephalopathy also adjusted for viral load and to evaluate the effect of HIV encephalopathy on mortality.

There were 2398 children, with a median of 6.4 years of follow up, included in this analysis. At baseline the 2272 children followed for incident HIV encephalopathy and survival analyses were equally divided between the sexes, the majority (85%) were less than or equal to 10 years of age, 24% had low birth weight, 56% had a CD4 percentage above 25% and there were no viral load data for 54%.

At the time of their first neurological examination 35% of children were on a HAART regimen and 27% were on a high CNS penetrating regimen. During the study period there were 77 incident cases of HIV encephalopathy, giving an incident rate of 5.1 per 1000 person years (95% CI 4-6.3).

The investigators reported a 10-fold decline in incidence of HIV encephalopathy. This began in 1996 and stablised after 2002. This decrease paralleled a significant increase in the use of HAART in the cohort.

They found the risk of developing HIV encephalopathy in children initiated on HAART was halved compared to those who were not on HAART (hazard ratio 0.5, 95% CI 0.29-0.86), p=0.01. Baseline CD4 less than 15% was associated with over 8-fold increase in risk of developing HIV encephalopathy (hazard ratio 8.41, 95% CI 4.79-14.76). Infants were also at greater risk, age less than or equal to 1 year at first neurological examination was associated with a over 3-fold increase in HIV encephalopathy (hazard ratio 3.38, 95% CI 1.36-8.44).

In the subanalysis looking at ranked CNS penetrating regimens, the investigators found a 41% reduction in incidence of HIV encephalopathy in high CNS penetrating regimens compared to low (hazard ratio 0.59, 95% CI 0.31-1.10). Due to the small sample size in this analysis, this association was not significant, p=0.64.

Across the cohort (n=2272) both HAART and high CNS penetrating regimens were associated with increased survival, hazard ratio 0.41 (95% CI 0.29-0.58), and hazard ratio 0.31 (0.22-0.45), both p<0.0001, compared to no HAART and low CNS penetrating regimens respectively.

Children with an HIV encephalopathy diagnosis had a 12-fold increase in risk of death compared to those without (hazard ratio 12.42, 95% CI 8.46-18.24).

There was a 50% increased survival benefit associated with HAART use among the 77 children with an incident diagnosis of HIV encephalopathy (hazard ratio, 0.51, 95% CI 0.25-1.05) but this was not statistically significant, p=0.07. High CNS penetrating regimens were associated with greater survival benefit, giving a 74% reduction in risk of death (hazard ratio 0.26, 95%CI 0.11-0.61, p=0.002) compared to low penetrating regimens.

COMMENT

Wood and colleagues write that their findings suggest that early HAART, initiated before the onset of symptomatic HIV, may be warranted to protect the developing CNS in children with HIV. For infants, they suggest that alongside CHER findings, and in keeping with some recent guideline changes, that HAART should be given to all infants immediately after birth. However, in an accompanying commentary, Marc Tadieu suggests that it is not possible to conclude directly from this study that very early treatment would have prevented class C events and possibly ensure normal cognitive and behavioural development, "although, it is tempting to do so."

Patel and colleagues found HAART use to be highly effective in reducing the risk of HIV encephalopathy. They suggest that among children with HIV encephalopathy diagnosis, treatment decisions should take into account the effectiveness of ARVs in penetrating the CNS, as high CNS penetrating regimens offered increased survival benefit (74% reduction in risk of death compared to low penetrating). Editorial commentary from Bruce Brew describes HIV, the brain, children and "neuro-HAART" as "a complex mix" and suggests it is time for randomised clinical trials to establish whether "neuro-HAART" treats brain disease better than standard HAART.

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PREVENTION

Making progress on prevention

A TAC policy briefing

A goal of the HIV & AIDS and STI Strategic Plan for South Africa 2007-2011 (NSP) is to reduce new infections by half over the five-year period of the plan. Is it difficult to measure progress towards this goal because of a lack of reliable data on HIV incidence. Nevertheless, policy improvements around voluntary male medical circumcision and prevention of mother-to-child transmission (PMTCT) will significantly reduce new infections.

This is the first part of a two-part TAC policy brief. This part deals with voluntary male medical circumcision and the next one, which will be released in early 2010, deals with PMTCT.

Part One: Voluntary Male Medical Circumcision (VMMC

Summary

It is two and a half years since TAC published its briefing on VMMC. [1] Since then, in Southern Africa, over 3,000 VMMCs have been carried out by the Family Life Association of Swaziland. Zambia has performed nearly 8,000 and Zimbabwe just under 1,300. Yet comparatively little progress has been made making this affordable intervention (about R300 per VMMC) available beyond Orange Farm in South Africa, where several thousand circumcisions have been performed in an ANRS sponsored research project. PEPFAR, the Global Fund and the Gates Foundation have committed to funding VMMC, but South Africa has not made use of this opportunity. [2]

The key recommendation of this brief is that the South African National AIDS Council (SANAC) needs to move quickly to adopt a policy that promotes the scaling up of VMMC and that the Department of Health must ensure this policy is implemented. It is at over four years since the results of the first circumcision trial were published; South Africa should have scaled up beyond Orange Farm by now.

Evidence for the benefts of VMMC

The evidence that circumcised heterosexual males have less risk of contracting HIV is compelling. Three randomised controlled clinical trials conducted in high-prevalence areas in sub-Saharan Africa, whose resuts have been published in reputable medical journals, have found that the risk of HIV-negative males contracting HIV is reduced by 50 to 60% when they are circumcised. [3, 4, 5] Evidence from two of these trial settings, Orange Farm and Rakai, Uganda, shows that VMMC also reduces the risk of men contracting Human Pappiloma Virus (HPV). [6, 7] A trial in Rakai also found that VMCC reduces the risk of men contracting Herpes Simplex Virus-2 (HSV-2). [7]

The benefits of VMMC for the female partners of circumcised men have also been shown. Women partners of circumcised men are less likely to contract trichomoniasis and bacterial vaginosis. VMMC also reduces the risk of symptomatic ulceration in HIV-negative men and women and HIV-positive men. [7, 8]

A UNAIDS/WHO/SACEMA expert review of mathematical models of VMMC found:

There would be large benefits of male circumcision among heterosexual men in low male circumcision, high HIV prevalence settings. The review found that one HIV infection would be averted for every five to 15 male circumcisions performed

They found that the cost of averting one HIV infection ranges from R1,125 (US$150) to R6,750 (US$900) using a 10 year time horizon.

Critically they found that women benefit indirectly from reduced HIV prevalence in circumcised male partners and that VMMC service scale-up "acts synergistically with other strategies to reduce HIV disease burden." [9]

A review of the risks and benefits of circumcision for women, published in *The Lancet* in July, states:

Although circumcision of HIV-infected men does not seem to directly reduce HIV risk for their female partners in the short term, women will benefit from male circumcision programmes. Wide-scale roll-out of male circumcision is expected to lead to decreasing HIV prevalence in communities over 10—20 years, in both men and women, by averting new infections in men and onward transmission to their partners.8 On a shorter timescale, a woman's HIV risk would be substantially reduced if circumcision prevents her male partner from acquiring HIV. Indeed, anecdotal reports suggest that interest in circumcision in young men in the first roll-out programmes in Africa is in part being driven by women's preference for circumcised partners. Finally, women with circumcised partners, irrespective of HIV serostatus, face decreased risk of sexually transmitted infections such as Trichomonas vaginalis, bacterial vaginosis, herpes simplex virus type 2, and human papillomavirus. [10]

Circumstances where VMMC has no proven benefits for HIV

There are circumstances where VMMC appears to have no proven benefits for HIV:

Circumcised HIV-positive men do not have a lower risk of passing HIV to their female partners. A trial testing this was ended early by its Data Safety Monitoring Board because of futility. (NB: The 2007 TAC briefing indicated that there was some evidence this was benefit of circumcision. This was based on the best evidence at the time, but is now not supported by the evidence.) [11]

There is no compelling evidence that VMMC reduces the risk of transmission in homosexual sex.

Evidence for the safety of VMMC

No surgical procedure is risk-free, but the evidence for the safety of VMMC is considerable:

Over 50,000 VMMCs have been performed in sub-Saharan Africa as part of trials and projects to reduce the risk of transmission from HIV. There are no reported cases of serious permanent adverse events.

The balance of evidence indicates that VMMC does not cause sexual dissatisfaction or dysfunction. [12]

No evidence for risk compensation

An argument offered against VMMC is that it will result in risk compensation behaviour, ie that men would take sexual risks in the belief that they are protected from HIV transmission. Furthermore, that this risk-taking would have negative effects on women's rights.

No evidence has been offered for this view. It is often simply asserted. But a study of risk compensation behaviour in one of the three trials found that it did not occur. [13] In a real world setting in Kenya, i.e. outside of a trial, no evidence was found of risk compensation behaviour. [14]

It is important that counselling at VMMC sites and public messaging on VMMC emphasises that VMMC is not completely protective against HIV transmission and using condoms for sex remains necessary to reduce the risk of contracting HIV.

Other arguments against circumcision are dealt with by Halperin et al. (2008). [15]

Promoting VMMC is consistent with human rights

VMMC is consistent with a human rights approach to health-care. It should always be implemented in accordance with these principles:

It must be voluntary or, in the case of infants, must be done with parental or guardian consent.

It must be accompanied by proper counselling on the need for practising safer sex, the offer of HIV testing and referral to treatment facilities for people who are HIV-positive.

It must not undermine women's health.

There are several projects in Sub-Saharan Africa that already meet these criteria, including the Orange Farm project in South Africa. They should be used as models for scaling up VMMC.

The slow progress in rolling out VMMC means we are losing an important opportunity. The delay in making this essential health intervention available is inconsistent with human rights, for both men and women, as well as sound public health care.

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OTHER NEWS

President Obama announces end to HIV-positive immigration ban in the US

On 2 November 2009, the US Department of Health and Human Services published final regulations that will remove HIV from its list of 'communicable diseases of public health significance' and will remove the HIV test from the routine medical exam for lawful permanent resident applicants. The regulations will go into effect on 4 January 2010, following a routine implementation period.

This was announced during the presidential press briefing for the fourth reauthorisation of the Ryan White CARE Act, and included the following statement:

"Twenty-two years ago, in a decision rooted in fear rather than fact, the United States instituted a travel ban on entry into the country for people living with HIV/AIDS. Now, we talk about reducing the stigma of this disease - yet we've treated a visitor living with it as a threat. We lead the world when it comes to helping stem the AIDS pandemic - yet we are one of only a dozen countries that still bar people from HIV from entering our own country. If we want to be the global leader in combating HIV/AIDS, we need to act like it. And that's why, on Monday my administration will publish a final rule that eliminates the travel ban effective just after the New Year. Congress and President Bush began this process last year, and they ought to be commended for it. We are finishing the job. It's a step that will encourage people to get tested and get treatment, it's a step that will keep families together, and it's a step that will save lives." (Applause)

Source: Obama B. Press Statement "Remarks by the President at signing of the Ryan White HIV/AIDS Treatment Extension Act of 2009. (30 October 2009).

http://www.whitehouse.gov/the-press-office/remarks-president-signing-ryan-white-hivaids-treatment-extension-act-2009

Related links:

Immigration resource with focus on HIV

http://immigrationequality.org/template.php?pageid=177

Report on Kaiser Network

http://globalhealth.kff.org/Daily-Reports/2009/November/02/GH-110209-HIV-Travel.aspx

IAS press release "IAS applauds White House announcement of repeal of the United States' discriminatory and ineffective HIV entry and immigration ban". (30 October 2009).

http://www.iasociety.org/Default.aspx?pageId=379

Global database on HIV travel restrictions

http://www.hivrestrictions.org

ON THE WEB

Conference reports and online abstracts:

BHIVA Autumn Conference and CHIVA Parallel Sessions

8-9 October 2009, London

Some of presentations from the BHIVA Autumn Conference are now posted on the BHIVA website:

http://www.bhiva.org/cms1224475.asp

5th IAS Conference on HIV Pathogenesis, Treatment and Prevention

19-23 July 2009, Cape Town

The conference website includes all abstracts and many PDF or powerpoint slides of posters and oral presentations, together with a limited amount of webcasts.

http://www.ias2009.org

WHO meeting: the impact of ARV treatment on prevention

A WHO consultation meeting held from 2-4 November 2009 focused on the increasingly important impact that HIV treatment has on reducing transmission. A report from the meeting will be produced, but the related papers and presentations from this meeting have also been posted online.

http://www.who.int/hiv/events/artprevention/day1/en/index.html

Reports and journals:

JAIDS Supplement: HIV scale-up and global health systems

Free online access to this supplement to JAIDS, guest-edited by Wafaa El-Sadr and Kevin De Cock.

November 2009 - Volume 52 - Supplement pp: S1-S68

http://journals.lww.com/jaids/toc/2009/11011

Returned to risk: deportation of HIV-positive migrants

The 27-page report was prepared by Human Rights Watch, Deutsche AIDS-Hilfe, the European AIDS Treatment Group, and the African HIV Policy Network. It describes cases in South Korea, Saudi Arabia, the United Arab Emirates, South Africa, and the United States in which HIV-positive migrants were deported, and describes the need to develop policies guaranteeing uninterrupted treatment for this population.

The report documents:

- In Saudi Arabia: mandatory HIV testing; detention for up to a year without access to medication; and deportation of HIV-positive migrants.
- In the United Arab Emirates: deportation of 1,518 non-citizen residents infected with HIV; hepatitis types B and C; or tuberculosis in 2008.
- In South Africa: the inability to continue treatment – amounting to a death sentence – for people living with HIV who are sent back to Zimbabwe.
- In the United States: poor access to treatment in detention and harsh conditions or lack of access to medical treatment for some HIV-positive individuals who are deported.
- In South Korea: mandatory HIV testing of migrants and the deportation of those found to be HIV positive, despite South Korea's international legal obligations and a recent Seoul High Court ruling that such deportation is not the most effective means of protecting public health.

To read the Human Rights Watch report visit:

http://www.hrw.org/en/node/85610

PLoS Medicine – November 2009

http://www.plosmedicine.org

Effects of genital ulcer disease and herpes simplex virus type 2 on the efficacy of male circumcision for HIV prevention: analyses from the Rakai trials

Gray RH et al.

The unintended consequences of clinical trials regulations

McMahon AD et al.

This article argues that recent EU trial regulations have dramatically reduced levels of noncommercial research in the UK, and that patients have suffered as a result.

FUTURE MEETINGS

2010 conference listing

The following listing covers some of the most important upcoming HIV-related meetings and workshops.

Registration details, including for community and community press are included on the relevant websites.

16-19 February: 17th CROI

http://www.retroconference.org/2010

8th European Drug Resistance Workshop

17-19 March 2010, Sorrento, Italy

http://virology-education.com

11th International Workshop on Clinical Pharmacology of HIV Therapy

7-9 April 2010, Sorrento, Italy

http://virology-education.com

6th International Workshop on HIV and Hepatitis Co-Infection

June 2010, Israel. The date and venue tbc.

http://virology-education.com

5th International Workshop on Hepatitis C - Resistance and New Compounds

and 5th International Workshop on Clinical Pharmacology of Hepatitis Therapy

June 2010, Boston, USA. The dates and venue tbc.

http://virology-education.com

5th International Workshop on HIV Transmission - Principles of Intervention

15-16 July 2010, Vienna

http://virology-education.com

2nd International Workshop on HIV Pediatrics

16-17 July 2010, Vienna

http://virology-education.com

18-23 July 2010, Vienna

XVIII International AIDS Conference (AIDS 2010)

http://www.aids2010.org

3rd International Workshop on Clinical Pharmacology of Tuberculosis Drugs

September 2010, USA. Date and venue tbc.

http://virology-education.com

HIV i-BASE

HIV i-Base is an HIV-positive led treatment information service. We produce information both for clinicians and other health workers and for people with HIV.

Our publications are used and have been adapted in many countries and settings.

Our fully searchable website is designed to be fast to access, easy to use, and simple to navigate.

All i-Base publications are available online.

http://www.i-base.info

i-Base produce five non-technical treatment guides, which are available online as web pages and PDF files.

http://www.i-base.info/guides

- Introduction to combination therapy
- A guide to changing treatment
- Avoiding & managing side effects
- HIV, pregnancy & women's health
- Hepatitis C for People living with HIV

The site also includes a web-based Q&A section for people to ask questions about treatment:

http://www.i-base.info/questions

Recent questions include:

- Is it OK to take probiotic cultures with HIV meds?
- Is d4T+3TC+EFV good enough?
- Can I take these supplements with my HIV treatment?
- Can I use Zyban to stop smoking if I'm on HIV treatment?
- What would happen if somebody starts with a CD4 count of zero and on entry inhibitor?
- Do I have a natural resistance to HIV?
- How to remove genital warts?
- Switching back to Kaletra after efavirenz…
- Is it OK to use muscle gain powder?
- Do we have to start using condoms?

We have also posted online a set of generic clinic forms, developed with the Royal Free Centre for HIV Medicine, which may be a useful resource for other hospitals.

http://www.i-base.info/clinicforms

HIV i-Base

www.i-Base.info

Southern African HIV Clinician's Society

www.sahivsoc.org

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