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EDITORIAL

Welcome to the November/December issue of HTB that includes selected reports from five conferences.

Of interest, three of these conference reports include studies looking at lipohypertrophy.

Although the side effect profile of ARVs has dramatically improved since 1996, including a better understanding of how to manage and avoid many of the symptoms of lipodystrophy, little progress has been made on fat accumulation.

No class of drugs, or individual drug, has been cleared from this association, and recent studies fail to show any correlation with plasma lipids. For example, even drugs with a relatively benign, or even favourable, lipid profile (nevirapine, atazanavir and raltegravir) have not shown differences in fat accumulation compared to standard of care control groups.

Genetics are likely to explain many interpatient differences but this has not so far resulted in sceening tests. We report differences by race and gender from a Canadian study that was presented at the Lipodystrophy Workshop, and this supports previously annectodal experience that lipohypertrophy may occur more frequently in African women.

Management options are also limited. Reductions in VAT from treatment with either rHGH or tesamorlin (neither of which are currently licensed in Europe for this indication) both return to baseline if either intervention is stopped.

A multifocus approach can be currently recommended: and diet, exercise, treatment switching and perhaps a therapeutic intervention, all being needed to attempt to shift the underlying mechanism responsible - and it is disappointing when research looks at single interventions in isolation.

Also in this issue, Richard Jeffreys from TAG provides an excellent analysis of the controversial results from the RV144 Thai Vaccine Trial - 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 conflicting press and media coverage.

Other articles include, drug interaction studies presented at ICAAC from the HIV Drug Interactions group in Liverpool and an overview of paediatric studies conducted in the South concludes our reports from IAS2009.

As this is the last HTB of the year we would also like to take the opportunity to thank our medical board and other advisors for their invaluable comments and feedback.

And to our readers, we would like to wish you all a Happy New Year!

CORRECTION

HTB Sep/Oct 2009: Low viral loads in elite controllers

The article that we included in the last issue of HTB erroneously stated that the correlation between viral load and neutralising antibody responses was inverse (there is a section heading in the paper that mistakenly cites the correlation as inverse instead of positive). This has since been corrected on both the original source website and the i-Base reprint.

CONFERENCE REPORTS

12th European AIDS Society Conference (EACS)

11-14 November 2009, Cologne

Introduction

This issue of HTB went to press just after the 12th ECAS conference and detailed reports from this meeting will be included in our next issue.

As a stop press we only include one article:

- EACS releases three updated management guidelines

Although the abstracts from the meeting are not currently available online, this year a comprehensive programme of lectures and sessions are due to become available as webcasts:

http://www.multiwebcast.com/eacs/2009/12th

EACS releases three updated management guidelines

Simon Collins, HIV i-Base

The European AIDS Clinical Society publishes three management guidelines that make extensive use of summaries, bullet point list and supportive tables to produce resources that are easy to follow resources. The three main updates (version 5) were launched at this year's conference.

PDF versions are now available to download from the societies website. Additional tables not included in the PDF and printed booklets are also available online.

http://www.europeanaidsclinicalsociety.org/

The main changes to each guideline are outlined below.

ARV guidelines

- A check list for initial and routine clinic management and a new flow chart for assessing and supporting a patients readiness to start ARV treatment. This includes the importance of asking about depression and mental health, and alcohol and recreational drug use.
- In primary infection, although a CD4 count <350 three months after infection is included as a criteria to start treatment, the guidelines recognise that most patients are likely to wait at least until six months.
- Treatment is recommended for any patient with a CD4 count <350, and at between 350-500 in patients older than 50 years, coinfection with HCV, HBV or other listed health complications.
- A new section focuses on HIV and TB coinfection.
- Switching drugs for toxicity is overly cautious for anyone other than naive patients, perhaps underestimating the importance of tolerability when modifying treatment however pre-treatment someone may be.
- PEP is recommended ideally within 4 hours of exposure, and not later than 48 hours. Surprisingly there is no reference to viral load of the HIV-positive partner as a factor in assessing risk.

Prevention and management of non-infectious comorbidities

This management guideline has expanded considerably, now addressing many of the comorbidities associated with an older HIV cohort, especially cardiovascular, renal, hepatic, metabolic, neoplastic, done and mental health complications. Recommendations are not graded based on the quality of evidence.

- Screening sections have been expanded for renal, bone, neurocognitive disorders, depression and cancer.
- Lipid management is covered in a separate table, which notably does not include triglyceride management due to less evidence suggesting elevated TG as an independent risk factor for clinical complications.
- Bone screening refers doctors to the FRAX calculator (www.shef.ac.uk).
- Kidney screening includes eGFR at baseline and a new recommendation to include dipstick testing.
- Many additional tables are available as web resources (ie for neurocognitive screening, lipoatrophy treatments etc).

Hepatitis coinfection

The main changes in the hepatitis coinfection guidelines include:

- To start appropriate ARVs when CD4 count is <500 c/mm3 in people who need HBV treatment.
- That this is likely to be lifelong unless the patient is HBV eAg+ who may clear HBV and that treatment could be cautiously stopped six months after conversion to eAg–.
- New information on hepatitis D (HDV) which increase the risk of fibrosis progression in HBV infection.
- That people with CD4 count < 350 should probably start ARVs prior to HCV treatment to increase the chance of success (SVR).
- Early HCV treatment is recommended for HIV-positive people identified in acute HCV infection.
- Non responders (< 2 log HCV RNA drop at week 12) should stop treatment to wait for new options.
- People who relapse can consider retreating with longer duration.
- That HIV is no longer a contraindictation for liver transplant and that timely referral to transplant lists is therefore important.

CONFERENCE REPORTS

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

26-28 October 2009, Philadelphia

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
- Visceral adipose tissue returns to baseline after stopping therapeutic rHGH
- Reduced levels of vitamin D in patients taking efavirenz
- Association between inflammation and sleep apnea in the MACS cohort
- Sports supplements impact on serum creatinine and eGFR markers of renal function

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 subcutaneous 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 waist: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 (median 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 in HIV-negative control cohort with similar adipose profile. [2]

C O M M E N T

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 analyses 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 reported fat loss more frequently 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).

C O M M E N T

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 the prevalence of lipodystrophy in a cohort of 468 children and adolescents (92% infected at birth). Data collected included demographic and clinical history and used standardised assessment 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. In this group, 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 having ever used d4T, indinavir, d-drugs 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 use (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.

Visceral adipose tissue returns to baseline after stopping therapeutic intervention with rHGH

Simon Collins, HIV i-Base

Central fat accumulation remains one of the most distressing but least understood metabolic complications, with very limited management options. Several studies have reported that recombinant Human Growth Hormone (rHGH) can reduce central visceral adipose tissue (VAT), although earliest studies at higher doses (4-6 mg/day) were associated with significant toxicity. Additionally, any benefit seemed dependent on maintaining treatment, and the optimal dose remained to be established.

It was important to see the 3-years results from a study from the Massachusetts General Hospital, presented by Steven Grinspoon, carried out in people with reduced growth hormone (GH) secretion (peak GH <7.5 ng/mL). [1] This was a randomised double-blind study of low dose rHGH (an average dose of 0.33 mg/day: starting at 2 mcg/kg/day but increasing to 6 mcg/kg/day, titrating to the upper quartile of normal IGF-1 range). After 18 months patients crossed over to either active drug or placebo, depending on their original randomisation. The 18 month initial results have already been published. [2]

Pooled analysis for both arms showed that 18 months treatment significantly reduced mean (±SD) VAT compared to placebo (-7.3 ±21.3% vs +4.8 ±22.7%, p<0.0001) and trunk fat (-3.2 ±15.3% vs +2.4 ±13.1%, p=0.003). rHGH also had a statistically positive effect on reducing systolic and diastolic blood pressure, triglycerides and LDL-cholesterol and increasing lower limb fat, but had a negative glyceamic affect: increasing fasting glucose and 2-hour glucose on OGTT (see Table 1). No impact for seen for intima media thickness, though this was not elevated at baseline.

During the crossover period, the benefits of rHGH on VAT reversed to baseline within 6 months. The increase in IFG-1 seen during 18 month treatment (approximately +100ng/mL increase from baseline) also dropped within 2-4 weeks of discontinuation.

Table 1: Pooled effect of rHGH vs placebo at 18 months (mean%, ±SD)

	rHGH	placebo	p
VAT	-7.3 ±21.3%	+4.8=±22.7%	<0.0001
Trunk fat	-3.2 ±15.3%	+2.4 ±13.1%	0.003
Lower limb fat	+4.9 ±13.3%	+1.1 ±11.8	0.03
Systolic BP	-2.0 ±13.9%	+2.6 ±12.0%	0.007
Diastolic BP	-1.1 ±13.7%	+5.8 ±17.1%	0.0009
Triglycerides	-0.9 ±43.4%	+11.0 ±52.9%	0.05
LDL-chol	-2.7 ±23.7%	+4.9 ±28.7%	0.03
Fasting glucose	6.7 ±11.7%	2.5 ±11.4%	0.007
2-hour glucose	16.5 ±48.6%	0.1 ±26.9%	0.002

C O M M E N T

The importance of continuing treatment in order to maintain any reduction in VAT has also been reported with tesamorelin, which although has reduced toxicity, appears to reverse benefits back to baseline VAT levels if discontinued. An FDA decision on approval of tesamorelin is expected in the second quarter of 2010.

References
1. Grinspoon S et al. Effects of treatment and discontinuation of low dose physiologic growth hormone in HIV patients with abdominal fat accumulation: a randomised, placebo-controlled 36-month crossover trial. 11th Intl Workshop on Adverse Drug Reactions. 26-28 October 2009, Philadelphia. Oral abstract O-02. Antiviral therapy 2009; 14 Suppl 2: A3.
2. Lo et al. Low-dose physiological growth hormone in patients with HIV and abdominal fat accumulation. JAMA 2008;300(5):509-519. (6 August 2008).
http://jama.ama-assn.org/cgi/content/full/300/5/509

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 $\pm$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 $\pm$7.2kg/m2) and waist circumference (98.6 +16.9cms) compared to the HAART (25.5 $\pm$4.5kg/m2 and 93.8 +11.5cm) and no-HAART (25.4 $\pm$4.1 kg/m2 and 91.8 $\pm$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, London. 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 an 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.

C O M M E N T

This study highlights the importance taking a history of supplement use to consider this as a cause for elevated creatinine or low eGRF.

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

Introduction

The AIDS Vaccine conference is one of the most important scientific meetings 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

Abstracts from the conference are 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 the vaccine and 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 participants aged 20-25, 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

Introduction

The following short reports are summaries from some 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 include:

- Smoking masks the long-term benefits of HAART on lung function
- Recent ARVs and the blood/brain barrier: CSF drug concentrations of darunavir/r and raltegravir
- Alcohol and marijuana may reduce drug levels of atazanavir and efavirenz
- Raltegravir body composition study: 48-week DEXA results

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.

C O M M E N T

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

Recent ARVs and the blood/brain barrier: CSF drug concentrations of darunavir/r and raltegravir

Simon Collins, HIV i-Base

The issue of drug penetration into the cerebrospinal fluid (CSF) is an increasing focus for all antiretrovirals, but has particular importance given the interest in nucleoside-sparing regimens. These include studies looking at boosted-PI monotherapy as a maintenance strategy after initial viral suppression with triple drug therapy and dual NNRTI + PI/r or raltegravir + PI/r combinations.

Scott Lettendre's group presented encouraging results from two studies at ICAAC: on darunavir/r and on raltegravir, supported by Tibotec and Merck respectively.

The darunavir study measured 29 CSF and plasma pairs from 16 HIV-positive patients between August 2006 and August 2008, and compared levels to the median IC50 for wild-type virus (2.75 ng/mL). [1]

Participants were a median 48 years, 62% were Caucasian and 19% had HCV co-infection. Median CD4 cell count was 197 cells/mm3. Viral load was detectable in 38% of blood and 10% of CSF samples. Median duration of darunavir was 7.5 months (IQR 3.6 - 14.6).

Darunavir was detected in all CSF specimens with a median concentration of 56.9 ng/mL (IQR 39.6 - 81.4). The median total plasma concentration (AUC) was 4,094 ng/mL (IQR 2,993 - 6,410) with a median CSF-to-plasma ratio of 1.4%. The median unbound plasma concentration was 542 ng/mL (IQR 376 - 971) with a median CSF-to-plasma unbound ratio of 9.4% (IQR 6.8 - 14.2%). DRV concentrations in CSF exceeded the IC50 of wild-type HIV in all specimens by a median of 20-fold.

The raltegravir study had a similar design, with 22 matched plasma/CSF samples from 18 HIV-positive patients. Demographics were also similar: median age 46 years, 89% Caucasian, 12% HCV coinfection with a median CD4 of 276 cells/mm3. [2] The median raltegravir inhibitory concentration (IC50) for wild-type HIV is 3.4 ng/mL.

Raltegravir was present in all CSF specimens with a median concentration of 14.5 ng/mL. The median plasma concentration was 260.9 ng/mL (IQR 2.0 - 640.4) with a median CSF-to-plasma ratio of 5.8% (IQR 2.1%-17.8%). CSF concentrations correlated with plasma concentrations ($r = 0.49$, $p = 0.02$) but not with post-dose sampling time ($p > 0.50$). Raltegravir concentrations in CSF exceeded the IC50 of wild-type HIV in all specimens by a median of 4.3-fold (IQR 2.7-7.7). HIV RNA levels were undetectable in 20 of 21 (95%) CSF specimens and in 13 of 21 (62%) plasma specimens.

Each study concluded that the study drug penetrated CSF in concentrations that are in the therapeutic range to suppress wild-type HIV and would be expected to contribute antiviral activity in the CSF as part of combination therapy.

Drug levels of both drugs in CSF correlated better with total levels in plasma suggesting that therapeutic drug monitoring could indicate effectiveness in the nervous system. Unbound plasma concentrations of darunavir were less closely correlated.

References

1. Best B et al. Darunavir concentrations in CSF exceed the median inhibitory concentration. 49th ICAAC, 12-15 September 2009, San Francisco. Poster abstract A1-1312.
http://www.posters2view.com/icaac/view.php?nu=A1-1312
2. Best B et al. Raltegravir concentrations in CSF exceed the median inhibitory concentration. 49th ICAAC, 12-15 September 2009, San Francisco. Poster abstract A1-1311.
http://www.posters2view.com/icaac/view.php?nu=A1-1311

Raltegravir body composition study: 48-week DEXA results

Simon Collins, HIV i-Base

While some aspects of the lipodystrophy syndrome are better understood and managed, fat accumulation (lipohypertrophy), principally central visceral adipose tissue (VAT), remains unexplained and is still associated with all families of antiretrovirals. While this mechanism is unknown, it appears to have little relationship to the atherogenic lipid and glucose changes that appear to be a separate set of lipodystrophy symptoms.

The DEXA results reported here are from a sub-set of 76/563 naive patients from the double-blind placebo-controlled STARTMRK trial, randomised to either raltegravir or efavirenz, each with tenofovir/FTC. This analysis compared baseline to week 48, with follow-up planned to week 96. Metabolic parameters included fasting lipid and glucose changes and relationship to NCEP goals.

Baseline characteristics for patients in the sub study were similar to the larger group and are summarised in Table 1. Median CD4 count and viral load (in the substudy) was approximately 200 cells/mm3 and 5 log copies/mL.

At 48 weeks there were few overall changes and no significant differences between the two arms. Total fat increased in both arms by around 16-20% in both limbs and trunk (see Table 2). Investigator reported observational changes were two cases of mild fat accumulation in the blinded efavirenz arm. No patients reported lipodystrophy symptoms.

Lipid changes were significantly great in the efavirenz group: TC +33 vs +10; HDL +10 vs + 4; LDL +16 vs +6; and TG +37 vs -3 mg/dL (all p<0.001). The change in the TC:HDL ratio was -0.1 vs -0.3 in the efavirenz and raltegravir groups (p=0.292).

Table 1: Baseline Characteristics in the DEXA Sub-Study

	raltegravir (n=54)	efavirenz (n=57)
Male, n (%)	50 (92.6)	48 (84.2)
Female, n (%)	4 (7.4)	9 (15.8)
White	33 (61.1)	33 (57.9)
Black	14 (25.9)	9 (15.8)
Median CD4 (range)	230 (1 to 573)	202 (6 to 567)
Median viral load, log (range)	4.9 (4 to 6)	5.0 (4 to 6)
B/line CD4 <50	8 (14.8)	9 (15.8)
B/line VL >100K	24 (44.4)	30 (52.6)

Table 2: Body composition changes in STARTMRK at 48 weeks

	raltegravir 400 mg bid			efavirenz 600 mg qd		
Region	n	Baseline mean (gm)	Mean % change † (95% CI)	n	Baseline mean (gm)	Mean % change † (95% CI)
Arms	35	1873.08	23.33 (5.95, 40.72)	41	1724.23	18.94 (11.80, 26.07)
Legs	35	7055.66	16.31 (3.85, 28.77)	41	6305.59	15.63 (9.59, 21.67)
Appendicular	35	8928.73	17.38 (4.34, 30.42)	41	8029.83	16.09 (10.15, 22.03)
Trunk	35	11683.73	17.01 (2.87, 31.15)	41	10142.54	20.46 (11.72, 29.19)
Total	35	20612.46	16.92 (3.52, 30.32)	41	18172.37	17.98 (10.89, 25.07)

N = # of patients in the treatment group. † Mean % changes from baseline are based on the measurements of the pts who were measured at baseline and the time point assessed.

C O M M E N T

The lipohypertrophy profile of each new drug should be included routinely in all Phase III antiretroviral trials. While raltegravir was originally approved over two years ago (October 2007 in the US), the first information on fat accumulation was only presented at ICAAC this year (September 2009). It is now unfortunate that this is based on DEXA rather than CT scans: while DEXA can provide information about limb fat loss, it is not able to separate visceral fat from subcutaneous fat.

While no signal of early problems is reassuring, 48-weeks is probably too early to see significant changes. As efavirenz has previously been linked to fat accumulation, similar results at this timepoint should be interpreted cautiously.

References

1. Berger D et al. Metabolic profiles and body composition changes in treatment-naïve HIV-infected patients treated with raltegravir (RAL)-based vs. efavirenz (EFV)-based combination therapy: 48-week data. 49th ICAAC, 12-15 September 2009, San Francisco. Poster abstract H-1571. http://www.posters2view.com/icaac/view.php?nu=H-1571

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.

References

1. Fehintola FA et al. Tobacco and marijuana uses significantly decrease atazanavir (ATV) trough concentrations in HIV infected individuals. 49th ICAAC, 12-15 September 2009, San Francisco. Poster abstract H-231.
http://www.posters2view.com/icaac/view.php?nu=H-231
2. Brazeau D et al. Effects of CYP2B6 single nucleotide polymorphisms (SNPs) and substance abuse on efavirenz (EFV) pharmacokinetics. 49th ICAAC, 12-15 September 2009, San Francisco. Poster abstract H-228.
http://www.posters2view.com/icaac/view.php?nu=H-228

Other drug interaction studies at ICAAC

HIV-druginteractions.org

These summaries are selected from a longer report published by this group on the Liverpool University site. All references are to the Programme and abstracts for the 49th ICAAC, 12-15 September 2009, San Francisco.

Interactions with vicriviroc

Drug interactions with vicriviroc (30 mg alone or with RTV) were studied in HIV-negative volunteers.

There was no effect on midazolam when administered with vicriviroc alone, but there was a marked increase when administered with ritonavir. Ketoconazole increased vicriviroc AUC by 136% when administered alone and by 503% when administered with ritonavir.

There was no effect on vicriviroc exposure with rifabutin when administered with ritonavir (200 mg once daily). Rifampicin markedly decreased vicriviroc exposure when coadministered with RTV (100 mg twice daily) - the relative oral bioavailability was 11.6% based on AUC. Coadministration of rifampicin with vicriviroc is not recommended.

Carbamazepine had no effect on vicriviroc when administered with ritonavir (100 mg twice daily). In the presence of ritonavir, addition of another CYP3A4 inhibitor or modestly potent CYP3A4 inducer will not require dose adjustment of vicriviroc. If carbamazepine or rifabutin are coadministered with vicriviroc in a RTV-boosted PI-containing regimen, no vicriviroc dose adjustment is required, but ritonavir should be increased to 100 mg twice daily or 200 mg once daily.

Ref: Kasserra C et al. Assessment of pharmacokinetic and safety interactions between vicriviroc and CYP3A4 substrates, inhibitors, and inducers. Abstract H-230.

Opiate substitution therapy and antiretrovirals

Three studies provided information on the interactions between opiate substitution therapy and ARVs.

The effect of darunavir/r (600/100 mg twice daily for 7 days) on the pharmacokinetics of buprenorphine was assessed in 17 HIV-negative subjects stable on buprenorphine/naloxone maintenance therapy (daily doses up to 24/6 mg). There was no effect on buprenorphine AUC, Cmax or trough concentrations; however, norbuprenorphine Cmax increased by 36% and AUC increased by 46%. No subject required dose adjustment of buprenorphine/naloxone. Given the increase in norbuprenorphine concentrations, close clinical monitoring of patients is recommended. [1]

The effect of raltegravir (400 mg twice daily) on the pharmacokinetics of methadone were investigated in 12 HIV-negative subjects stable on methadone. This study reported that there was no change in either methadone AUC or Cmax in the presence of raltegravir and no dose adjustment is required. [2]

The interaction between buprenorphine and ddI, 3TC and tenofovir was investigated in 27 HIV-negative, buprenorphine/naloxone maintained subjects. Data for ddI and tenofovir were compared to values obtained from 20 control subjects not receiving buprenorphine; 3TC was compared to control data. No significant changes in buprenorphine pharmacokinetics were observed when coadministered with ddI, 3TC and tenofovir. When compared to controls, buprenorphine had no statistically significant effect on NRTI concentrations. [3]

References

1. Sekar VJ et al. Pharmacokinetic (PK) Interaction between darunavir in combination with low-dose ritonavir (DRV/r) and buprenorphine/naloxone (bup/nlx). Abstract H-232.
2. Anderson MS et al. Effect of raltegravir (RAL) on the pharmacokinetics (PK) of methadone. Abstract A1-1295.
3. Baker K et al. Interactions between buprenorphine and antiretrovirals: nucleos(t)ide reverse transcriptase inhibitors (NRTI) didanosine, lamivudine and tenofovir. Abstract A1-1306.

Darunavir and food

The oral bioavailability and steady state pharmacokinetics of a paediatric oral suspension of darunavir were assessed in two studies in 23 HIV-negative adult subjects. Firstly, ritonavir (100 mg twice daily) was administered on days 1-5 and a single 600 mg dose of darunavir on day 3 as a) tablet with food, b) suspension fasted, and c) suspension with food. In the second part, darunavir pharmacokinetics were assessed following administration of the suspension (600 mg twice daily) with ritonavir (100 mg twice daily) for 7 days. In the first study the criteria for bioequivalence (90% CI of LSM ratios within limits of 80-125%) were met for Cmax and AUC when comparing tablet (with food) and suspension (with or without food). Pharmacokinetic data obtained with the suspension in the second study were comparable to historical data obtained with the same dose in the tablet formulation. The oral suspension will be further evaluated in paediatric HIV-positive subjects.

Ref: Sekar VJ et al. Bioavailability and food effect of darunavir (DRV) following administration of an oral suspension. Abstract H-233.

Raltegavir and rifabutin

Coadministration of raltegravir (400 mg twice daily) and rifabutin (300 mg once daily) was investigated in 16 HIV-negative subjects. Raltegravir AUC increased by 19%, Cmax increased by 39% and Ctrough decreased by 20%. These changes were not deemed to be clinically significant and no dose adjustment is required.

Ref: Brainard DM et al. Lack of a Clinically important effect of rifabutin (RFB) on raltegravir (RAL) pharmacokinetics. Abstract A1-1296.

Raltegavir and fosamprenavir or fosamprenavir/ritonavir

The interaction between raltegravir and atazanavir or atazanavir/ritonavir and the effect of food was studied in HIV-negative subjects. Raltegravir (400 mg twice daily) and fosamprenavir (1400 mg twice daily) or fosamprenavir/ritonavir (700/100 mg twice daily or 1400/100 mg once daily) were administered alone and in combination with and without a light meal. The effects are summarised in Table 1 below.

Table 1. PK interactions of fosamprenavir doses with raltegravir

	raltegravir			*amprenavir*		
	AUC	***Cmax***	***Cmin***	***AUC***	***Cmax***	***Cmin***
FPV 1400 mg twice daily + light meal:						
	-29%	***-5%***	***-68%***	***-19%***	***-17%***	***-33%***
FPV 1400 mg twice daily, fasted:						
	-37%	***-28%***	***-38%***	***-36%***	***-27%***	***-43%.***
FPV/r 700/100 mg twice daily + light meal:						
	-30%	***-15%***	***-41%***	***+13%***	***+27%***	***-27%.***
FPV /r 700/100 mg twice daily, fasted:						
	-15%	***+6%***	***-25%***	***-24%***	***-18%***	***-50%.***
FPV/r 1400/100 mg once daily + light meal:						
	-254%	***-56%***	***-54%***	***-25%***	***-25%***	***-33%.***
FPV /r 1400/100 mg once daily, fasted:						
	-55%	***-51%***	***-36%***	***-16%***	***-14%***	***-19%.***

Although raltegravir exposure decreased with fosamprenavir, especially at higher doses of ritonavir, raltegravir Cmin were 3- to 9.4-fold higher than the IC95 for WT HIV (14.6 ng/ml). Amprenavir concentrations were decreased, however, Cmins for the boosted regimens were 2.1- to 7.8-fold higher than the EC90 for PI-naïve HIV+ patients (228 ng/ml). The clinical implications of these results have yet to be determined.

Ref: Luber A et al. Steady-state pharmacokinetics (PK) of fosamprenavir (FPV) and raltegravir (RAL) alone and combined with unboosted and ritonavir-boosted FPV Abstract A1-1297.

Etravirine and lopinavir/r

This study looked at the interaction between etravirine (200 mg twice daily) and the tablet formulation of lopinavir/ritonavir (400/100 mg twice daily) in 16 HIV-negative subjects. Coadministration decreased etravirine AUC, Cmax and Cmin by 35%, 30% and 45%, respectively; lopinavir AUC, Cmax and Cmin decreased by 13%, 11% and 20%, respectively. There was no change in the pharmacokinetics of ritonavir. These etravirine results are in contrast to previous data obtained with capsule formulation of lopinavir/ritonavir which showed increased etravirine exposure. No dose adjustment of etravirine is required as the effect of lopinavir/ritonavir tablets is similar to the effect of darunavir/ritonavir seen in clinical trials which demonstrated favourable etravirine efficacy and safety. The decrease in lopinavir concentrations was similar to earlier data and is not considered clinically relevant.

Ref: Scholler-Gyure M et al. Pharmacokinetic (PK) Interaction between etravirine (ETR) and lopinavir/ritonavir (LPV/r). Abstract A1-1298.

Etravirine and fluconazole or voriconazole

The pharmacokinetic interaction between etravirine (200 mg twice daily) and fluconazole (200 mg once daily) or voriconazole (200 mg twice daily) was studied in HIV-negative subjects. Fluconazole increased etravirine AUC, Cmax and Cmin by 86%, 75% and 2.09-fold, respectively (n=16); fluconazole AUC, Cmax and Cmin decreased by 6%, 8% and 9%, respectively (n=15). Voriconazole increased etravirine AUC, Cmax and Cmin by 36%, 26% and 52%, respectively (n=16); voriconazole AUC and Cmin increased by 14% and 23%, but Cmax decreased by 5% (n=14). Combinations were generally safe and well tolerated.

Ref: Scholler-Gyure M et al. Pharmacokinetic (PK) interaction between etravirine (ETR) and fluconazole (FLU) or voriconazole (VOR) in HIV-negative volunteers. Abstract A1-1299.

LPV/r and echinacea

The effect of echinacea (500 mg three times daily for two weeks) on the pharmacokinetics of lopinavir/ritonavir (400/100 mg twice daily) was studied in 16 HIV-negative subjects. Neither lopinavir nor ritonavir pharmacokinetics were altered by coadministration of echinacea (lopinavir AUC decrease by 4% and there was no change in Cmax). Although echinacea has been shown modulate P450 3A4 in vitro, these data suggest a clinically significant interaction is unlikely.

Ref: Malati CY et al. Echinacea purpurea does not alter the steady state pharmacokinetics of lopinavir or ritonavir in healthy human volunteers. Abstract A1-1307.

"Quad" fixed-dose combination and food

A "quad" fixed dose combination tablet containing emtricitabine (200 mg), tenofovir (300 mg), elvitegravir (150 mg) and the boosting agent GS-9350 (150 mg) is currently in development. This evaluated the effects no food, or light (373 kcal, 20% fat) or high (800 kcal, 50% fat) meals on single doses of the "quad" tablet in 24 HIV? subjects. The pharmacokinetics of emtricitabine were equivalent when given fasted or with either meal. Compared to the fasting state, tenofovir AUC increased by 24% with a light meal and by 23% with a high fat meal; Cmax increase by 20% with a light meal, but was similar to fasting with a high fat meal. Elvitegravir AUC and Cmax increased by 34% and 22% with a light meal and increased by 87% and 56% with a high fat meal (all compared to fasting). The AUC of GS-9350 was similar with a light meal, but decreased by 17% with a high fat meal (all compared to fasting).

Ref: German P et al. Effect of food on pharmacokinetics (PK) of elvitegravir (EVG), emtricitabine (FTC), tenofovir DF (TDF) and the pharmacoenhancer GS?9350 as a fixed dose combination tablet. Abstract A1-1300.

GS-9350 or ritonavir to boost GS-9350

GS-9350 is CYP3A4 inhibitor currently in development as an alternative boosting agent to ritonavir. The study compared the effects of GS=9350 (100 or 150 mg once daily) and ritonavir (100 mg once daily) on the pharmacokinetics of atazanavir (300 mg once daily) in 33 HIV-negative subjects. The higher dose of GS-9350 was found to be bioequivalent (80-125%) to 100 mg ritonavir (atazanavir GMRs of 1.01 for AUC, 0.92 for Cmax and 0.98 for Cmin). Atazanavir exposure was lower with the lower dose of GS-9350.

Ref: Ramanathan S et al. Pharmacokinetic boosting of atazanavir with the pharmacoenhancer GS-9350 versus ritonavir. Abstract A1-1301.

NVP extended release formulation

Nevirapine is licensed for twice daily administration, but is frequently given once daily. Two extended release formulation of nevirapine are currently in development. Patients who were stable on twice daily nevirapine were switch to one of two extended release formulations (XR25% and XR20%). In the 92 patients treated with XR, absorption was decreased - Tmax increased from <2h with the twice daily dosing to 6.7-8.6 h with the XR formulations. Cmin of XR formulations were comparable to the twice daily formulation, whereas Cmax of the XR formulations were lower. Relative bioavailability (based on AUC0-24) was 80% for the XR25% formulation and 71% for the XR20% formulation. No virological failures were observed. The XR25% formulation has been selected for further development due to its increased bioavailability and decreased variability compared to XR20%.

Ref: Quinson A et al. Steady state evaluation of two extended release (XR) nevirapine (NVP) tablets 400 mg QD compared with immediate release (IR) NVP tablets 200 mg BID in HIV-1 infected patients. Abstract A1-1310.

CONFERENCE REPORTS

5th IAS Conference on HIV Pathogenesis, Treatment and Prevention

19-23 July 2009, Cape Town

Introduction

We conclude our reports from this important conference with the following article on paediatric studies.

- Overview of paediatric studies

Overview of paediatric studies

Polly Clayden, HIV i-Base

A wealth of paediatric data was presented at IAS 2009 held in Cape Town in July. Also preceding the conference was the 1st International Workshop on HIV Pediatrics, which looks as if it will become an annual fixture on the conference calendar and gave an additional opportunity to present and discuss the state of the art in the field.

Overall, far too much was presented to review here. Abstracts, some slides and, for IAS2009, webcasts can be viewed on the respective conference websites.

Several themes occurred over and over again at both meetings.

National capacity for early infant diagnosis, which not only enables early initiation of treatment but also gives a clearer picture of how well prevention of mother-to-child transmission (PMTCT) programmes are performing, with the goal of vastly reducing cases of paediatric HIV, is not yet nearly sufficient in most places.

Where infants are diagnosed in time, early initiation of treatment is not without its difficulties. It can, however, be extremely beneficial in young children.

Treatment of children who are HIV-infected despite exposure to single-dose nevirapine through PMTCT is another challenge, as is what to do in the longer term with exposed children initiated on a protease inhibitor-containing HAART to overcome the risks of NNRTI resistance.

Strategies to simplify regimens, including paediatric fixed-dose combinations and once-a-day dosing, are essential for successful management of children with HIV, as are strategies to enable co-treatment of tuberculosis in this population.

The research summarised below addresses these issues.

Early infant diagnosis

Several guidelines now recommend universal treatment for HIV-infected infants. However, in resource-limited settings early infant diagnosis (EID) is frequently an obstacle to early initiation of antiretrovirals.

A survey by World Health Organization (WHO) asked, "What is available for early infant diagnosis?" and found the number of laboratories in several countries mismatched to the estimated number of HIV-exposed infants and necessary tests. This assessment of national capacity was conducted to inform revisions to their guidelines for infant diagnosis and treatment. [1]

For this survey, a questionnaire on clinical and laboratory capacity was sent to HIV experts in 34 high-burden countries and data were collected between February and April 2008. Replies were received from 18 of the 34 selected countries: 12 African, two South American, two Asian and one Middle Eastern.

This revealed huge variation in the number of children assessed per laboratory (range 7 - 190 000 during the study period). When virological tests were offered, the entry points were usually inpatient/outpatient services, prevention of mother-to-child transmission (PMTCT) or antiretroviral therapy (ART) sites, and laboratories were centralised and usually located in capital cities. Six countries surveyed implement HIV DNA polymerase chain reaction (PCR), 5 RNA PCR and 7 both. Ten countries used filter paper with dried blood spots (DBS) to transport samples. All the countries that responded had capacity to measure CD4% and absolute CD4 cell counts.

Although the survey confirmed that several high-burden countries are building capacity for EID, it showed that at present in many countries capacity does not reflect estimated need.

In many resource-limited countries it is only possible to use a single diagnostic test. The optimal time to perform this is unclear, however, particularly when children are breastfed. The WHO researchers used a model to calculate the number of children becoming infected and being diagnosed at different time points from birth in order to estimate the optimal time to diagnose the maximum number of children but at the same time minimise mortality. [2]

This modelling showed a decreasing trend of infant survival at 6 months, depending on the time the test was performed. The investigators suggested that 4 - 6 weeks of age is the optimal time for infant testing in a breastfeeding population.

With greater laboratory capacity and newer technology, testing earlier than 6 weeks could mean earlier initiation of treatment. But the sensitivity of viral detection tests before 6 weeks of age is unknown, particularly when performed on infants with antiretroviral exposure for PMTCT.

A South African study looked at the sensitivity of assays at earlier time points in infants born to HIV-positive women at Rahima Moosa Hospital, Johannesburg.[3] Blood was sampled at birth and at 2, 4, 6 and 10 weeks, and stored. HIV-exposed infants were routinely tested at 6 weeks with HIV DNA PCR using a liquid blood sample.

Stored DBS samples from each time point were tested with HIV DNA PCR (Amplicor v1.5), TaqMan HIV-1 (CAP/CTM) and APTIMA HIV-1 (GEN-PROBE) assays. The investigators used samples from two age-matched, PCR-negative infants as controls.

Mothers received a range of PMTCT interventions: no antiretrovirals, single-dose nevirapine (NVP), single-dose NVP plus zidovudine (AZT) or HAART.

At 9 months of the study, 253/373 (68%) infants had 6-week PCR results; the remaining 120 (32%) did not return for testing. Eighteen (7.1%) were HIV infected at 6 weeks despite the majority receiving formula milk exclusively and all receiving NVP and AZT PMTCT prophylaxis.

Of the 17 infected infants with complete results, both CAP/CTM and APTIMA assays were positive in 11/17, 13/13 and 14/14 birth, 4- and 6-week samples, respectively.

The quantitative CAP/CTM assay showed lower viral load results at 2 weeks of age (the only time point when false negatives occurred). The investigators noted that this was probably due to PMTCT prophylaxis increasing the proportional number of infants infected in utero who can therefore be diagnosed at birth.

Both assays were more sensitive for earlier HIV detection than HIV DNA PCR, which detected 9/17 birth samples. CAP/CTM had the highest specificity (100%) and HIV DNA PCR the lowest (95%).

Although this is a small sample, newer technologies appear to be more sensitive than standard PCR. These initial results suggest that the majority of in utero and perinatal infections can be detected by using either CAP/CTM or APTIMA assays if they are available.

There were also reports from programmes using DBS.

A sub-study of the PMTCT Keso Bora trial conducted in Burkina Faso used a quantitative HIV RNA assay (Biocentric) and assessed DBS samples compared with paired plasma samples obtained from HIV-exposed infants aged up to 6 weeks, 3 - 6 months and 9 - 18 months.[4] All measurements were performed locally.

The study investigators reported 100% sensitivity (102/102) and specificity (105/105) (95% confidence interval (CI) 97.2 - 100%, correlation 0.906) using DBS. Of note, Biocentric is the homebrew ANRS assay, so they would have to develop their own probes, reagents, etc.

A Cambodian study assessed the feasibility of very early diagnosis (0 - 3 days of age) using heel-prick samples on DBS and a real time DNA assay (Bicentric). [5] A second DBS was performed at week 6. Infants with positive results at 0 - 3 days or 6 weeks were followed up with HIV RNA quantification as soon as possible.

At 0-3 days, 3/370 (0.8%) infants had positive results (1 infant died before week 6). 327/333 were confirmed negative at 6 weeks and 6 were DNA positive (1.8%) and subsequently confirmed RNA positive.

The investigators suggested that these preliminary results demonstrate the feasibility of a minimally invasive very early diagnosis using DBS.

Difficulties with implementation

A study from Swaziland, conducted by the national ART programme and the Clinton Foundation, highlighted the difficulties of treatment initiation in infants following early diagnosis. [6]

Since March 2007 the EID programme using DNA PCR was expanded in response to high infant mortality in HIV-infected children. By November 2008, however, this had led to neither an increase in infants receiving treatment nor a decrease in mortality.

The study was a retrospective record review of all infants testing positive at 15 health facilities in the Manzini Region from January to August 2008. The investigators reported that 78% of results were available at the facility, and 44% of results were documented as having been received by the caregiver. Only 58/176 (33%) of children were enrolled at an ART centre and 34 initiated on treatment. Of those with data available 81% were eligible for ART, and among eligible children, 82% initiated treatment. Overall 19% of infants testing positive were initiated on treatment at the time of the evaluation.

This study found that the greatest points of loss are return of the result to caregivers and infant enrollment at the ART centre for treatment.

Infant outcomes

There are limited data describing outcomes for infants initiating treatment at less than 1 year.

The MTCT Plus Initiative showed data from sites in eight African countries and Thailand comparing infants with older children initiated between February 2003 and September 2008. [7]

The investigators looked at change in CD4 percentage from baseline using linear modelling adjusted for duration of highly active antiretroviral therapy (HAART), country, baseline CD4 percentage, NVP exposure for PMTCT, and age at initiation.

Of 542 children initiating treatment and followed up for a median of 30 months (intraquartile range (IQR) 12 - 39), 190 (35%) were aged <12 months at initiation and the remainder >12 months (median 36 months, IQR 19.5 - 67), 51% were male, and18% had Centers for Disease Control (CDC) stage C disease.

The infants had a higher mortality rate than the older children, 7.5 v. 3.2/100 person-years. Of 31 (54%) infant deaths, 81% occurred within 3 months of treatment initiation.

Among the children for whom data were available there was no difference between infants and older children in change of CD4 percentage from baseline. Baseline CD4 percentage ($p<0.01$) and time on HAART ($p<0.001$) were significantly associated with an increase in CD4 percentage in multivariate analysis.

In this analysis, although infants initiating HAART had a higher mortality at the start of treatment, the infants who survived had good immunological response over >3 years of follow-up, similar to that of older children.

A South African review of infants initiated on HAART at the Family Clinic for HIV at Tygerberg Hospital and Ikwezi community clinic

from June 2007 to August 2008 showed high levels of virological suppression to 24 weeks. [8]

Infants received lopinavir/ritonavir (LPV/r) with stavudine (d4T) and lamivudine (3TC) in accordance with South African guidelines. Of 98 initiated, 47 had 24 weeks of follow-up. Of the remainder, 6 (6%) were lost to follow-up, 6 (6%) died and 33 (33.7%) were transferred.

The median age at initiation was 4.5 months and 33 (70%) infants were ≤6 months old (median age 3.68 months). All had immunological or clinical criteria for treatment. The majority, 42/47 (89.4%) of all infants and 30/33 (91%) ≤6 months of age, had WHO stage 3 or 4 disease.

Tuberculosis (TB) is a common co-morbidity in this population, and 11/47 infants required co-therapy with rifampicin (given with additional ritonavir).

At 24 weeks 37/47 children (79%) in the > 6 months age group and 26/33 (82%) aged <6 months had viral loads <50 copies/mL.

The investigators noted that the low age of initiation of treatment in this cohort reflected young infants with severe HIV disease rather than early initiation of treatment to prevent mortality and morbidity.

mproved neurodevelopmental outcomes

The developing brain is a major target for HIV. It is not yet known whether timing of initiation of antiretroviral therapy will affect neurodevelopmental outcomes in infants.

A substudy of CHER compared neurodevelopmental outcomes of 115 infants in this study from Tygerberg Children's Hospital with 84 control infants enrolled in a linked vaccine study, CIPRA-SA Project4. [9]

In this prospective study, the investigators looked at the neurodevelopmental profile, according to the Griffiths Mental Developmental Scales (GMDS), at 10 - 15 months of age in four groups of infants:

- HIV-unexposed, uninfected

- HIV-exposed, uninfected

- HIV-infected, HAART initiated before 12 weeks of age

- HIV infected, HAART deferred until eligibility criteria met.

The investigators were blinded to the infants' groups and a translator was used for Xhosa-speaking participants.

Of 115 infants from CHER enrolled, 13 withdrew from the study and/or were not co-enrolled (10 early, 3 deferred), 8 died (all deferred) and 4 were excluded (3 early, 1 deferred).

The investigators found that infants initiated on early ART have significantly better locomotor and general scores on the Griffiths Mental Development Scales at a median age of 11 months compared with infants on deferred HAART. Although mean quotients were lower on the other subscales in the deferred group, the differences were not significant. The mean scores on all subscales in the unexposed, uninfected group and the early HAART group were similar. They noted these results were "despite careful monitoring and ready access to ART in the latter" (Table I).

Table I. Mean quotients of infants for deferred vs early HAART and HIV- exposed uninfected and unexposed infants

	Deferred ART	Early ART	HIV-exposed uninfected	HIV-unexposed	p-value early vs deferred
No. assessed	26	66	28	34	
Median age in months (range)	11.0 (10.1 - 14.4)	11.0 (10.0 - 15.5)	11.4 (10.1 - 15.5)	11.5 (9.9 - 13.6)	
Mean locomotor quotient (± 1 SD)	88.9 (±16.3)	97.6 (±12.5)	105.3 (±14.3)	101.6 (±3.7)	0.01
Mean general quotient ± 1 SD	100.1 (±13.8)	106.3 (±10.6)	106.0 (±10.1)	106.9 (±11.7)	0.02

Treating children exposed to single dose nevirapine for PMTCT

Two studies looked at treatment of HIV-infected children with prior exposure to NVP to prevent MTCT.

Preliminary findings from IMPAACT 1060 confirmed concerns that NVP-exposed children could do less well receiving NVP containing HAART than protease inhibitor (PI)-containing HAART. [10, 11]

This was a randomised trial of treatment-eligible children aged 6 months - 3 years conducted in seven African countries. NVP-exposed (cohort 1, n=288) and unexposed (cohort 2, n=288) children received either LPV/r or NVP, plus 3TC and AZT. Children were stratified by age <12months v. ≥12 months with an equal number to be enrolled in each age group.

A similar study of exposed and unexposed mothers had also been conducted (A5208). In this trial, the arm in which exposed mothers received NVP-containing HAART, was stopped early by the Data Safety Monitoring Board (DSMB). This was due to superior performance of the LPV/r-containing HAART arm. [12, 13]

Following a scheduled DSMB review of IMPAACT 1060 on 20 April 2009, enrolment to cohort 1 also closed prematurely owing to a trend towards consistency with the A5208 results. At 24 weeks, virological failure (<400 copies/mL) was observed in 40% of the 60 infants <12 months v. 23% ≥12 months receiving NVP and LPV/r, respectively. Among the older children, 29% out of 22 and 17% of 19 receiving NVP and LPV/r experienced failure.

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

The NEVEREST study investigated whether NVP-exposed children, initially suppressed on LPV/r-based HAART, can safely switch to a NVP-based regimen. [14, 15]

In this study children aged 6 weeks - 2 years and eligible for treatment (n=323) were initiated on LPV/r plus 3TC and d4T. Children achieving a viral load <400 copies/mL and stable for ≥3 months were randomised (*N*=195) to either remain on LPV/r (control, n=99) or switch to NVP (switch, n=96), and then followed up to 52 weeks.

When the investigators looked at viral load <50 copies/ml to 52 weeks they found that 42.4% of children in the control group and 56.2% in the switch group sustained viral suppression (p=0.01). However, 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 <1 000 copies/mL, 98% v. 80% of children in the control and switch groups achieved this (p=0.001).

The investigators suggest 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.

This group also showed data from an evaluation of lipid profiles in children in the control and switch groups. [16]

They found no difference between the two groups at randomisation. But at 9 months after the change in regimen non-fasting total cholesterol (TC) and high-density lipoprotein (HDL) were significantly higher among the switch group (mean TC 4.13, HDL 1.36 mmol/l) compared with the control group (mean TC 3.73, HDL 1.07 mmol/l). Significantly lower triglyceride (TG) levels were found in the switch group (mean TG 1.36 mmol/l) compared with the control group (mean TG 1.53 mmol/l).

They noted that the clinical significance of these non-fasting lipid changes requires further investigation.

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.

Another NEVEREST trial of efavirenz (EFV) vs LPV/r is planned in nevirapine-exposed children >3 years old.

These studies all underscore the limited treatment options available for children, particularly in resource-limited settings.

Using a nevirapine-containing fixed dose combination in the CHAPAS trial

Paediatric fixed dose combination (FDC) tablets provide simpler alternatives to liquids for children.

Cipla have produced scored, dispersible tablets of d4T/3TC/NVP (baby and junior Triomune) with the correct dose ratios for children.

A sub-study of the CHAPAS trial (Children with HIV in Africa Pharmocokinetics and Adherence of Simple Antiretroviral Regimens), in Zambia, evaluated the need for dose escalation of NVP.[17] This strategy is currently recommended but requires dosing with separate tablets, making initial treatment more complex.

Children were randomised to start antiretroviral therapy with full-dose NVP (Triomune am/pm) vs dose escalation, using an initial 14 days of half-dose NVP (Triomune am; Lamivir-S (combined d4T/3TC) pm) followed by full dose. Children were dosed in accordance with WHO weight band tables. The primary endpoint was clinical/laboratory grade 3/4 adverse events (AEs) related to NVP.

In this comparison, 211 children aged 2 - 9 years with a median CD4 percentage of 13% were followed for a median of 92 weeks. Severe stunting, wasting and immunosuppression were common in the children. Seventeen children were lost to follow-up.

The investigators reported 31(18 per 100 person-years) vs 29 (16.5 per 100 person-years) grade 3/4 AEs definitely/probably or uncertainly NVP-related in children receiving full-dose vs dose-escalation (incidence rate ratio (IRR) 1.09 (95% CI 0.63 - 1.87), p=0.74).

Twelve (11%) full-dose vs 2 (2%) dose escalation children had grade 2 disseminated skin rash and 1 receiving full dose had grade 1 rash. Two children (one from each arm) substituted with EFV; 3 continued full-dose NVP; 9 (8 full dose and 1 dose escalation) stopped NVP and restarted with successful dose escalation; and 1 full dose stopped, started a lower NVP dose, had another rash and substituted EFV.

Overall 90% of children who started with full-dose NVP continued uninterrupted in this study. As dose escalation requires provision of separate drug formulations, the evaluation of policy implications for dose escalation of NVP in fixed-dose combination HAART is ongoing.

The CHAPAS trial also investigated the pharmacokinetics of NVP in children treated with Triomune Baby/Junior and rifampicin-based tuberculosis treatment. [18]

EFV-based regimens are currently recommended for concomitant use with rifampicin, but EFV is not currently indicated for children below 3 years of age. Earlier CHAPAS data suggest that the higher dose ratio of NVP to NRTI in Triomune Baby/Junior may compensate for the dose reduction induced by rifampicin.

Pharmacokinetic sampling was performed in 22 children after 4 weeks of concurrent NVP and rifampicin-containing regimens. Rifampicin was dosed at 10 - 20 mg/kg per day. Samples were pre-dose (C_0) and 1, 2 and 6 hours post-dose, and nevirapine plasma concentrations were determined using LC-MS/MS. NVP pharmacokinetics in children without TB treatment (n=16) were compared in multivariate linear regression analysis. The median age of the 21 children analysed was 1.55 (range 0.66 - 3.18) years, and 10 were girls.

The investigators found that only 11 (52%) of the children receiving TB treatment reached sufficient NVP trough levels (C_0 <3.0 mg/L). Multvariate analysis revealed a 41% (95% CI 24 - 55%) reduction in nevirapine AUC with concomitant rifampicin. They noted a 3.4% increase in AUC for each 10 mg/m2 increase in NVP dose/m2.

They recommend caution with this approach in young children until more efficacy and safety data are available. They suggest that an increased NVP dose is likely to be necessary and requires further evaluation.

Once a day lamivudine and abacavir, and abacavir hypersensitivity in the ARROW trial

Simplification of HAART regimens provides benefit for children, caregivers and health workers. To date there are no data on once-daily use of 3TC and abacavir (ABC) in resource-limited settings.

A substudy from the ARROW trial (a randomised trial of monitoring and first-line induction-maintenance strategies) compared the PK of once- v. twice-daily 3TC and abacavir (ABC) (Kivexa).[19] This was a cross-over study performed in 41 Ugandan children aged 3 - 12 years receiving HAART, dosed according to weight bands. The ARROW trial uses scored tablets of ABC/3TC to ensure better accuracy of division and more flexible dosing. Total daily doses were 150+300 mg, 225+450 mg and 300+600 mg for children weighing 12 - 20 kg, 20 - 25 kg and >25 kg, respectively.

PK sampling was performed for twice-daily dosing at steady state (36 weeks) pre-dose, and 1, 2, 4, 6, 8 and 12 hours post dose. Children were then switched to the once-daily dose and further sampling was performed at 4 weeks with an additional sampling at 24 hours.

Daily area under the curve (AUC0-24) and peak level (Cmax) were compared by geometric mean ratios (GMR). GMR with 90% CI within 0.80 - 1.25 was considered to be bioequivalent.

PK parameters were available for 35 and 36 children for 3TC and ABC, respectively. Approximately half were in the younger age group.

The investigators reported that in children 3 - 12 years, AUC_{0-24} of both 3TC and ABC were bioequivalent with once and twice daily regimens but Cmax was 76% and 64% higher for 3TC and ABC respectively. No grade 3/4 adverse events were reported and no child discontinued after the switch to once-daily dosing.

In this analysis, in contrast to data from European children in PENTA 13, 3TC AUC levels in 3 - 6- and 7 - 12-year-old children were similar for both once- and twice-daily dosing and similar to levels in older children. The investigators noted that many younger children in PENTA 13, whose 3TC levels were lower, received syrups, but ARROW children received tablets. They concluded that these results suggest that once-daily dosing of 3TC and ABC is feasible in resource-limited settings.

The ARROW investigators also showed data describing successful management of hypersensitivity reactions among children in this trial in Uganda and Zimbabwe.[20]

The WHO recommends ABC for paediatric first-line treatment. Hypersensitivity reactions (HSR) occur in 2 - 5% of people receiving ABC in clinical trails and are strongly associated with the presence of the HLA-B*5701 allele. Prospective screening for HLA-B*5701 is sometimes recommended, but this pharmacogenetic test is rarely available in resource-limited settings.

Clinical diagnosis and management may be complicated in this setting due to widespread use of NVP and cotrimoxazole and febrile infections.

Health workers and caregivers were trained in recognition and management of ABC-HSR and all suspected HSR underwent independent clinical review. ABC was only discontinued in 7 cases.

The investigators reported that suspected ABC-HSR was rare (3/1 207, 0.2% (95% CI, 0.05 - 0.7%)) in this trial, consistent with reports of a lower prevalence of HLA-B*5701 in black populations. Clinical symptoms (fever, rash) occurred 9 - 13 days after initiation of HAART; 2/3 cases had additional gastro-intestinal and respiratory symptoms and required hospitalisation.

ABC-HSR was successfully managed despite co-administration of cotrimoxazole and NVP, and the investigators recommend that ABC can be used safely in resource-limited settings.

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TREATMENT ACCESS

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

C O M M E N T

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.org

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

ANTIRETROVIRALS

Tibotec issues Dear Doctor letter in Europe concerning severe etravirine reactions: three case reports

Following the approval of etravirine, three cases of severe skin rash or hypersensitivity in patients on etravirinecontaining regimens resulted, in August 2009, in the issuing of a Dear Healthcare Professional (DHCP) letter in the United States, that we published in the last issue of HTB. [1]

On 19th October, Tibotec issued a similar letter to healthcare workers in the UK. As this letter has not been published online, please see the September/October issue of HTB for the US letter. [2]

The three case studies that led to the US letter are summarised below.

Case 1: A 49 year old HIV positive female developed TEN, resulting in her fatality. First symptoms of rash (widespread rash with intense itching) appeared 10 days after starting etravirine/darunavir/raltegravir. Four days later, the rash was described as papular and pruritic. A further 4 days later, pruritus was increasingly widespread with fine macropapular erythema on the patient's back. Darunavir was withdrawn after 19 days of treatment and lopinavir/r was prescribed. At this time, the oral cavity was clear. After 3 days, the rash had improved but the patient experienced ongoing cutaneous irritation. The rash had settled seven days later; however, the patient still experienced cutaneous irritation and developed headache and arthralgia. All medications were withdrawn (etravirine was withdrawn after 29 days of treatment). The patient was hospitalized with erythroderma, oral ulceration, and a fever (40.5°C). The patient experienced a rash that involved more than 30% of her body surface area, mucosal ulceration, likely vaginal involvement, and hemorrhagic conjunctivitis. TEN was diagnosed. The patient underwent an emergency tracheotomy and died. The reporting physician felt that the cause of TEN was an Adverse Drug Reaction (ADR), as there was no obvious preceding infection or alternative cause.

Case 2: A 49 year old HIV positive female experienced severe hypersensitivity reaction with hepatic failure, from which she recovered. The patient had a history of increased hepatic enzymes while on nelfinavir and nevirapine therapy, and hypersensitivity to efavirenz, indinavir, and sulfamethoxazole/trimethoprim. ARV treatment with lopinavi/r, raltegravir, and etravirine was started simultaneously. Seventeen days after starting ART, she developed a rash (not further specified regarding severity or clinical aspect). All ARVs were stopped 2 days later. Seven days later, the patient was hospitalised for hepatitis. The patient's liver function tests (LFTs) peaked at 3,000 u/L and she subsequently developed progressive hepatic encephalopathy. The patient responded to highdose steroids and recovered from the events. Liver biopsy results revealed progressive diffuse active destructive hepatitis with global lobular disarray, infiltrating mononuclear cells, and extensive hepatocellular necrosis. These findings were not compatible with a viral or toxic/metabolic/druginduced hepatitis.

Case 3: A 31 year old HIVpositive male experienced TEN (reported as Lyell's syndrome) while on etravirine treatment for HIV infection. The subject experienced a grade 4 rash with mucosal involvement, 22 days after starting treatment with ETR. Full blood count and biochemistry were reported normal. Treatment with ETR was stopped 8 days later. The patient was hospitalised 2 days later with generalized erythematous rash, itchy, with pink and hydrated mucous membranes with diffuse confluent erythematous rash on the trunk and limbs. There were no lesions in the oral mucosa, but there were mucosal lesions in the genital and perianal region. This was diagnosed as Toxicodermatosis (subsumed under Lyell's syndrome). Approximately two weeks after stopping treatment with etravirine, the patient died from myocardial infarction. The physician considered the relationship between Lyell's syndrome and etravirine as possible and the death from myocardial infarction as not related to etravirine. In september 2009, the investigator downgraded the case to a StevensJohnson Syndrome. The subject's medical history and concurrent conditions included alcoholism, cardiac insufficiency, coronary angioplasty and dilated myocardiopathy.

For further information please contact the Medical Virology departments at Tibotec directly on +44 (0)1494 56 8313.

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   http://www.tibotectherapeutics.com/tibotectherapeutics/documents/INTELENCE_DHCP.pdf
2. Etravirine (Intelence) label change in the US due to severe hypersensitivity reactions. HTB September/October 2009.
   http://www.i-base.info/htb/v10/htb10-9-10/Intelence.html

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

DRUG 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 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.”

C O M M E N T

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.

DRUG INTERACTIONS

Essential news from Liverpool University drug interaction resource (HIV-druginteractions.org). See also the comprehensive drug interaction and pharmacology reports from the 49th ICAAC earlier in this issue of HTB.

Reduced etravirine levels after direct switch from efavirenz

This study in 25 healthy volunteers assessed the pharmacokinetics of etravirine (400 mg once daily and 200 mg twice daily) without and with a preceding efavirenz intake period (600 mg once daily for 14 days). Etravirine pharmacokinetics were assessed before and after efavirenz intake.

Steady state etravirine pharmacokinetic parameters were significantly lower after efavirenz intake in the once daily and twice daily arms. Etravirine AUC, Cmax and Ctrough when given once daily decreased by 29%, 22% and 33%, respectively. When given twice daily, etravirine AUC, Cmax and Ctrough decreased by 28%, 21% and 37%, respectively. All subjects had detectable efavirenz concentrations 7 days after stopping efavirenz intake; 5/25 had concentrations above the suggested minimum effective concentration of 1000 ng/ml.

The authors conclude that the induction effect of efavirenz persists for at least 2 weeks after stopping drug intake, but that the decrease in etravirine is not likely to be clinically significant. However, further clinical data are warranted.

Ref: Boffito M, Jackson A, Lamorde M, et al. Pharmacokinetics and safety of etravirine administered once or twice daily after 2 weeks treatment with efavirenz in healthy volunteers. J Acquir Immune Defic Syndr, 2009, 52(2): 222-227.

http://www.ncbi.nlm.nih.gov/pubmed/19620877

Gemfibrozil significantly reduced by lopinavir/r

This was an open label, single sequence study in 15 healthy volunteers comparing gemfibrozil pharmacokinetics parameters before and after two weeks of lopinavir/ritonavir (400/100 mg twice daily).

The GMR (90% CI) for gemfibrozil AUC after 14 days of lopinavir/ritonavir compared with base line was 0.59 (0.52 to 0.67) ($P<0.001$). GMR (90%CI) for gemfibrozil apparent oral clearance and Cmax were 1.69 (1.41 to 1.97) and 0.67 (0.49 to 0.86), respectively ($P<0.0001$ and $P<0.01$, respectively). There was no change in gemfibrozil half life.

It is not clear what the mechanism is for the reduction in the systemic exposure of gemfibrozil. However, clinicians treating HIV-infected patients for hypertriglyceridemia should be aware of this interaction.

Ref: Busse KH, Hadigan C, Chairez C, et al. Gemfibrozil concentrations are significantly decreased in the presence of lopinavir-ritonavir. J Acquir Immune Defic Syndr, 2009, 52(2): 235-239.
http://www.ncbi.nlm.nih.gov/pubmed/19648824

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 sceptics 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

Reference

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.

http://content.nejm.org/cgi/content/full/361/16/1548

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 10 September 2009 edition of AIDS, examine long-term neurocognitive and psychiatric outcomes of vertically infected adolescents and the impact of HAART on HHIV 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.

C O M M E N T

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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2. Patel K et al. Impact of HAART and CNS-penetrating antiretroviral regimens on HIV encephalopathy among perinatally infected children and adolescents. AIDS 2009, 23:1893-1901.

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

Community resources and publications:

UK patient survey: you, your GP and HIV

This survey has been compiled by the Forum Link Project – a network that currently links patient support groups from 15 HIV clinics. The survey has been designed by HIV-positive people to help understand the relationship with GPs and how to develop Primary Care services in the future.

The group believe that this is the first online survey in the UK of GP services in relation to HIV care that has been organised, compiled and run by HIV-positive people. The data collected will be used by Forum Link members during consultations currently being undertaken by Patient Groups and PCTs.

The survey is anonymous and is online here:

http://www.forum-link.org/research/gp/survey

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

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-Base.info

All i-Base publications are available online, including editions of the treatment guides. The site gives details about i-Base, the UK Community Advisory Board (UK-CAB), our phone service and meetings, as well as access to our archives and an extensive range of links. It can be used to order publications and regular subscriptions to be delivered by post or email (as PDF files).

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

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

RSS news feed has been introduced for HIV Treatment Bulletin for web and PDA access - we welcome your feedback on this new way to provide treatment updates.

A section on Education, Advocacy and Training includes our training manual for advocates with eight 2-hour modules that include questions and evaluation. Training modules start with basics, including CD4, viral load and other monitoring tests, combination therapy and side effects, and include overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment.

An average of 6000 pages are served from the site each day.

i-Base announcements list

A free email News and Announcements list. By subscribing you can be kept up-to-date on new and revised publications from i-Base. This is an announcement only list with low traffic, mainly to announce new and updated publications and services. Messages will contain a link to a PDF file of the publication and/or a link to the web version.

To subscribe please fill out the form at this link:

http://www.i-base.info/forms/newssub.html

Training manual – revised, updated and now fully online

This established training resource has been revised and updated and is now online in new format.

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

The Training Manual for Advocates provides entry-level curriculum relating to HIV and treatment.

It is made up of 8 modules for learning about aspects of HIV care has been updated and published online as an interactive resource. It provides entry-level curriculum relating to HIV and treatment.

Additional support material is included on how to understand aspects of science that might be new to a lay reader.

http://www.i-base.info/manual/en/index.html

Sections include:

1. Immune system and CD4 count
2. Virology, HIV and viral load
3. Introduction to antiretrovirals (ARVs)
4. Side effects of ARVs
5. Opportunistic infections and coinfections
6. HIV and pregnancy
7. Drug users and HIV
8. Clinical trial design and the role of advocates

Each module includes learning objectives, non-technical review material, test questions, an evaluation and a glossary.

We hope this will be useful for training advocates and other related healthcare workers as well as for HIV-positive people who want to know more about aspects of their healthcare.

The training manual was previously only available online as a PDF document and has been widely translated. Earlier editions are available in Russian, Portuguese, Hindi and Nepalese as are available as PDF files.

Generic clinic forms

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.

These PDF files include record sheets to track CD4 and viral load results, cardiovascular risk, hepatitis, first patient visit, patient update, day case and summary notes.

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

Please contact the i-Base office if you would like help adding your own hospital or Trust logo to these forms.

Report assessing the treatment information needs African people in the UK living with HIV

This report by Winnie Sseruma and i-Base includes an analysis from workshops held last year and details African use and experience of current treatment information resources.

http://www.i-Base.info/pdf/africantreatmentneeds.pdf

i-Base Book: "Why we must provide HIV treatment information"

Photography by Wolfgang Tillmans

i-Base has worked as a treatment literacy project for over six years. Over this time we have always produced copyright-free material and encouraged other organisations to use, translate and adapt our material. Through this work, we have been very lucky to develop links to many other advocacy projects outside the UK.

A recent meeting, held in Cape Town earlier this year, focused on how to raise the profile of treatment literacy. One result from the meeting is a publication "Why we must provide HIV treatment information".

With text provided by activists from 25 countries and 50 full colour photographs by Wolfgang Tillmans, this limited edition 100-page publication is being sold by i-Base to raise funds to help support our international treatment literacy projects.

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting since 2002. It now includes over 300 members form over 100 organisations. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted. Membership is free,

http://www.ukcab.net

World CAB - reports on international drug pricing

Two reports from meetings between community advocates and pharmaceutical companies, that focused on pricing issues and global access to treatment, and that are now available online.

Both are available to download as a PDF file from the i-Base website.

http://www.i-base.info/wcab/index.html

Introduction to combination therapy

June 2009 edition

This non-technical patient guide to treatment explains combination therapy, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and how to avoid drug resistance.

Printed and/or PDF versions of earlier versions of this booklet are available in other languages.

Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support

March 2009 edition

This is a new i-Base guide. It is a non-technical patient guide to Hepatitis C and coinfection with HIV.

This booklet mainly covers treatment related aspects of coinfection including transmission, natural history, tests and monitoring, HCV treatment and side effects, research into new drugs and living with coinfection. It also includes contributions from a wide range of people with direct experience of coinfection. The online version of this guide includes additional text.

Guide to changing treatment: what to do when your treatment fails

September 2008 edition

This is a non-technical patient guide to changing treatment, drug resistance and what to do if treatment fails. It is updated to include recent advances in new treatments and strategies, especially in relation to use of new and expanded access treatments.

This booklet helps patients in discussions with doctors, and covers what can be done if viral load starts to rise, and the importance of considering or finding out why the current combination failed, treatment strategies and new pipeline treatments.

Guide to HIV, pregnancy & women's health

January 2009 edition

Updated and revised, this patient guide helps women get the most out of HIV treatment and care before, during and after pregnancy. It should help whether on therapy or not and includes information for the mothers health and for the health of the baby.

The guide gives information on medication, Caesarean section and breastfeeding, as well as details of other sources of help. It is aimed at people in a wide range of circumstances including positive women thinking about having children and pregnant women who have recently been diagnosed HIV-positive.

Guide to avoiding & managing side effects

May 2008 edition

This is a comprehensive 72-page A5 guide that is aimed at helping anyone using HIV drugs to get the most out of their treatment, the most out of their relationships with their doctor and other health professionals, to get better medical care to improve their health and, most importantly, to enjoy a better quality of life.

Translations of i-Base guides

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 35 languages.

More information about this process is available on the i-Base website.

In addition, PDF files of some of the translated publications are available on the i-Base site.

Please be aware that some of these translations are from earlier editions of the treatment guides, and check the publication date before relying on all information.

http://www.i-base.info/about/downloads.html

Languages currently include:

Bosnian, Bulgarian, Chinese, Czech/Slovak, Croatian, French, Greek, Hindi, Indonesian, Italian, Kosovo, Macedonian, Nepali, Polish, Portuguese, Romanian, Russian, Serbian and Spanish.

Treatment 'Passports'

These popular booklets are for HIV-positive people - whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Like all i-Base publications, they are available free as single copies, or in bulk.

HIV Treatment Bulletin (HTB)

This is the journal you are reading now: a review of the latest research and other news in the field. HTB is published 10 times a year in a printed version, in a pdf file that we can email to you, and on our website.

The printed version is available at most HIV clinics in the UK and is available free by post.

HTB South

A quarterly bulletin based on HTB but with additional articles relevant to Southern Africa. HTB South is distributed in print format by the Southern African HIV Clinicians Society (www.sahivsoc.org) to over 20,000 doctors and healthcare workers. It is also available as a PDF file and is posted online to the i-Base website.

ARV4IDUs

An electroniv publication, produced in English and Russian language editions, to provide an overview of research related to IV-drug use and antiretroviral treatment.

Treatment information request service - 0808 800 6013

i-Base offers specialised treatment information for individuals, based on the latest research.

We can provide information and advice over the phone, and we can mail or email copies of the latest research studies relevant to the caller.

For further details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesdays from 12 noon to 4pm. All calls are in confidence and are free within the UK.

Online Q&A service

An online 'question and answer' service that now has over 900 questions online. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

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

Recent questions include:

- Can d4T be replaced by AZT?
- How can I deal with my GP?
- What food shall I eat with my combination?
- Do HIV-positive pregnant women have to have an abortion?
- Will stopping meds reduce fatigue?
- Why are scientists not able to find a cure for HIV?
- Shall they use a condom again?
- I have often oral thrush regardless that I am on ARVs; what shall I do?
- My CD4 is 350; what can my viral load be?
- Can I have a glass of wine with my meds?
- How can I decrease viral load?
- If we are both HIV-positive, how can we have a baby that is not infected?
- What shall I switch to?
- Is sperm-washing needed if both partners are HIV-positive?
- How often should my viral load be tested?
- What can I do about my high cholesterol levels?
- Can I work as a massage therapist?
- Is there a problem working as a waiter and being HIV-positive?
- Worrying about life expectancy…
- Does having psoriasis mean that your CD4 count is very low?
- I have itching in my groin area, what shall I do?
- Does this mean that I am progressing to AIDS?
- My friend has neurological problems on Atripla…

Find HTB on AEGiS

AEGiS.org - the longest established and largest global resource of online HIV information - includes HTB in the regular journals that it puts online. You can find us at:

http://www.aegis.org/pubs/i-base/2009

The AEGiS daily email news service also carries i-Base conference reports.

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Copies of publications can also be ordered by post or fax using the form on the back page of HTB. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), HTB South, Treatment 'Passports' and all our guides to managing HIV and additional reports.

h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website: http://www.i-Base.info; by fax or post using the form on the back page by sending an email to: subscriptions@i-Base.org.uk

Editor: Simon Collins

Contributing Editor: Polly Clayden

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.

HIV i-Base receives unconditional educational grants from Charitable Trusts, individual donors and pharmaceutical companies.All editorial policies are strictly independent of funding sources.

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