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EDITORIAL

This double issue of HTB has arrived slightly later than usual in order to include reports from the Lipodystrophy Workshop held in Dublin at the end of November, together with early reports from the EACS conference that followed afterwards. Further reports from these meetings, together with coverage from the rescheduled 45th ICAAC that will now be held from 16-19 December in Washington, will be included in the January 2006 issue of HTB.

In terms of treatment access in the UK, TMC114 is now available on a named-patient programme. Use of either TMC-114 or tipranavir/r, if used with T-20, should offer many people two sensitive drugs. This provides the best opportunity in many years, for viral suppression <50 copies/mL to be a realistic goal for treatment-experienced patients.

Several other reports in this current issue relating to antiretroviral treatments highlight difficulties with the development programmes of pipeline compounds. GSK's CCR5 inhibitor has been shelved, and Phase II trials for Schering's compound in the same class have been stopped in treatment naïve patients, though the studies in treatment-experienced patients continue. The decision over the GSK compound was related to hepatic toxicity. So far, this has not so far been seen the other CCR5 inhibitors currently being developed. The Schering decision was based on efficacy. As this issue went to press, Tibotec announced that one of their phase II studies of the NNRTI TMC125 was being stopped early due to poor antiviral efficacy in treatment naïve patients, although the Phase III studies are not so far affected, and toxicity issues have not been raised.

In the run up to these Phase II trials, many European treatment advocates, in discussion with the companies and the regulatory agencies, argued that patients with advanced HIV (CD4 count <100-150 cells/mm³) should not be enrolled into trials of investigational agents before efficacy or a dose had been established. The caution was to ensure that patients with more advanced disease are more dependent on achieving an optimal response with their first treatment, and that they should not receive a treatment that was less successful than the minimum standard of care. This was supported by independent investigators and national regulatory agencies in some countries.

It is always very disappointing when unforeseeable problems limit development of promising compounds. In the examples above, the companies developing these drugs appear to have acted swiftly to reduce the risk to patients enrolled in their studies. However, they remain sobering examples of when access to investigational agents is not the same as access to better treatment. For patients with more advanced HIV, many of whom may have been recently diagnosed, and who may be more vulnerable in terms of giving informed consent for a trial of a new drug, and less aware of the choice of drugs that are already approved, then advocating for greater safety in the earliest Phase II studies appears justified.

To end on an optimistic note, in the US, where ARVs are generally approved six months or so before Europe, there is now a newly approved paediatric formulation of FTC, and approval of the long awaited 'meltrex' formulation of lopinavir/r. Both are covered in this issue.

Finally, as the year draws to a close, we would like to wish all our readers seasonal greetings, and best wishes for 2006.

CONFERENCE REPORT

7th Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

13-16 November 2005, Dublin

This annual workshop – linked in alternate years to either the EACS or ICAAC conferences in Europe and the US respectively - provides an opportunity for clinicians, researchers, industry and community advocates to focus on side effects, especially those associated with lipodystrophy and metabolic complications.

Although there were no dramatic breakthroughs at this meeting, a few studies had interesting implications for clinical practice and these are reported below.

Unless stated otherwise, all references are to the programme and abstracts from the meeting. They will go online as part of the aegis conference database at:

<http://www.aegis.org>

<http://www.aegis.org/conferences/lipo/>

Monitoring side effects in resource limited countries

Simon Collins, HIV i-Base

Immediately prior to the Lipodystrophy Workshop, the Forum for Collaborative HIV Research (FCHR) organised a roundtable discussion to focus on side effects in resource-limited settings. A report from this meeting was included in the programme

of the main Workshop, and was given by Veronica Miller, the director of the Forum. [1]

Nearly two million people receive ARV thanks to recent treatment access programmes. The majority receive drugs for which the side-effects are well described, but which are no-longer recommended as first-line therapy in US treatment guidelines. The lack of information on safety and tolerability from these rollout problems is disturbing. Studies reported at medical conferences are largely from smaller single investigator sites. Virologic and clinical results are optimistic, but the side-effects generally also reflect earlier use of these treatments in the economically developed countries. There is certainly no indication that treatments should be any safer in these programmes than in a Western setting. In fact, the likelihood is a higher incidence of toxicity, driven by patients starting treatment at more advanced disease stage when tolerability is worse. This may be complicated by overlapping of side effects with symptoms of other illnesses, and by a healthcare workers who have less experience in the use of HAART.

In the case of stavudine, the side effects are often irreversible (lipoatrophy, neuropathy and lactic acidosis), and so problematic that the drugs are rarely used in Western countries. This may also become the case with AZT, as anaemia frequently complicates use of AZT as an alternative first-line choice. Many doctors and advocates recognise the importance of switching away from d4T in resource-limited settings. However, this is unlikely to occur given the additional cost, unless there are adequate data. A proposal to start collecting data now, even while advocating for change, will provide the necessary support for the range of healthcare providers – funders, governments and healthcare systems – to justify additional costs for safer and more tolerable treatment.

WHO and the Global Fund were invited to the meeting but did not attend. The concern was also expressed that the goal of 'numbers on treatment' now drives access programmes both on national and international agendas, at the expense of individual patient care. Speakers at both meetings highlighted the importance of including data and safety provision within all programmes and of funders including PEPFAR and GFATM recognising and supporting this. Lipoatrophy and neuropathy are stigmatizing and debilitating no matter which country you receive your treatment in. Fatal side-effects including lactic acidosis and hepatic failure will similarly contribute to undermining the benefits that ARV treatment undoubtedly provides. Using treatment with high levels of toxicity will only build problems for the future. No-one expects any of the corrective procedures to ever become available. These patients trust their doctors, just like patients in the West. Collecting accurate data on the incidence of side effects in roll-out programmes will also provide a clearer picture of the overall benefits over the risks for the majority of people who use ARV treatment.

The Forum meeting included presentations on the importance of long-term monitoring, regulatory considerations, agreements on standardisation on the way that data will be collected and use of both traditional and newer technologies (SMS, mobile phone, and internet).

A working group from the meeting will take this project forward.

Slide presentations are already posted to the FCHR website and a full report from the meeting will follow:

<http://www.hivforum.org>

References:

1. Miller V et al. Report from Forum meeting on drug toxicity in resource-poor settings 7th Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 13-16 November 2005, Dublin.

Uridine supplement reverses thymidine-induced lipoatrophy

Simon Collins, HIV i-Base

Two years ago at the Lipodystrophy Workshop, Ulrich Walker presented in vitro data that supported uridine supplementation to reduce or reverse lipoatrophy induced by thymidine analogue associated mitochondrial toxicity. Last years Workshop saw further in vitro data [1, 2]. There was therefore considerable interest in the first in vivo results, presented in by Sutinen and colleagues from the same research group, in an oral presentation at this years workshop. [3]

Twenty patients who were taking d4T- or AZT-containing HAART for >18 months, were randomised in 1:1 ratio to receive either three cycles of NucleomaxX (a dietary supplement given at a dose of 36g, three times daily, for the first ten days of each month, for three months) or a taste-matched placebo. Body composition was measured by DEXA and MRI and liver fat was quantified by proton spectroscopy on day 90.

Patients in the NucleomaxX arm gained statistically significant increases in limb fat after 3 months (range 400g – 1500g) compared to both baseline and placebo patients (both $P < 0.05$). Total body fat and intra-abdominal fat also increased. The proportion of limb fat to total fat increased from 19% to 25% in the uridine arm. This change was not clinically noticeable by patients. No significant changes occurred in the placebo group. One patient receiving placebo died from myocardial infarction during the study, and one patient discontinued due to its bad taste.

HDL (good) cholesterol fell from 1.24 to 1.15 mmol/L in the uridine group but there was no effect on triglycerides, lactates, or

insulin resistance. CD4 counts remained stable and no patients experienced viral rebound. PK confirmed that the supplement provided increased levels of uridine in plasma.

A second study using NucleomaxX was presented as a poster by McComsey and colleagues from Case Western Reserve University, Ohio. [4] Sixteen patients on d4T-containing HAART were given 36g NucleomaxX three times a day, every other day, for 16 weeks, with follow-up at 32 weeks after 16 weeks off-uridine. As this study only recorded patient and doctor perceptions about improvements in lipoatrophy (both groups reported benefits) rather than a physical measure, it is difficult to comment on the results.

C O M M E N T

Uridine is not a potential treatment for lipoatrophy in itself – it only reverses fat loss in people who are using lipoatrophy-causing treatment. Nevertheless, it is very interesting to know that a protective agent is available for people who are dependent on either d4T or AZT. The highest needs for such a treatment however is in resource-limited countries where d4T is still a cornerstone of treatment, and the cost of NucleomaxX, at 84 euros for three days (nine 36g sachets, approximately 240 euros/month) may be higher than the discounted price for tenofovir or abacavir, the switch treatments of choice. Optimal dosing may also not have been established, given the different design of the two studies above.

Taken together these two studies suggest that uridine supplements maybe a new treatment tool in managing lipoatrophy. Their use beyond persons receiving pyrimidine NRTIs (and specifically thymidine analogs) has not been evaluated. Furthermore, it is important to note that the studies reported involved small numbers of individuals and did not use endpoints that could be considered standard or part of the established lipodystrophy case definition approach. In particular, self-report of lipoatrophy is widely thought by physicians working in this area to be of limited value. Larger placebo-controlled studies using established objective endpoints such as DEXA scanning are now required.

In addition, limited safety data have been reported with this supplement and details of possible drug interactions with life-saving antiretroviral medications have not been evaluated.

A number of supplements, notably garlic supplements and St John's Wort, are known to have important interactions with some HIV medications. Before individuals rush to buy expensive uridine supplements over the Internet, they should consider that evaluation of potential risks, or establishment of potential benefits, i.e. not to standards normally used by regulatory agencies.

It is unclear why NucleomaxX should be so expensive. Raw materials are cheap and the production process likely to be of low complexity. In addition, the lack of having to submit to clinical trial and regulatory approval means the development process is also low cost. Someone is making an extortionate profit margin here.

There are other strategies to raise plasma uridine levels: 10mL of regular beer contains 0.5mg of uridine - this includes low, or non-alcoholic beers - and drinking 10mL of beer per kilo of body weight was found to raise uridine plasma concentrations by 1.8 fold. Administering uridine itself also raises plasma uridine levels at a cost of about £1.50 a gram. Lastly, another "supplement", citicoline (Cytidinediphosphocholine), has also been found to be an efficient agent in raising uridine plasma levels and can be purchased for less than £1.40 per gram.

Further information:

<http://www.nucleomaxX.com>

<http://www.mitochnol.com>

References:

1. Blanchard P. Uridine as a potential treatment for NRTI related mitochondrial toxicity. HIV Treatment Bulletin, Vol 4 No7, August 2003. <http://www.i-base.info/pub/htb/v4/htb4-7/potential.html>
2. Potential for uridine to treat mitochondrial toxicity: still only in vitro data. HIV Treatment Bulletin, Vol 6 no 1, January 2005. <http://www.i-base.info/htb/v6/htb6-1/Potential.html>
3. Sutinen J, Walker K et al. Uridine supplementation increases subcutaneous fat in patients with HAART-associated lipodystrophy: a randomized placebo controlled trial. 7th Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 13-16 November 2005, Dublin. Abstract 7.

Pravastatin increases limb fat in HIV-positive patients with hypercholesterolaemia

Simon Collins, HIV i-Base

Paddy Mallon and colleagues from University of New South Wales always produce important studies at the Workshop. This year was no exception, with a study looking at changes in body composition in patients with elevated cholesterol who were treated with 40mg/day of pravastatin. Although pravastatin is often used in HIV-positive patients to reduce cholesterol, and is preferred over other statins due to fewer drug interactions with ARVs, this was the first study to look at whether it has an

impact on body composition.

Thirty-three HIV-positive men on stable PI-containing HAART who had fasted cholesterol > 6.5 mmol/l were given dietary advice and started on a lipid-lowering diet for four weeks. They were then randomised to receive either pravastatin or placebo from week 4 to week 16. The primary endpoint of the study was time adjusted change in total cholesterol from baseline, with secondary endpoints looking at change in cholesterol from week 4, body composition using DEXA and abdominal CT, and additional lipid and cardiovascular risk markers.

Results are summarised in Table 1 below.

Table 1: Changes in cholesterol and body fat in patients treated with pravastatin or placebo

	Pravastatin	placebo	p
Chol AUC			
0-16 week (mmol/l-wk)	- 0.6	-0.4	0.8
4-16 week (mmol/l-wk)	- 0.82	-0.34	0.04
Total fat (kg)	+ 1.03	-0.09	0.01
Limb fat (kg)	+ 0.72	+0.19	0.04
% IAF	- 2.90	0.08	0.70

Although the decreases in cholesterol were modest, with the difference between the pravastatin and placebo group only becoming significant from week 4 to 16 (a secondary endpoint of the study), body fat increased significantly in the pravastatin group, and this was predominantly driven by an increase in limb fat.

Homocysteine was the only cardiovascular risk marker to be reduced during the study (in the pravastatin group) with no significant differences occurring in other cardiovascular, lipid, glucose or dietary parameters.

C O M M E N T

Statins in general, and pravastatin in particular, have other pharmacological actions in the body other than lipid lowering, which may impact favourably on lipotrophy.

Pravastatin has been shown to have protective role against the development of diabetes in one large clinical trial. Moreover, a recent clinical study revealed that pravastatin treatment improved insulin sensitivity in 25 women with the metabolic syndrome who had impaired glucose intolerance.

Additionally, statins are immunologically active and also act as anti-inflammatories. These pathways may also be involved in their beneficial action on lipotrophy.

Ref: Mallon PWG, Miller J, Carr A et al. Changes in body composition and cardiovascular measures in hypercholesterolaemic HIV-infected men treated with pravastatin: a randomised, placebo-controlled study. 7th Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 13-16 November 2005, Dublin. Abstract 23.

Evidence that facial fat can return after switching from either d4T or AZT, to abacavir or tenofovir

Simon Collins, HIV i-Base

Although it is now well established that switching from a thymidine analogue to either abacavir or tenofovir can slowly reverse limb fat loss improvements in facial lipotrophy have not been clearly established. [1, 2, 3]

Paul Benn and colleagues reported results from using 3D facial imaging to measure changes in facial volume over 48-weeks, in a sub-study of 47 patients enrolled in a UK switch study (RAVE). [4] All patients were virologically suppressed (11 on AZT and 36 on d4T) prior to switching to abacavir (n=24) and tenofovir (n=23). At baseline 39/47 patients in the sub-study (85%) reported facial lipotrophy with 32/47 (68%) reporting either no worsening, or a perceived improvement in facial lipotrophy at week 48.

Mean volume difference in both cheek areas at week 48 was +2539mm³ (SD 5346) (just over 1cm³ in each cheek) although fat in forehead area decreased by -138mm³ (SD 347) over the same period. Mean limb fat, measured by DEXA, also increased by 2.9kg (SD 0.9) and 3.4 kg (SD 2.1) in the abacavir and tenofovir groups respectively. There was a correlation between increases in cheek fat and limb fat that remained significant after adjusting for weight gain (p=0.02) but there were no statistically significant differences between the abacavir and tenofovir arms.

References:

1. Moyle GJ, Baldwin C, Langroudi B et al. A 48-week, randomised, open-label comparison of three abacavir-based substitution approaches in the management of dyslipidaemia and peripheral lipoatrophy. *Journal of Acquired Immune Deficiency Syndromes* May 1, 2003; 33(1):22-28.
2. Carr A, Martin A, Ringland C et al - Long term changes in lipodystrophy after switching from thymidine nucleoside analogues to abacavir. Programme and abstracts from the 5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 8-11 July 2003, Paris Abstract 16.
3. Moyle G et al. A randomised, open-label comparative trial of abacavir or tenofovir DF as replacement for a thymidine analogue in persons with lipoatrophy and suppressed HIV RNA on HAART. 12th Conference on Retroviruses and Opportunistic Infections (CROI), Feb 22-25, 2005, Boston, Abstract 44LB.
4. Benn P, Sauret V, Cartledge J et al. Improvements in facial lipoatrophy at 48 weeks following substitution of a thymidine analogue with tenofovir (TDF) or abacavir (ABC): a randomised, open-label study in people with lipoatrophy and virological suppression on HAART. 7th Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 13-16 November 2005, Dublin. Abstract 8.

Niacin has beneficial effect on lipids but no reduction in abdominal fat

Simon Collins, HIV i-Base

Michael Dubé from Indiana University reported results from a 48 week study looking at whether extended release niacin (ERN), also known as nicotinic acid or vitamin B3, would be safe and effective in dyslipidaemic HIV-positive patients on HAART.

This was a single arm open label study in 33 men (median age 43 years, 67% white). After a 4-week course of diet modification and exercise, ERN was started at 500mg daily for the first 4-6 weeks as tolerated and titrated in 500mg doses until either the target dose of 2000mg/day or improved lipid targets were reached. 23 patients reached the 2000mg dose and eight reached 1500mg, four patients discontinued, one each for flushing, grade 3 ALT, diarrhoea and HIV progression. Three patients had grade 2 and three had grade 3 flushing.

Results are summarised in Table 1 below.

Table 1: Lipid changes at week 24 and 48

	Baseline	%Δwk24	%Δwk48
Total-C	6.5	-0.6	-0.12 *
HDL-C	0.9	+0.08	+0.13 *
TG	5.6	-0.8	-0.5 *
Non-HDL-C	5.4	-2.0	-1.7 *

* $P < 0.01$

No significant changes in ALT or uric acid were reported. At week 12 fasting glucose increased transiently by 5%, but changes were not significant at week 24 or 48. Fasting insulin was greater than baseline at all time points.

Dubé concluded that extended-release niacin might be considered for treatment of high triglycerides, high non-HDL cholesterol, or low HDL cholesterol without major elevations of low-density lipoprotein cholesterol.

Other commentators however stressed the importance of careful monitoring of glucose regulation and the liver if niacin is used in lipid management for HIV-positive individuals.

Although the study design included using MRI scans to monitor intra-abdominal fat (IAF) these results were not included in the presentation. As part of the discussion after the presentation, it was reported that no change in IAF was seen in this study.

C O M M E N T

Side effects from high dose regular niacin include flushing, and rarely, acanthosis nigricans - a black furry rash on the chest and underarms, which can result from insulin resistance, and which resolves after discontinuation/dose reduction.

Diabetes can be exacerbated and require dose adjustments of diabetes medication. Liver function also requires careful monitoring.

Niacin can increase levels of growth hormone and this may explain some of the benefits seen in this study. A previous report from Fessel and colleagues reported reductions in intra-abdominal fat and softening and shrinkage of buffalo hump making the lack of effect on IAF important. [2]

Niacin is reported to appear in human milk and may cause serious side effects in nursing infants.

References

1. Dubé MP, Wu JP, Aberg JA et al. Safety and efficacy of extended release niacin for the treatment of dyslipidaemia in patients with HIV infection: a prospective, multi-centre study (ACTG5148). 7th Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 13-16 November 2005, Dublin. Abstract 12.
2. Fessel J - Effects of Niacin upon Fat Expansion in HIV-Positive Patients Who Have the Fat Redistribution Syndrome (FRS). Abstract 703-T. See HTB Volume 3 Number 3. April 2002.
<http://www.i-base.info/pub/htb/vol3/htb3-3/index.html>

Gluteal implants used to replace lost buttock fat

Simon Collins, HIV i-Base

One of the posters presented at the workshop provided details of implants used to correct buttock lipoatrophy in seven women treated at University of Barcelona. The surgeon, Dr Fontdevila has treated HIV-related lipoatrophy for over four years, predominantly using autologous fat transfer to correct facial lipoatrophy, with approximately 60% of procedures carried out in the plastic surgery department in HIV-positive individuals.

Buttock augmentation is inherently more difficult and more complicated to correct for two main reasons: the area to be filled is much larger than other areas affected by lipoatrophy, and that an implant in this area is subjected to significant daily stress and consequently a higher risk of migration or breakage. Very few studies have reported on successful buttock correction in patients with HIV, although earlier lipodystrophy workshops have sometimes included experimental approaches - usually using high volume fillers – in small numbers of patients.

The Spanish researchers use soft silicone implants manufactured by Silimed in Brazil and distributed in Europe by Polytech Silimed, Germany. Company literature says 'the implants consist of a highly resilient silicone elastomer filled with a highly cross-linked silicone gel so that even in case of a rupture the gel would not leak'. Round implants were used for women with Grade 1 or 2 lipoatrophy and larger oval implants for women with Grade 3 fat loss. It is significant that in this procedure, the implants are inserted in intramuscular pockets, in order to minimise any chance of migration. The muscle fibre is used to hold and seal the implants. However this is a painful procedure and patients are advised that they should allow for at least one month for pain to subside and before they are able to walk normally. Non-HIV buttock augmentation insert implants under, not inside the muscle.

The only major complication reported occurred in the patient with the most severe atrophy, where a hip prosthesis migrated to the gluteal pocket, requiring surgical repositioning.

The study reported that all women were satisfied with the results, but some were worried then by the contrast between the treated area and the extreme thinness of their legs and thighs.

Although lost buttocks can be distressing, and can include physical discomfort, this procedure is likely to only appeal to a minority of people. From a safety perspective, there is concern that the trauma experienced by normal activity will require the implants to degrade, requiring replacement sooner than similar implants used for breast augmentation. This is estimated at every 8-10 years for buttock implants, with current follow-up protocol requiring monitoring for degradation by MRI scan after 5 years.

C O M M E N T

Patient support email discussion lists routinely include posts about the discomfort and psychological distress associated with losing buttock fat. It is important to follow any procedures being reported, though with the limited data on current options, for most people the invasive nature of this procedure, combined with the uncertainty of the results, will probably encourage a conservative approach towards this treatment.

Severe loss of buttock fat, especially if compounded by muscle loss, can certainly have a negative impact on quality of life, but the difficulty and pain associated with normal sitting is possibly still best countered by using padded underwear or a cushion.

Ref: Fontdevila J et al. Surgical treatment of the buttocks and hip atrophy in feminine lipodystrophic patients. 7th Intl Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 13-16 November 2005, Dublin, Ireland. Abstract 41.

CONFERENCE REPORT

10th European AIDS Conference

17-20 November 2005, Dublin, Ireland

The 10th European AIDS Conference (EACS) was held in Dublin just as this issue of HTB was going to press, immediately following the Lipodystrophy Workshop. Further reports from this meeting will therefore be included in the January issue of HTB.

The conference organisers have not yet published abstracts from the meeting online, although they will go online at:

<http://www.aegis.org>

However, webcasts of several of the presentations are included, though free registration is required, and access is not instant:

<http://www.eacs-conference2005.com/>

Pregnancy studies at EACS

Polly Clayden, HIV i-Base

Triple antiretroviral regimens in pregnancy

Three posters looked at triple antiretroviral regimens in pregnancy. The majority of the women studied had higher CD4 counts and received treatment for mother to child transmission.

Historically in the UK, pregnant women with higher CD4 counts would generally receive nevirapine-containing regimens, but following the hepatic toxicity warning from Boehringer Ingelheim, alternative strategies are needed. BHIVA pregnancy guidelines recommend short course protease inhibitor containing regimens for women in this situation. Two posters looked at saquinavir-containing (SQV) regimens and another at triple nucleosides. Saquinavir, tenofovir and FTC are all FDA pregnancy category B drugs.

Short course boosted saquinavir

David Hawkins' group at Chelsea and Westminster Hospital in London presented results from an observational study on the use of boosted saquinavir in pregnancy from December 2002 to July 2005 [1].

Data were available for 13 women (15 pregnancies). Following the BHIVA START (Short Term Triple Antiretroviral Therapy) protocol, women received SQV hard gel-capsules (hgc)/ritonavir (1000/100mg BID) plus Combivir from a median of 21 weeks (range 13-25 weeks) until delivery.

The median age of the women was 32 years (range 19-39 years); the median CD4 count at initiation of therapy was 437 cells/mm³ (range 237-637 cells/mm³) and viral load 7901 copies/mL (range 117-55460 copies/mL). Seven women had received HAART previously in pregnancy. One woman was switched from nevirapine/Combivir due to nevirapine-associated hepatic toxicity.

All women had a CD4 count of <50 copies/mL at delivery. The median period of gestation was 37 weeks and 73% of women had a caesarean delivery.

Sixteen HIV negative infants including one set of twins were born during the study period. The investigators noted no additional resistance mutations from baseline were detected on stopping therapy post delivery.

Low dose boosted saquinavir once-daily (QD)

Luis Lopez-Cortes and co-workers from Seville, Spain reported data from a cohort of pregnant women receiving therapeutic drug monitoring (TDM) guided boosted saquinavir containing therapy [2].

Women received an initial SQV/r dose of 1200/100 mg QD. TDM was used to maintain a SQV C_{min} of 100ng/mL (24 +/- 5 hours post dose).

Data were available for 38 women. Their median age was 31 years (range 21-38 years). At inclusion 15 (44.1%) women were drug naïve, 33 (86.8%) had no prior PI failure and 11 (32.3%) were already on treatment. Their median CD4 was 508 cells/mm³ (range 42-1158 cells/mm³) and viral load 3,905 copies/mL (range <50-181,000 copies/mL). Therapy was initiated at a median of 20 weeks (range 0-35 weeks) of pregnancy and 30 (78.9%) women received AZT and 3TC as their nucleosides.

SQV Cmin from 24-39 weeks of pregnancy (n=72); 34 women: 239ng/mL (range 80-2235 ng/mL). The SQV dose was increased to 1600 mg QD in two women.

After a median of 17 weeks (range 3-39 weeks), 29 people had undetectable viral load at delivery. Three women had viral loads of 110 copies/mL, 400 copies/mL and no data respectively after only 3-4 weeks of therapy. Mode of delivery was vaginal in 16 pregnancies and 16 by caesarean section (11 of these were for gynaecological reasons). The authors reported no mother to child transmissions.

They wrote: "Although SQV plasma levels are lower, low dose SQV/r is an effective and low risk therapeutic option in HIV-infected pregnant women with no prior or limited experience on PIs. TDM is advisable to maintain appropriate levels throughout pregnancy."

Triple nucleosides

Annette Haberi and co-workers reported data from 10 women receiving AZT plus tenofovir with either FTC or 3TC in pregnancy who had CD4 counts >250 cells/mm³ or a history of adherence problems. Of this group, three women received Combivir plus tenofovir, three women tenofovir+FTC (Truvada) plus AZT and four women received tenofovir, FTC and AZT as single drugs.

The median age of the women was 31 years (range 25-43 years) at baseline and 6 women were treatment-naïve. Initiation of therapy was at a median of 32 weeks (range 14-33 weeks); the median CD4 count and viral load was 335 cells/mm³ (range 45-605 cells/mm³) and 48,200 copies/mL (range 60-229,000 copies/mL) respectively.

All ten women in this group delivered by caesarean section. The median CD4 count at delivery was 424 cells/mm³ (range 74-652 cells/mm³) and viral load was 25 copies/mL (range 19-50 copies/mL). The median time to <= 50 copies/mL was 4.6 weeks (range 2-12 weeks). There were no cases of mother to child transmission.

The authors wrote: "Further evaluations should be implemented to make this regimen an addition to current recommendations for MTCT prophylaxis."

C O M M E N T

Luis Lopez-Cortes et al report that most women (36/38) taking saquinavir during pregnancy have adequate (>100ng/ml) plasma concentrations when prescribed saquinavir/ritonavir 1200mg/100mg bd. This is a higher dose than routinely recommended and it is of interest to note that despite this 2/36 mothers had a TDM-driven dose increase to 1600mg bd.

Tung MY et al report on 13 mothers taking a more conventional boosted saquinavir/r regimen and note effective viral suppression. It would be interesting to know how many mothers might have had apparently sub-optimal trough plasma concentrations at this lower dose, and whether dose adjustment is required on the basis of total (free and bound) concentrations. The data, whilst not conclusive, adds to the body of evidence that boosted saquinavir is a reasonable option in pregnancy, especially for Short-Term ART. It should be noted that in both studies the median CD4 counts and viral loads were favourable for a good response to ART.

Habert A et al, report their findings treating ten women with a more controversial (triple NRTI) regimen. Clearly a much larger study is required to assess the long-term impact on viral suppression, and there are still few data on the safety of tenofovir in this setting.

References

1. Tung MY, Khan W, Hawkins DA. The clinical outcome of using saquinavir hard-gel capsules/ritonavir (SQV/r) with two nucleosides (NRTIs) in HIV-infected pregnant women. 10th European AIDS Conference. November 2005, Dublin, Ireland. Abstract PE14.2/2.
2. Lopez-Cortes R, Ruiz-Valderas R, Rivero A et al. Therapeutic drug monitoring and efficacy of low-dose saquinavir/ritonavir QD in HIV-infected pregnant women. 10th European AIDS Conference. November 2005, Dublin, Ireland. Abstract PE14.4.1.
3. Habert A, Linde R, Faul-Burbes C et al. Effective MTCT-prophylaxis with AZT, TDF plus FTC or 3TC. 10th European AIDS Conference. November 2005, Dublin, Ireland. Abstract PE14.2/3.

Brazilian deal with Abbott is challenged in courts

On 11 October, Brazil reached an agreement with Abbott Laboratories to lower the price of Kaletra, according to a report by Associated Press, although this story changed several times over the previous few months and did so again as we went to press.

Originally Brazil proposed manufacturing lopinavir/r without recognizing the patent - unless Abbott negotiated a price closer to the estimated production costs for the generic formulation. This was due to the strain on its healthcare system relating to the cost of ARV treatment and the large numbers of people requiring treatment. The Brazilian government and Abbott have been at loggerheads on this issue. A deal agreed in June was undermined by a change of health minister in Brazil a few weeks later.

Many community advocates see Brazil as one of the few countries that would be able to use the exceptions outlined in the TRIPS agreement to enable a country to manufacture patent medications due to national emergency, even though Brazil is not technically a low-income country.

In a statement, the health ministry reported that the deal would reduce the price of Kaletra to 63 cents a pill down from its current price of \$1.17, saving the government \$339 million over six years.

However on 1 December, as this issue of HTB went to press, less than two months after the agreement, Brazilian public prosecutors have asked a federal judge to void Abbott Laboratories' patent on the Kaletra. The lawsuit, supported by seven non-governmental organisations representing AIDS patients and 40 international non-governmental organizations such as Doctors Without Borders means that this case may still not be settled.

The Brazilian government's response to HIV is considered a model AIDS programme and provides free ARV treatment currently to around 160,000 patients, cutting mortality to similar levels as Western countries. Progressive and open approaches to HIV prevention ensure that health education starts when children are in primary school, well before they are expected to be sexually active.

Source: AP and other reports, October - December 2005

C O M M E N T

The new Brazilian price for Kaletra (USD 0.63) was proposed to start in March 2006 and may only last until the meltrex formulation is launched. The meltrex formulation is likely to be priced with an 8-10% increase in Brazil. Brazilian government laboratories had committed to produce Kaletra locally for USD 0.41 if compulsory licensing was implemented.

The technology transfer discussed in earlier negotiations was dropped from the new deal. This deal will also send a signal to other companies including Gilead and Merck who are currently negotiating voluntary licensing for tenofovir and efavirenz with the Brazilian government.

ANTIRETROVIRALS

Named-patient access programme available in UK for new protease inhibitor darunavir (TMC114)

Over the last month named-patient programmes for darunavir (TMC114) have opened in Europe. The drug, produced by Tibotec is currently being reviewed for fast-track approval in the US, based on impressive results in Phase II studies.

The results from the 24-week combined interim analysis of the phase IIB trials of darunavir were presented at the 12th Conference on Retroviruses and Opportunistic Infections (CROI) in February this year and were covered in HTB April 2005. [1]

The study looked at people who had experienced at least 3 classes of antiretrovirals with prior use of at least 1 PI, had at least one primary PI mutation, and viral load >1,000 copies/mL.

Patients were randomised to receive optimal background therapy (OBR, at least 2 NRTIs with or without T-20) and one of 4 doses of darunavir/ritonavir (400/100mg once a day, 800/100mg once a day, 400/100mg BD or 600/100mg BD) or chosen PI (CPI). Based on the 24-week results, the selected dose of darunavir/r for treatment-experienced patients in phase III trials was 600mg/100mg BID.

Baseline median CD4 count and viral load were 141 cells/mm³ and 4.6 log₁₀ copies/mL respectively.

Patients in the highest dose group, 600mg/100mg BID, plus optimised background regimen, experienced a mean reduction in plasma HIV RNA of -1.85 log, compared to a reduction of -0.27 log in the control group.

The 600/100mg twice-daily dosing produced a greater mean change in viral load, a greater percentage of subjects with 1log or more reduction, a marginally greater percentage with fewer than 400 copies/mL, and a greater percentage with fewer than 50 copies/mL than any other group. Mean change in CD4 was +75 cells/mm³ for darunavir/r 600/100 twice-daily vs +15 cells/mm³ for CPI.

Darunavir is being distributed by Janssen-Cilag, a subsidiary of Johnson and Johnson, which in turn is the parent company of Tibotec Therapeutics.

For participation or additional information in the UK please contact the Medical Information Team at Janssen-Cilag on 01494 567444.

C O M M E N T

As with every new antiretroviral drug darunavir will only provide limited short-term results if added to an existing failing regimen, or if it is not used in combinations that include other active drugs.

However when darunavir was used with enfuvirtide (T-20), in T-20-naïve patients resulted in 63% patients achieving viral suppression <50 copies/mL.

If these results are supported in other studies then this will shift the paradigm for the management of treatment-experienced patients where viral suppression has often been seen as an unrealistic goal. This now show that changing treatment for experienced patients can realistically lead to maximal suppression in the majority of patients, as with other stages of treatment.

Reference

1. McKerrow G. 24-week efficacy of TMC114: dramatic early activity in heavily-experienced patients, HIV Treatment Bulletin Vol6No4, April 2005. [12th CROI, Boston, 2005. Abstract 164LB.]
<http://www.i-base.info/htb/v6/htb6-4/24.html>

Source:

<http://www.tibotec.com>

<http://www.tibotec.com/bgdisplay.jhtml?itemname=EAP2>

Tibotec discontinues TMC125 study C227: phase III studies continue

On 29 November 2005, Tibotec issued a press release that announced the discontinuation of a single exploratory open-label phase II study of one TMC125, their NNRTI that is most developed. Phase III studies of TMC125, which are currently enrolling in highly treatment-experienced patients, have not been affected by this announcement.

The discontinued study, TMC125-C227, randomised PI-naïve patients failing a first line NNRTI-containing regimen to receive either TMC125 or a PI, together with two RTIs.

After 12 weeks a difference in the proportion of patients achieving or maintaining an undetectable viral load (<50 copies/ml) in favor of the control group, indicted a sub-optimal virologic response of patients receiving TMC125. No safety concerns were identified. The company decided to stop the trial based on these data. The study's Data Safety Monitoring Board endorsed that decision.

Tibotec researchers believed that it was in the best interest of trial participants, including those presently responding to TMC125 therapy, to be switched to a regimen based on approved antiretrovirals as soon as possible, in order to minimize the chances of compromising future treatment options.

Given the antiviral activity demonstrated with TMC125 thus far in studies involving patients with NNRTI-resistant virus, Tibotec researchers are confident in the design and conduct of the phase III trials, TMC125-C206 and TMC125-C216 (DUET 1 and DUET 2), which are currently enrolling patients.

C O M M E N T

Until further analysis are performed and reported, or the exact details of this study are released, it is difficult to comment on this press release. We assume that the difference must have been significant for the study to have been closed.

Source:

Tibotec Press Release: Tibotec discontinues exploratory trial with TMC125: Phase III registration studies continue, (29 November, 2005).

<http://www.tibotec.com>

New Kaletra tablet formulation (meltrex) approved by FDA

On 28 October 2005, the Food and Drug Administration (FDA) approved a new formulation of Kaletra. Kaletra (lopinavir/ritonavir) is now available in the US as a film-coated tablet (200mg/50mg) that provides advantages over the currently marketed capsule formulation for HIV-1 infected patients. Specifically, the tablet formulation:

- does not require refrigeration,
- can be administered without regard to meals

- does not require dose adjustments for concomitant use with certain NNRTIs and PIs in treatment-naïve patients
- has a decreased pill burden compared to the capsule formulation (2 tablets twice daily or 4 tablets once daily in treatment-naïve patients only vs 3 capsules twice daily or 6 capsules once daily in treatment-naïve patients only)

Selected changes to the SPC for the tablet formulation are included below. Please refer to the full SPC for full details of the changes.

- Two 200/50 mg lopinavir/r tablets are similar to three 133.3/33.3 mg KALETRA capsules under fed conditions with less pharmacokinetic variability.

No clinically significant changes in C_{max} and AUC were observed following administration of lopinavir/r tablets under fed conditions compared to fasted conditions. Relative to fasting, administration of lopinavir/r tablets with a moderate fat meal (500 - 682 Kcal, 23 to 25% calories from fat) increased lopinavir AUC and C_{max} by 26.9% and 17.6%, respectively. Relative to fasting, administration of lopinavir/r tablets with a high fat meal (872 Kcal, 56% from fat) increased lopinavir AUC by 18.9%, but not C_{max}. Therefore, lopinavir/r tablets may be taken with or without food.

- Lopinavir/r oral solution must be taken with food.
- Lopinavir/r tablets should be swallowed whole and not chewed, broken, or crushed.

The 'dosage and administration' section was revised to include the following information:

- Although the label includes an option to dose lopinavir/r once-daily for treatment naïve patients, once-daily administration of lopinavir/r is not recommended in therapy-experienced patients.

Drug interactions with the tablet and capsule formulation are similar and require similar dose adjustments.

The 'how supplied' section was revised to include storage information for the Kaletra tablets as follows:

- Recommended storage for the film-coated tablets is at 20°- 25°C (68°-77°F); excursions permitted to 15°-30°C (59° to 86°F) [see USP controlled room temperature]. Exposure of this product to high humidity outside the original container for longer than 2 weeks is not recommended.

Abbott plan to phase out the capsule formulation of lopinavir/r

C O M M E N T

European approval is not expected until early Summer 2006. However a named patient programme is being planned within the next month, that will enable earlier access for patients who currently have adherence or storage problems associated with the current formulation.

The cost premium in the US for the new formulation was an 8% increase, although this is not expected in Europe. Once the meltrex formulation is available, Abbott will discontinue production of the current formulation.

Source: FDA list serve

An archive of past list serve announcements is available on the FDA web site at:

<http://www.fda.gov/oashi/aids/listserve/archive.html>

GSK closes Phase 3 studies of its CCR5 inhibitor aplaviroc and terminates development programme

Simon Collins, HIV i-Base

In the last issue of HTB, we reported that GSK suspended naïve studies of their CCR5 inhibitor aplaviroc (GW873140) due to two cases of serious but non-fatal hepatotoxicity. On 25 October the company issued a press announcement that all Phase 2b and 3 trials including those in treatment experienced patients are also to be terminated.

Phase 3 development started in July 2005 for the treatment of HIV-1 infection in treatment-experienced patients. In September 2005, all Phase 2b clinical trials in HIV treatment-naïve patients, as well as studies in healthy volunteers, were terminated due to cases of severe hepatotoxicity. Phase 3 studies in treatment-experienced patients with multi-drug resistant virus and limited treatment options remained open, although further enrollment was on hold while data from the Phase 2b studies were reviewed. Patients who were already in the Phase 3 studies had the option to continue therapy and were closely monitored for any adverse events during that time.

GSK recently received a report of a patient in one of the Phase 3 trials who experienced elevated liver enzymes (AST, ALT) and total bilirubin. Based on a review of this case in the context of the previous reports from the Phase 2b studies, GSK has stopped all Phase 3 studies of aplaviroc. No further clinical studies of the compound are planned at this time.

It is GSK's intention to stop therapy with aplaviroc for all current trial participants. However, treatment-experienced patients who are currently on aplaviroc and receiving clinical benefit, as determined by their physician, may elect to continue aplaviroc therapy until an alternative regimen can be devised or until they are no longer deemed to be deriving benefit from the drug. These patients will continue to be monitored closely for signs or symptoms of liver toxicity, and elevations in liver function tests. Clinical trial investigators and their Institutional Review Boards or Ethics Committees have been notified of the situation and have received instructions for transitioning of patients participating in the Phase 3 trials.

GSK is actively reviewing the aplaviroc safety data, and follow-up on all patients is ongoing.

C O M M E N T

An additional unscheduled oral presentation at the EACS conference in Dublin, enabled GSK to present a more detailed review of the details behind the decision to stop development of aplaviroc.

Four cases of hepatic toxicity, defined by dramatic increases in ALT levels, were complicated by similar increases in bilirubin. According to Hy's law, when both ALT and bilirubin increase in the same patient, there is a 10-50% risk of the reaction being fatal. Fortunately, none of the cases in the GSK study were fatal.

After the GSK presentation, and in response to a question from Stefan Mauss, a spokesperson from Pfizer read a short pre-prepared statement relating single case of hepatic toxicity associated with maraviroc (the Pfizer CCR5 inhibitor). The limited details released about this case, including it being a single case from over 1000 patients exposed to the compound, that it involved a recent coinfection with hepatitis C, and the use of other hepatic-toxic drugs. This suggests that similar safety concerns to the GSK compound may not be occurring, creating the possibility that this may be a drug-specific rather than a class effect.

Source: GSK press release 'GSK terminates patient enrollment for Phase 3 studies of investigational HIV entry inhibitor aplaviroc (GW873140)'. 25 October 2005.

Schering discontinues Phase II studies of vicriviroc in treatment naïve patients

On 27 October 2005, Schering-Plough issued a press release that it has discontinued a Phase II study with its investigational CCR5 receptor antagonist, vicriviroc, used in combination with AZT and 3TC (Combivir) in treatment-naïve HIV patients. This decision was due to a return of detectable virus in some patients late in therapy compared to the standard-of-care control regimen of AZT/3TC/efavirenz.

The company noted that this decision was not based on hepatotoxicity or other significant safety issues in patients receiving vicriviroc in the study or in a second Phase II study in treatment-experienced HIV patients, which is continuing. The Phase II study in U.S. treatment-experienced patients is being conducted by the NIH-sponsored AIDS Clinical Trials Group (ACTG) and is fully enrolled.

Schering-Plough said that it discontinued its Phase II treatment-naïve study following a recommendation from the independent Data Safety Monitoring Board (DSMB), which has been meeting regularly to conduct reviews of the safety and efficacy data. The increased incidence of detectable virus was only seen in some patients after several weeks of treatment. The study had been under way since spring 2004 in 23 centers in Europe and Canada, with 92 patients enrolled. Patients already enrolled in the treatment-naïve study will continue to receive vicriviroc until they can be switched to an alternative regimen in consultation with their physician. Clinical trial investigators for the study, their Ethics Committees and Health Authorities are being notified.

Source: Press release from Schering Plough: Schering Plough discontinues Phase II study of vicriviroc in treatment-naïve HIV patients, continues Phase II study in treatment-experienced patients. 27 October 2005.

<http://www.schering-plough.com>

FDA issues approvable letter for Bioject needle-free injection device

On 23 November, Roche and Trimeris announced that they had received an approval letter from the U.S. Food and Drug Administration (FDA), in response to their request for inclusion of information about the Biojector® 2000 (B2000) needle-free injection device in the T-20 (enfuvirtide, Fuzeon) labeling. In the approval letter, the FDA has requested additional information from the ongoing ENF-404 or WAND (With A Needle-Free Device) study, a randomized, open-label, two-way,

cross-over study assessing the tolerability of the B2000 device for administration of T-20.

The B2000, made by Bioject Medical Technologies Inc., is a needle-free, CO₂-powered injector that disperses liquid medication beneath the skin. T-20 is the first and only entry inhibitor available for the treatment of HIV and is currently approved for administration with a needle and syringe.

<http://www.roche.com>

<http://www.trimeris.com>

RESISTANCE TESTING

Cost effectiveness of resistance testing for treatment-naïve patients

Simon Collins, HIV i-Base

In the 1st November issue of *Clinical Infectious Diseases*, Paul Sax and colleagues from Massachusetts General Hospital and the Harvard Medical School presented their analysis of the cost-effectiveness of resistance testing in treatment-naïve patients prior to starting treatment.

They used a model of HIV disease to project life expectancy, costs, and cost-effectiveness in a hypothetical cohort of antiretroviral-naïve patients with chronic HIV infection and assumed baseline prevalence of 8.3% drug resistance.

Results from the study showed that the model predicted that a strategy of genotype-resistance testing at initial diagnosis of HIV infection increased per-person quality-adjusted life expectancy by one month, with an incremental cost-effectiveness ratio of \$23,900 per quality-adjusted life-year (QALY) gained, compared with no genotype testing. The cost-effectiveness ratio for resistance testing remained less than \$50,000 per QALY gained, unless the prevalence of resistance was 1%, a level lower than those reported in most regions of the United States and Europe.

In sensitivity analyses, the cost-effectiveness remained favorable through wide variations in baseline assumptions, including variations in genotype cost, prevalence of resistance overall and to individual drug classes, and sensitivity of resistance testing.

The study concluded that 'genotype-resistance testing of chronically HIV-infected, antiretroviral-naïve patients is likely to improve clinical outcomes and is cost-effective, compared with other HIV care in the United States' and that 'resistance testing at the time of diagnosis should be the standard of care'.

C O M M E N T

The cost-effectiveness of resistance testing prior to starting HAART has already been reported in HTB, together with the high estimated prevalence of transmitted drug resistance in the UK (10-18%).

This use of resistance testing was first recommended in BHIVA treatment guidelines in 2003, and this recommendation was strengthened in 2005.

However, results from the 2005 BHIVA national audit, presented at its conference in October, showed that over the last year only fifty percent of treatment-naïve patients across the UK were given resistance testing on diagnosis or prior to starting treatment. It is a real concern that patients are losing the opportunity to identify risk of treatment failure prior to initiating treatment regimens, that are likely to be suboptimal, and more likely to lead to additional accumulated mutations.

Ref: Sax PE, Islam R, Walensky RP et al. Should resistance testing be performed for treatment-naïve HIV-infected patients? A cost-effectiveness analysis. *Clin Inf Dis*, Volume 41 (2005) 9: 1316-1323.

DRUG LEVEL MONITORING

Improved clinical outcome in 80% patients who modified an NNRTI or PI dose following therapeutic drug monitoring (TDM)

Simon Collins, HIV i-Base

An analysis of the use of TDM interventions and clinical benefits at the Hospital Carlos III, Madrid during a three-year period, were published by Rendón and colleagues in the September 2005 issue of *HIV Medicine*.

The investigators retrospectively looked at 151 requests for TDM from 137 patients from October 2000 to August 2003.

Plasma samples were drawn at routine appointments prior to a morning dose, when levels were at steady-state, but without patients knowing that drug levels were going to be measured.

Almost sixty percent (89/151) of the requests were for suspected drug-related toxicity, and apart from three requests relating to drug interactions, the remainder related to virological failure. Suspected high drug levels relating to drug toxicity were more often requested for patients using NNTRIs (68% of NNRTI requests) and suspected suboptimal levels related to virological failure was more commonly requested for PIs (61% PI requests). TDM was requested more frequently for NNTRIs than PIs (73% vs 27%).

Around one third of the tests for toxicity (32/89) showed elevated plasma levels (this was slightly higher at 40% of the NNRTI-related toxicity tests). Sixty percent of patients with liver toxicity had elevated levels and 30% had suspected efavirenz toxicity (insomnia, dizziness). Only 2/12 patients with elevated triglycerides on lopinavir/r-containing regimens showed elevated drug levels.

Around half of the patients tested for toxicity had plasma levels within the normal range and eight percent were paradoxically below the reference range.

When TDM was requested in relation to virological failure, 37% of requests (22/59) showed suboptimal levels. This included 9/12 patients using lopinavir/r, 3/8 using amprenavir, 6/14 using efavirenz and 4/20 using nevirapine. Again though, around half of the requests showed levels within the therapeutic reference range.

Of more interest are the results reported following a dose modification in 20 of the patients at this clinic (8 efavirenz and 2 nevirapine-related dose reductions; 3 efavirenz, 4 lopinavir/r and 1 nevirapine-related dose increases; and 2 regimen changes). Following these dose-modifications, outcomes improved in 80% cases, and a similar percentage of patients whose drug-plasma levels were retested (11/14) were within the therapeutic range.

Individual results presented for the patients in this study are probably more important than pooled data. Follow-up in patients reducing efavirenz from 600mg to 400mg/day, or nevirapine from 400mg to 200mg once a day maintained virological suppression <50 copies/mL (one patient showed 65 copies/mL), though follow-up in these patients ranged from 1-8 months. Longer term confirmation is clearly important and required.

Viral suppression <50 copies/mL in 4/4 patients increasing efavirenz to 800/mg/day (follow-up range 3-8 months) but in only in 1/4 patients who increase the lopinavir/r dose to 533/133mg-twice-daily (follow-up 2-5 months).

C O M M E N T

Other studies looking at clinical benefits of TDM have reported a similarly low level of active dose modification after identifying either excess or sub-optimal levels. In this study only 20/54 potential interventions were made.

The high rate of reported clinical benefits where the results of TDM were implemented in patients who were followed longitudinally, indicates that this is a resource that is still under-utilised on an individual patient level.

Ref: Rendón AL, Núñez M, Soriano V et al. Clinical benefit of interventions driven by therapeutic drug monitoring. HIV Medicine (September 2005), 6, 360-365.

PREGNANCY AND PMTCT

US pregnancy guidelines updated

The "Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States" have been revised to include:

- Updates to Clinical Scenario #3. The new information discusses a 3 to 7 day "tail" of postpartum maternal ZDV/3TC following single dose maternal/infant nevirapine; this "tail" may reduce the risk of nevirapine resistance.
- Updated information on the role of cesarean delivery in preventing mother-to-child transmission of HIV.
- An updated Supplement: Safety and Toxicity of Individual Antiretroviral Agents in Pregnancy, including a new section on tipranavir.
- A Perinatal Antiretroviral Guidelines Working Group Conflict of Interest Disclosure (Appendix).

Updated information appears highlighted in yellow.

You can download the updated guidelines, or request to receive them by e-mail or hard copy from the AIDSinfo Web site:

http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=66

The AIDSinfo website is also a useful source of other information related to HIV/AIDS, including other treatment and prevention guidelines, downloadable databases for PDAs (Personal Digital Assistants), fact sheets, and HIV/AIDS-related clinical trials information.

Source: FDA list serve

An archive of past list serve announcements is available on the FDA web site at:

<http://www.fda.gov/oashi/aids/listserve/archive.html>

OTHER NEWS

European activists denounce pricing increases for HIV drugs as ‘unbearable’

European treatment activists condemned the ever-increasing cost of life-saving antiretroviral treatment at the 10th European AIDS Conference in Dublin.

“HIV drug prices are getting higher and higher. This threatens to cause European HIV patients serious difficulties accessing their medication in the near future,” said David Haerry, one of the chairs of the European Community Advisory Board, a working group of EATG.

“This has been a trend since the early days of HIV treatment, but it has accelerated in the last couple of years; nowadays it seems unstoppable.”

His comments followed the announcement by drug company Boehringer Ingelheim that tipranavir (Aptivus), its recently registered protease inhibitor, will cost up to 24 euros a day in Europe - though adding in the other drugs needed for this compound to be effective will at least triple that price.

Introducing new drugs into HIV treatment must be a cost-effective use of national health budgets. The new drugs should be more effective, work against drug-resistant virus and have fewer side effects that need managing.

However the new drugs are also more expensive, and with the number of people living with HIV in Europe likely to continue rising for the foreseeable future, their cost to national health systems threatens to become unsustainable.

Aptivus is the latest in a series. Efavirenz (Sustiva/Stocrin) from BMS/Merck, tenofovir (Viread) from Gilead, Ipinavir/r (Kaletra) from Abbott, T-20 (enfuvirtide, Fuzeon) from Roche and atazanavir (Reyataz) from BMS - each of them previously set a new price record in its class when it was licensed. The HIV drug bill is increasing as more Europeans with HIV are living longer.

“Unless there is a fair drug price policy for all disease areas, including HIV, national health systems are going to bear an excessive burden”, explained Wim Vandevelde, a member of EATG’s Board of Directors.

“This case is not hypothetical: EU countries such as Belgium or regions like the Basque Country in Spain are already restricting access to HIV medication for reasons of cost.”

EATG Board member Smiljka Malesevic comes from Serbia. She said: “Even if these drugs are licensed in Central and Eastern Europe, they are completely unaffordable for the vast majority of patients in the part of the world currently experiencing the fastest-growing epidemic. This threatens lives at a time these new drugs should be saving them.”

The scaling up of HIV drug prices is leading local reimbursement authorities to question the entire licensing system and the value and authority of the European Medicine Evaluation Agency (EMA). This is contributing further to an already fragmented picture of access to HIV drugs. What is happening is against the spirit of the European Union, says the EATG.

Nikos Dedes, Chairperson of the EATG, concluded: “We call all stakeholders –companies, regulatory agencies, governments and patient groups - to treat this issue with urgency. We must collaborate on a serious policy for a sustainable HIV drug pricing system in Europe. This is a duty we owe to people living with HIV and to our society.”

For more info, please contact Joan Tallada, EATG, External Communications Officer (English, Spanish, French, Italian) on + 34 637 464 803 or at joan@eatg.org

Source: EATG Press release, November 2005.

<http://www.eatg.org>

ON THE WEB

Treatment guidelines:

Guidelines for the use of antiretroviral agents in pediatric HIV infection

National Pediatric and Family HIV Resource Center (NPHRC), Health Resources and Services Administration (HRSA), and National Institutes of Health (NIH), updated November 3, 2005.

http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=51

See also the supporting slide sets from the AIDS Education and Training Centers National Resource Center:

<http://aidsetc.org/aidsetc?page=et-01-00#S1.1X>

Conference reports:

American Association For The Study of Liver Diseases (AASLD)

November 11-15, 2005 San Francisco

A wide range of reports from the AASLD conference are online on the NATAP.org website:

<http://www.natap.org>

<http://www.natap.org/2005/AASLD/aasld.htm>

Reports include studies of new treatments, transplantation and monitoring fibrosis in liver disease:

- Consensus Interferon: study results at AASLD
- Alfaferon-Alpha (Albumin-Interferon Alpha) (11/17/05)
- REPEAT Study: Non-responders to ≥ 12 weeks' treatment with standard-dose pegylated interferon alfa-2b (PegIntron) plus ribavirin received standard dose of Pegasys + ribavirin or double dose Pegasys + ribavirin (11/15/05)
- Alfaferon + ribavirin in PegIFN non-responders: phase 2 study (11/15/05)
- SCH 503034 HCV protease inhibitor monotherapy in HCV genotype 1 IFN non-responders (11/15/05)
- VX-950 hepatitis C Protease inhibitor (11/15/05)
- Combination therapy with SCH-503034 HCV protease inhibitor & PegIntron in non-responders: phase 1b study results (11/15/05)
- Performance of APRI for the diagnosis of significant hepatic fibrosis is improved by a simple modification (11/14/05)
- Long term results after therapy with pegylated interferon alpha-2a (Pegsys) in HCV-positive liver transplant recipients.
- Predicting outcome in patients with HCV after organ liver transplant: a 15-year follow-up. (11/14/05)
- Recurrent hepatitis C is a risk factor for poor outcome after liver retransplantation. (11/14/05)
- Multicentred randomised trial of HCV treatment with PegInterferon-alpha 2a (Pegasys) and ribavirin after liver transplantation: one year report (11/14/05)
- On treatment virological response of 70% in 100 patients treated with combination antiviral therapy for recurrent HCV following liver transplantation. (11/14/05)
- Is liver biopsy justified in hepatitis C genotype 2 and 3? (11/14/05)
- Fibroscan, monitoring liver stiffness: a new tool to measure liver fibrosis during therapy. (11/14/05)
- Telbivudine (LdT) Phase 3 One Year Study Results (11/14/05)
- Liver Cancer developed Among SVRs; Sexual Dysfunction among HCV+ (11/14/05)
- Virological and histological features of HCV in patients with normal ALT: results of a ten year prospective follow-up study. (11/14/05)
- African-American patients had fewer office visits and were less likely to return for a second office visit (11/14/05)

- Coffee drinking decreases the risk of chronic liver disease in the US population. (11/14/05)
- Impact of caffeine consumption on ALT and histological activity in patients with chronic active HCV. (11/14/05)
- Troglitazone significantly reduced tumor growth in vivo, and caused tumor regression in liver cells (11/14/05)
- Study evaluations of non-invasive fibrosis tests (11/14/05)
- Liver histology in hepatitis C patients with normal ALT levels. (11/14/05)
- Hispanics developed cirrhosis more quickly due to the presence of fatty liver & diabetes (11/14/05)
- Cannabinoids block interferon-mediated suppression of hepatitis C virus (HCV) replication. (11/14/05)
- Cryoglobulinemia is associated with steatosis and fibrosis in chronic HCV. (11/14/05)
- Independent validation and comparison with fibroscan, fibrotest and liver biopsy of clinical glycomics for the non invasive assessment of liver fibrosis in chronic HCV. (11/14/05)
- New hepatitis C polymerase inhibitor HCV-796 study in patients - (11/11/05)

Medscape articles and online papers:

The following journal articles are available online in full. Medscape requires a simple one-time free online registration.

AIDS

<http://www.medscape.com/viewpublication/744>

- **AIDS events among individuals initiating HAART: do some patients experience a greater benefit from HAART than others?**
- **Clinical management of depression and anxiety in HIV-infected adults**

JAIDS: Journal of Acquired Immune Deficiency Syndromes

http://www.medscape.com/viewpublication/878_index

- **HIV infection does not affect the performance of noninvasive markers of fibrosis for the diagnosis of hepatitis C virus-related liver disease**

Noninvasive markers of hepatic fibrosis hold great promise to stage liver fibrosis and to monitor disease progression. This study concluded: "the diagnostic performance of the evaluated noninvasive markers of liver fibrosis is equivalent in HCV/HIV-coinfected and HCV-infected subjects. These tests may be of value for the clinical evaluation of HCV/HIV-coinfected patients and warrant further study."

- **Prednisolone pharmacokinetics in the presence and absence of ritonavir after oral prednisone administration to healthy volunteer**

Study showing a significant interaction that may require caution given side effects associated with corticosteroid use that concluded: "Ritonavir significantly increased the systemic exposure of prednisolone in healthy subjects. Results from this investigation suggest that corticosteroid exposure is likely elevated in HIV-infected patients receiving protease inhibitors".

HIV Medicine

http://www.medscape.com/viewpublication/1008_index

- **Impact of antiretroviral choice on hypercholesterolaemia events: the role of the Nucleoside Reverse Transcriptase Inhibitor back bone**
- **The effect of low-dose ritonavir monotherapy on fasting serum lipid concentrations**

The AIDS Reader

http://www.medscape.com/viewpublication/93_index

- **Multidrug-resistant HIV**
- **Memory loss in persons with HIV/AIDS: assessment and strategies for coping**
- **Effect of recombinant human growth hormone on exercise capacity in patients with HIV-associated wasting on HAART**

AIDS Clinical Care

<http://www.medscape.com/viewpublication/880>

- **Diabetes drugs for HIV lipodystrophy**
- **An added value of rapid testing: improved quality of care**

Online Medical Resources:

HIV inSite Knowledge Base

Updates form October and November 2005

- **Cardiac manifestations of HIV** - Rakhlin N, Hsue P

<http://hivinsite.ucsf.edu/InSite?page=kb-04-01-06>

- **Coping with the psychological stressors of HIV:** related resources - Journal articles, presentations, and patient information on depression and stress in people living with HIV

<http://hivinsite.ucsf.edu/InSite?page=kbr-03-01-05-01>

- **Substance abuse and HIV:** related resources - Journal articles, presentations, and patient information on substance abuse issues and HIV infection.

<http://hivinsite.ucsf.edu/InSite?page=kbr-03-03-08>

Other recently updated resource pages:

- **Treatment access**

<http://hivinsite.ucsf.edu/InSite?page=kbr-08-01-03>

- **HIV/AIDS and the workplace**

<http://hivinsite.ucsf.edu/InSite?page=kbr-08-01-14>

- **HIV transmission and prevention in gay men**

<http://hivinsite.ucsf.edu/InSite?page=kbr-07-04-04>

Updated antiretroviral drug profiles:

- **Ritonavir (Norvir)**

<http://hivinsite.ucsf.edu/InSite?page=ar-03-02>

- **Emtricitabine (Emtriva, FTC)**

<http://hivinsite.ucsf.edu/InSite?page=ar-01-08>

See all drug profiles:

<http://hivinsite.ucsf.edu/InSite?page=ar-drugs>

Community newsletters and journals:

The Stop TB Primer

The first of two documents being produced from the Stop-TB eForum discussions is now available on the HDN eforums website:

<http://www.healthdev.org/eforums/stop-tb>

Fighting TB on the front lines: Key findings and recommendations on the crucial role played by front-line health workers in TB control

The people fighting against tuberculosis (TB) are clearly the best-placed to talk about the challenges they face on a daily basis and how to improve the DOTS programmes so that they function at optimum level. They need a louder voice and more visibility - and those working at the health policy level need to learn from them.

As a member of Stop TB Partnership, Health and Development Networks moderated and managed a six-month discussion on the Stop TB eForum on the 2005 theme of World TB Day: Key roles and needs of front-line health workers in stopping tuberculosis.

The overall aim of the discussion was to share information and assess the critical role that front-line health workers play in turning back the tide of TB. The discussion built upon the recognition that government services cannot defeat TB alone

and that further improvements in case detection and cure rates need the active and local engagement of people involved in care provision on a daily basis.

This document is a distillation of the experiences and expertise of the many people who contributed to the discussion. These key findings and recommendations highlight the vital role played by front-line health workers in TB control.

Available online at:

<http://www.healthdev.org/eforums/stop-tb>

IAVI Report – September 2005

<http://www.iavireport.org/Vax/CurrentVAX.asp#1>

- **An industrial incentive:** Several organizations are pursuing new ways to encourage the pharmaceutical industry to increase investment into the research and development of an AIDS vaccine.
- **US Senators introduce bill on accelerating AIDS vaccine research**
- **First meeting of Clinton Global Initiative draws funding and attention for development issues**
- **Vice President of Uganda addresses major AIDS vaccine meeting**
- **Understanding test of concept trials: why are Phase IIb trials an important step in evaluating AIDS vaccine candidates?**

European AIDS Treatment News

Volume 14, 02 . Autumn 2005 . English Edition

- **Ethics and clinical trials**
- **HIV research for drug users**
- **New obstacles for cheaper drugs**
- **Methadone and buprenorphine as essential drugs**
- **How to stop a worldwide pandemic**

EATN is published in English and Russian in printed and PDF format, and in a variety of other languages, including Spanish, only in PDF format.

PDF download at the EATG website:

<http://www.eatg.org>

Community resources:

Amedeo HIV Medicine

Amedeo HIV Medicine 2005 is now available in PDF format (762 pages, 5.1 MB).

Download:

<http://www.hivmedicine.com/textbook/download.htm>

Under certain conditions, the editors and the authors agree to remove the copyright on their book for all languages except English and German.

MEETING ANNOUNCEMENTS

Conference on Retroviruses and Opportunistic Infections, 2006

The 13th Conference on Retroviruses and Opportunistic Infections will be held February 5-9, 2006 at the Colorado Convention Center in Denver, Colorado.

Please visit the updated 2006 website, for information regarding dates and deadlines, abstract submission, travel grants, international scholarships and the community educator programme:

<http://www.retroconference.org>

PUBLICATIONS AND SERVICES FROM i-BASE

i-Base website redesigned

<http://www.i-Base.info>

The website has been redesigned to be faster, easier to use, and more accessible for those with impaired sight. For those who understand these matters, all pages conform to at least the W3C-WAI Level A and most to level AAA.

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.

There is a new section on Education and Training with treatment training for advocates. This includes our training manual 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 brief overviews of the main opportunistic infections. There is a module on pregnancy and another module on IV drug users and treatment

All i-Base publications are available at our website, including 2005 editions of the treatment guides. The site gives details about i-Base, the UK Community Advisory Boards (UK-CABs), 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).

A new page has been added on how to adapt and translate treatment resources, and included examples from projects we have worked with outside the UK.

An average of 2000 pages a day are served from the site.

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 for three years. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

Reading material, reports and presentations from these meetings (the 15th meeting was on 25 November 2005) are posted to the i-Base website and are available in printed format.

The November meeting included presentations on HIV treatment in Eastern Europe, and a training on hepatitis and coinfection from Dr Mark Nelson. UK-CAB members gave reports back from the the EACS and BHIVA conferences, the Lipodystrophy Workshop, and the Global Fund; and the group met with Pfizer to discuss entry inhibitors as a class including maraviroc.

<http://www.i-base.info/ukcab/index.html>

<http://www.i-base.info/ukcab/nov05/index.html>

World CAB - reports on international drug pricing

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

The latest report focusses on a meeting held in January 2005 with four Indian generic manufacturers.

An earlier report is from a meeting in February 2004 with three major brand manufacturers.

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 2004 edition

This non-technical patient guide to treatment is available in 12 languages. It explains what combination therapy is, 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 Bulgarian, Chinese, English, French, Georgian, Italian, Latvian, Macedonian, Portuguese, Russian, Slovak, and Spanish. Please see the 'translations' page or the website for more details.

Introduction to Combination Therapy - New Portuguese edition

The June 2004 edition of this i-Base guide is now available in Portuguese as a pdf file posted to the i-Base website.

Guide to HIV, pregnancy & women's health

Spring 2005 edition

Updated and revised in April 2005, 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 changing treatment: what to do when your treatment fails

April 2005 edition

Also updated and revised in April 2005, this is a non-technical patient guide to changing treatment and what to do if treatment fails.

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 avoiding & managing side effects

February 2005 edition

This is a comprehensive 44-page 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.

New sections are included on heart disease, lipodystrophy, and information relating to newer drugs including T-20, atazanavir, tenofovir, FTC and fosamprenavir.

Chinese, French, Italian and Spanish translations of the previous edition are still available.

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.

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.

This service is available in English and French.

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/2004>

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

Order i-Base publications via the internet, post or fax

People with internet access can use our website to order and receive publications. You can access our publications online or subscribe to receive them by email or by post; and you can order single copies or bulk deliveries by using the forms at:

<http://www.i-base.info/forms/index.html>

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), 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 sending an email to:

subscriptions@i-base.org.uk

or by fax or post using the form on the back page.

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

Some articles are reproduced from other respected sources and copyright for these articles remains with the original authors and sources, as indicated at the end of each article.

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

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HIV i-Base

All publications are free, including bulk orders, because any charge would limit access to this information to some of the people who most need it.

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REFUNDS FROM THE TAX MAN

From April 2005 the Inland Revenue is operating a system whereby you can request that any refunds from them should be paid to a charity of your choice from the list on their website. If you feel like giving up that tax refund we are part of this scheme and you will find us on the Inland Revenue list with the code: **JAM40VG** (We rather like this code!) Any amount is extremely helpful.

Whichever of the above schemes you might chose to donate to i-Base we would like to thank you very much for your support.

