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EDITORIAL

The last issue of HTB this year – a double issue for November and December – includes a report from the latest BHIVA audit, together with reports from the recent Glasgow conference.

We like to take this opportunity to thank all our readers and funders for continuing to support i-Base through 2006, and to send you seasonal good wishes for the coming holidays, and new year ahead.

New 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 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.

We are asking for minimum donation price of £10.00 plus £2.50 p&p.

Please contact the i-Base office for more details:

T: 020 7407 8488

or email: bookoffer@i-Base.org.uk

or post the donation form on the inside back page of this issue of HTB, using either ‘standing order’ or ‘one-off donation’ as appropriate.

Thank you for your support.

CONFERENCE REPORTS

BHIVA Autumn conference

13-14 October 2006, London

Causes of death in the UK: results from BHIVA audit

Simon Collins, HIV i-Base

The annual BHIVA audits are an essential mechanism for highlighting issues relating to management of HIV-positive patients in the UK. Over 130 clinics (80% from outside London), participate by providing information on an aspect of care. A wide range of clinics are involved: roughly 20% of participating clinics in this audit treat <50, 50-100, 101-200, 201-500 and >500 patients.

This audit addressed causes of death, and results were detailed in an oral presentation by Sebastian Lucas at the years Autumn BHIVA Conference.

Data was analysed from case note reviews from 90 centres that included 387 deaths among adults with HIV during the audit period of October 2004 – September 2005. Although the date of death was missing for eight patients, these were still included in the analysis.

It is positive that the annual rate of deaths in the UK patients diagnosed patients under care is relatively low. 40 centres reported no deaths among their adult HIV patients in the preceding year, including 52% of those serving 100 or fewer patients.

Demographic breakdown included: roughly three-quarters of deaths were men and one quarter women; 57% white, 33% African, 2% Caribbean, rest unknown; age: 65% between 30-50 years old and 27% were over 50; 72% occurred in a

UK hospital and 22% in a community setting in the UK; 80% had no history of injection of non-prescribed drug, 9% had discontinued prior to their final illness, and 5% continued injecting drug use until their final illness.

CD4 count in the preceding 6 months was less than 50 cells/mm³ in 35% cases and over 200 cells/mm³ in around 25% cases. Viral load was >50 copies/mL in 60% patients but only high (over 100,00) in 25%, with just over 30% cases having an undetectable viral load. Deaths of patients who were effectively responding to ARV treatment largely overlapped with the 32% categorised as being unrelated to HIV. These included: 30 malignancies (7.8% of all deaths), 22 liver disease (5.7%), 17 cardiovascular disease (4.4%), 7 suicide (1.8%), 7 sepsis (1.8%), 6 accident/injury (1.6%), including one homicide, 4 (1.0%) overdose, 1 (0.3%) renal disease and 29 (7.5%) other or not stated.

Although 25 people died of cardiovascular disease, 17 of these were recorded by the centre under 'unrelated to HIV'. Similarly, 26 deaths recorded as due to liver disease were also categorised as non-HIV related. A comment from the presenter suggested that this was an area where more careful categorisation in the future could relate these to an HIV-related complication.

The second largest category related to around 25% deaths (n=93, one-third of all HIV-related deaths) being due to late diagnosis. This accounted for >40% of deaths at clinics treating less than 200 patients, compared to 13% of the deaths at centers with >500 patients. This was reported as a minimum estimate as some deaths attributed to untreatable complications of HIV involved conditions which early treatment could have prevented. Also, there may be under-ascertainment of deaths occurring without involvement of HIV specialist services.

Late diagnosis disproportionately affected younger people (10% of these deaths vs 5% related to other causes) and non white patients (31% were white compared to 65% in other causes of death). Deaths attributed directly to late diagnosis of HIV were: PCP (28), opportunistic infections (16), TB (9), lymphoma (8), sepsis (8), multi-organ HIV (7), Kaposi's Sarcoma (3), cardiovascular disease (3), renal (2), malignancy (1), other or multiple HIV related (6) and unknown (2). 16 cases suggested a possible clinician delay in diagnosing HIV.

Eleven deaths (3%) were due to multiple drug resistance and running out of treatment options.

Six deaths related to worsening HIV-related symptoms shortly after starting HAART, suggesting IRIS.

Five deaths were related to possible or probably adverse reactions to HIV treatment (3 lactic acidosis, 1 fulminant liver failure (isoniazid), 1 pneumonia possibly associated with non-Hodgkins lymphoma chemotherapy-related bone marrow suppression).

Patient factors included 18 deaths where people had refused treatment (only 3 of whom had used ARVs at some time). 31 deaths were also reported as being directly linked to poor adherence, mainly including bacterial infections (sepsis 12), and included 3 relating to MDR-HIV.

Only 12 patients were known to have arrived in the UK in the prior 6 months, nine of whom died as a result of late diagnosis.

This reinforces other evidence that immigration to the UK is not driven by access to HIV treatment: the majority of late diagnoses were in people who were established in the UK. However, although no deaths were reported as being related to ineligibility for NHS treatment, concern for this is very likely to be a factor for not accessing care. Importantly, deaths of UK patients who have been denied leave to remain in the UK, and have been deported to countries with very limited access to ARVs, are clearly not included in these figures.

Part of the rationale for each audit is to raise awareness and improve standards of care. This study has identified some specific issues, including: mechanisms for informing centres when patients have died in the community or at tertiary referral centres, the importance of good communication and prompt, effective referral pathways, the value of death reviews (used in less than half the deaths reported), and the need for improvement in death certification (information was missing from 50% of certificates, and HIV was also commonly not directly recorded).

Some centres reported that data gathering for this study was an instructive exercise in itself, and identified issues of communication and record-keeping that could be improved.

C O M M E N T

This audit does attempt to provide information on all deaths, but information on incidence and reporting from a wide range of clinics across the UK.

In general, it is positive that death rates are low, with one third unrelated to HIV – though both cardiovascular and renal causes may be seen as HIV-related in the future – and that only 3% were related to multiple drug resistance

A high risk associated with late diagnosis is still a serious concern. Without appropriate treatment, HIV is still a potentially fatal illness.

Ref: Lucas S. 25 years on: the causes of HIV-related death: results of BHIVA audit. BHIVA Autumn conference. 13-14 October, 2006.
Slides and supporting information relating to previous audits are available on the BHIVA website:
<http://www.bhiva.org>

CONFERENCE REPORTS

8th International Congress on Drug Therapy in HIV Infection

12–16 November 2006, Glasgow

This biannual meeting is popular for its single-track programme and useful treatment overviews.

Reports in this issue of HTB include:

- d4T associated with significantly increased risk of type-2 diabetes mellitus
- Saquinavir/r vs lopinavir/r: interim results from the Gemini study
- Explanation for failure of TMC-125 (etravirine) in TMC227 study
- Wide disparity in switch to second-line therapy among children in CHIPS cohort
- Multi-drug resistance in vertically infected children
- Viral load blips in children from the CHIPS cohort
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- Drug interactions with etravirine (TMC-125)
- Community meeting on criminalisation of HIV transmission: jailing people for passing on HIV may threaten public health

Unless stated otherwise, references refer to abstracts and programme of the 8th International Congress on Drug Therapy in HIV Infection. All abstracts are available online:

<http://www.abstracts2view.com/hiv/>

GLASGOW: ANTIRETROVIRALS

d4T associated with significantly increased risk of type-2 diabetes mellitus

Simon Collins, HIV i-Base

The use of d4T (stavudine) has dramatically fallen in most Western countries, primarily due to high risk of lipoatrophy, and additive mitochondrial-related toxicity with other reverse transcriptase inhibitors. However, globally it remains one of the most widely ARVs prescribed first line therapy (in d4T/3TC/nevirapine), as the basis for the least expensive WHO-recommended fixed dose combinations (FDCs).

Further caution against use of d4T as a long-term treatment option was highlighted in an analysis of the use of d4T and the risk of diabetes mellitus (DM) from the D:A:D Study, given in an oral presentation by Stephane de Wit

D:A:D is a prospective observational study of 23,437 HIV patients that has a focus on toxicity and safety issues relating to ARV treatment, including lipodystrophy, cardiovascular risk and hepatotoxicity and where DM is collected as a study endpoint.

The incidence of diabetes mellitus (DM) in the D:A:D study is comparable to that in HIV-negative populations, and this analysis aimed to identify whether specific antiretrovirals (ARV) were associated with new onset DM.

However, the rate of DM (/1000 PY) increased from 3.96 in those unexposed to d4T to 8.20 in those exposed for 2-3 years and then decreased. No other ARV was significantly associated with DM after controlling for d4T use.

Time-updated total cholesterol, HDL-cholesterol and triglycerides were all associated with DM. Adjusting for each of these

separately reduced slightly the relationship between d4T and DM. While lipodystrophy was significantly associated with DM (1.37, $p=0.008$), adjustment for this did not modify the relationship between d4T and DM. This led the authors to conclude that 'd4T potentially directly contributes to insulin resistance, rather than through lipodystrophy'.

Ref: De Wit S, Sabin CA, Weber R et al. Relationship between use of stavudine and diabetes mellitus. 8th International Congress on Drug Therapy in HIV Infection, 12-16 November 2006, Glasgow. Oral abstract PL9.5.

Saquinavir/r vs lopinavir/r: interim results from the Gemini study

Simon Collins, HIV i-Base

Results were presented in Glasgow by Slim and colleagues from a planned interim analysis of the first 150/337 treatment naïve patients randomised to either saquinavir/r (1000/100mg BID) or lopinavir/r (400/100mg BID) in a prospective open-label study.

All patients received tenofovir/FTC as background RTIs. The trial is being run in the USA, Canada, Puerto Rico, France and Thailand. The primary endpoint of the study is the percentage of patients with viral load <50 copies/mL at week 48.

The study enrolled 75% men and 25% women. Baseline characteristics were generally balanced between both arms and included mean CD4 count 114 cells/mm³ and viral load 5.1 log copies/mL, median age 36 years (range 20-63), 11% HCV coinfecting. There is a slight trend in the lopinavir/r arm for patients to be more advanced compared to the saquinavir arm (40% vs 32% with CD4 counts < 50 cells/mm³; and 37% vs 28% with a prior AIDS defining event).

At week 24, there were 5 virologic failures in the saquinavir group (6.8%) versus 2 (2.6%) in the lopinavir group. 69% of saquinavir/r patients compared to 75% of lopinavir/r patients had achieved viral suppression < 50 copies/ml ($p=0.43$, NS between arms). Results were 74% vs 84% for ITT <400 copies/mL assay. Mean changes in CD4 and viral load were + 279 vs +294 cells/mm³ and -3.2 vs -3.5 logs copies/mL in the saquinavir/r vs lopinavir/r arms respectively.

Fourteen patients discontinued saquinavir/r (3 due to side effects, 11 for non-safety reasons) vs 13 with lopinavir/r (4 side effects, 9 non-safety). There were no significant differences in Wk 24 efficacy measures.

Fasting lipid parameters were similar at baseline but changes by week 24 favoured the saquinavir arm. Total cholesterol increased above ≥ 5.2 mmol/L (grade 1 or higher) in 7.9% patients on saquinavir vs 25% of patients on lopinavir arm ($P<0.01$); triglycerides increased to over 4.5 mmol/L (grade 2 or higher) in 1% vs 9% lopinavir/r patients ($P<0.05$).

C O M M E N T

Although this data is interesting, we need to wait for full 48-week analysis in order to see whether some of the small differences between the arms become more significant by the end of the study, and for a full comparison of the safety profile.

The question was also raised in a question after the presentation, about whether interim results should be presented.

As there is little recent data from randomised trials that compares saquinavir/r to other boosted PI-regimens, these results will be important. Results from the MaxCmin2 study, presented as a late breaker at the IAS conference in Paris in July 2003, had a similar design and showed results that benefited lopinavir/r. [2]

This study will show whether new formulations of both drugs have any impact on earlier results (Fortovase was used in the MaxCmin2 trial).

Reference

1. Slim J, Avihingsanon A, Ruxrungtham K et al. [PL2.5] Saquinavir/r (SQV/r) BID vs lopinavir/r (LPV/r) BID plus emtricitabine/tenofovir (FTC/TDF) QD in ARV-naïve HIV-1 infected patients: GEMINI Study. 8th ICDTHI, 12-16 November 2006, Glasgow. Oral abs PL2.5.
2. Youle M, Gerstoft J, Fox Z et al. Final week 48 analysis of a Phase IV, randomized, open-label multi-centre trial to evaluate safety and efficacy of lopinavir/ritonavir (400/100mg BID) versus saquinavir/ritonavir (1000/100mg BID) in adult HIV-1 infection: the MaxCmin2 trial. 2nd IAS Conf HIV Pathog Treat 2003 Jul 13-16. Abs. LB23.
<http://www.aegis.com/conferences/iasshivpt/2003/lb23.html>

Explanation for failure of TMC-125 (etravirine) in TMC227 study

Simon Collins, HIV i-Base

An oral presentation by Brian Woodfall provided an analysis of why Tibotec's TMC227 study had performed so poorly. [1] This trial was closed in November 2005 by the trial Data and Safety Monitoring Board (DSMB) because treatment-experienced patients in Thailand randomised to the new NNRTI etravirine (TMC-125) failed to show minimum -1 log virological response after 12 weeks. [2]

The study randomised patients failing their first-line NNRTI-based regimen and who were PI-naïve, to either the new NNRTI (n=59) or an investigator chosen PI-based regimen (n=57; 61% lopinavir/r, 32% atazanavir/r). The study took place in Argentina, Brazil, Spain, Thailand and South Africa.

Resistance tests were used to guide treatment choices and the study protocol included using two investigator selected sensitive nucleosides in the new regimen.

Pooled data from all sites showed that an initial viral load response of -1.3 logs at week 8 in the NNRTI arm (compared to >2 log reductions in the PI group) was not sustained to week 12. In Thailand the rebound occurred before week 4, and occurred after week 8 in South Africa and after week 12 in Argentina and Spain. For patients reaching week 12, only 57% of the TMC-125 groups compared to 91% in the PI group achieved at least -1.0 log viral load decline.

The baseline resistance profiles of patients in the NNRTI arm were slightly more advanced compared to the PI group, but the significant differences in response was probably more related to the fragility or an unsupported NNRTI, compared to boosted PI regimens which even shows reasonable success rates when used as monotherapy in several small trials, especially in PI-naïve patients. Although TMC-125 retains activity against NNRTI-resistant virus, it is clearly as vulnerable to rapid resistance when used as virtual monotherapy as existing drugs in this class.

At baseline, the median number of NNRTI mutations was 2 (range 0-4) and median fold change (FC) to TMC125 was 2.0. The median number of NRTI mutations was 1 (range 0-7). However 9% and 12% of subjects in TMC125 and control groups, respectively, did not receive two sensitive NRTIs. Only patients with less than 2 TAMS/M184V maintained viral suppression.

Patients with higher NNRTI and RTI-associated resistance had higher FC to TMC-125. Thai patients had more extensive RTI and NNRTI resistance, and this correlated with a higher FC phenotypic resistance to TMC-125 (5.6 vs \leq 2.0 in other countries). Increased resistance to RTIs tended to increase with increased NNRTI mutations.

In a multivariate analysis, increased numbers of NRTI and NNRTI mutations, use of inactive NRTIs, and higher TMC125 FC were all independently associated with virologic failure.

C O M M E N T

The failure of TMC-125 in this study seems to be convincingly explained by extensive RTI and NNRTI resistance, and recycling of RTIs. It also showed that accumulating NNRTI mutations can compromise chance of benefiting from pipeline NNRTIs.

This is particularly important in countries using NNRTI-based first line regimens where there is limited or no access to viral load monitoring, where patients are treated until clinical failure. Unfortunately, this the exactly the setting that would benefit most from a second generation NNRTI.

Other Phase III trials TMC125 in NNRTI and PI experienced patients are ongoing.

TMC-125 is currently available in the UK in an expanded access programme.

References

1. Woodfall B, Vingerhoets J, Peeters M et al. Impact of NNRTI and NRTI resistance on the response to the regimen of TMC125 plus two NRTIs in Study TMC125-C227. 8th International Congress on Drug Therapy in HIV Infection, 12-16 November 2006, Glasgow. Oral presentation PL5.6.
2. Tibotec discontinues TMC125 study C227: phase III studies continue. HIV Treatment Bulletin November/December 2005.
<http://www.i-base.info/htb/v6/htb6-11-12/TMC125.html>

GLASGOW: PAEDIATRICS

Wide disparity in switch to second-line therapy among children in CHIPS cohort

Polly Clayden, HIV i-Base

Kate Lee from the MRC presented data from the Collaborative HIV Paediatric Study (CHIPS) - a multicentre cohort of HIV positive children receiving care in 39 hospitals across the UK and Ireland since 1996. The CHIPS cohort includes 90% of HIV positive children in the UK and Ireland.

The study investigated characteristics of switch to second-line treatment in children who had initiated therapy HAART naïve. This included predictors of earlier switch; CD4 and viral load at switch; and timing of switch with respect to viral load thresholds. Switch was defined as substituting either \geq 3 drugs in the regimen or 2 drugs with recorded reason for failure, with viral load $>$ 50 copies/mL.

Of a group 595 children initiating therapy HAART naïve, 132 (22%) children switched to second line therapy after a median

7.2 years (rate 7.8/100 child-years (CY) [95%CI 6.6-9.2]).

The total population of children was a median age of 4.7 years (IQR: 1.5-8.8 years) with median CD4% 14% (IQR: 8-20.5%), absolute CD4 366 (IQR: 159-700) cells/mm³ and viral load 138,201 (IQR: 123,722-154,373) copies/mL. The median follow up was 3.1 (range: 0-8.2) years. 78% children had had an undetectable viral load <400 copies/mL at any time during first line therapy. The children had received 40 different antiretroviral combinations: 61% had received an NNRTI; 32% a PI; 1% both and 8% NRTIs only.

The investigators reported that the median CD4 count at switch was 485 (IQR: 217-840) cells/mm³ and 20% (IQR: 12-26%) but only 63 (48%) had achieved viral load <400 during first-line therapy.

Viral load at switch was 8,206 copies/mL (IQR: 5,382-12,512) in children who had suppressed on first line vs. 79,569 copies/mL (IQR: 62,127-101,907) in those who had not. The also found that time to switch was longer in those who had suppressed (median >7 vs. 3.1 years respectively, adj HR=0.12 [0.08-0.19]).

Evaluating independent predictors of earlier switch they found: failure to ever achieve undetectable viral load to <400 copies/mL on first line (HR: 7.0 [4.7-9.8], p<0.001); older age at HAART initiation (HR: 1.1[1.0-1.2] per year older, p=0.006); lower CD4% at HAART initiation (HR: 0.87 [0.78-0.97] per 5% higher, p<0.001) and later calendar year at HAART initiation (HR: 1.5 [0.9-3.0] for 2002 vs. 1997-99, p=0.15) were associated.

They reported that sex; current age, viral load or prior adverse events at HAART initiation were not independently associated with earlier switch.

By 3 years after HAART initiation, 14% and 18% of children switched before reaching viral load thresholds of 1000 and 30000 copies/mL respectively (as in the PENPACT 1 trial); 3% & 1% reached thresholds and switched within 6 months with 15% & 3% remaining on 1st-line for >6 months after confirmed viral load >1000 or >30000 copies/mL. Median time to switch after thresholds was 3.3 and 1.0 year respectively.

The investigators noted that children were "Switching somewhere between 1000 and 30,000 copies/mL but no clear level." There was "No clear threshold being used to trigger switch.

Overall they found a low rate of switching to second line, with children never achieving undetectable viral load switching sooner than those who had; older children switching sooner than younger and children starting HAART more recently or with lower CD4% also switching sooner.

They added that there was little consistency in CD4 and viral load at switch.

"Paediatricians seem to be fairly conservative about switching ART for all children", and "There is an urgent need for evidence on which to base switching to guide management for the future", they wrote.

Ref: Lee KJ, Lyall H, Walker AS et al. Wide disparity in switch to second-line therapy in HIV-infected children in CHIPS. 8th International Congress on Drug Therapy in HIV Infection, 12-16 November 2006, Glasgow. Oral abstract PL2.4.

C O M M E N T

It would be wrong to extract from these findings that a child's first line regimen should last for an average of seven years before switching (in those who had ever suppressed) as this will have depended on the child's ability to tolerate a detectable viral load.

This study concludes that paediatricians have been fairly conservative about switching. It was important that there was an analysis by calendar year, as between 1996 and 2000 there were fewer options and more reluctance to switch and this shows a non-statistically significant trend (p=0.15) towards switching at lower viral loads in more recent calendar years. There is also a growing understanding of the implications of resistance (see below).

Several paediatricians have suggested that these results provide additional support for PENPACT 1, which looks at PI vs NNRTI and has a second randomisation looking at switching children at a low viral load (1000 copies/mL) and 1.5 log higher (30,000 copies/mL). This study is now fully enrolled with 260 children.

Multi-drug resistance in vertically infected children

Polly Clayden, HIV i-Base

Vertically infected children are now surviving to adolescence and adulthood; in the CHIPS cohort the median age is now approaching 10 years.

A poster from St Mary's Hospital and Chelsea and Westminster Hospital family clinics evaluated the prevalence of triple class genotypic resistance and clinical outcome in a paediatric cohort between 1 November 2005 and 31 October 2006,

in a retrospective case note review.

This cohort has 220 HIV positive children with a median age 9.9 years (range 0.4-17.7 years), 47% male, 80% Black African. 179 (81%) had ever received antiretroviral therapy: 4 NRTIs alone; 91 had received 2 classes and 84 had received 3 classes of ART. At latest follow up 156 children were on HAART and 127 (81%) had viral loads of <50 copies/mL and median CD4%, 35% (IQR 29-40%).

95/214 children (44%) had ever had a resistance test including 11 who had baseline resistance testing prior to initiation of therapy and all had wild type virus. Of the 84 children having had resistance testing after initiation of therapy 32 (38%) had wild type virus, 31 (37%) had M184I/V mutations and 46 (55%) had non M184V mutations most frequently thymidine-associated mutations, 52 (62%) had NNRTI-associated mutations, most commonly 181C/I and 11 children had major protease mutations.

Of the 179 children who had ever received ART, 34 (19%) had dual class and 6 (3%) had triple class resistance, 2 of whom died during the study.

Of the multi drug resistant children 4/6 children were male, all of black African origin, born between 1988 and 2000 with 3.9-14.9 years on ART and 5/6 had received mono/dual ART prior to HAART. Median number of drugs ever received 13 (range 9-14) and 3 had received T20. Two children died during the study period. Of the remaining children, at latest follow up, all have detectable viral load (range 587 to >500,000 copies/mL) half have a CD4 count of 0 cells/mm³ (range 0-450 cells/mm³).

One patient was receiving 3TC alone; one abacavir+tenofovir+lopinavir/r; one tenofovir+FTC+abacavir+T20+TMC114/r and one tenofovir+FTC+ddI+tipranavir/r (T20 was stopped).

The investigators wrote: "Perinatally infected children with MDR HIV living in the UK urgently require access to novel salvage therapies if they are to survive."

C O M M E N T

Although these data are depressing this is a small snapshot from a cohort historically treated with suboptimal regimens, lack of options and evidence. Hopefully the future is brighter for kids starting therapy now. CHIPS is now looking at resistance across the whole cohort.

Many questions are arising, now that children with HIV are living much longer, around how to stop kids getting resistance by adolescence so that they can start their adult life well with treatment options.

However this experience from London is replicated across western Europe and north America and for this group of young people novel salvage therapies are a priority. In this regard there was a poster at this conference documenting a case study of using TMC114 and T20 in a heavily treated 12 year old (Bamford et al). PK data revealed the need for three times a day dosing with TMC 114. Tibotec is undertaking a PK study of TMC114 in children and the results will be ready in January 2007.

Ref: Foster C, Mackie N, Seery P et al. Emerging multi-drug resistance in children with perinatally acquired HIV-1. 8th International Congress on Drug Therapy in HIV Infection, 12-16 November 2006, Glasgow. Poster abstract P 360.

Viral load blips in children from the CHIPS cohort

Polly Clayden, HIV i-Base

A poster from CHIPS evaluated the characteristics, predictors and consequences of transient increases in viral load "blips" in children on HAART in the UK and Ireland.

For this evaluation blips were defined as ≥ 1 viral load ≥ 50 copies/mL between two undetectable viral loads <50 copies/mL, <280 days apart, during sustained viral suppression, without a change in treatment (excluding single drug substitutions for simplification/personal reasons and single drug interactions).

The investigators found of the 595 of the 1065 children enrolled in CHIPS to December 2005 initiating HAART naive, 347 (58%) achieved sustained viral load <50 copies/mL on either first or second line treatment.

Of these, 78 experienced an overall total of 109 blips (between 1-4 per child) with median viral load 137 copies/mL (IQR: 73-374 copies/mL); 17 blips were >1000 copies/mL (max 39,838 copies/mL).

The investigators found blips were more common during second-line therapy (28/100 child-years (CY) [95%CI 16-38]) and

following a previous blip (19/100CY [12-30]) compared to during first-line therapy without prior blips (10/100CY [8-13]).

Blipping occurred at all ages from 1-15 years but rates decreased with age at HAART initiation (IRR=0.94 [0.89-1.00] per year older, $p=0.06$), but were higher in children on PI (75% nelfinavir) regimens (IRR=1.62 [1.10-2.39], $p=0.02$), and in those remaining below detection for longer (IRR 1.21 [1.05-1.39] per extra year suppressed, $p=0.009$).

The children's CD4 and CD8 counts were similar pre/post blip (median difference CD4 -33 cells/mm³ (IQR -230,304 cells/mm³), $p=0.89$ and CD8=10 cells/mm³ (-236,315 cells/mm³), $p=0.51$). 43% of detectable viral loads during periods of suppression were blips rather than virological failure.

The investigators found no evidence for a higher rate of virological failure in children who had ever blipped (adjusted HR: 0.74 [95% CI 0.46-1.17] $p=0.20$, for having blipped compared to never blipped. Additionally children who blipped in the last year (adjusted HR 0.93 [0.59-1.47], $p=0.77$) or blipped to >1000 copies/mL (adjusted HR 0.84 [0.35-2.06], $p=0.71$) were not at higher risk of subsequent failure.

They concluded that blips are fairly common in children occurring in 22% with otherwise undetectable viral load <50 copies/mL. Blipping is more common in children: starting HAART at younger age; on second line therapy; after a previous blip; on non-NNRTI containing regimen and in children with undetectable viral loads for more than one year.

They noted that this contrasted to at least one adult study that found no significant predictors of blipping. "But blips have little effect on CD4 and CD8 and do not increase rate of virological failure" they wrote.

Ref: Shingadia D, Lee KJ, Pillay D et al. Viral load blips in HIV-infected children from the CHIPS cohort: what do they mean? 8th International Congress on Drug Therapy in HIV Infection, 12-16 November 2006, Glasgow. Poster abstract P359.

GLASGOW: SIDE EFFECTS

Switching from PIs to NNRTIs has similar effect on TC/HDL ratio as use of lipid lowering drugs in the management of dyslipidaemia

Simon Collins, HIV i-Base

Marc van der Valk presented an analysis comparing results from different approaches to the management of dyslipidaemia in an analysis from the D:A:D cohort. [1]

The study primarily looked at the different effect from using lipid lowering drugs (LLD) compared to switching from PI- to NNRTI-based regimens. This was informed by an earlier randomised study (Calza, AIDS 2005) that reported greater reductions in mean total cholesterol from baseline of -46% with pravastatin, and -38% with bezafibrate, compared to -27% and -10% after switching from a PI to either nevirapine or efavirenz respectively. [2] Concerns raised in the Calza study include seeing a greater than expected effect from use of lipid lowering agents, compared to results from clinical trials with these drugs

In the D:A:D study, patients were identified who were NNRTI-naïve and who had confirmed total cholesterol >6 mmol/l on PI-based regimens for > 6 months. They compared results from 221 patients using LLD to 208 patients who switched their PI to an NNRTI, and to 1,463 control patients who made no intervention. Baseline values and results at 12 months are summarised in Table 1. The changes reported remained significant after adjustment for sex, age, HIV RNA and CD4, smoking, history of CVD, use of CVD drugs, diabetes, previous PI exposure and ethnicity. P values reported below refer to strategy arm compared to control.

Each strategy produced different effects on lipid parameters. Total cholesterol fell in all groups, but reductions were greater with LLD compared to switching. Both strategies were significantly better than the control arm ($p<0.0001$ and $p=0.02$, compared to control, respectively). Increases in HDL were only significant compared to control in the switch group ($p=0.0001$; compared to $p=0.27$ in LLD group). Both groups had a similar effect in reducing TC:HDL ratio ($p=0.03$, LLD; $p=0.06$ switch). Changes in LDL were greater in the LLD group ($p=0.0004$) compared to the switch group ($p=0.06$); while reductions in triglycerides were greatest in the switch group ($p=0.0001$) vs LLD ($p=0.0007$).

Because of the significant differences in some baseline parameters, the researchers then analysed results stratified by baseline values. LLD resulted in most pronounced effect on total cholesterol and LDL, especially in those with highest baseline values, with minimal effect on HDL. Switching resulted in greater increases in HDL, irrespective of baseline values. And both strategies led to similar reductions in TC/HDL ratio.

The study noted that the changes observed in controls could suggest some regression to the mean, or possible selection of those in whom intervention was withheld in view of declining lipid values, perhaps related to changes in diet and exercise (not recorded in the study). Limitations of the study also include problems of selection bias (with LLD drugs chosen for patients with greater dyslipidaemia) and no ability to look at role of individual LLDs.

Table 1: Baseline characteristics and results

	LLD		Control	p-value
N	221	208	1463	
Baseline (median, mmol/l):				
Total chol	7.6	7.1	6.7	0.0001
LDL-chol	5.4	5.1	4.9	0.0001
TG	3.6	2.6	2.6	0.0001
HDL	1.1	1.1	1.2	0.003
TC:HDL chol	6.6	6.1	5.8	0.001
Results (mean changes at 12 months, mmol/l)				
Total chol	-1.02	-0.66	-0.40	
LDL	-0.92	-0.71	-0.45	-0.45
TG	-0.82	-1.10	-0.18	-1.10
HDL	+0.08	+0.18	+0.01	+0.01
TC/HDL ratio	-1.48	-1.48	-0.48	

References

1. Van Der Valk M, Friis-Møller N, Sabin C et al. Effect of interventions to improve dyslipidaemia. 8th International Congress on Drug Therapy in HIV Infection, 12-16 November 2006, Glasgow. Oral abstract PL12.2.
2. Calza L, Manfredi R, Colangeli V et al. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. AIDS 2005 July 1; 19 (10): 1051-1058.

GLASGOW: HEPATITIS COINFECTION

Higher doses of ribavirin increases response rate to HCV treatment in coinfecting patients: results from PRESCO study

Simon Collins, HIV i-Base

An oral presentation of the results from the PRESCO trial by Vincent Soriano was one of the most interesting late-breaker presentations in Glasgow. PRESCO used higher doses of ribavirin with pegylated interferon alfa-2a (180µg/week) in HCV coinfecting patients, and was also designed to look at longer duration of HCV treatment.

This was a prospective, multicenter, open-label trial, in 389 patients with CD4 >300 cells/mm³ and elevated aminotransferases who were HCV-treatment naïve. Ribavirin was dosed at 1000 mg daily for people weighing <75 Kg; and 1200 mg daily if >75 kg. People with HCV genotypes 1 and 4 were treated for 48 or 72 weeks, and patients with HCV genotypes 2 and 3 were treated for 24 or 48 weeks.

Baseline characteristics included 75% male, median age 40, median CD4 count 456 cells/mm³, 74% on HAART (nearly all suppressed <50 copies/mL). Baseline HCV parameters included 28% patients with F3/F4 stage fibrosis and 67% with HCV RNA >500,000 IU/mL. HCV genotype was 49% G1/12% G4 and 1% G2/38% G3. Exclusion criteria included active drug addiction, alcohol abuse, decompensated liver cirrhosis, hepatitis B virus infection, or treatment with ddI. AZT use was actively discouraged to minimise ribavirin-related toxicity.

Sustained virological response rates (SVR) were significantly higher in patients with G2/3 compared to G1/4, and were approaching monoinfection rates (see Table 1). The 44% (174/389) discontinuation rates were largely due to virological failure, mainly at week 24 (66/174) and voluntary withdrawal (64/174). 32 people discontinued treatment due to serious events and 12 were lost to follow-up.

Table 1: Response rates by genotype and duration of treatment

	n	ETR	SVR	short	long
Overall	389	67%	50%		
G1/4	237	53%	30%	31%	53%
G2/3	152	90%	72%	67%	82%

These rates were higher than achieved previously in the APRICOT study using 800mg ribavirin, and were the same as those seen in the HCV monoinfection FRIED study using weight-based RBV for genotype 1 and 3, and gave an improved for genotype 4 (G2 data was not shown).

45/101 patients allocated to the extended therapy arms refused to continue therapy after completing the standard treatment period (data from ICAAC poster).

However, voluntary discontinuations were higher in the extended arms, especially in G1/G4 patients (80% vs 8% in patients using treatment for 72 weeks rather than 48 weeks). In G2/G3 patients, discontinuation rates were 16% and 4% in the 48 week and 24 week treatment arms respectively. This significantly reduces the power of the study to look at the effect of duration of treatment.

Despite rates of voluntary discontinuations, tolerability was reported as good, and this was largely explained by low use of AZT. 15% and 22% of patients reduced their interferon and ribavirin doses respectively.

The impact of ribavirin exposure on SVR was analysed in a sub-group of patients and median levels of 2.8 ug/mL were found in 21 non-responders compared to 3.3 ug/mL in 42 responders. The range of RBV concentrations significantly overlapped though the trend to higher RBV levels and SVR was statistically significant ($p=0.01$).

Infection with HCV-2/3 (RR 2.48; 1.45-4.24; $p=0.001$), lower baseline HCV-RNA (RR 2.61: 1.54-4.43, $p<0.0001$), and HCV-RNA <50 IU/ml at week 12 (RR 4.97: 2.71-9.11, $p<0.0001$) were independent predictors of SVR in the multivariate analysis. Extended treatment duration was not (RR 1.78: 0.83-3.81, $p=0.14$).

C O M M E N T

In general, the PRESCO trial is encouraging, demonstrating that ribavirin doses higher than 800mg can be used safely in HIV-coinfected patients, and that this may have contributed to higher success rate. As in mono-infected patients, the dose of ribavirin is an important determinant of SVRs. However, about 75% of the patients only had fibrosis stage F0-2 (Metavir), which may also have contributed to the better success rate.

The findings that show a superiority of the extended treatment arms are remarkable considering the high proportion of patients (45%) who never entered the extended treatment period. Only 45 many people completed 72 weeks of treatment in the G1/4 arm and only 24 achieved SVR, and the 80% is quite a stunning non-completion rate. Although extending the duration to 72 week in 'difficult to treat' patients has been a useful strategy in monoinfection, as this study shows, tolerability may be a limiting issue for many patients. Nevertheless, for motivated individual patients with slow reduction in viral load this may be a useful strategy.

This study also starts to add weight to the fact that in some G2/3 patients shorter duration of therapy may suffice.

The dose-reduction rate of 22% due to ribavirin is still on the high side despite no AZT use. EPO use is not mentioned but is a useful adjunct to minimise symptomatic anaemia.

However, despite the additional burden of toxicity, this approach should be investigated further, in particular, in patients with slow viral response or high viral load. Both these characteristics frequently observed in coinfected patients.

Treatment of HCV in HIV co-infected patients is moving towards the concept of 'individualised' therapy, where in the future the duration of therapy with pegIFN and ribavirin will be determined by baseline host and viral characteristics and early viral kinetics.

Ref: Nuñez M, Miralles C, Berdún MA et al. The PRESCO trial: role of extended duration of therapy with pegylated interferon alfa-2a plus weight-based ribavirin dose in 389 HCV/HIV co-infected patients. 8th International Congress on Drug Therapy in HIV Infection, 12-16 November 2006, Glasgow. Oral abstract PL13.1.

NNRTI levels high in HCV co-Infected patients with cirrhosis

Mark Mascolini, for natap.org

Plasma concentrations of non-nucleosides (NNRTIs) - especially nevirapine - proved high in hepatitis C virus (HCV)-coinfected patients with liver cirrhosis in a single-center Spanish study [1]. Cirrhosis did not affect protease inhibitor (PI) levels in this analysis.

Pablo Barreiro and colleagues from Madrid's Carlos III Hospital ran this cross-sectional study on 279 HCV/HIV-infected patients taking standard doses of efavirenz, nevirapine, lopinavir/ritonavir, atazanavir/ritonavir, or unboosted atazanavir for at least 6 months. No one was taking drugs that may affect levels of these antiretrovirals, except for tenofovir. Everyone had adherence above 95%, as rated by pharmacy records. Barreiro determined liver fibrosis with the noninvasive FibroScan test; he excluded patients with a Child-Pugh class C liver disease prognosis.

The study group had an average age of 45 years, 78% were men, and 85% were injecting drug users. One third were alcohol abusers, and body mass index averaged 22.6 kg/m². The group's mean CD4 count stood at 511 and mean viral load at 2.01 log copies/mL (about 100 copies). Alanine aminotransferase averaged 54 IU/mL and HCV-RNA 5.3 log. Two thirds of the study group had HCV genotype 1, and one quarter had genotype 3.

FibroScan determined that 103 people (37%) had cirrhosis, 80% of them with a Child-Pugh class A score and 20% with Child-Pugh B. Fibrosis did not correlate with PI levels, but Barreiro charted positive correlations between liver stiffness (measured as KPa) and levels of efavirenz ($\rho = 0.47$) and nevirapine ($\rho = 0.22$). The correlation with efavirenz was statistically significant ($P = 0.001$), whereas the correlation with nevirapine was not ($P = 0.14$). Child-Pugh class (A versus B) did not affect median concentrations of any antiretroviral studied.

Efavirenz levels lay above 4 microg/mL in 5 of 16 people (31%) with cirrhosis versus 1 of 30 (3%) without cirrhosis. Among people taking nevirapine, 5 of 14 (36%) with cirrhosis had levels above 8 microg/mL, compared with 8 of 31 (26%) without cirrhosis.

Barreiro concluded that HCV-coinfected people with compensated cirrhosis may have higher than normal concentrations of NNRTIs, especially efavirenz. He proposed that patients with cirrhosis may benefit from therapeutic drug monitoring to avoid NNRTI toxicity. Barreiro also suggested his findings show that noninvasive tools like FibroScan can identify HCV/HIV-infected people who may need antiretroviral dose adjustments.

References

1. Barreiro P, Rodriguez-Novoa S, Labarga P, et al. Influence of the stage of liver fibrosis on plasma levels on antiretroviral drugs in HIV-infected patients with chronic hepatitis. 8th International Congress on Drug Therapy in HIV Infection, November 12-16, 2006, Glasgow. Abstract PL6.2.

GLASGOW: DRUG INTERACTIONS

Drug interactions with darunavir (TMC-114)

Simon Collins, HIV i-Base

An overview of clinical studies of drug interactions with the protease inhibitor darunavir (TMC-114), already approved in the US, was given in an oral presentation by David Back.

TMC114/r was studied with atazanavir (ATV), indinavir (IDV), lopinavir/r (LPV/r), saquinavir/r (SQV/r), efavirenz (EFV), nevirapine (NVP), tenofovir disoproxil fumarate (TDF), atorvastatin (AVS), omeprazole (OME), ranitidine (RAN), sildenafil (SIL), clarithromycin (CLA), sertraline (SER), paroxetine (PAR), oral contraceptives (OC) and ketoconazole (KTZ).

Results are summarised in Table 1 below. TMC114/r increased exposure to EFV (21%), NVP (27%), TDF (22%), IDV (23%), LPV (37%), KTZ (212%), CLA (57%), AVS and SIL (4-fold), and decreased exposure to SER (49%), PAR (39%) and ethinyl estradiol (44%). There was no change in ATV or SQV. TMC114 exposure increased by 21%, 24% and 42%, respectively, when combined with TDF, IDV and KTZ, decreased by 13%, 13%, 26% and 53%, respectively, when combined with EFV, CLA, SQV/r and LPV/r, and was unchanged when combined with ATV, NVP, AVS, OME, RAN, SER and PAR.

The study concluded that combining TMC114/r with LPV/r or SQV/r is not recommended and that some co-administered drugs may require dose adjustments (SIL, AVS, KTZ and IDV). Additional contraception should be used when OC are combined with TMC114/r.

Table 1: Summary of drug interaction studies with darunavir (TMC-114)

	Interaction effect with TMC-114	Recommendation
<i>ARVs</i>		
Efavirenz	EFV increased by 21% TMC-114 decreased by 13%	Not clinically relevant
Nevirapine	NVP increased by 27% TMC-114 no change	Not clinically relevant
Tenofovir	TDF increased by 22% TMC-114 increased by 21%	Not clinically relevant
Indinavir	IDV increased by 23% TMC-114 increased by 24%	Consider TDM for IDV
Lopinavir.r	LPV increased by 37% TMC-114 decreased by 53%	Do not coadminister

Saquinavir	SQV no change TMC-114 decreased by 26%	Do not coadminister
Atazanavir	ATV no change TMC-114 no change	No interaction
<i>Antibiotics</i>		
Ketoconazole	KTZ increased by 212% TMC-114 increased by 41%	Consider reducing KTZ
Clarithromycin	CLA increased by 57% TMC-114 decreased by 13%	Only relevant with renal impair,
<i>SSRI's</i>		
SER	SER AUC decreased by 49% TMC-114 no change	Monitor clinically, titrate SSRI
PAR	PAR AUC decreased by 39% TMC-114 no change	Monitor clinically, titrate SSRI
<i>Other</i>		
Atorvastatin	AVS increased by 400% TMC-114 no change	Start with lowest AVS dose
Pravastatin	PVS increased by 81% (23-166%)	Start with lowest PVS dose
Sildenafil	SIL increased by 400%	Reduce SIL dose
ethinyl estradiol	EE exposure decreased by 44%	Use other contraception
Ranitidine	TMC-114 no change	No dosing change
Omeprazole	TMC-114 no change	No dosing change

Ref: D Back, V Sekar, E Lefebvre et al. Use of TMC114 in combination with other drugs: guidance from pharmacokinetic studies. 8th International Congress on Drug Therapy in HIV Infection, 12-16 November 2006, Glasgow. Oral abstract PL5.1.

Drug interactions with etravirine (TMC-125)

Simon Collins, HIV i-Base

An overview of drug interactions with the investigational NNRTI etravirine (TMC-125) was presented by Thomas Kakuda. Etravirine is a substrate and inducer of CYP3A4 and a substrate and inhibitor of CYP2C, and has a different interaction profile compared to nevirapine and efavirenz.

Two-way PK interaction studies at steady-state were conducted with TMC125 and didanosine (ddI), tenofovir (TDF), the ritonavir (rtv)-boosted PIs darunavir (DRV), fosamprenavir (FPV) and tipranavir (TPV). The 1-way effect of omeprazole (OME) and ranitidine (RAN) on TMC125, and the 1-way effect of TMC125 on lopinavir (LPV) with saquinavir (SQV), methadone (MET) and sildenafil (SIL) were also studied.

Table 2: Summary of drug interaction studies with etravirine (TMC-125)

	TMC-125	Recommendation
Fosamprenavir	FPV inc by 69% TMC-125 no change	Consider dose reduction of FOS using TDM
Atazanavir	TMC Cmin, Cmax, AUC all inc by 50% (30% with ATZ/r) ATZ Cmin red. by 47%, AUC by 17% (ATZ/r by 38% & 14%)	Do not use unboosted ATZ. Use 300mg ATZ/ 100mg RTV.
Sildenafil	SIL reduced by 57%	Consider increasing dose of SIL
N-desmethyl-SIL	N-sSIL reduced by 41% No significant effect on TMC-125	
Tipranavir/r	TMC-125 reduced by 75% No significant effect on TPV/r	Do not administer together
Darunavir/r	TMC-125 reduced by 37% No significant effect on DRV	Not clinically relevant
Omeprazole	TMC-125 increased by 41%	Not clinically relevant

Results are summarised in Table 1. TMC-125 should not be coadministered with nevirapine, efavirenz, tipranavir/r, full dose ritonavir or unboosted PIs. Fosamprenavir and sildenafil may require dose adjustment. Coadministration with clarithromycin is not recommended for treatment of MAI. No significant effect on levels of either drug were seen with ddI, tenofovir, lopinavir/r, saquinavir/r, methadone, and oral contraceptives ethnylestradiol (exposure slightly increased) and norethindrone (similar PK with slightly lower Cmin by 22%).

Ref: Kakuda T, Schöller-Gyüre M, Woodfall B et al. TMC125 in combination with other medications: summary of drug-drug interaction studies. 8th International Congress on Drug Therapy in HIV Infection, 12-16 November 2006, Glasgow. Oral presentation PL5.2.

C O M M E N T

Both these overviews highlight the complexity of drug interactions and the important of expert interpretation.

Effects on individual drugs need to be interpreted in the context of the pharmacokinetics of that compound – a 25% reduction for example may have clinical implications for one drug and not another.

Although both TMC-114 and TMC-125 are relatively free of clinically important interactions, it is essential to be aware of the few

contraindications with these new agents, and of the potential interactions that may require monitoring or dose modification.

GLASGOW: TRANSMISSION

Community meeting on criminalisation of HIV transmission: jailing people for passing on HIV may threaten public health

The European AIDS Treatment Group (EATG) organised a satellite session at the beginning of the conference, and issued the following press release afterwards.

The conviction and imprisonment of people with HIV for transmitting their virus is counterproductive and may even threaten public health, the Eighth International Congress on Drug Therapy in HIV Infection was told this week. HIV criminalisation experts were addressing the conference's community workshop, organised by the European AIDS Treatment Group.

Matthew Weait of the Research Institute for Law, Politics and Justice at Keele University said that there was a difference between believing that transmitting HIV, especially to partners unaware of the risk, was morally bad and that the law should be used to prosecute such cases. "We need to challenge that linkage," he said.

Weait stressed the possible adverse consequences of the criminalisation of HIV transmission:

- It could act as a disincentive for people to test, as ignorance of status might be a defence.
- It made it difficult for HIV positive people to disclose or recommend post-exposure prophylaxis to a partner if there had been unprotected sex.
- Since recklessness means that people knew there was a risk of transmission and decided to take it, the use or attempted use of a condom could even be used as prosecution evidence.

Research was urgently needed to find out if criminalisation was already affecting people's testing and disclosure behaviour, he said. Lisa Power of the Terrence Higgins Trust said that there had been prosecutions for HIV in 26 European countries. She said that many countries had prosecuted people who had had unprotected sex even when they had not transmitted their virus. Most countries had imposed custodial sentences with sentences of 5-10 years not uncommon.

However the meeting also heard that some countries there had been successful challenges both to the underlying law on criminalisation and the scientific evidence used to prove transmission.

Roland Brands, Policy Officer for the Social and Legal Aspects of HIV for the Dutch SOOAIDS Project, said that between 2001 and 2005 the Netherlands prosecuted 10 people with HIV who had unsafe sex and did not disclose to their partners for attempted manslaughter and attempted GBH. There was only one HIV transmission in these 10 cases.

However after appeals by AIDS activists, the Dutch Supreme Court in January 2005 decided that prosecuting people for exposure was unjust since exposure did not inevitably mean infection.

Virologist Anna-Maria Geretti said that individual cases could be successfully challenged on the basis of the scientific evidence. She said that though genetic testing could rule out an HIV transmission, it was very difficult to prove, without corroborating evidence, that one person *did* infect another.

The issue was twofold: firstly, the way samples from the alleged victim and perpetrator were compared with control samples tended to exaggerate their similarity, and secondly, it was often difficult to exclude the possibility that a third party may have infected both people or served as an intermediary.

This was demonstrated in one specific UK case recently, which was as a result dismissed.

Bernard Forbes, Chair of the UK Coalition of People Living with HIV and AIDS, co-moderating the session, commented that the UK Department of Health had recently launched a campaign stressing that young people had a responsibility to protect themselves from sexually transmitted infections. Criminalisation, on the other hand, made it the entire responsibility of the infected person.

"These two ideas just don't fit," he said. "Maybe we should suggest that the Crown Prosecution Service indicts the Department of Health for encouraging GBH."

Srdan Matic, STD/HIV programme advisor for the World Health Organisation European office, presented a personal perspective, because the WHO does not as yet have a position on criminalisation, though it is expected to produce one in 2007. Matic said that society should intervene in individual behaviour only if it was the only way to ensure public health. Experience with injecting drug users showed exactly the reverse – the more severely countries punished the use and supply of drugs, he said, the worse their drugs and HIV problem tended to be. He said that the severity of the sentences handed down in HIV transmission cases may violate the UN Declaration on Human Rights. "We know where criminalisation starts," he said. "But where does it end?"

All presentations from the Community Workshop on the Criminalisation of HIV Transmission can be downloaded from:
<http://www.eatg.org/pages/article.php?id=383>

ANTIRETROVIRALS

TMC 114 recommended for conditional approval in Europe

On 14 December the European Medicines Agency (EMA) recommended granting of a conditional marketing authorisation for the protease inhibitor darunavir (brand name Prezista, formerly TMC-114).

This means that darunavir may be fully approved within 90 days and be available in the 25 countries of the EU.

Conditional marketing authorisations are granted for medicines that are likely to have a significant benefit for patients, before all of the formal studies into its efficacy and safety have been completed.

Darunavir needs to be used with a boosting dose of 100mg ritonavir and was approved in the U.S. in June.

The most common reported adverse reactions included diarrhoea, headache, fatigue, vomiting and hypertriglyceridaemia. A pharmacovigilance plan for darunavir, as for all medicinal products, will be implemented as part of the marketing authorisation.

Detailed recommendations for the use of this product will be described in the Summary of Product Characteristics (SPC) which will be published in the European Public Assessment Report (EPAR) and will be available in all official European Union languages after the conditional marketing authorisation has been granted by the European Commission.

Source: EMA report, 15 December 2006

Atazanavir 300mg capsule approved in US

On October 16, 2006, the Food and Drug Administration approved a new 300 mg capsule form of atazanavir (Reyataz).

Atazanavir is now available in the US as 100mg, 150 mg, 200 mg, and the new 300 mg capsules.

The new 300 mg capsules give treatment-experienced patients the option to take either one 300mg capsule, or two 150 mg capsules of atazanavir, once daily plus ritonavir 100 mg once daily, with food.

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>

TREATMENT ACCESS

A summary of treatment access-related news since the last issue of HTB.

Clinton price for new paediatric treatment

The Clinton Foundation announced a deal with Cipla and Ranbaxy to make 19 antiretroviral products available for treating paediatric HIV at an average price of \$60 a year.

The statement from the foundation says that these prices will be available to 62 developing countries and will make treatment possible for an additional 100,000 people in 2007.

\$15 million from the Clinton Foundation and a further \$35 million grant Unitaids, a drug purchasing consortium, formed in September by France, Brazil, Chile, Norway and the UK, will be combined to assure the Indian generic companies sufficient volume of drug sales to justify the lower prices.

Antiretroviral products to be purchased include new fixed dose combinations (FDCs) Pedimune and Triviro-LNS kids for older children (see HTB volume 7 number 9 page 15-16).

These formulations still need to be licenced and pre-qualified by the WHO.

The WHO has produced simple dosing tables for each product for children based on weight bands.

<http://www.who.int/entity/hiv/paediatric/generictool.xls>

Generic FDC of efavirenz/tenofovir/FTC launched by Cipla

Cipla has launched a new fixed dose combination pill called Viraday

Viraday is a combination of three anti-HIV drugs efavirenz 600 mg, tenofovir 300 mg and emtricitabine 200mg (a generic equivalent of Atripla).

At retail price of 5,200 rupees a month, Viraday is a fraction of the wholesale international price of approximately US\$ 1,100 (approximately 52,800 rupees) a month.

<http://www.cipla.com>

Indian generic heat-stable ritonavir

Indian generic manufacturer Emcure Ltd has announced the production and availability of a heat-stable formulation of ritonavir called Empetus.

Emcure has produced other genetic ARVs, including atazanavir under voluntary license from BMS, which has recently been introduced.

Empetus is available in bottles of 30 tablets costing about \$20 per month and still requires WHO pre-qualification.

This generic formulation has been produced prior to a heat stable version of ritonavir from Abbott.

<http://www.emcureaidsinfo.com>

Compulsory license for efavirenz in Thailand

Thailand will issue a compulsory license for use by the government to improve access to efavirenz.

The price that patent holder Merck charges in Thailand (1,500 baht/month – US \$41) is double that charged by Indian generic manufacturers (800baht/month – US \$22)

The compulsory license will apply both to import and local production of the drug. The Thai Government Pharmaceutical Organisation (GPO) who manufacture antiretrovirals for use in Thailand is developing its own production of efavirenz which is scheduled begin next year.

In the meantime, the compulsory license will allow Thailand to import generic efavirenz from India.

Thai activists and MSF welcome this development.

FDA tentative approvals 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/formulation	Manufacturer	Date
abacavir 300 mg	Cipla, India	6 Nov 2006
d4T/3TC/NVP (FDC)	Cipla, India	17 Nov 2006

“Tentative Approval” means that FDA has concluded that a drug product has met all required quality, safety and efficacy standards, though it may not be marketed in the U.S. because of existing patents and/or exclusivity rights. Tentative approval, however, does make the product eligible for consideration for purchase under the PEPFAR program.

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to almost 30 since the programme was launched.

An updated list of generic tentative approvals is included as a table on the i-Base website:

<http://www.i-base.info/itpc/fdageneric.html>

Whilst generic approval and competition have produced a side range of NNRTI-based options for first-line therapy, protease inhibitors and second-line RTIs, or other drugs effective for treatment experienced patients, are clearly missing from this list.

Source: FDA list serve

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

An archive of past list serve announcements is available on the FDA web site at:
<http://www.fda.gov/oashi/aids/listserve/archive.html>

GUIDELINES

WHO EURO releases European clinical protocols for HIV/AIDS care and the report of the consultation on criminalisation of HIV/AIDS

On 1 December the WHO released eleven European Clinical Protocols for HIV/AIDS Treatment and Care:

1. Patient evaluation and Antiretroviral treatment for Adults and Adolescents
2. Management of Opportunistic Infections and General Symptoms of HIV/AIDS
3. Palliative Care for People Living with HIV/AIDS
4. Management of Tuberculosis and HIV Coinfection
5. HIV/AIDS Treatment and Care for Injecting Drug Users
6. Management of Hepatitis C and HIV Coinfection
7. Management of Hepatitis B and HIV Coinfection
8. Prevention of Hepatitis A, B, C and other Hepatotoxic Factors in People Living with HIV/AIDS
9. Support for Sexual and Reproductive Health in People Living with HIV/AIDS
10. Prevention of HIV Transmission from HIV Infected Mothers to their Infants
11. Paediatric HIV/AIDS Treatment and Care (forthcoming)
12. Immunisation of People Living with HIV/AIDS and People at Risk of HIV Infection
13. Post Exposure Prophylaxis for HIV Infection (forthcoming)

All the Protocols can be accessed and downloaded at:

http://www.euro.who.int/eprise/main/WHO/Progs/SHA/treatment/20060801_1

A technical consultation on the criminalisation of HIV and other sexually transmitted infections held in Copenhagen on 16 October 2006. The Report is accessible at:

http://www.euro.who.int/Document/SHA/crimconsultation_latest.pdf

The press release from WHO EURO on the occasion of the World AIDS Day 2006 is available at:

http://www.euro.who.int/mediacentre/PR/2006/20061129_1

US adult treatment guidelines updated

On October 10, 2006, the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents released a new revision of the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

Most of the changes to the previous edition (highlighted in yellow in the pdf file) relate to recommendations for preferred and alternative antiretroviral components in treatment-naïve patients and on safety data that have emerged since the last revision.

Two boosted PI-regimens have been added to recommended first-line regimens: atazanavir/ritonavir (once daily) and fosamprenavir/ritonavir (twice-daily), both plus 2 RTIs. Previous recommendations only included efavirenz plus 2 RTIs or lopinavir/ritonavir plus 2 RTIs.

The recommendations for choice of nucleosides are fixed dose combinations of either tenofovir/FTC or AZT/3TC. Alternative options are abacavir/3TC or ddI with either 3TC or FTC.

Tables 28 and 29 have been revised according to updates in the Perinatal Guidelines to incorporate preclinical and clinical data relevant to the use of darunavir during pregnancy and new recommendations on antiretroviral use during pregnancy.

Table 30 has been updated to include information on expanded access programs for two investigational agents, TMC125 and MK-0518.

The complete October 10, 2006, version of the adult treatment guidelines is available on the AIDSinfo web site at:

<http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

C O M M E N T

It is noticeable that AZT remains a first-line preferred nucleoside and that no reference is made to the evidence linking AZT to lipotrophy, which led to UK guidelines in July 2005 downgrading the use of AZT to that of an alternative option.

Download guidelines:

<http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

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>

US perinatal guidelines updated

On October 12, the Public Health Service Task Force updated its 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.

Changes in this edition include:

Postpartum haemorrhage, antiretroviral drugs, and methergine use.

“Methergine should not be co-administered with drugs that are potent CYP3A4 enzyme inhibitors, including protease inhibitors and the NNRTIs efavirenz and delavirdine...”

An update on preconceptual counseling and care for HIV-1-infected women of childbearing age.

It is recommended that all women of child-bearing age are offered the opportunity to receive preconception counseling and care as a component of routine primary medical care.

Lopinavir/r (Kaletra) was added as a first-line preferred PI in HIV+ women who are pregnant; prior to this update nelfinavir (Viracept) was the only preferred PI.

There is an **update on abacavir**; in Table 3, “pharmacokinetics are not significantly altered in pregnancy; no change in dose is indicated”. The Guidelines are updated with information on the use of **Darunavir (TMC114)**. In addition, there is an update on Kaletra: in Table 3, “pharmacokinetic studies of standard dose of lopinavir/ritonavir capsules a (3 capsules twice daily) during 3rd trimester indicated levels were significantly lower than during postpartum period and in non-pregnant adults; an increased dose of 4 capsules of lopinavir/ritonavir twice daily starting in the 3rd trimester resulted in adequate lopinavir exposure; by 2 weeks postpartum, standard dosing was again appropriate. Pharmacokinetic studies of the new lopinavir/ritonavir tablet formulation are underway, but data are not yet available.” And there is additional information in the Guidelines.

Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women in PDF:

<http://aidsinfo.nih.gov/ContentFiles/PerinatalGL.pdf>

US guidelines for the use of antiretroviral agents in paediatric HIV infection revised

<http://aidsinfo.nih.gov/ContentFiles/PediatricGuidelines.pdf>

The Guidelines for the Use of Antiretroviral Agents in Paediatric HIV Infection have also been revised. The revision represents a major rewriting of the main document to improve its organisation and readability. Because the main document has been almost completely rewritten, there is no highlighting of changes to either its text or tables.

The document’s Appendix: Characteristics of Available Antiretroviral Drugs, and Supplement I: Paediatric Antiretroviral Drug Information, have also been updated. Changes to those sections appear highlighted in yellow.

Changes in recommendations include:

- Revised guidelines on when to initiate therapy in antiretroviral-naive children, with recommendations for four age categories (< 12 months, 1 to < 4 years, 4 to 12 years, and > 13 years).
- Revised discussion and tables of rationale for antiretroviral drug choice for antiretroviral-naive children, with revised preferred and alternative treatment regimen recommendations.
- Revised recommendations for adolescents, including issues related to drug dosing, use of contraception, pregnancy, and transition into adult care.

- Updated Characteristics of Available Antiretroviral Drugs drug dosing appendix and updated Supplement I: Paediatric Antiretroviral Drug Information, including information on newly approved antiretroviral agents, such as darunavir, and new paediatric studies.
- Recommendations for antiretroviral resistance testing for all antiretroviral-naïve children prior to initiation of antiretroviral therapy.
- New section and table on monitoring of children on antiretroviral therapy and management of antiretroviral toxicity/intolerance.
- New section on management of the treatment-experienced child.
- New section and tables on assessment and management of antiretroviral treatment failure and choice of new antiretroviral regimen in children with treatment failure.
- New section on therapeutic drug monitoring.
- New section on discontinuation or interruption of antiretroviral therapy.
- Inclusion of darunavir information.

The updated guidelines are available on the Paediatric Guidelines page of the Clinical Guidelines section of AIDSinfo
<http://www.aidsinfo.nih.gov/Guidelines/>

Source: FDA list serve. An archive of past list serve announcements is available on the FDA web Site:
<http://www.fda.gov/oashi/aids/listserve/archive.html>

ON THE WEB

Guidelines and reports:

HIV and poverty in the UK

Also on 1 December, Crusaid and the National AIDS Trust launched a report into the rising numbers of people living with HIV in extreme poverty in the UK.

This report highlights the effect of stigma and discrimination in driving people living with HIV into poverty. Hate crime and discrimination not only have a damaging effect on the physical and mental health of people living with HIV, but can also lead to isolation and poverty. Recent research shows that a third of people living with HIV have experienced discrimination.

The report calls for action in tackling the root causes of poverty among people living with HIV, including addressing high levels of hate crime, unemployment and poor housing among people living with HIV. It is available online:

<http://www.crusaid.org.uk/poverty>

Online medical resources:

Management of metabolic and morphologic sequelae of HIV and Its treatment – November 2006

<http://www.medscape.com/viewprogram/6286?src=mp>

- Management of HIV-associated lipodystrophy: emerging data in clinical context - Andrew Carr
- Cardiovascular disease: prevention in patients with HIV infection - Pablo Tebas
- Cosmetic interventions for HIV-associated lipodystrophy - Graeme J. Moyle

HIV inSite Updates

Herpes Simplex Virus and HIV-1 - November 2006

<http://hivinsite.ucsf.edu/InSite?page=kb-05-03-02>

Sexual Transmission of HIV - October 2006

<http://hivinsite.ucsf.edu/InSite?page=kbr-07-02-01>

Safer Sex Methods - September 2006

<http://hivinsite.ucsf.edu/InSite?page=kbr-07-02-02>

HIV Transmission and Prevention in Adolescents

<http://hivinsite.ucsf.edu/InSite?page=kb-00&doc=kb-07-04-03>

HIV InSite Overview of the President's Emergency Plan for AIDS Relief.

Core documents, program management tools, and related resources. Updated July 2006.

<http://hivinsite.ucsf.edu/InSite?page=pr-rr-10>

PRN notebook – October 2006

<http://www.prn.org>

Lu: New Antiretrovirals In Development: The View In 2006

Siegel: New Perspectives In Hiv Treatment Interruption: The Smart Study

Dumond: Understanding Primary And Secondary HIV Prophylaxis

Liza King: Tb And HIV Coinfection: Current Trends, Diagnosis And Treatment Update

Alejandra Gonzalez-Duarte: Selected Neurologic Complications Of HIV And Antiretroviral Therapy

Conference coverage online:

IAPAC European Sessions 2006

The presentation slides from the recent IAPAC European Sessions 2006 can now be downloaded at the following link:

<http://www.iapac.org/home.asp?pid=7567>

Presentations include:

IMPLICATIONS OF A DECADE OF HAART

- EuroSIDA: What Do the Numbers Tell Us? - Jens D. Lundgren
- 10 Years of Progress: State of the HAART - Jose M. Zuniga
- Future Directions in HAART - Schlomo Staszewski

NAVIGATING ARV DRUG RESISTANCE

- The Role of Newly Approved and Investigational ARV Drugs - Jurgen Rockstroh
- Is there a Future for Structured Treatment Interruptions? - Bernard Hirschel

SOCIOBEHAVIORAL ASPECTS OF HIV CARE

- Prevention with Positives - Gus Cairns
- Promoting Adherence to HAART - Carmina Fumaz
- Addressing Substance and Alcohol Abuse in HIV-Positive Patients - Fabrizio Starace

EMERGING ISSUES IN HIV CARE

- Adolescents and HIV: The Unmet Challenge - Carlo Giaquinto
- Hepatitis B/C Coinfection: Doubling the HIV Management Challenge - Stefan Mauss
- Putting Non-Occupational PEP Into Practice: What Are The Implications? - Jesus Almeda

Vaccine research:

IAVI Vax news

Promising results from clinical trials presented at this year's AIDS Vaccine conference

The near thousand researchers who gathered at the start of the annual AIDS Vaccine Conference in Amsterdam from 29 August to 1 September were greeted with a spirit of optimism that has become quite unusual for this field. Lawrence Corey of the HIV Vaccine Trials Network in Seattle called 2006 "a vintage year for vaccine development" when he gave a presentation on the AIDS vaccine pipeline at the conference's opening plenary session.

<http://www.iavireport.org/vax/VAXOctober2006.asp#1>

FUTURE MEETINGS

14 Retrovirus Conference (CROI)

February 25-28, 2007, Los Angeles

The 14th Conference on Retroviruses and Opportunistic Infections will be held February 25-28, 2007 at the Los Angeles Convention Center in Los Angeles, California.

The CROI 2007 website, will be updated this summer to include information including details and deadlines for international scholarships and community educator programme. Deadline for abstract submission is 3 October 2006.

<http://www.retroconference.org>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The website has been redesigned to be faster, easier to use, and simpler to navigate.

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

A new section has been added about adapting and translating i-Base materials in other countries:

<http://www.i-base.info/education/adapting.html>

To coincide with the new publicity material for the treatment phonenumber, we are also launching a web-based Q&A section for people to ask questions about their own treatment:

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

The site is also 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, Advocacy and Training. This 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.

All i-Base publications are available at our website, including 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 3000 pages are served from the site each day.

Treatment training for advocates

i-Base have produced a training manual for advocates that is available online as a PDF document. It provides a basic entry-level curriculum relating to HIV and treatment. Each module includes non-technical review material, test questions, an evaluation and a glossary.

The manual is available in English, Russian, Portuguese, Hindi and Nepalese.

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

<http://www.nkplus.org>

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 18th meeting was on 1 September 2006) are posted to the i-Base website.

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

<http://www.i-base.info/ukcab/feb06/index.html>

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.

The latest report is from 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 2006 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.

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.

New Italian translation of Introduction to Combination Therapy

A new translation of the Introduction to Combination Therapy has just been produced by the HIV-organisation Nadir.

It is available as a pdf file on the i-Base website (see below).

Translations of i-Base guides

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 30 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>

Chinese

- Avoiding & managing side effects [3.8 Mb] Aug 02
- Changing treatment: second line & salvage therapy [284 Kb] Aug 02
- Introduction to combination therapy [236 Kb] Aug 02

Bulgarian

- HIV, pregnancy & women's health [304 Kb] Mar 06

French

- HIV, pregnancy & women's health [1 MB] April 06
- Avoiding & managing side effects [344 Kb] Jun 06
- Introduction to combination therapy [132 Kb] Jun 01

Greek

- Changing treatment: second line & salvage therapy [180 Kb] Mar 03
- Introduction to combination therapy Nov 01 [1 Mb]

Italian

- Avoiding & managing side effects [1 Mb]
- Changing treatment PDF [1 Mb]
- HIV, pregnancy and women's health [1.2 Mb]
- Introduction to combination therapy [1 Mb] June 06

Portuguese

- Introduction to combination therapy [696 Kb] Sep 05

Russian

- Introduction to combination therapy [448 Kb]
- HIV, pregnancy and women's health [668 Kb]

Serbian

- Introduction to combination therapy [227 Kb]

Spanish

- Avoiding & managing side effects [210 Kb]
- Introduction to combination therapy [192 Kb]

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.

New online Q&A service

A new 'question and answer' service has been added to the i-Base website. 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/index.html>

Recent questions include:

- How quickly does HIV progress?
- Can I know when I caught HIV?
- My partner is HIV-positive...
- Should I start treatment: newly diagnosed with CD4 200 and viral load 375,000
- What is the risk of diabetes from HIV drugs, especially PIs?
- Is there an HIV vaccine?
- Which diet can prevent muscle wasting?
- Why is there more research on treatment rather than a cure?
- Can Truvada affect my kidneys?
- Question of oral sex risk with a fissured tongue
- How many antiretrovirals are there and why do we need so many?

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/2006>

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 fax or post using the form on the back page by sending an email to: subscriptions@i-base.org.uk

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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.

However, any donation that your organisation can make towards our costs is greatly appreciated.

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Since many employers match their employees donations a donation through Give-As-You-Earn could double your contribution. For more information on Give-As-You-Earn visit www.giveasyouearn.org

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.

