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EDITORIAL

Welcome to the July/August issue of HTB and summer reading that includes reports from the International HIV Resistance Worshop held recently in Sitges. We continue with additional reports from the BHIVA spring conference and conclude, finally, our coverage from the Retrovirus conference held back in February.

Antiretroviral news includes European approval for boosted atazanavir for first-line therapy and the online publication of the BHIVA Guidelines for Treatment of HIV-1 Infection in Adults.

As a supplement to this issue, we also include the June 2008 edition of Introduction to Combination Therapy.

This booklet is a short summary of information for someone to gain the maximum benefit from their treatment and their clinicians. It is widely used in clinics for newly diagnosed patients or patients about to start treatment.

The new edition updates the pull-out colour reference chart on individual drugs, includes the latest recommendations from the 2008 BHIVA guidelines, and includes pages for patients to record their CD4, viral load, resistance test and other personal notes.

This booklet is available free, including in bulk, to all UK clinics and individuals. Please order what you need either directly online or using the fax-back form on the back cover of HTB.

Regular readers will have learnt that the London HIV Commissioners declined to support this or any of our other projects.

While we continue to challenge this decision and will update you on this progress in the next issue, we would like to emphasise that i-Base is still very much alive and fighting - any rumours of our demise are extremely premature!

The next issue will also bring our first reports from the International IAS AIDS Conference due to be held in Mexico City at the begining of August. As the largest HIV conference, and having broader focus than purely medical advances, is sure to include important studies and advances.

CONFERENCE REPORTS

XVII International Resistance Workshop

10-13 June 2008, Sitges

Introduction

Despite the fall in the value of the dollar, European delegates are fortunate that this specialist resistance workshop still alternates between European and North American sites. This years meeting in Sitges included a healthy balance between basic science and studies with more direct clinical importance.

Several themes emerged and they were covered by multiple presentations, including integrase resistance (14 posters with 3 oral presentations and a programmed discussion), susceptibility to etravrine (8 studies), resistance to other new drugs (another 15 or so studies) and co-receptor tropism assays (10 studies).

The remaining 100 studies covered all aspects of drug resistance, only a few of which we are able to cover below.

Reports in this issue of HTB include:

- Integrase inhibitor resistance and cross-resistance: weighing viral fitness and the option to benefit from second-generation compounds
- Understanding etravirine susceptibility: new weighted genotype score and phenotypic cut-offs
- Promising pipeline antiretrovirals: IDX899, CHX157 and beviramat
- Lack of virological impact of treatment intensification in suppressed patients supports latent viral reservoir as source of residual viraemia
- Detecting viral tropism: impact of a more sensitive Trofile (ES) assay
- NNRTI resistance in infants prophylaxed with single-dose nevirapine varies by the timing of infection
- Low frequency K103N mutations are associated with poor virological response to NNRTI based therapy

Unless stated otherwise, references are to the Programme and Abstracts of the XVII International HIV Drug Resistance Workshop (IHDRW), 10-14 June 2008, Sitges, Spain published as Supplement 3 in Anitviral Therapy Volume 13 Issue 4.

Thanks to Anna-Maria Geretti for advice and comments on these reports.

Integrase inhibitor resistance and cross-resistance: weighing viral fitness and the option to benefit from second-generation compounds

Simon Collins, HIV i-Base

Several research groups presented results on generally small groups of highly treatment experienced patients who are no longer responding to raltegravir-based regimens.

The key questions for these patients who already have limited options involves identifying when the risks of remaining on a less than suppressive treatment outweigh any residual benefits from treatment.

- Do integrase inhibitors (INIs) have class properties that are stronger than individual drug profiles (generally like NNRTIs or PIs)?
- Does resistance accumulate slowly enough for reduced viral fitness to have a clinical benefit?
- Does the risk of accumulated mutations compromise the future option to benefit from second generation INIs?

An understanding of the integrase resistance, first reported at last years meeting, emphasised that primary resistance follows two main pathways – based on either Q148H/R/K or N155H, leading to >10-fold resistance, with one group this years reporting that these mutations are not found on the same genome. Indeed, four distinct pathways appear to develop, with different implications for viral fitness. This year Y143R/C emerged in several studies as a further primary mutation.

While resistance generally has an impact on reducing viral fitness, and immunological benefits were reported as continuing 3 and 6 months after treatment failure, questions were asked to each presenter about the degree to which patients maintained on a failing integrase-based regimen may be compromising their options to use second-generation integrase compounds.

This issue will not be resolved until they are greater data available on the viral responses of patients who stop integrase treatment – and this is currently limited to single case reports.

Michael Miller presented Merck's longitudinal genotyping and cloning analysis from 35/133 patients (28%) failing raltegravir at 48 weeks in their Phase II study. [1]

Three additional patients had showed no INI changes. Of the 35, 2 subsequently resuppressed their viral load, leaving 33 patients with a second genotype. Of these, a further 2 resuppressed and 4 were lost to follow-up, 4 remained stable with Q148H and G140S and 23 provided data from a third genotype.

At first failure only 9 patients had single mutations, with most having 2 or more, and these increased in number over time. The genotype at first failure showed 20 patients with mutations at Q148 + combinations and 14 with N155 plus combinations. No patients failed with mutations at both these key sites. One patient failed with Y143R alone.

Over time, four pathways were reported: i) a consistent preference for the Q148H at each stage, including Q148H/G140S (n=13) that remain stable; ii) patients with N155H alone, which generally developed to Q148 (n=5); iii) mixed N155H/Q148H viral populations that resolved to Q148H over time, often with G140S (n=7); and iv) patients with other mixed patterns including N155H but who accumulated additional mutations but not Q148 (n=7).

Q148 viruses, especially with secondary mutations, displayed the greater levels of resistance and the least benefit from impaired fitness.

Addressing this small dataset, without details on the time of sampling, Miller was optimistic that second generation Merck compounds would be active against Q148 and N155, but also did not expect to see pharmacologically acceptable formulations available for at least several years.

Most importantly, he also recognised that there were no data to support maintaining raltegravir in patients who were virologically failing treatment.

Signe Fransen and colleagues from Monogram, also working with the Merck team presented results from a subset of 69 samples from the Phase III Benchmrk studies. [2]

Nine patients had mutational changes at both Q148 and N155, but the changes at each point were mixtures and they were never found on the same genome. Secondary mutations - E92Q with N155H, and G140S(A) with Q148R(H/K) – were related to the primary resistance pathway. A few patients were reported with E92Q but without changes at N155 or Q148.

Four patterns in this analysis broadly followed the Miller study: i) Q148R(H/K) with or without additional changes including N155H and Y143R/C; ii) N155H with or without additional mutations, including Q148R(H/K) and Y143R/C; iii) Y143R/C with or without changes at N155 or Q148; and iv) 1 patient with no primary mutations.

Clonal analysis from these patients showed a variable impact of mutation patterns on viral fitness. Both Q148 and N155 reduced replicative capacity and this was either further reduced or, in some cases improved, depending on the secondary mutation pattern.

However, there is unlikely to be any significant clinical relevance from what are likely to be transitory changes in fitness, especially if a trend to developing Q148 is confirmed, as this mutation has little impact on fitness.

Clinical experience from raltegravir use was also provided by several independent research groups.

Steven Deeks group from University of San Fransisco, presented results from 13 patients who remained unsuppressed on raltegravir-containing regimens. [3]

These were multiple experienced and advanced patients (baseline CD4 count was 66 cells/mm3) followed for a median of over 12 months. Most notably, CD4 increases persisted despite virological non-suppression (with increases of +37 and +71 cells/mm3, at 3 and 6 months respectively).

Three patients with intermittent adherence in this group lacked mutations, but otherwise G140S+Q148H and T97A+Y143R patterns were seen, and they were associated with high-level phenotypic resistance.

One patient, who only showed isolated N155H, interrupted only the raltegravir componant of treatment while maintaining their background regimen. Plasma levels initially remained stable, suggesting an effect of viral fitness, but they subsequently rebounded by over 1 log as the proportion of raltegravir-associated mutations declined in the absence of selective drug pressure.

Christine Katlama from Pitié-Salpêtrière Hospital, Paris, reported on a cohort of 50 treatment-experienced patients who started raltegravir between September 2006 and November 2007. 34 patients successfully suppressed viral load to <40 copies/mL by week 24. 11 patients had low-level viraemia >40 - <400 copies/mL and 3 had persistent viraemia >400 copies/mL.

4/13 patients with genotype results showed integrase mutations: G140S+Q148H (n=2), N155H (n=1) and a switch fromN155H to G140S+Q148H (n=1).

Several studies also addressed cross-resistance between raltegravir and elvitegravir, and no researchers either directly involved in these studies or in the general discussions expected patients who fail on one of these drugs to benefit from subsequent use of the other.

Olivia Goethals and colleagues from Tibotec used selected in vitro emergence of resistance to raltegravir and elvitegravir and site directed mutagenesis of selected mutations against a panel of integrase inhibitors. [5]

Q148R was selected by both raltegravir and elvitegravir and conferred resistance to other compounds. The researchers concluded that Q148H, together with E92Q and T66I, which were both also selected by elvitegravir, should be considered to confer class-wide resistance.

The discussions on cross-resistance were closely tied to interest in second-generation integrase inhibitors, and awareness of the pipeline is important for patients who have already devloped integrase resistance. Merck say they have already designed molecules with activity against 148 and 155 mutations - and that rational drug design should also be able to overcome changes at position 143. The bottleneck is overcoming pharmacokinetic problems of delivery and tolerability though, and Daria Hazuda also estimated that they are still likely to be at least 2-3 years away from clinical studies.

Finally, a study from Anne-Genvième Marcelin and colleagues from Pitié-Salpêtrière Hospital, Paris, compared integrase sequences from 72 clade-B and 66 CRF02-AG strains for the difference in naturally occurring polymorphisms. [6]

While several studies have reported that polymorphisms in subtype B infection are not limiting responses in integrase-naïve patients, including two studies at this workshop [7, 8], there are little data from non-B subtypes.

They found 13 amino acid changes that could affect the functional properties of integrase with clustering suggesting these may include compensatory mutations, concluding that virological response to integrase inhibitors by viral sub-type should be studied in clinical trials.

C O M M E N T

This focus on resistance should be seen against the background of raltegravir also producing some of the strongest treatment responses in multiple-experienced and advanced patients.

For patients failing integrase-based treatments though, these questions are critical. Unlike the US, which needs to wait for a validated integrase resistance test, integrase resistance is already being sequenced in many UK and European labs, and is being validated as part of a European quality control programme.

Documenting resistance history for selection of future drugs is important. The limited data, and expert opinion from the researchers involved with these compounds suggest no specific benefit from remaining on integrase inhibitors once viral load has rebounded, and that the risk of accumulating mutations will compromise use of future INIs and that this risk should be taken seriously.

The data on viral fitness suggests any benefit is likely to be short term, and unlikely to outweigh the risk from accumulating further resistance, especially once Q148 changes have occurred.

References:
1. Miller M et al. Longitudinal analysis of resistance to the HIV-1 integrase inhibitor raltegravir: results from P005, a Phase 2 Study in treatment-experienced patients. XVII IHDRW 2008, Sitges. Abstract 6.
2. Fransen S et al. Loss of raltegravir susceptibility in treated patients is conferred by multiple non-overlapping genetic pathways. XVII IHDRW 2008, Sitges. Abstract 7.
3. Hatano H et al. Virological and immunological outcomes in a cohort of patients failing integrase inhibitors. XVII IHDRW 2008, Sitges. Abstract 10.
4. Katlama C et al. Virological evolution on HIV treatment-experienced patients with raltegravir-based salvage regimens. XVII IHDRW 2008, Sitges. Abstract 11.
5. Goethals O et al. Resistance mutations in HIV-1 integrase selected with raltegravir or elvitegravir confer reduced susceptibility to a diverse panel of integrase inhibitors. XVII IHDRW 2008, Sitges. Abstract 9.
6. Marcelin A-G et al. Natural variation of integrase sequences form subtype B and CRF02-AG HIV-1 antiretroviral naïve patients and possible effect on susceptibility to integrase inhibitors. XVII IHDRW 2008, Sitges. Abstract 63.
7. Buzón MJ et al. Fitness progression and phenotypic susceptibility to raltegravir of HIV-1 integrase are not restricted in long-term HAART treated patients. XVII IHDRW 2008, Sitges. Abstract 76.
8. Ji H et al. Tracking HIV-1 integrase polymorphisms from the pre-antiretroviral therapy era up to the introduction of integrase inhibitors. XVII IHDRW 2008, Sitges. Abstract 78.

Understanding etravirine susceptibility: new weighted genotype score and phenotypic cut-offs

Simon Collins, HIV i-Base

Although etravirine (ETV) was approved in the US in January 2008, [1] the indication to not rely on ETV with only two new RTIs, and its interaction profile with other ARVs, have limited it's use, other than with darunavir as in the DUET registrational studies.

The workshop included several studies addressing both genotypic and phenotypic resistance, that will hopefully help interpret a patients susceptibility to this new NNRTI.

Johan Vingerhoets and colleagues from Tibotec presented a new and updated weighted list of mutations associated with reduced virological response from the DUET studies.

Until now, presence of three or more mutations from the 13 key mutations V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V, G190A/S, indicated likely high-level resistance. This year, four additional mutations were added to this list: K101H, E138A, V179T and M230L. Virologic responses still decreased with increasing numbers of mutations, with 77%, 61%, 56% and 38% patients achieving <50 copies/mL in the presence of 0, 1, 2 and ≥3 of mutations respectively.

However, V179F, G190S and Y181V had the greatest impact with only approximately 12%, 20% and 32% of patients with only one of each these single mutations achieving <50 copies/mL, indicating the importance of developing a weighting score.

Relative weighting was determined using random forest and linear model techniques, applied to matched phenotypic/genotypic samples and a panel of recombinant isolates. A multivariate analysis adjusted for baseline viral load, darunavir fold-change (FC) and NRTI sensitivity.

A new weighted score of 0-2, 2.5-3.5 and ≥4 corresponded to 74%, 52% and 38% virological response rates. This significantly improved the correction between genotype score and etravirine phenotypic sensitivity, especially at lower scores, shown in Table 1.

Table 1: Genotypic weighting scores and associated phenotypic sensitivity to etravirine

Mutation	FC in single site directed mutant	Effect on FC in model	Weight factor
Y181V	12.5	High	3.0
Y181I	17.4	High	3.0
K101P	6.2	High	2.5
L1001	1.8	Medium	2.5
Y181C	3.9	Medium	2.5
M230L	3.4	High	2.5
E138A	2.0	Medium	1.5
V106I	NA	Low	1.5
G190S	0.2	Low	1.5
V179F	0.1	Medium	1.5
V90I	1.5	Low	1.0
V179D	2.6	Low	1.0
K101E	1.7	Low	1.0

K101H	1.3	Low	1.0
A98G	2.5	Low	1.0
V179T	0.8	Low	1.0
G190A	0.8	Low	1.0

Phenotypic sensitivity cut-offs for etravirine were evaluated by Monika Peeters and colleagues from Tibotec who looked at samples from almost 600 patients from the DUET studies to determine clinical cut-offs for the Virco Antivirogram phenotypic assay. Excluding patients who discontinued before week 24 or who used T-20 as a new drug, this left 403 patient samples for this analysis which looked at a continuum of responses. [3]

Baseline etravirine EC50 was a significant predictor of response at week 24 and data mining techniques set a lower cut-off a ≤ 3.0 fold change. However, the data set could not establish an upper cut-off with > -1.0 log reductions seen at 13 fold changes, leading the researchers to call this 'intermediate' rather than an 'upper' cut-off. At baseline, 67%, 18% and 15% of patients had etravirine fold-changes of < 3, 3-13 and >13 fold; with 71%, 50% and 37% of patients in the same groups respectively, achieving viral suppression <50 copies/mL at week 24.

Eoin Coakley presented the results from the Monogram clinical cut-offs for etravirine, derived from evaluating week 2, 4, 8 and 24 viral responses from the DUET studies in relation to baseline fold change in 200 samples from patients not starting new T-20. Although they arrived at a similar lower clinical cut-off of 2.9, they failed to report an upper cut-off due to a limited number of sample with higher phenotypic resistance.

They reported that from their analysis of the DUET data, median etravirine fold change at baseline was 0.75 (range 0.06-200), with a third of sample showing hypersensitivity (<0.04 FC).

Lee Batchelor and colleagues from Virco, classified phenotype responses as maximal (MA), reduced (RR) or minimal (Min) for the VircoTYPE vitual phenotype, using clinical cut-offs of 1.6, 5.0 and 27.6 fold change for IC50 (associated respectively with 20%, 50% and 80% losses of predicted wild-type response). [5]

In a subset of routine clinical samples from the Virco database, the percentage associated with MA, RR or Min was 73%, 24% and 2.4% respectively, with 38% of samples having at least one NNRTI-associated mutation. When just looking at this subset of NNRTI-resistant samples, 48%, 46% and 6% had etravirine values classified as MA, RR or Min.

The percentage of patients achieving <50 copies/mL by fold change in the DUET studies were found to be 69% (FC<1.6), 59% (FC 1.6 - <5.0), 49% (FC 5.0 – 27.6) and 44% (FC > 27.6).

C O M M E N T

Workshop organiser John Mellors commenting on the new etravirine data emphasised that clinicians just want an easy way to know whether a drug will work, and collaboration between research groups would help his situation as an expert responsible for interpreting these results.

Several clinicians at the meeting, including Jonathan Shapiro found the upper cut-off levels unconvincing as an aid for clinical decisions.

In the UK, where phenotype tests are used less frequently, the new genotypic weighed score analysis will be of most relevance.

References

1. See HIV Treatment Bulletin, Jan/Feb 2008. http://www.i-base.info/htb/v9/htb9-1-2/Etravirine.html
2. Vingerhoets J et al. An update on the list of NNRTI mutations associated with decreased viralogical response to etravirine: multivariate analysis on the pooled DUET-1 and DUET-2 clinical trial data. XVII IHDRW 2008, Sitges. Abstract 24.
3. Peeters M et al. Determination of phenotypic clinical cut-offs for etravirine: pooled week 24 results of the DUET-1 and DUET-2 trials. XVII IHDRW 2008, Sitges. Abstract 121.
4. Coakley E et al. Biological and clinical cut-off analyses for etravirine
5. Bacheler L et al. Exploring etrivirine resistance among recent routine clinical samples submitted for resistance testing. XVII IHDRW 2008, Sitges. Abstract 110.

Pipeline antiretrovirals: IDX899, CHX157 and beviramat

Simon Collins, HIV i-Base

IDX899: an NNRTI in development with Idenix

An oral presentation by Rob Murphy [1] summarised two posters at the workshop that presented information on a new NNRTI being developed by Idenix. [2, 3]

Antiviral activity was shown in results from a seven-day Phase I/IIa dose finding study in Argentina, 40 treatment-naïve patients were randomised 8:2 to once-daily monotherapy with 800mg, 400mg, 200mg or placebo. All patients switched to 28 days monotherapy or started HAART at the end of the study period.

Results were available for all but two patients in each of the 200mg and placebo arms. Viral activity was similar in each of the active drug groups which saw steady, linear viral load reductions reaching -1.8 log at day eight (using COBRAS Amplicor 1,5) from mean baseline of approximately 4.3-4.6 log copies/mL.

No clear relationship was seen between drug exposure and response and although the current formulation only has 50% bioavailability, all doses achieved drug trough concentrations that exceeded the protein adjusted EC50 by greater than 10-40 fold (with individual ranges from 5-140 fold).

Mean CD4 count increased by around +65 cells/mm3 in all groups compared to a reduction of -85 cells/mm3 in the placebo arm.

Side effects occurring in ≥ 2 patients were mild, infrequent and distributed equally between the placebo and active drug groups, with no clear dose-related toxicity, and no grade3/4 laboratory changes. There were no cases of rash, which commonly do not show after only 7 days, but also no cases of CNS disorientation which would be expected, if induced. Toxicity has not been seen in preclinical animal studies.

A second poster presented by Jocelyn Jakubik expanded on the likely resistance and cross-resistance profile of IDX899 in a set of in vitro studies. [2]

IDX899 was shown to remain sensitive (<4 fold change from wild-type) to 20/23 single, double and triple site directed mutations, with greater resistance seen to Y181C (14 fold), E138K/Y181I (11 fold) and E138K/Y181I/M230L (900 fold). It also retained sensitivity to viral pools selected through exposure to efavirenz and etravirine (TMC-125), and retained greater sensitivity to each pool compared with efavirenz, etravirine of TMC-278 (rilpivirtine)

High level resistance to IDX899 was selected in vitro after ≥29 passages with two independent pathways initiated by mutations at either E138K or V90I/Y181C.

While showing potential benefits of IDX899 against NNRTI-resistant virus, the results also tentatively suggested that naïve patients failing IDX899 might retain sensitivity to efavirenz.

This poster expanded on the first presentation of these studies at the Retrovirus Conference earlier this year. [4]

Idenix are still in negotiation with potential companies to take forward the clinical development programme of IDX899 in 2009, based on an improved formulation and possibly also a 100mg dose.

C O M M E N T

These promising early results should help start the Phase I/II studies. Although the in vitro data support potentially different resistance patterns to both existing NNRTIs and other pipeline drugs, this also needs to be studied in the clinical programme.

References

1. Murphy R et al. In vitro cross-resistance profile, antiviral activity, safety and pharmacokinetics in HIV-i-infetected of IDX899, a novel HIV-1 NNRTI with high barrier to resistance. XVII IHDRW 2008, Sitges. Abstract 5.
2. Murphy et al. Antiviral activity, safety and pharmacokinetics of IDX899, a novel HIV-1 NNRTI with high barrier to resistance, in treatment-naïve HIV-1-infected subjects. XVII IHDRW 2008, Sitges. Poster 25.
3. Jakubik J et al. In vitro cross-resistance profile for a next-generation NNRTI: IDX899. XVII IHDRW 2008, Sitges. Poster 26.
4. Richmann D et al. Genotypic Resistance and Phenotypic Cross-resistance Profile in vitro for a Novel NNRTI: IDX899. 15th CROI, Boston, 2008.
http://www.retroconference.org/2008/Abstracts/32674.htm

http://www.retroconference.org/2008/PDFs/729.pdf

CHX157: a prodrug similar to tenofovir-DF

Randall Lanier, formerly with GSK and now with Chimerix, presented results on hexadecyloxpropyl tenofovir (CMX157), a new compound similar to Gilead's tenofovir disoproxil fumerate. [1]

Differences claimed for this new compound include activity against K65R and that this prodrug is less efficiently cleaved to free tenofovir in plasma, which should increase tenofovir diphosphate levels in target cells, lower the apparent IC50 and reduce the rate of secretion into the kidney (and related toxicity). The primary elimination pathway is thought to be hepatic,

IC50s for CMX157 were determined against a panel of 30 NRTI single and multiple isolates including K65R, M184V, TAMS, K70E, Q151M and 69-SXX insertion and are detailed in Table 1.

Similar results were also reported against a separate panel of 14 NRTI-resistant and wild-type clinical isolates in PBMCs.

Table 1: Examples of IC50s for CMX157 and tenofovir-DF against NRTI-resistant isolates

	CMX157	tenofovir-DF
L74V/M184V	0.66nM	227nM
T69SSG/M184V/L210W/T215Y	57nM	~17,000nM
M41L/L210W/T215Y	6.3nM	2,240nM
M41L/L210W/T215Y/M184V	2.2nM	770nM

The poster reported that tenofovir diphosphate levels were 33-fold higher in PHA/IL-2 stimulated human PBMCs after 24 hours compared to tenofovir-DF and that no toxicity has been observed in rats administered up to 100mg/kg/day for 7 seven days.

References

1. Lanier ER et al. Hexadecyloxpropyl tenofovir (CMX157) has enhanced potency in vitro against NRTI resistant HIV relative to tenofovir and a favorable preclinical profile. XVII IHDRW 2008, Sitges. Poster 4.

Beviramat (PA-457): baseline gag polymorphisms determine treatment response

Scott McCallister from Panacos presented an analysis of the impact of baseline Gag polymorphisms together with individual drug exposure levels on virological response to the maturation inhibitor beviramat. [1]

Results of early studies were complicated by formulation difficulties and disappointing virological responses. In fact, the latest virological information from ongoing Phase IIb results has only trickled out in a series of company press statements containing 'forward-looking statements'. [2, 3]

The analysis at this years workshop was from 44 treatment-experienced patients on currently failing treatment who added beviramat in escalating dose groups as functional monotherapy for 14 days.

	Responders >0.5 log reduction	non-responders <0.5 log reduction
N	20	24
Trough >20ug/mL	19/20	19/24
Mean VL response	-1.26 log	-0.05 log
Baseline Gag polymorphisms	5.9	7.3

Viral responses by presence of baseline polymorphisms in Gag at positions 369, 370 or 371 were -0.16 (n=9), -0.24 (n=22) and -0.32 logs (n=11) respectively. Patients with absence of the same mutations had viral responses of -0.69, -0.79 and -0.73 respectively. Patients with no changes at 369-371 had a reduction of -1.08 logs.

Panacos are now planning to restrict future research to patients without baseline Gag polymorphisms at the three points, citing the approximate 60% naïve patients from the 567 patients in the University of British Columbia database as guide to proportion of patients likely to be eligible. They will also plan to restrict studies to patients who achieve minimum trough levels >20ug/mL.

C O M M E N T

Predefining a patient group likely to benefit from beviramat is similar to use of a tropism assay prior to prescribing CCR5 inhibitors and should not be a block to future drug development, especially if it can reliably result in a -1.2 log drop in viral load.

References

1. McCallister S et al. HIV-1 gag polymorphisms determine treatment response to beviramat (PA-457). XVII IHDRW 2008, Sitges. Abstract 8.
2. Panacos press statement: Results of bevirimat 350 mg cohort, data support further dose escalation in Phase 2b study (10 Dec 2007) http://phx.corporate-ir.net/phoenix.zhtml?c=75423&p=irol-newsArticle&ID=1085851&highlight=
3. Panacos press statement: Greater than 1 log10 mean reduction in 300 mg bevirimat cohort. (25 October 2007). http://phx.corporate-ir.net/phoenix.zhtml?c=75423&p=irol-newsArticle&ID=1067968&highlight=

Lack of virological impact of treatment intensification in suppressed patients supports latent viral reservoir as source of residual viraemia

Simon Collins, HIV i-Base

Frank Maldarelli from the US HIV Drug Resistance Programme, and colleagues, presented results from a small treatment intensification study looking to clarify the source of residual viraemia in patients with viral load suppressed to <50 copies/mL. [1]

This group has previously reported that long term suppression < 50 copies/mL still results in 80% patients have viraemia >1 copy/mL (when tested on an assay with this sensitivity), but that median levels are only 3.1 copies/mL once patients have been on stable treatment for 60 weeks, and that no further suppression occurred from week 60 to 120. This study also found that the level at week 60 correlated with pre-treatment viral load but not with choice of treatment regimen. [2] They concluded that "these data suggest that the persistent viraemia on current antiretroviral therapy is derived, at least in part, from long-lived cells that are infected prior to initiation of therapy".

The new study intensified treatment for 30 days in 6 patients who had been suppressed to <50 copies/mL for at least the previous year on standard 3-drug regimens but who still had detectable virus using a 1 copy/mL assay. The four patients on PI-based therapy intensified with efavirenz and the two patients on NNRTI-based therapy added lopinavir/r. Doses were modified appropriately to allow for ARV drug interactions.

These patients (5 men, 1 woman) had been diagnosed a mean 9 years (range 4-16) and on treatment for a mean of 4 years (range 1-10). Mean baseline viral was 4.5 copies/mL.

No significant changes occurred in viral load or CD4 count over the 30 day intensification period, and treatment was well tolerated with no serious side effects reports. Mean viral load during and after intensification were 5.2 and 5.3 copies/mL respectively, showing no impact of the intervention. This was supported by individual responses of the 6 patients that were all included in the poster.

The researchers concluded that failure to find a decrease from intensification in this study was inconsistent with the idea that persistent vireamia at low levels was the result of ongoing complete cycles of replication and that the results supported the source being from latently infected reservoirs.

C O M M E N T

This study supports research first presented at the resistance workshop several years ago by Lisa Frenkel, who found that 8/11 children with generally suppressed viraemia had no evolution of viral divergence since starting treatment, implying ongoing viraemia was seeded from latently infected cells rather than a partially activated reservoirs as suggested by others.

This has been one of the theoretical foundations behind the drive to achieve suppression to <50 copies/mL. rather than at any higher (or lower) level. The absence of viral evolution shows effective treatment stopping, rather than slowing, HIV progression, with a clearly different and more important impact on clinical outcome.

References

1. Maldarelli F et al. Intensification with efavirenz or lopinavir/r does not reduce residual HIV-viraemia in patients on standardised ARV therapy. XVII IHDRW 2008, Sitges. Abstract 72.
2. Maldarelli F et al. ART suppresses plasma HIV-1 RNA to a stable set point predicted by pretherapy viremia. PLoS Pathogens 3(4): e46. doi:10.1371/journal.ppat.0030046.
3. Tobin NL, Frenkel L et al. Evidence that low-level viremias during effective HAART result from two processes: expression of archival virus and replication of virus. J Virology, Aug. 2005, p. 9625–9634.

Detecting viral tropism: impact of a more sensitive Trofile (ES) assay

Simon Collins, HIV i-Base

It is unfortunate that the viral tropism assay available to screen patients for maraviroc and vicriviroc studies was insufficiently sensitive to identify patients with clinically important R5/X4 mixed populations, and treatment failure in these patients impacted on the trial efficacy results.

Trofile is still the only FDA approved test, but sensitivity has now been improved and a reanalysis of results from the ACTG 5211 vivriviroc study using the new assay (Trofile ES) was presented at the workshop.

Jacqueline Reeves and colleagues from Monogram presented screen and entry samples for the 118 patients, originally all classified as R5, and reported virological responses by the new tropism results. With the new test, 25 patients were now classified as mixed R5/X4. Four samples were not available, and the remaining 89 were all R5.

The virological results for R5 patients at day 14 and week 24 now improved to -1.10 and -1.85; -1.31 and -2.09; and -0.93 and -1.75 logs in the 5mg, 10mg and 15mg arms respectively. This was approximately a 0.2-0.3 log difference in the 5mg

and 10mg arms, but did not affect the 15mg results.

While most patients are now thought to have a mix of R5/X4 viruses, the clinical cut-off for the percentage of X4 that becomes clinical important is still to be determined.

Treatment responses were significantly different in the 64 patients with confirmed R5 at screening and entry: -1.15 and -1.95 log reductions at day 14 and week 24. Responses in 5 patients who switched from R5 to mixed R5/X4 between screening and enrollment had reductions were -1.15 and -1.20; and in the 15 patients now identified with mixed tropism at screening of -0.66 and 0.57, at day 14 and week 24.

Several studies looking at determining tropism from genotyping the V3 and V2 loops showed that these results are improving and that using this faster and significantly less costly technology, with an X4 result screening out and an R5 result requiring confirmation, may be more likely in the next year or two. [2]

C O M M E N T

This more sensitive tropism test is welcome as accurate identification of tropism prior to using CCR5 inhibitors is clearly key to treatment outcome. Trofile ES will routinely replace Trofile from July 2008.

One important aspect of the genotype V3 approach is the potential to use this as a screening test for patients who are virally suppressed on their current treatment, but who wish to switch to CCR5 inhibitors due to tolerability issues on their current regimen. While phenotype tests require detectable viral load (>500 copies/mL) the genotype tests can work with plasma RNA and proviral DNA.

References

1. Reeves J et al. Response to vicriviroc in HIV-1 infected, treatment-experienced individuals using an enhanced version of the Trofile HIV co-receptor assay [Trofile (ES)]: reanalysis of ACTG 5211 results. XVII IHDRW 2008, Sitges. Abstract 88.
2. Moores A et al. Improved detection of X4 virus by V3 genotyping: application to plasma RNA and proviral DNA. XVII IHDRW 2008, Sitges. Abstract 89.

NNRTI resistance in infants prophylaxed with single-dose nevirapine varies by the timing of infection

Polly Clayden, HIV i-Base

Ana Blanco and co-workers from the Mozambique Ministry of Health, Health Alliance International, Seattle, University of Washington, Seattle and Seattle Children's Hospital Research Institute showed findings from an evaluation of infants infected with HIV despite receiving single dose nevirapine (sdNVP) prophylaxis.

The investigators hypothesised that the timing of nevirapine selective pressure relative to when the HIV first infects infants, effects the selection and persistence of NVP resistant virus. They suggest that:

- NVP pressure during "acute" (peri-partum) infection will result in transmission or significant selection of mutations that will populate long-lived viral reservoirs and mutations will persist over time.
- NVP pressure during "established" (in utero) infection will select mutations, however, as HIV-1 reservoirs are already established, fewer will be archived so mutant population will fade over time.

This report was from a prospective observational cohort study of 741 infants of whom 100% received single dose NVP (73% mothers). The investigators estimated the timing of infection using nested PCR for HIV-1 pol in dried blood spots, collected by heel stick, at birth and every 2 weeks for the first 2 months of life, and then every 4-8 weeks until one year of age.

Concentrations of resistant virus were determined using quantitative PCR oligonucleotide ligation assays (OLA) for K103N, V106M, Y181C and G190A.

HIV infection was detected by PCR in 53 infants followed between 0-8 weeks of age. 29 were infected in utero (HIV detected at birth), all had wild type virus and 23 had high and stable viral load at birth ie "established" infection, and 6 had low viral loads that later increased, suggesting "acute" infection at the time of birth.

The investigators reported that the selection and decay of NVP-resistant HIV-1 varied by timing of infection.

Infants with "established" infection had frequent selection of NVP-resistant HIV-1 (87%, 95%CI 66-97%).

Postpartum infant AZT+sdNVP vs. NVP decreased NVP-resistant HIV-1 (3/6 vs. 0/17, p=0.013). NVP-resistant viruses decayed rapidly compared to infants with peri-partum infection.

Compared to "established", infants with "acute" in utero infection (ie low viral load at birth) had infrequent (33%) selection of NVP-resistant HIV-1, p=0.01. In this group of infants NVP-resistant HIV-1 appeared to decay more slowly.

Among infants with peripartum infection (n=24) there was infrequent selection of NVP-resistant HIV-1; (38%, 95%CI 19-59%) compared to "established", p=0.001. Few infants with NVP-resistance, initially had exclusively wild-type viruses vs. "established" (2/9; 22%, 95%CI 3-60% vs. 21/21 ; 100%, 95%CI 84-100%), p< 0.001. Also, most infants had 100% NVP-resistant HIV-1 in the first sample with detectable resistance vs. "established", (6/9; 67%, 95%CI 30-93% vs. 0/22 ; 0%, 95%CI 0-15%), p< 0.001.

The investigators noted a non-significant trend for less NVP-resistance when mothers did not take sdNVP (0/5 vs. 9/19, p= 0.12).

They summarised:

- With "established" in utero infection, viral replication in utero generates mutations that are selected by sdNVP. AZT appears to reduce the selection of NVP mutations, "theoretically by increasing the genetic barrier and decreasing viral replication". Rapid decay of NVP-resistant virus suggests that after an (undefined) interval, NVP-based HAART may be effective.
- With "acute" in utero infection there is frequently too little viral replication in utero to generate mutations, so there are no NVP-resistant mutations to select. But if selected NVP-resistant HIV-1 decays slowly suggesting that it populates long-lived reservoirs.
- With peri-partum infection, infections with 100% resistant virus suggests transmission of NVP-resistant HIV-1. Persistence of mutations at high concentrations suggests it populates reservoirs. Persistence of mutations suggests that NVP-containing HAART may fail.

The investigators noted a low rate of mother-to-child transmission among infants whose mothers received pre-partum AZT in addition to sdNVP. But this was only a minority of women and access needs to be improved.

Ref: Miceck MA, Blanco AJ, Beck IA et al. The selection, transmission and persistence of drug-resistant HIV-1 in infants prophylaxed with single dose nevirapine varies by the timing of infection. XVII IHDRW 2008, Sitges. Abstract 71.

Low frequency K103N mutations are associated with poor virological response to NNRTI based therapy

Polly Clayden, HIV i-Base

Gilian Hunt and co-workers showed findings from an observational epidemiological study comparing HIV-positive women from Johannesburg clinics exposed (n=94) and unexposed (n=60) to single-dose nevirapine (sdNVP) for mother to child transmission prophylaxis 18-36 months earlier.

In this study, pre-treatment samples were tested for K103N mutations using an allele-specific real time PCR (AS-PCR). Population sequencing was performed on samples from women who did not achieve a viral load <50 copies/mL or did not sustain viral suppression to 78 weeks.

All women received South African first-line regimens (d4T/3TC plus either nevirapine or efavirenz).

The investigators found K103N mutations detected by AS-PCR in 10.6% samples from the sdNVP exposed and 15% reportedly unexposed women. 57.8% of women with baseline resistance had an inadequate virological response. Only 36.7% of the 30 women across both groups with an inadequate virological response had K103N mutations detected pre-treatment.

The investigators then performed an analysis of other minority mutant populations in the earliest failing samples and found different mutation patterns between the two groups of women. K103N was more frequent among the exposed women (9/18, 50%) than the unexposed women (3/12, 33%) and M184V/I was more frequent among the unexposed (9/12, 75%) than the exposed (6/18, 33%). In both groups most women had at least one NNRTI mutation 13/18 (72%) exposed women and 10/12 (83%) unexposed women in their failing sample.

The investigators concluded that in this study exposure to sdNVP was not associated with reduced likelihood of achieving undetectable viral load <50 copies/mL or with sustained response at 78 weeks.

However K103N mutations were strongly associated with compromised response. Most women were initially undetectable but this was not sustained and K103N mutations were associated with a >3-fold risk of viral rebound. They wrote: "The consequences of underlying resistance mutations were not apparent within the fist 6 months of therapy but clearly affected the durability of viral suppression after 6 months."

They noted that despite comparable levels of K103N in both groups s/dNVP exposed women appeared to fail with K103N and unexposed M184V.

They suggested that possibly the K103N is archived in previously exposed women at undetectable levels. In unexposed

women they suggest that M184 mutation, which is known to appear rapidly but results in a compromised virus, subsequently delays the development of other resistance related codons. 'These discrepancies in virus evolution between the two groups warrant further investigation." they added.

Reference: Hunt G, Coovadia A, EJ Abrams et al. Low frequency K103N mutations are strongly associated with inadequate virological response to non-nucleoside reverse transcriptase inhibitor based therapy. XVII IHDRW 2008, Sitges. Abstract 120.

CONFERENCE REPORTS

14th Annual BHIVA Conference

23–25 April 2008, Belfast

Introduction

The annual BHIVA spring conference held this year in Dublin, has two main aims. In addition to presenting overview lectures on important aspects of HIV care and management - often given by international experts, it aims to encourage UK-based research and case studies by presenting research from junior doctors and researchers.

In the last issue of HTB we covered the latest BHIVA audit, current MRC studies and a range of other posters and presentations.

In this issue we continue with the following reports:

- Bone problems raised in several UK studies
- Late diagnosis in adolescence of vertically acquired HIV infection
- Case study of multi-drug resistant woman receiving newer antiretroviral drugs in pregnancy
- Predictors of treatment failure in Western Cape, South Africa
- Late pregnancy loss in HIV-positive women
- Renal tubular dysfunction with tenofovir-based HAART in four vertically infected adolescents

Bone problems raised in several UK studies

Simon Collins, HIV i-Base

Several small studies looked at markers of bone metabolism in patients on HAART.

M Rosenvinge and colleagues from St Georges reported an unexpectedly high rate of vitamin D deficiency in a retrospective case note review of 132 consecutive patients attending their out-patients clinic from November 2007. [1]

They reported 58% patients (76/132) had 25-hydroxycholecalciferol (25(OH)D) deficiency including 8% (11 patients) who were severely deficient (<25nmol/L). A further 27% had borderline deficiency (50-75nmol/L) and only 16% of patients had optimum levels.

Multivariate analysis identified associations with black race (OR 0.14 95%CI 0.02-0.88, white vs black), younger age (OR 0.87, 95%CI 0.78-0.97, for every increase in age by one year) and higher random blood glucose (OR 3.21 95%CI 1.32-7.8 for every increase by 1mmol/L).

No association was found with diagnosis date, CDC stage, use/duration of tenofovir/HAART, weight, kidney/bone profile or parathyroid hormone levels.

Klassen and colleagues from Imperial College reported a case study of severe vitamin D deficiency in a 67 year old Somalian patient who had presented with bone pain, hypophosphatemia (0.64 mmol/L) and raised alkaline phosphatase (>500U/L) while on tenofovir-based HAART. [2]

Vitamin D levels were severely deficient (<15 nmol/L) and she had secondary hyperparathyroidism. Pelvic x-ray was normal.

Vitamin D supplement (dosed 15ug/day) rapidly improved clinical symptoms and normalised phosphate and alkaline phosphatase levels, and Truvada/efavirenz was maintained.

A second poster from this group looked at risk factors for low vitamin D in a group of 79 patients who had been assessed for 25(OH)D levels over a 2-year period. [3]

Mean age of the group was 41 (range 17-72), 70% were on HAART, median CD4 was 380 (range 0-930. 53% were women, 49% were African (33% Caucasian),

Median vitamin D levels were 31 nmol/L (range <15-145). 23% patients had severe deficiency (<25 nmol/L) and 70% has less than optimum levels (25-74 nmol/L). Higher levels were associated with Caucasian origin (P=0.025), current use of HAART (p=0.010) and duration of HAART (p=0.026). CD4 count, season, gender, PI or tenofovir use had no significant association (p>0.064 for all).

S Hill and colleagues from St Mary's and Hillingdon Hospitals presented an analysis of markers of bone metabolism and the clinical impact in a retrospective review of 205 patients (45% women, 55% black) seen in their cohort during 2007. [4]

From a mean of almost four calcium tests during the year, 42% patients had ≥1 low calcium level, 23% had ≥1 low phosphate and 20% had ≥1 high phosphate.

Low calcium and phosphate levels were more common in patients on HAART and were seen in 47% vs 32% (p=0.06), and 30% vs 5% (p<0.0001) patients, but were not related to tenofovir use. Low vitamin D levels were more common in women than men (8% vs 2%), all of whom were non-Caucasian.

References

All references are to the Programme and Abstracts of the 14th Annual BHIVA Conference, Dublin, 2008, published as Supplement to HIV Medicine, Volume 9.

1. Rosenvinge MM et al. Unexpectedly high rates of vitamin D deficiency in an inner-city London HIV clinic. Oral abstract O15.
2. Klassen K et al. Vitamin D deficiency presenting with hypophosphatemia, bone pain and a raised alkaline phosphatase in a patient on tenofovir. Poster P83.
3. Klassen K et al. Risk factors for hypovitaminosis D in HIV-positive individuals. Poster P95A.
4. Hill S et al. How common are abnormalities of serum calcium, phosphate and vitamin D in an HIV-positive cohort and what is their clinical significance. Poster 96.

Late diagnosis in adolescence of vertically acquired HIV infection

Polly Clayden, HIV i-Base

In an oral presentation, M Prime and coworkers presented findings from an investigation of clinical characteristics and circumstances in a group of vertically infected adolescents diagnosed in the UK or Ireland at 13 years of age or above. This study was conducted by investigators from: St George's Hospital, London, London School of Hygiene and Tropical Medicine, St Mary's Hospital, London, MRC Clinical Trials Unit, UCL Institute of Child Health and Mortimer Market Centre, London.

In the UK and Ireland, HIV positive children diagnosed at <16 years of age are reported to the National Study of HIV in Pregnancy and Childhood and followed up through the Collaborative HIV Paediatric Study. New HIV diagnoses made at adult services are reported to the Health Protection Agency and the Survey of Prevalent HIV Infections Diagnosed collects annual data on patients receiving care.

This study was an analysis of data to the end of 2005.

The investigators identified 38 cases; of these 19 (50%) were male and 36 (95%) were black African. 34 (89%) were born in sub-Saharan Africa, and three of these were diagnosed before arrival in the UK/Ireland.

The median age of the adolescents at diagnosis was 14.3 years (IQR: 13.6–15 years) with a median of 1.8 years (IQR: 0.2–5.6 years) between arrival in the UK and HIV diagnosis. 24 (63%) of those diagnosed presented with symptoms; the others were tested for HIV as part of screening for STIs or following diagnosis of a family member. Their median CD4 count at diagnosis was 208 cells/mm3 (IQR: 23–251 cells/mm3) and 11 developed AIDS before or within 2 years of diagnosis.

Thirty two patients began antiretroviral therapy (ART), the majority (88%) within a year of their HIV diagnosis.

The investigators wrote: "Young people with vertically acquired HIV infection are surviving childhood without ART and being diagnosed in adolescence. In this cohort a third were asymptomatic, highlighting the importance of testing all children born to HIV infected women, regardless of age or symptoms." They added: "Increased awareness amongst clinicians is urgently required to prevent presentation with advanced disease and to reduce ongoing transmission as this population become sexually active."

Ref: Prime K, Ferrand R, Foster C et al. First presentation of vertically acquired HIV infection in adolescence. 14th Annual BHIVA Conference, Dublin, 2008. HIV Medicine, 9 Suppl. 1. Abstract O2.

Case study of multi-drug resistant woman receiving newer antiretroviral drugs in pregnancy

Polly Clayden, HIV i-Base

A poster from Furco and coworkers from Northwick Park Hospital, Harrow, St Mary's Hospital, London and Chelsea and Westminster Hospital, London reported a case study of a multi-drug resistant HIV-positive pregnant woman receiving a combination of newer antiretroviral drugs.

This patient was a 38-year-old African woman, pregnant with twins, who presented with a viral load of 4,660 copies/mL and CD4 count 471 cells/mm3) in early trimester.

She had previously been treated with different combinations of NRTIs (5), NNRTIs (2) and protease inhibitors (2). Genotypic sequencing showed the following mutations - RT: D67N, V118I/V, M184V, Y188L, L210W, T215Y; protease: L10I, I13V, G16E, K20I, M36I, M46I, I47V, F53L, I54V, D60E, D63T, H69K, I84V, L89M. A confirmatory phenotypic test showed high-level antiretroviral resistance.

At 25 weeks gestation, she received a combination of tenofovir/emtricitabine, darunavir/ritonavir, etravirine and enfuvirtide. After 4 weeks her viral load was undetectable (<50 copies/mL).

PK studies for enfuvirtide, etravirine and darunavir were performed and all drug concentrations were within the expected therapeutic ranges.

At 34 weeks, her viral load was still undetectable and she delivered two HIV negative infants by caesarean section.

The infants received ARV prophylaxis with enfuvirtide, nevirapine and ddI. The investigators noted that enfurvirtide was undetectable and darunavir/ritonavir and etravirine were detectable in cord blood. The infants' adverse events included injection site reactions, hypertriglyceridaemia, anaemia, transient hypereosinophilia and raised alanine transferase.

Ref: Furco A, Gosrani B, Nicholas S et al. Use of newer antiretroviral (ARV) drugs (darunavir, etravirine and enfuvirtide) in HIV-positive pregnant woman with pan-class resistance failure. 14th Annual BHIVA Conference, Dublin, 2008. HIV Medicine, 9 Suppl. 1. P60.

Predictors of treatment failure in Western Cape, South Africa

Polly Clayden, HIV i-Base

In an oral abstract, Mohammed Ishaaq Datay presented findings from a preliminary analysis of predictors of treatment failure in patients receiving HAART in rollout cohorts in Western Cape Province, South Africa. Investigators from the University of Oxford and the University of Cape Town conducted the study.

As of June 2006, over 18,000 patients from 44 clinics were receiving HAART in this province. Approximately 1.5% experienced treatment failure (defined as two viral load results >1000 copies/mL and a switch to second line HAART).

This was a retrospective case control study. The control group maintained viral load <400 copies/mL at time of case failure and continued on first line HAART. The two groups were matched for treatment duration and clinic attended.

The investigators sampled 368 eligible patient records (130 cases and 238 controls) from eight clinics (representing 9249 patients receiving care). Of the 238 controls, 174 (73%) had a baseline CD4 count of less than 150 cells/mm3.

In the multivariate analysis, the predictors of failure were: low baseline CD4 <150 cells/mm3 (OR 3.2, 95%CI 1.5-6.9), previous antiretrovirals for MTCT (OR 3.0, 95%CI 1.4-6.3); treatment interruptions (OR 3.7, 95%CI 2.2-6.4) and nevirapine-based HAART (OR 2.0, 95%CI 1.2-3.5).

The investigators found that treatment interruptions were strongly associated with travel/migration p=0.001; 48/78 (62%) of treatment interruptions were due to defaulting (lost to follow-up?); 29/48 (60%) of defaulters travelled and 21/29(72%) of travelling was to Eastern Cape Province.

They also reported that prior use of MTCT drugs within 12 months of starting HAART and the use of NVP as the MTCT drug were more strongly associated with treatment failure.

They concluded: "The high prevalence of a very low baseline CD4 is concerning in light of its association with failure. Our study adds insight into the role of treatment interruption, choice of NNRTI and MTCT exposure. Further study of treatment interruption and travel is needed working towards intervention".

Ref: Datay MI, Boulle A, Yudkin P et al. Predictors of virological treatment failure in the HIV roll-out cohorts of the Western Cape Province, South Africa. 14th Annual BHIVA Conference, Dublin, 2008. HIV Medicine, 9 (Suppl. 1). Oral Abstract 013.

Late pregnancy loss in HIV-positive women

Polly Clayden, HIV i-Base

Data were presented from a retrospective case note review of HIV-positive women receiving antenatal care at Homerton Hospital, East London between 2000 and 2007, whose pregnancies resulted in either late miscarriage or interuterine death.

The investigators reported 242 pregnancies during the study period, of these19/242 (8%) in 18 women resulted in late pregnancy loss. 15 of these were late miscarriages (defined as loss at 14–24 weeks gestation) and 4 intrauterine deaths (beyond 24 weeks gestation).

The mean maternal age was 31.6 years (range 23.3–39.4 years). 14/18 (78%) women were originally from sub-Saharan Africa and 11/18 (61%) were of uncertain immigration status.

Significant psychosocial problems were reported in 7/18 (39%) of the women.

10/18 (56%) of women received their HIV diagnosis during this pregnancy. 14/18 (76%) were CDC Stage A; their mean nadir CD4 was 327 cells/mm3 (393 cells/mm3 at pregnancy loss). 38% of women had viral load <400 copies/mL and 56% between 400 and 100,000 copies/mL). 8/18 (42%) of women were receiving HAART during their pregnancy. The median gestational age at loss was 18 weeks (range 14 to 39 weeks).

14/19 postmortems were performed. 10/14 post-mortems showed chorioamnionitis; Group B Streptococcus was identified in one. One post-mortem showed toxoplasma placentitis.

The investigators noted that all women in the study group attended for HIV follow-up following their pregnancy loss. They concluded: "We advocate further large-scale research to elucidate the mechanisms underlying late pregnancy loss in HIV".

C O M M E N T

The investigators described the rate of late loss in pregnancy as high (8%) compared to background general population rate of 2% (4% in east London).

Although they were unable to confirm cause of this rate of late loss, they highlight the need for sexual health screening during pregnancy, which in this cohort only occurred in 53% of women undergoing review.

Ref: J Anderson, R Evans-Jones, D Janga, et al. Pregnancy loss in HIV-positive women attending antenatal care at a London centre. 14th Annual BHIVA Conference, Dublin, 2008. HIV Medicine, 9 (Suppl. 1). O14

Renal tubular dysfunction with tenofovir-based HAART in four vertically infected adolescents

Polly Clayden, HIV i-Base

A poster authored by Onyeador and coworkers from Imperial College and St Mary's Hospital, London described renal tubular dysfunction in four adolescents receiving tenofovir-based HAART.

This was a retrospective case note review of children <18 years old who have ever received tenofovir. In this clinic, all children receiving tenofovir undergo prospective screening by annual renal ultrasound scanning (USS), three monthly serum electrolytes and urine Ca/Cr, albumin/Cr or protein/Cr and retinal binding protein.

In this cohort of 139 HAART experienced, vertically infected children, 51 (37%) had received tenofovir. Four (8%) patients, all female, had documented renal tubular leak at a median age of 16.9 years (range 12.3–18 years). The children's ethnicity was: black african (2), caucasian (1) asian/caucasian (1). None of the children had hepatitis B/C coinfection, prior renal disease, family history of renal disease or hypertension.

Their median duration of HAART prior to tenofovir-based HAART was 9 years (range 9–14 years), in three regimens (range 2–8 regimens). The tenofovir-based HAART was started at a median CD4 count of 335 cells/mm3 (range 20–1360 cells/mm3) and median viral load 77,000 copies/mL (~range 1,200–172,000 copies/mL).

The children all received the adult tenofovir dose of 300 mg once daily, at initial weights of 32, 33, 36 and 59 kg with a dose range of 5.1–9.4 mg/kg for a median duration of 37 months (range 18–54 months) prior to stopping tenofovir. All children were asymptomatic, identified on screening, with biochemical resolution within 4 months of tenofovir cessation.

The authors wrote: "Although unlicensed, tenofovir is widely used in HAART experienced paediatric cohorts resulting in cases of renal tubular dysfunction. Paediatric formulations and pharmacokinetic studies are currently recruiting with results eagerly awaited."

Ref: Onyeador N, Patel D, Lyall H et al. Renal tubular dysfunction associated with tenofovir based HAART in perinatally acquired HIV: the need for paediatric formulations and pharmacokinetic studies. 14th Annual BHIVA Conference, Dublin, 2008, HIV Medicine, 9 (Suppl. 1). P61.

CONFERENCE REPORTS

15th Conference on Retroviruses and Opportunistic Infections

Boston, 2-6 February 2008

Introduction

The last three issues of HTB included reports on antiretrovirals and treatment strategies, prevention of mother-to-child transmission (PMTCT), paediatrics, hepatitis coinfection, opportunistic infections and treatment access from this important conference.

This issue includes our final reports:

- The unmet need for contraception services for women receiving ART
- Valacyclovir decreases plasma and genital viral loads in HSV-2/HIV-1 co-infected women
- HPV genotypes in HIV-positive women in Zimbabwe and Uganda

Abstracts for the meeting are online as soon as the conference opens, and many of the most important oral abstract sessions and overview sessions are posted as webcasts within a day or so. We encourage readers to go directly to the source for many of these sessions.

www.retroconference.org

The unmet need for contraception services for women receiving ART

Polly Clayden, HIV i-Base

Two oral presentations clearly highlighted the importance of contraception services for HIV positive women receiving ART and PMTCT services.

DITRAME Plus

Valeriane Leroy presented findings from a study of the ANRS 1201-1202 Ditrame Plus Cohort in Abidjan, Côte d'Ivoire, looking at the incidence of a new pregnancy among HIV-positive women followed postpartum over 24 months after a PMTCT intervention, who chose either replacement or breast feeding. The study hypothesis was that non-breastfeeding women are exposed to a greater risk of unwanted pregnancy.

The analysis included all women in the Abidjan cohort between March 2001 and July 2003, age <49 years, who received a short course ARV prophylaxis regimen (AZT + single-dose NVP+/-3TC), delivered a live infant and initiated one of the two infant feeding options offered (replacement feeding or exclusive breastfeeding for 4 months).

Contraceptive methods were promoted and provided free of charge according to the infant feeding option: replacement feeders used oral or injectable contraception; breast feeders followed the lactational amenorrhea method for 4 months, then injectable or oral contraception. Condoms were provided to both feeding groups.

The study evaluated the occurrence of first new pregnancy within the 24 months follow-up period. The start of pregnancy was estimated using the reported date of last menstrual period and the gestational age as assessed by ultrasound.

724 women were assessed, 332 (46%) replacement feeders, and 392 (54%) breast feeders. Use of a contraceptive method was similarly high in both groups: formula feeders, 78.1% vs. 77.5% breast-feeders (p=0.87).

The investigators reported 79 new pregnancies over 24 months. At 12 months, the incidence of a new pregnancy was similar between the two groups: 4.4% (95% CI: 2.7-7.2%) in breast-feeders and 4.1% (CI: 2.4-7.0%) in formula-feeders. They found correlates of incidence of a new pregnancy within 12 months were an advanced WHO clinical stage 3-4 vs 1-2 (adjusted relative risk: 0.2; 95% CI: 0.1-0.8, p=0.02) and the death of the last-born child (adjusted RR: 6.6; 95% CI: 2.6-16.6, p<0.0001)

At 24 months the incidence of a new pregnancy was significantly lower in formula feeders than in breast feeders, 10.0% vs. 16.5% (adjusted RR: 0.5; 95% CI: 0.3-0.9, p=0.02). Factors associated with pregnancy at this time point were: the follow-up clinic, the number of live-born children and the death of the last-born child (adjusted RR: 3.5; 95% CI: 1.4-8.7, p=0.008).

The investigators concluded: "Replacement feeding is not responsible for a greater incidence of pregnancy in this urban West African population. Our results highlight the public health importance to deliver appropriate family planning services for HIV-infected women".

HBAC

Jaco Hornsy then showed findings from a cohort of 733 HIV-positive women enrolled in the Home Based AIDS Care (HBAC) study in Uganda and receiving HAART.

This was a prospective cohort study of women age 18-49 who initiated HAART from March 2003 – June 2006, in which trends and predictors of pregnancy, desire for children, and use of family planning were analysed.

Women were counselled on the effect of HAART on restoring fertility and sexual activity, HIV prevention and family planning. They received free condoms on request.

The investigators conducted detailed social and behavioral questionnaires in the women's homes. These were quarterly the first year after initiating HAART, and every 6 to 12 months thereafter.

There was no provision or referral for termination of pregnancy in this study; abortion is illegal in Uganda. However, women who aborted were asked about their experiences and treated for any complications.

The analysis included 708 women with a median follow-up of 2.05 years (IQR 2.0 to 2.1). After initiation of HAART, 120 (16.9%) women had 140 pregnancies (20 repeat pregnancies). The median time to conception was 12.4 months (IQR 7.9-18.0). There were 144 pregnancy outcomes (4 sets of twins); 106 live births (74%), 4 (3%) miscarriages, 8 (5%) still births and 26(18%) induced abortions.

The investigators reported an increased incidence in pregnancy from 3.46/100 person-years in the first quarter of HAART to 11.71/100 person-years in the fourth quarter (p=0.0001). They noted that this paralleled an increase in the proportion of women reporting sexual activity in the past 3 months from 24.4% to 32.5% over 24 months of follow-up, p=0.001.

Predictors of pregnancy were: age (per 10 year decrease) (adjusted HR 2.7, 95% CI 1.9-3.8, p<0.001), having a body mass index >18.5 (adjusted HR 1.1, 95% CI 1.0 to 1.1, p=0.02), and inconsistent condom use (adjusted HR 1.8, 95% CI 1.0 - 3.2).

Despite 93% to 97% of all women in this study reporting that their pregnancies were unwanted or unplanned, only 14% and 13% of women used permanent or semi-permanent family planning methods and 3.5% and 4.3% used dual contraception at 18 and 24 months respectively.

The investigators recommended:

- Family planning services should be an integral part of HAART interventions in Africa.
- Counselling is critically needed to explain the restorative effect of HAART on fertility and sexual activity.
- Younger women and their partners should be particularly targeted.
- Dual contraceptive services should be available to all for free.

C O M M E N T

The first part of the conclusion from the Abijan study was curious; the effectiveness of the lactational amenorrhea method of contraception has been well documented and is reported to be 98% effective "with perfect use".

Surely any differences in pregnancy incidence between the two feeding groups would be masked by the high rate of uptake of contraception by all the women in this study, which at 78% is to be applauded and is considerably higher than the background rate in Cote d'Ivoire (<10%) and most African countries.

As Karen Beckerman remarked following the presentation, "free contraception and counselling works, it contributes to pregnancy spacing and, if offered, women will take up this life saving intervention".

With regards to the finding that women with WHO stage 3-4 vs 1-2 were more likely to become pregnant within 12 months, it would be useful to know if these women were receiving HAART (baseline variables in this study included maternal eligibility for HAART but these data were not presented).

In the second study, the HBAC investigators describe an "unmet need" for family planning services as part of ART programmes. The rate of unwanted pregnancy (93% - 97%) in this cohort was scary - even within the Ugandan setting with a fertility rate of 6.7 children.

This presentation ended with quotes from HBAC women, which made uncomfortable listening, and included: "I wanted to abort so badly. I tried all the methods I was told locally but I failed. And there was no way I could ask the doctors to do an abortion. That is why I carry the pregnancy today…"

Policy makers and healthcare providers have responsibilities to include contraception services alongside ART and PMTCT programes, and the need becomes even greater in settings where termination of pregnancy is illegal.

Although not really discussed in either study, it deserves mentioning that, in addition to considerable advantages to women's health, even a minimal reduction in unplanned pregnancies can have the equivalent impact to PMTCT interventions in reducing infant infection. One previous study suggested that in Kenya and Zambia, lowering the pregnancy rate by 5.6% and 6.6%, respectively would have the equivalent impact to providing single dose nevirapine. [3]

These two studies highlight both the need for and the potential uptake of such services.

References

1. Viho I, Becquet R, D Ekouevi D et al. Alternatives to prolonged breastfeeding and incidence of pregnancies among HIV-infected women: The ANRS 1201-1202 Ditrame Plus Cohort in Abidjan, Côte d'Ivoire, 2001 to 2005. 15th CROI. February 2008. Boston, US. Oral abstract 73.
2. Homsy J, Bunnell R, Moore D et al. Incidence and determinants of pregnancy among women receiving ART in Rural Uganda. 15th CROI. February 2008. Boston, US. Oral abstract 74.
3. Clayden P. Time to Move On: More Questions about Single-dose Nevirapine. GMHC Treatment Issues November/December 2004. http://www.gmhc.org/health/treatment/ti/ti1811.html#3

Valacyclovir decreases plasma and genital viral loads in HSV-2/HIV-1 co-infected women

Polly Clayden, HIV i-Base

A poster authored by Jared Baeten and coworkers from the University of Washington, Seattle, US; Assn Civil Impacta Salud y Educacion, Lima, Peru; and Fred Hutchinson Cancer Reserach Centre, Seattle, WA, US showed findings from a study to assess whether HSV-2 suppressive therapy reduces HIV-1 plasma and genital viral loads. [1]

This was a randomised, placebo-controlled, cross-over trial of 500 mg valacyclovir received orally twice daily by 20 HSV-2/HIV-1 co-infected women in Lima, Peru who had CD4 counts >200 cells/mm3 and were not receiving ART.

The women were randomised to receive valacyclovir or placebo for 8 weeks. Then following a 2-week washout period, they received the alternative regimen for a further 8 weeks.

Plasma samples were taken weekly and endocervical swabs were collected three times a week for measurement of HIV-1 viral load. Additionally, the women collected genital swabs themselves daily for HSV DNA PCR. The women's median CD4 count was 372 cells/mL (range 229- 850).

The investigators reported detection of genital HSV on 3.7% of days receiving valacyclovir versus 22.1% of days receiving placebo ($p<0.001$). HIV-1 plasma viral load was significantly lower during the valacyclovir arm compared to the placebo arm, 4.34 vs 4.61 log copies/mL, $p<0.001$; a difference of -0.27 log copies/mL, (95%CI -0.34 to -0.20). Cervical HIV-1 was detected at 54.3% of visits while receiving valacyclovir versus 71.1% of visits while receiving placebo, $p<0.001$. Cervical HIV-1 levels were significantly lower while receiving valacyclovir vs placebo, 2.87 vs 3.23 log copies/swab, $p<0.001$; a difference of –0.35 log copies/swab, (95% CI –0.46 to –0.25).

The investigators concluded: "Daily valacyclovir therapy (500 mg twice daily) for HSV-2 suppression significantly reduced plasma and genital HIV-1 concentrations among HSV-2/HIV-1 co-infected women. Suppressive HSV-2 therapy has the potential to reduce HIV-1 infectiousness and the rate of disease progression; these outcomes are under evaluation in ongoing clinical trials."

C O M M E N T

Results from the HPTN 039 study conducted by the same group were also presented at this conference [2]. This was a randomised, placebo-controlled trial to determine whether HSV-2 suppression with twice-daily acyclovir reduces the risk of HIV acquisition among women in Africa and men who have sex with men (MSM) in the Americas (n=3251).

This study found that acyclovir did not reduce HIV acquisition among women with HSV-2 and MSM, despite evidence from multiple epidemiologic studies that HSV-2 infection increases HIV susceptibility by 2- to 3-fold, even with excellent retention and adherence among the trial participants. The investigators wrote "..acyclovir (400 mg twice daily) suppresses HSV-2, but does not prevent HIV acquisition. Further research is needed to elucidate the disparity between extensive data on epidemiologic and biologic interactions between HSV-2 and HIV and these trial results."

Although the investigators suggest that suppressive HSV-2 therapy with valganciclovir has the potential to reduce HIV-1 infectiousness and the rate of disease progression, the results from ongoing research with valganiclovir are needed.

References

1. Baeten J, Strick L, Lucchetti A et al. Herpes simplex virus suppressive treatment decreases plasma and genital HIV-1 viral loads in HSV-2/HIV-1 co-infected women: A randomised, placebo-controlled, cross-over trial 15th CROI. February 2008. Boston, US. Poster abstract 676.
2. Celum C, Wald A, Hughes J et al., HSV-2 suppressive therapy for prevention of HIV acquisition: Results of HPTN 039. 15th CROI. February 2008. Boston, US. Oral abstract 32.

HPV genotypes in HIV-positive women in Zimbabwe and Uganda

Polly Clayden, HIV i-Base

Two posters evaluated HPV genotypes in HIV-positive from Zimbabwe and Uganda. HIV is known to be risk factor for human papillomavirus (HPV) prevalence and persistence. Both current HPV vaccines however are only known to be effective against types 16 and 18 of HPV.

David Hill and coworkers (from Stanford University School of Medicine, Wake Forest University Baptist Medical Centre, Caradon Consulting San Carlos and University of California), looked at HPV genotypes in HIV-positive pregnant Zambian women with subtype C HIV-1 and assessed cervical HPV infection and HIV-1 virus shedding. [1]

In this study, women were evaluated for HIV and HPV infection by assays of cervical swab samples. For HPV, real-time polymerase chain reaction (RT-PCR) was performed followed by a generic HPV probe using DNA hybridisation. Positive samples were re-probed for 29 individual HPV types and a probe mixture of 10 types. Cervical HIV RNA was measured using RT-PCR.

119 women were enrolled (5 were excluded from HPV analyses due to insufficient DNA).

The investigators found, 82% (94/114) of samples were HPV-positive. Re-probing revealed 27 unique HPV types in 72 women. 58% (66/114) of women had high cancer risk genotypes: HPV 58 in 19 women, followed by HPV 66, in 14 women.

Additionally, HIV cervical virus was detected in 88% (46/52) of cervical samples tested. The median cervical viral load was 3.54 log copies/mL.

The investigators found no correlation between HIV-1 shedding and the presence of HPV, or specific HPV types in cervical samples tested.

The investigators wrote: “A high proportion of HIV-positive pregnant women in Zimbabwe shed HIV-1 RNA and carried high risk cervical HPV types associated with increased cervical cancer risk. However, only 16 of 94 (17%) were infected with HPV-16 or -18, types against which current vaccines are known to be protective.”

They added: “These data suggest that current HPV vaccines may not prevent HPV infections or provide protection against the high risk HPV types prevalent among HIV-infected women in Zimbabwe.”

In the Ugandan study Janis Taube and coworkers from Johns Hopkins Medical Institute, Baltimore, MD, US; Makerere University, Johns Hopkins University Research Collaboration, Kampala, Uganda; and Makerere University, Kampala, Uganda looked at HPV genotype prevalence in HIV-positive and HIV-negative women in Kampala. Additionally they wished to determine which genotypes are associated with cervical pathology in this population. [2]

200 women aged 18 to 30 years were recruited to the study at 4 to 12 weeks post-partum at Mulago Hospital. The women underwent rapid HIV testing and a pelvic exam. Cervical cytology samples were collected and processed.

Among these women, the investigators reported an HIV prevalence of 19% and an HPV prevalence of 65%. The most frequent high-risk HPV genotypes were 16 (9%), 33 (9%), 35 (6.5%), 45 (6.5%), and 58 (6%). The most frequent low-risk genotypes were 62 (22%), 61 (11%), 81 (11%), 70 (10%), and 53 (10%). The prevalence of HPV 6, 11, and 18 was 2.5%, 1%, and 4%, respectively.

They found there was no significant difference between the presence of HPV 16 or HPV 18 in HIV-positive or HIV-negative women (13.9% vs 7.3%, p=0.20 and 3.7% vs 5.6%, p=0.64, respectively). HIV-positive women were more likely to have other HPV genotypes (both high and low risk) than HIV-negative women (72.2% vs 40.9%, p<0.001 and 63.9% vs 36.6%, p= 0.0046, respectively).

They also found HIV-positive women had a greater median number and range of HPV genotypes vs HIV-negative women (median of 2, range 0-8 vs median of 1, range 0-6, p<0.001). HIV-positive women were significantly more likely to have an abnormal Pap smear vs HIV negative women (43% vs 11%, p<0.001). And HPV prevalence was 58% in women with normal cytology and 97% in women with abnormal cytology. They noted that HPV 16 and 18 prevalence in women with normal cytology was 9.9% and in women with abnormal cytology was 28%.

They concluded: “Our results show that while HPV types 16 and 18 may be seen in association with cervical pathology, preventative, or therapeutic vaccines will need to target a broad-spectrum of HPV genotypes to effectively combat cervical disease in this population”.

C O M M E N T

Both these studies and another from Zambia [3] highlight the question of whether current HPV vaccines will be effective in populations with a significant diversity and multiplicity of HPV types. HPV vaccine development of the future needs to consider a broader range of HPV types if these advances are to have a wider global impact.

References
1. Hill D, Katzenstein D, Shetty A et al. Cervical human papillomavirus infection in HIV-1-infected pregnant women in Zimbabwe. 15th CROI. February 2008. Boston, US. Poster abstract 1023.
2. Taube J, Kamira B, Motevalli M et al. Human papillomavirus prevalence and genotype correlation with cervical cytopathology in Ugandan women. 15th CROI. February 2008. Boston, US. Poster abstract 1024.
3. Parham G, Sahasrabuddhe V, Vermund S et al. Prevalence and predictors of squamous intraepithelial lesions of the cervix in HIV-infected women in Lusaka, Zambia. XVI International AIDS Conference, Toronto, Canada.13-18 August 2006. Oral Abstract TUAB0303.

TREATMENT ACCESS

FDA approval of generic ARVs

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

Drug and formulation	Manufacturer, Country	Approval date
Nevirapine (200mg tabs)	Matrix, India	25 May 2008
3TC/d4T 30mg/6mg & 60mg/12mg paediatric tablets and oral suspension	Cipla, India	19 June 2008
AZT oral solution (50 mg/5 mL)	Cipla, India	26 June 2008

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

Effective patent dates are listed in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations, also known as the Orange Book:

http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=3D021360&TABLE1=3DOB_Rx

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to 70 since the programme started. An updated list of generic tentative approvals is available on the FDA website:

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

Source: FDA list serve:
http://www.fda.gov/oashi/aids/listserve/archive.html

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

Access to generic efavirenz in South Africa: MSD agrees to grant licenses on reasonable terms

TAC statement

Even though efavirenz is not the preferred first-line option for treatment in South Africa, being reserved for nevirapine intolerance or contraindication, it accounts for over 60% of the total South African ARV drug budget.

Legal action from community groups has resulted in the manufacturer making significant changes to address efavirenz supply and cost. [1]

Acting on behalf of TAC, the AIDS Law Project (ALP) lodged a complaint with the Competition Commission of South Africa in

late 2007 alleging that MSD (Pty) Ltd – the South African subsidiary of multinational drug company Merck – was unlawfully refusing to license the antiretroviral (ARV) medicine efavirenz (EFV) on reasonable terms. [2]

In a statement on I June, TAC recognise that MSD is now no longer acting in an anticompetitive way, and that this paves the way for the market entry of a wide range of affordable efavirenz products.

According to the ALP's records and recent correspondence from the Commission, MSD has:

- Licensed four generic drug companies – two local producers and two locally-based importers – to bring stand-alone EFV products to market;
- Agreed that all four licensees are entitled to bring co-packaged products containing EFV to market;
- Agreed that all four licensees will not unreasonably be refused consent to bring co-formulated products containing EFV to market;
- Agreed that all licensed products can be sold to both public and private sectors in South Africa and 10 other southern African countries (Angola, Botswana, DRC, Lesotho, Madagascar, Mauritius, Namibia, Seychelles, Swaziland and Zimbabwe); and
- Waived any right to a royalty.

On the basis of these significant developments, the Commission believes that there is no reason to refer the complaint to the Competition Tribunal for adjudication on what is now largely a historical complaint.

In practical terms, this means that there are now a sufficient number of competitors to ensure that efavirenz prices are kept as low as is reasonably possible. It also means that the public sector, which until relatively recently was paying 64 cents in every rand spent on first-line ARV treatments for efavirenz alone, can now choose to procure from up to five suppliers.

This also has the potential to enable the numerous co-packaged and co-formulated generic products commonly used in sub-Saharan Africa to be able to be used in South Africa.

Impact on price reductions

When TAC and the ALP first started to engage MSD on this issue as far back as May 2002, the company sold a year's supply of EFV for one adult for US$500. That price has dropped significantly. Today, MSD's best international price for a year's supply is US$237.25. In contrast, the best international price for a generic equivalent of proven quality, safety and efficacy is US$150. In the South African private sector, MSD's EFV sells for R166.90 (VAT inclusive) for a 30 days' supply. In contrast, the cheapest registered generic equivalent sells for R136.80. These prices are expected to drop even further.

Price differentials in respect of FDCs are even greater. MSD has committed to sell Atripla at US$613.20 per patient per year. In contrast, the Clinton Foundation HIV/AIDS Initiative (CHAI) has managed to secure a commitment from a reputable Indian company to bring generic TDF/FTC/EFV to market for only US$349 per patient per year. The same company has also committed to bringing generic TDF/3TC/EFV – which is considered as therapeutically equivalent to the FTC version of the FDC – for US$299 per patient per year. South Africa is entitled to purchase drugs through CHAI.

References

1. TAC statement: 'TAC complaint increases access to efavirenz: MSD finally agrees to grant licenses on reasonable terms'. (1 June 2008) http://www.tac.org.za/community/node/2329
2. TAC Statement: "TAC complains to the Competition Commission about the anti-competitive conduct of the world's largest pharmaceutical company" http://www.tac.org.za/community/node/2127

Reaching '3 by 5'…. by 7: new report on universal access

On 2 June 2008, the World Health Organization (WHO), UNAIDS and UNICEF launched the joint report, 'Towards Universal Access: Scaling up HIV Treatment, Care and Prevention Interventions in the Health Sector'.

The new report contains the latest numbers on access to HIV treatment, and to key prevention interventions such as antiretrovirals to prevent mother-to-child HIV transmission in low- and middle-income countries worldwide.

It marks the significance of getting 3 million HIV-positive people on treatment, which although originally tied to the '3x5 campaign' shows that persistently working and focusing on treatment programmes, together with the infrastructure they require, has achieved health outcomes that few people thought possible when combination therapy was first available in the West from the late 1990's.

Download report:
http://www.who.int/hiv/mediacentre/2008progressreport/en/index.html

Oxfam criticises DFID's new strategy as a "missed opportunity"

As the government launched its new AIDS strategy for developing countries on 2 June, Oxfam was quick to praise the long-term commitment of substantial funding to strengthen health systems but expressed disappointment that the strategy lacked a specific spending target for tackling HIV and AIDS.

Speaking at the launch, Douglas Alexander, the Secretary of State for International Development, announced that DFID will spend £6 billion on improving health systems and services in poor countries in the run-up to 2015. This announcement is in addition to the £1 billion over 7 years committed last year to the Global Fund to Fight AIDS, Tuberculosis and Malaria.

He also announced that DFID would provide £100 million over the next six years to help improve Nigeria's national response to HIV.

"The announcement of this much needed long-term financial commitment to help strengthen health systems in the developing world is a very welcome one. It could help to pay the salaries of millions of health workers worldwide," said Phil Bloomer, Oxfam's Director of Campaigns and Policy who attended the launch. "But we have to remember that tackling the AIDS epidemic is about more than just health systems. It is also about factors such as education, awareness raising, counselling, and the provision of security of food and income for all those who need it, whether infected or affected.

"While many will welcome today's announcement, some will feel that the abandonment of a clear spending target sends out a worrying signal to other international donors who look to the UK's example to help define their response.

"The Government is right to point to the strong leadership role it has repeatedly played in shaping the global response to tackling HIV and AIDS," said Bloomer. "But by not having a specific spending target for HIV, the government has missed an opportunity to put pressure on other donors to scale up their response to the HIV epidemic."

C O M M E N T

This is a very welcome statement from Oxfam on this very unwelcome development from DfID. It is disturbing and shocking that DfID thinks that AIDS can be handled under the larger umbrella of budget support to individual countries for health and development.

In reality, HIV-positive citizens in most countries are rarely prioritised and this policy shift will have an impact on the direct health gains and lives saved that are the direct results of 'vertical' HIV programmes.

Most HIV-positive advocates in resource-limited settings owe their lives to HIV-specific programmes.

This threatens to reduce contributions to the Global Fund, to dedicated AIDS, TB or malaria funding despite the wider positive impact that HIV programmes have had on overall health infrastructure in the countries where they operate.

Source: Oxfam press statement 2 June 2008

ANTIRETROVIRALS

Boosted atazanavir approved in Europe as first-line therapy

On 24th June 2008, the European Commission granted marketing authorisation for atazanavir boosted by ritonavir (300mg/100mg once daily), in combination with other antiretrovirals, as a first-line treatment HIV-1 infected adults. [1]

Previously, atazanavir/r was only recommended in treatment-experienced patients.

This decision was based on results from the non-inferiority CASTLE study which randomised almost 900 naïve patients to either once-daily atazanavir/r or twice-daily lopinavir/r with background tenofovir+FTC. Results were first presented at the Retrovirus conference in February and were reported in the March April issue of HTB. [2]

Efficacy was similar in both study arms; 78% vs 76% patients in the atazanavir/r and lopinavir/r arms respectively achieving viral load <50 copies/mL at week 48.

Safety events in the study were consistent with prior experience, and patients taking atazanavir/r experienced lower rates of Grade 2-4 adverse events such as diarrhoea (2%) and nausea (4%) than those taking lopinavir/r (11% and 8% respectively). Additionally, the atazanaivr/r arm was associated with significantly lower increases from baseline compared to the lopinavir/r arm in total cholesterol, triglycerides and non-HDL cholesterol at 48 weeks (all $p<0.0001$).

As with previous observation, 34% of the patients in the atazanaivr/r arm and less than 1% of patients in the twice-daily lopinavir/r arm experienced elevations in total bilirubin (hyperbilirubinaemia) greater than 2.5 times the upper limit of normal. This elevation was not associated with liver dysfunction as the rates of Grade 3-4 liver enzyme elevations were similar between treatment groups (2% in once-daily atazanaivr/r arm vs 1% in the twice-daily lopinavir/r arm).

Atazanavir 300mg boosted with 100mg ritonavir is now available in the UK for use in naive patients.

References:

1. Bristol-Myers Squibb press release. 'European commission approves boosted Reyataz ' 24 June 2008.
2. Atazanavir/r vs lopinavir/r in treatment-naïve patients: 48 week results. HTB March/April 2008. http://www.i-base.info/htb/v9/htb9-3-4/Atazanavir.html

C O M M E N T

Many UK clinics were already using atazanavir/r as first line therapy as a once-daily PI option to efavirenz, and improved tolerability due to only requring 100mg dose of boosting ritonavir.

Atazanavir/r is now recommended as an alternative to efavirenz in the new BHIVA treatment guidelines (July 2008).

BMS and Merck discontinue 100mg capsule formulation of efavirenz used for paediatric treatment

Simon Collins, HIV i-Base

In June 2007, the 100mg capsule formulation of efavirenz (Sustiva), was discontinued by Bristol-Myers Squibb (BMS), the European manufacturer and distributor. This alarmed UK doctors and pharmacists. Pharmacists only learnt of this through a news item in The Pharmaceutical Journal, rather than from any direct communication from BMS. This was without prior notification.

i-Base have since learnt that BMS and Merck (who manufacture and distribute efavirenz outside the US and five European countries), actually discontinued this formulation in 2006 due to their analysis of low patient usage, and that the existing stocks were then used until they eventually ran down.

This has caused significant difficulties for children on this formulation, including increasing pills counts, use of higher doses, and increased use of therapeutic drug monitoring (TDM), for which doctors are hoping that BMS agree to fund.

The lack of 100mg capsules predictably increased for the 50mg formulation. This resulted in problems in the supply chain leading to patients being juggled between capsule sizes and formulations, being unable to receive standard three-month prescriptions, and the emergency importation and use of the US packaged formulation (which is not approved in Europe) at the end of 2007.

Efavirenz is now available for paediatric use in an oral solution and in 50mg and 200mg capsules. For many children, for example those using a 350mg dose, the withdrawal of the 100mg formulation has increased the pill count from 4 to 7 capsules. Some children, who are able to swallow the larger 200mg capsules are now using higher doses than clinically recommended to reduce pill count and improve this aspect of their quality of life.

In France, following complaints by patient organisations including TRT-5, BMS responded by maintaining the 100mg formulation until December 2008. After meeting with TRT-5, who are raising this with the French regulatory agency, BMS France are preparing a letter and leaflet to accompany the switch.

BMS UK say their "decision to discontinue 100mg capsules in June 2007, was based on very low usage of the capsule and the ability to substitute two 50 mg capsules for the 100 mg dose" … and that "50 mg capsules, 200 mg capsules and 600 mg tablets, as well as 30 mg/ml oral solution are still available".

The company statement, issued on 10 July, continued "the discontinuation was communicated through the medical press … and that the MHRA and Department of Health were informed. We recognise that we did not communicate directly with the HIV advocacy community about this decision and in the future we will do this".

C O M M E N T

It is strange that a paediatric formulation of one of the most important antiretroviral drugs could have been discontinued without broader community and provider awareness. It is also disconcerting that many of these details are only now coming to light.

With many public and private organisations now at last recognising the importance of more and better paediatric formulations, even with relatively low patient numbers, it is a worrying signal for BMS to stop an existing one.

If the 100mg formulation is permanently discontinued, some activists in France are calling for children to be able to use the FDA-approved generic version of efavirenz, produced by Aurobindo.

Saquinavir (Invirase) interactions with digoxin, garlic capsules, methadone, tipranavir and omeprazole: US label changes

Roche has updated their US package insert for saquinavir (Invirase) to include the following drug interaction information and include new warnings regarding coadministration of Invirase/ritonavir and digoxin (used in the treatment of various cardiac conditions).

Updated drug interaction information has been added on five products in the product package insert revision:

1. Digoxin. A new warning has been added. Caution should be exercised when saquinavir and digoxin are coadministered. Coadministration results in a significant increase in serum concentration of digoxin; therefore, the serum concentration of digoxin should be monitored and the dose of digoxin may need to be reduced.
2. Garlic capsules. No data are available for the coadministration of saquinavir/ritonavir with garlic capsules. A warning has been added that the coadministration of garlic capsules and saquinavir is not recommended due to the potential for garlic capsules to induce the metabolism of saquinavir, which may result in subtherapeutic saquinavir concentrations.
3. Methadone. Methadone levels are decreased and the dosage of methadone may need to be increased when coadministered with saquinavir/ritonavir.
4. Tipranavir/ritonavir. Combining saquinavir with tipranavir/ritonavir is not recommended due to a decrease in saquinavir levels with coadministration.
5. Omeprazole. When saquinavir/ritonavir is coadministered with omeprazole, saquinavir concentrations are increased significantly. If omeprazole or another proton pump inhibitor is taken concomitantly with saquinavir/ritonavir, caution is advised and monitoring for potential saquinavir toxicities is recommended, particularly gastrointestinal symptoms, increased triglycerides, and deep vein thrombosis.

Source: FDA list serve (11 June 2008).
http://www.fda.gov/oashi/aids/listserve/listserve2008.html#61108

US label changes for nevirapine paediatric solution

On 24 June 2008, FDA approved labeling changes to the Viramune (nevirapine) oral solution and tablets to reflect various updates, including:

- Dosing recommendations for paediatric patients 15 days to 2 months of age.
- Dose recommendations for all pediatric age groups are now based on body surface area (BSA) instead of weight-based dosing. Studies were conducted comparing weight-based dosing and BSA-based dosing. While comparable drug concentrations are achieved with either method, BSA dosing allows for smoother dose transitions between pediatric age groups and is therefore preferred.
- Addition of data from a pharmacokinetic hepatic impairment study
- Revision of the recommendation that nevirapine not be administered to patients with severe hepatic impairment to a recommendation that nevirapine not be administered to patients with moderate (Childs Pugh B) or severe (Childs Pugh C) hepatic impairment.
- Revision of recommendations for the occurrence of rash during the once daily lead-in phase of dosing. The label now states that lead-in dosing should not be extended beyond 28 days of dosing.

Source: FDA list serve (27 June 2008).
http://www.fda.gov/oashi/aids/listserve/listserve2008.html#62708

New US pediatric dosing for lopinavir/r

The lopinavir/r (Kaletra) tablet and oral solution labels were updated to include dosing recommendations for pediatric patients 14 days to 6 months of age and from 12 to 18 years of age.

Dosing in children (14 days – 18 years of age) is based on body weight or body surface area (size) see Table 1. For full details see the FDA announcement and new product information.

Table 1. Pediatric dosing recommendations for patients 6 months to 18 years of age *

Body Weight (kg)	Body Surface Area (m^2)	Recommended number of 100/25 mg Tablets Twice-Daily
15 to 25	≥0.6 to <0.9	2
>23 to 35	≥0.9 to <1.4	3
>35	≥1.4	4 (or two 200/50 mg tablets)

* Based on body weight or body surface area for lopinavir/r tablets (without concomitant efavirenz, neviraprine, fosamprenavir, or nelfinavir)

Source: FDA list serve (23 June 2008).
http://www.fda.gov/oashi/aids/listserve/listserve2008.html#62308

New US pediatric dosing for tipranavir/r

On June 23, 2008, FDA approved a new Aptivus (tipranavir) oral solution (100 mg/mL). The product label has been updated to include dosing recommendations for pediatric patients 2-18 years of age.

In addition, information regarding oral and parenterally administered midazolam was updated in the Contraindication and Drug Interactions section.

Source: FDA list serve (23 June 2008).
http://www.fda.gov/oashi/aids/listserve/listserve2008.html#062308

DSMB stops ACTG study due to suboptimal responses

NIAID press release

An independent Data and Safety Monitoring Board (DSMB) has determined that the experimental, once-daily antiretroviral drug regimen of FTC (emtricitabine), atazanavir and ddI enteric-coated (ddI-EC) is inferior to a standard antiretroviral drug regimen and therefore should be discontinued in an ongoing clinical trial. The National Institute of Allergy and Infectious Diseases (NIAID), the part of the National Institutes of Health that oversees the trial, concurs with this recommendation and has stopped this component of the study.

This development arose from the DSMB's recent review of safety and efficacy data from a Phase IV clinical trial sponsored by NIAID. The trial is examining whether certain regimens of antiretrovirals taken once a day are at least as good as a standard antiretroviral regimen containing a drug combination taken twice a day. The study involves 1,571 HIV-infected volunteers on four continents who were randomly assigned to take one of three drug regimens:

- 3TC/AZT taken twice daily + efavirenz taken once daily
- FTC + atazanavir + ddI-EC (an experimental regimen taken once daily, with atazanavir taken separately from ddI-EC)
- FTC/tenofovir + efavirenz

The DSMB found conclusive evidence that the second regimen, FTC + atazanavir + ddI-EC, is inferior to the control regimen primarily because it is less effective at controlling HIV. Based on this finding, the decision has been made to discontinue the emtricitabine + atazanavir + ddI-EC component of the study. All study participants are being notified of the development.

C O M M E N T

It is unclear why anyone would have expected FTC/ddI/un-boosted atazanavir to work as well as boosted - and what would be the advantage to someone risking this.

The press statement uses psuedo-medical language as if everything is so reasonable, eg 'NIAID concurs with DSMB' - they have no choice and certainly couldn't go against a DSMB recommendation; or using 'conclusive evidence' rather than just say 'the study found'.

More critically, the ddI and atazanavir interaction should have been sufficient for this not to have been studied - especially with unboosted atazanavir. It is also difficult to see how option 2 is a once-daily regimen if it required separating the ddI and atazanavir doses.

Source: NIAID press release: Monitoring Board Recommends Stopping Experimental Treatment Regimen in International Study of Patients New to HIV Treatment.
For more information on this announcement, go to:
http://www3.niaid.nih.gov/news/newsreleases/2008/ACTG_5175.htm

GUIDELINES

UK (BHIVA) 2008 Treatment Guidelines published online

The 2008 BHIVA guidelines are now published online and are a significant revision of the 2006/7 guidelines.

Changes include:

- Earlier discussions about starting treatment (ie once CD4 is <500 cells/mm3)
- New tables to estimate progression risk
- Recommendations to start treatment earlier (ie once CD4 count is <350 cells/mm3)
- Consideration to start treatment when CD4% is <14%, even when absolute CD4 count remains >350 cells/mm3
- In addition to symptomatic AIDS, starting or considering treatment with >350 cells/mm3 is also recommended for patients with hepatitis B or C coinfections, and importantly, patients with high cardiovascular risk (>20% 10-year Framingham risk).
- Efavirenz is recommended as consideration for first-line therapy for all patients. Those with contraindications for efavirenz are recommended to use a boosted PI.
- Atazanavir/r is now included as first-line treatment option.
- Although Truvada and Kivexa are both recommended as dual-nuke backbone, the guidelines caution against using Kivexa for patients with baseline viral load >100,000 copies/mL or who have high cardiovascular risk (Framingham)
- Resistance testing is routinely recommended for newly diagnosed patients, prior to starting treatment and prior to switching treatment, once viral rebound has been confirmed. Results should be communicated to patients, permanently recorded in patient notes and included in notes forwarded to other treatment centres should the patient change their clinic for any reason.
- Broadening availability to earlier HIV testing

The guidelines are already available to download in PDF format:
http://www.bhiva.org

They will also be published in the Autumn issue of HIV Medicine.

Major updates to US guidelines on prevention and treatment of OIs

Two important new long-awaited guidelines relating to the management and treatment of opportunistic infections were published online in June.

At over 200 pages each (plus references), both documents, available as searchable PDF files, are significant reference resources.

- Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents
- Guidelines for Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected Children

Major changes to the 2004 edition of the adult guidelines include:

- More emphasis on the importance of ART for prevention and treatment of OIs, especially those for which specific chemoprophylaxis and treatment do not exist;
- Information on diagnosis and management of immune reconstitution inflammatory syndromes (IRIS);
- Information on interferon-gamma release assays (IGRAs) for the detection of latent *Mycobacterium tuberculosis* infection;
- Updated information on drug interactions affecting use of rifamycin drugs for prevention and treatment of tuberculosis (TB);
- The addition of a section on hepatitis B virus (HBV) infection; and
- The addition of a section on malaria to the OIs of geographic interest.

The paediatric guidelines include similar revision to the previous 2005 guidelines.

The focus for both guidelines reflect the most common opportunistic infections experienced by patients treated in the US.

Both documents are available to view and download from:
http://www.aidsinfo.nih.gov

PREGNANCY & PMTCT

Low rates of MTCT in UK and Ireland

Polly Clayden, HIV i-Base

A paper authored by Claire Townsend and co-workers published in the May 11, 2008 edition of AIDS reported very low rates of mother-to-child transmission (MTCT) of HIV in UK and Ireland, 2000-2006. [1]

Findings from this analysis were first reported in a poster at the 15th Conference on Retroviruses and Opportunistic Infections in February and summarised in the March/April issue of HTB. [2,3]

This national surveillance study found an overall transmission rate of 1.2% (61/5151, 95% CI: 0.9–1.5%). The rate was lower in 2003-2006, 1% (938/3695) than in 2000-2002, 1.6% (923/1456), p=0.069. The transmission rate for women who received antiretrovirals for at least the last 14 days of pregnancy was 0.8% (40/4864, 95% CI: 0.6-1.1%), regardless of type of antiretroviral treatment or prophylaxis or mode of delivery.

In multivariate analysis (n=4892) including receipt of antiretrovirals, mode of delivery, gestational age and sex, the authors found receiving no antiretrovirals, AOR: 9.08, p=0.001 was the greatest risk factor for transmission. Girls were more likely to be infected than boys, AOR:1.91, p=0.023.

Preterm delivery (<32 weeks) was also a significant risk factor, AOR: 3.55, p=0.01. However, the authors noted that of the seven women with infected premature infants, three were received no antiretrovirals and four for <3 weeks (range: 1-19 days) and six had vaginal deliveries. Preterm delivery was not a significant risk factor for women receiving HAART, AOR:1.32, 95% CI: 0.3-5.82, p=0.714.

There was a non-significant overall 1.8 fold increased risk of transmission associated with vaginal delivery compared to elective Caesarean section, AOR: 1.82, p=0.076. In this cohort information on whether vaginal deliveries were planned or unplanned was available for 69.1% (775/1122) of women. After adjusting for receipt of antiretrovirals, gestational age and sex, unplanned vaginal delivery was associated with a significantly increased transmission risk, AOR: 4.16, 95%CI: 1.66-10.41, p=0.002 but planned delivery was not, AOR:1.56, 95% CI: 0.65-3.72, p=0.319.

The MTCT rate for women receiving HAART was 1.0% (40/4120). The rate did not differ significantly when HAART contained an NNRTI, 90.9% (18/1959), a PI, 1.1% (20/1795), p=0.625, both 0.8% 92/258) or neither 0% (0/108), p=0.847.

When the authors compared NNRTI and PI regimens, after adjusting for mode of delivery, sex and viral load (gestational age was excluded from this analysis, because, as noted earlier, it was not a significant risk factor for women receiving HAART in this cohort), AOR:1.31, 95% CI: 0.62-2.76, p=0.482, there was no difference in MTCT rates between the two types of regimens.

Already receiving HAART at conception showed a modest advantage, AOR: 0.18, 95% CI: 0.02-1.33, p=0.093. Women who transmitted and initiated HAART in pregnancy (n=34) began treatment later than those who did not, with median gestational age 30.1 weeks (IQR: 27.4-28.7 weeks) for those who transmitted vs. 25.9 weeks (IQR: 22.4-28.7 weeks) for those who did not, p=0.001.

The authors noted that each additional week of treatment gave a 10% reduction in transmission risk, AOR: 0.09, 95% CI; 0.84-0.97, p=0.007 (after adjusting for viral load closest to delivery, mode of delivery and sex).

For women receiving HAART there was no difference between transmission rates with elective Caesarean (0.7%, 17/2286) or planned vaginal delivery (4/559, AOR: 1.24, 95% CI: 0.34-4.52), p=0.746.

Viral load was undetectable in 58.7% (1135/1934) of women having elective Caesareans and 79.0% (417/528) of those having planned vaginal deliveries, p=0.001.

There were 3/2117 transmissions reported from women receiving HAART with undetectable viral load (0.1%, 95% CI: 0.0-0.4%). Two were delivered by elective Caesarean (0.2%, 2/1135) and one by planned vaginal delivery p=0.001. One positive infant born by elective Caesarean section and one by planned delivery had positive PCR results within 72 hours of birth suggesting transmission in utero.

Transmission rates were higher in women receiving HAART, with both emergency Caesareans and unplanned vaginal deliveries, p=0.027 and 0.019 respectively.

Eighteen other women had positive infants despite HAART and either planned delivery or elective Caesarean section. For

10 women the authors found an association with either: short duration of treatment, high viral load near delivery (range 8500-285,000) or adherence problems. Six women had low but detectable viral load (</=50 and <1000 copies/mL and two women received HAART for at least a month but there were no viral load data.

For women receiving AZT prophylaxis and elective caesarean section, the transmission rate was 0% (0/464, 95% CI: 0-0.8%). Overall 3/638 (0.5%, 95% CI: 0.1-1.4%) infants were born to women receiving AZT prophylaxis. All three women received AZT for less than 1 month, had detectable viral load (range 474-3000 copies/mL) and had vaginal deliveries.

The authors conclude: "Our findings suggest that offering HIV-infected women choices about HIV treatment and mode of delivery according to current guidelines has led to very low rates of MTCT."

References

1. Townsend CL, Cortina-Borja M, Peckham CS et al. Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000–2006. AIDS 2008, 22:973–981.
2. Townsend C, Cortina-Borja M, C Peckham C et al. Very low risk of MTCT in women on HAART who achieve viral suppression: The UK and Ireland, 2000 to 2006. 15th CROI. February 2008, Boston. Poster abstract 653.
3. See: HIV Treatment Bulletin, March/April 2008.
http://www.i-base.info/htb/v9/htb9-3-4/Very.html

PAEDIATRIC CARE

WHO recommends treating all HIV-infected infants aged less than 12 months

Polly Clayden, HIV i-Base

Following a meeting In April 2008 of the WHO Technical Reference Group for Paediatric HIV/Antiretroviral therapy and Care to consider the implications of recent research findings, the WHO have revised their guidelines for treatment and care of infants infected with HIV.

Of particular importance is the new recommendation: "All infants under 12 months of age with confirmed HIV infection should be started on antiretroviral therapy, irrespective of clinical or immunological stage." This was made in light of findings from the CHER study, in which dramatic reduction in mortality (75%) was observed in infants treated immediately irrespective of immunological or clinical criteria compared to infants whose treatment was deferred until criteria as outlined in the previous treatment guidelines were met.

Other research and observational data also suggest that early antiretroviral therapy in infancy dramatically reduces the risk of death and disease progression.

The full report from the meeting and new recommendations can be accessed at:
http://www.who.int/hiv/events/paediatricmeetingreport.pdf

Plasma concentrations and virologic evaluations after stopping NNRTI treatment in PENTA 11

Polly Clayden, HIV i-Base

A paper authored by Tim Cressey and co-workers from the PENTA-11 study group, published in the 15 May 2008 edition of Clinical Infectious Diseases, showed findings from an evaluation plasma concentrations, viral load, and development of drug resistance after a planned treatment interruption of a NNRTI–containing regimen in HIV-positive children.

PENTA-11 is an ongoing, randomised, phase II trial evaluating the role of planned treatment interruptions (PTI) in the treatment of HIV-positive children with a good response to antiretroviral therapy.

In this study children on stable HAART for at least 6 months with viral loads <50 copies/mL and CD4 percentages of 30% (for children aged 2–6years) or CD4 percentages of 25% and CD4 counts of 500 cells/mm3 (for children aged 7–15 years) were randomised to either a PTI or to continuous therapy.

The PTI arm used one of two strategies for stopping NNRTIs:

1. Treatment with nevirapine or efavirenz was stopped, and treatment with the remaining drugs was continued for 7–14 days.
2. Nevirapine or efavirenz were replaced by a protease inhibitor, and all drugs were stopped after 7–14 days.

Choice between the strategies was at the discretion of the paediatrician.

Sampling for plasma concentrations, viral load, and drug resistance testing were performed on days 0, 7 (drug concentrations

only), 14 and 28 after interruption of treatment with an NNRTI.

Of 110 children enrolled in PENTA-11 between November 2004 and December 2006, 56 were randomised to the PTI arm. Of these children, treatment with an NNRTI was stopped for 35 children of which 20 were receiving nevirapine, and 15 were

receiving efavirenz). The median age of the children was 8.9 years (range, 3.6-15.9).

Median time from stopping treatment with an NNRTI to stopping all drugs was 9 days (range, 6–15 days) for nevirapine and 14 days (range, 6–18 days) for efavirenz.

The investigators reported that at 7 days, 1/19 (5%) and 4/8 (50%) children had detectable nevirapine and efavirenz concentrations respectively. Efavirenz remained detectable in 3/12 (25%) children at 14 days. At 14 days, viral load was 50 copies/mL in 6/16 (38%) children interrupting treatment with

nevirapine (range, 52–7000 copies/mL) and in 2/12 (17%) children interrupting treatment with efavirenz (range, 120–1600 copies/mL).

They found that no new NNRTI or mutations were detected. Additionally, they reported no detection of 3TC-associated mutations.

The investigators concluded that in virologically suppressed children who interrupt an NNRTI-based regimen during their first PTI cycle, staggered or replacement stopping strategies for a median of 9 days for nevirapine and 14 days for efavirenz were not associated with the selection of NNRTI resistance mutations.

They noted that in this study it could not be determined whether a replacement or staggered stopping strategy is preferable. They suggest however that there are theoretical reasons to prefer a replacement stop strategy, particularly for efavirenz.

Ref: Cressey TR, Green H, Khoo S et al. Plasma drug concentrations and virologic evaluations after stopping treatment with nonnucleoside reverse-transcriptase inhibitors in HIV type 1–infected children. Clinical Infectious Diseases 2008; 46.1601-8.

BASIC SCIENCE AND VACCINE RESEARCH

A selection of articles relating to basic science and vaccine research from Richard Jeffreys excellent basic science blog.

Elite control of a virus that caused AIDS in the transmitting partner

Richard Jeffreys, TAG

From the online first section of J. Virology, a new paper from Justin Bailey and colleagues provides evidence that a virus that is clearly pathogenic in one individual can be controlled in another. The paper describes a couple in which the male partner received an AIDS diagnosis 10 years ago after developing PCP and cerebral toxoplasmosis; he started antiretroviral treatment and recovered with a first documented CD4 count of 266 cells. The female partner tested HIV-positive at the same time, and had no other risk factors. She has since consistently maintained CD4 counts over 800 and a viral load of less than 50 copies/mL.

Bailey and colleagues cultured several HIV isolates from the latent CD4 reservoir of both individuals, conducted full length genetic sequencing and found that the viruses are closely phylogenetically related and also contain a mutation in the tat gene that is present in less than 1% of the clade B isolates in the Los Alamos HIV sequence database. These data offer extremely strong evidence of transmission even though, as the authors note, the samples were taken many years after transmission likely occurred (the couple had been together for 17 years prior to the AIDS diagnosis). Both individuals possess the HLA B*57 allele that has been associated with elite controller status; the female partner also has another allele, HLA B*27, that has been shown to be overrepresented among elite controllers.

Additional analyses of viral sequences revealed that there were escape mutations in HLA B*57-restricted CD8 T cell epitopes in both partners. In the female partner, these mutations were present in every proviral gag clone studied, a phenomenon not observed by these authors in their larger cohort of elite controllers, suggesting that she was infected with a virus already containing the escape mutations. The authors speculate that the infecting virus may have been somewhat attenuated as a result, and subsequently the CD8 T cell response suppressed HIV replication sufficiently to prevent the development of compensatory mutations which can restore viral fitness. They also found that this individual's CD8 cell response had selected for another mutation in an epitope called KK10 which is known to impact viral fitness; this was associated with the presence of polyfunctional CD8 T cell responses aganst both the wild-type and mutant epitope.

In further studies of immune responses, HIV-specific CD8 T cells from the female partner were shown to be able to proliferate in response to HIV antigens while those from male partner could not. The capacity for unstimulated CD8 T cells from both partners to inhibit HIV replication in vitro was also assessed (against the HIV Ba-L isolate and a virus isolated from the male

partner); again, CD8 T cells from the female partner "dramatically inhibited" the replication of both viruses whereas those from the male partner did not. The researchers looked at neutralizing antibody responses to the autologous Env protein (generated by cloning the env gene from each individual's provirus) and found that titers were low, ranging from

In discussing their results, the study authors state: "In sum, we conclude that the immune system of ES9 is controlling viral replication by at least two different mechanisms: there is direct inhibition of viral replication by polyfunctional HIV-1-specific CD8 T cells that proliferate in response to autologous viral peptides and there is selection for and maintenance of escape mutations that have a negative impact on viral fitness. Vaccines that elicit CD8 T cells with both properties may be very effective at controlling HIV-1 replication."

Source: TAG Basic Science Blog 21 May 2008

Reference: Bailey JR et al. Transmission of HIV-1 from a patient who developed AIDS to an elite suppressor. JVI Accepts, published online ahead of print on 21 May 2008.
http://jvi.asm.org/cgi/content/abstract/JVI.00800-08v1

Presentations from the May 21-23 HIV Vaccine Trials Network (HVTN) Meeting

The HVTN has made available the Powerpoint files of presentations from their recent meeting in DC. [1]

Of particular interest, Surojit Sarkar from Emory presents data indicating that - as suggested by the longitudinal data from trials of Merck's HIV vaccine - CD8 T cell responses induced by Ad5 vectors do no contract in the way that typically occurs during the development of protective memory T cell responses, and that this is associated with the persistence of the vector. [2]

As a result, Ad5-induced CD8 T cell responses appear functionally compromised and display poor proliferative capacity and protective efficacy in Sarkar's murine studies.

David Watkins also contrasts the breadth of T cell responses that he observes in macaque vaccine studies (6-18 CD8 T cell epitopes) with those observed in the Merck vaccine efficacy trial (3 CD8 T cell epitopes), and several other presenters discuss strategies for improving the number of epitopes targeted by HIV-specific T cell responses. Based on a prior comment to this blog by Ian York, it is to be hoped that members of relevant NIH study sections are being educated about the potential importance of improving the breadth of vaccine-induced T cell responses in humans. [3, 4]

References

1. http://www.hvtn.org/meeting/may08.html
2. http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2008/04/after-the-fact.html
3. http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2008/04/hints-of-correl.html#comment-110221934
4. http://www.iayork.com/MysteryRays

   http://jvi.asm.org/cgi/content/abstract/JVI.00800-08v1

Source: TAG Basic Science Blog (4 Jun 2008)

Failure of STEP leads TAG to criticise the proposed PAVE100A vaccine trial

Simon Collins, HIV i-Base

The failure of STEP trial, using Merck's adenovirus serotype 5 (Ad5)-based HIV vaccine, has implications for using another Ad5 candidate in the proposed PAVE100A Phase IIb efficacy trial.

The STEP trial neither reduced infection or post-infection viral load, and potentially increased infection rates among a subset of trial participants.

Treatment Action Group (TAG), a influential community-based policy think-tank published a Position Statement that raises serious concerns about continuing with the PAVE100A trial.

This includes an analysis of the scientific likely hood that this new candidate will produce a different response, and questioning both the relevance and safety of such a restricted study population:the PAVE trial is limiting recruitment to circumcised gay men with no detectable antibody responses to Ad5.

TAG proposes abandoning plans for this particular clinical trial and Ad5 vaccine candidate in favour of supporting research to rapidly address two key issues:

1. The use of an alternate vector or DNA approach for the boosting immunisation that could be studied in a broader population.
2. Inducing broader responses to proteins contained in the vaccine, particularly HIV-1 Gag.

They argue against spending human and fiscal resources on PAVE100A, and instead suggest focusing on improving T cell-based immunogens so they can be studied in a broader population with a greater chance of success.

Source: TAG Basic Science Blog (30 May 2008)

The full statement "TAG position statement on the proposed PAVE100A vaccine trial" is available online:
http://www.aidsinfonyc.org/t

OTHER NEWS

Free osteopathy for people with HIV at the British School of Osteopathy

Since 2001, the British School of Osteopathy (BSO) has been running a free Friday morning treatment programme called the Chapman Clinic for HIV positive patients from its premises on Borough High Street, south east London.

Senior BSO tutor Paul Blanchard and his team have also, since 20005, run a free Friday afternoon osteopathy service at the Ian Charleston Day Centre at the Royal Free Hospital in Hampstead, north west London. From 1 April 2008 treatment at the BSO Chapman Clinic will be offered from the new clinical centre that the BSO is opening at 98-118 Southwark Bridge Road (SE1 0BQ) just a few minutes' walk from its existing premises.

The BSO is keen to ensure that anyone living with HIV who might be helped by osteopathic treatment are aware of the free treatment it can offer them. Osteopathy is a primary healthcare system, complementary to other medical practices. It is suitable for almost anyone and can contribute to alleviating an enormous range of conditions.

Osteopaths primarily work mostly on muscles and joints, and pay special attention to how the internal organs affect, and are affected by, that system. Relevant psychological and social factors also form part of the diagnosis. Another important principle of osteopathy is that the body has its own self-healing mechanisms, which can be utilised as part of the treatment.

Osteopathic treatment at the BSO Chapman Clinic and at the Ian Charleston Day Centre is provided by osteopathic students supervised and supported by tutors who are qualified osteopaths, and who have a specialist interest in HIV, drug therapies, associated pathologies and the musculo-skeletal presentation of HIV. Anyone living with HIV can refer themselves to these clinics.

Osteopathic treatment for people living with HIV/AIDS can bring great improvements in quality of life by addressing the particular musculo-skeletal dysfunction they often experience. It also complements the drug therapies used to manage HIV/AIDS and may also help in coping with the side effects they can bring.

To book treatment contact either clinic directly.
BSO Chapman Clinic: 020 7089 5360
clinicappointments@bso.ac.uk

Ian Charleston Day Centre: 020 7830 2062
Website: www.bso.ac.uk

Source: BSO press release

AIDS denialists shut out of Senate hearing after winning "whistleblower" award

A pair of high-profile AIDS denialists were disinvited from testifying at a May 14 U.S. Senate committee hearing on laws to protect whistleblowers, people who speak out publicly against wrongdoing within an organisation.

Peter Duesberg and Celia Farber had travelled to Washington, D.C., from California to receive an award for their efforts to discredit factual evidence about HIV and HIV treatment. "These aren't whistleblowers," said a Washington DC, HIV activist. "They're divergent thinkers who are 21st century snake-oil salesmen."

Source: thebody.com

MTV internet game challenges ignorance and assumptions about who has HIV

It's impossible to know whether a person has HIV just by looking at them, but too many people in the world still believe you can. That's where a new Internet game comes in: "Pos or Not" invites people to look at photos and short profiles of a wide range of people and guess whether they have HIV. Of course, there's no way to tell for sure -- and that's the point. "We feel it's another kind of activist tool to get out the word about HIV protection," explained the general manager of mtvU, the MTV network offshoot that launched the site.

Want to test your luck at "Pos or Not"?
http://www.thebody.com/content/art46888.html?mtrk=8203834

ON THE WEB

Overview of mucosal transmission

In the June issue of Nature Reviews Immunology, Florian Hladik and Juliana McElrath review the current state of knowledge regarding mucosal transmission of HIV infection and the current concepts of the immediate events that follow viral exposure at genital mucosal sites where most documented transmissions occur. Thy also discuss the gaps in knowledge that are relevant to future studies, which will shape strategies for effective HIV prevention.

Access to the full text of the paper is free of charge but requires registration with the Nature website.

http://www.nature.com/nri/journal/v8/n6/full/nri2302.html

Hladik F and McElrath JM. Setting the stage: host invasion by HIV. Nature Reviews Immunology 8, 447-457 (June 2008) | doi:10.1038/nri2302

PRN notebook

Four excellent articles have been recently posted online by this leading resource.

http://www.prn.org

The gastrointestinal tract in HIV-1 infection: questions, answers, and more questions! - Saurabh Mehandru

The GI tract is targeted during all stages of HIV disease, and this is especially so during acute and early HIV infection. CD4 cells are preferentially lost from the GI tract within weeks of HIV infection. Despite long-term antiretroviral therapy, CD4+T-cell reconstitution remains deficient in the GI tract in spite of the reconstitution seen in the peripheral blood.

HIV-1 integrase inhibitors – Teresa Evering and Martin Markowitz

The integrase inhibitors are a welcome addition to the treatment armamentarium for HIV/AIDS in treatment-experienced patients failing available antiretroviral regimens. The promising efficacy and tolerability profile of the integrase inhibitors, absence of cross-resistance with other antiretroviral classes, and demonstrated synergism of the integrase inhibitors in combination with approved antiretroviral agents place them in a position to become important components of effective combination antiretroviral regimens in individuals living with HIV/AIDS.

Osteoporosis and adrenal insufficiency - Todd T. Brown

The care of HIV-infected patients has become increasingly complex. Endocrine problems, such as osteoporosis and AI, have been frequently reported in the HAART era. Additional considerations may be required regarding the etiologies, diagnosis, and treatment compared with the general population. Further research is required to understand the intricacies of these problems in HIV-infected patients in order to provide optimal care.

Update on CCR5 inhibitors: scientific rationale, clinical evidence, and anticipated uses - Athe Tsibris

The CCR5 antagonists are a welcome addition to the therapeutic armamentarium available for antiretroviral-experienced patients. Currently, their use in antiretroviral-naive patients should be restricted to enrollment in ongoing or planned clinical trials. The CCR5 antagonist maraviroc is FDA-approved for treatment-experienced patients with R5 virus (only), and no patient should receive maraviroc without first undergoing a tropism assay.

JACI special issue on prospects for eradication

The Journal of Allergy & Clinical Immunology's new issue has a special focus on HIV/AIDS, in recognition of the upcoming International AIDS Conference in Mexico City. There are several free full-text articles, including this review by Lin Shen and Robert Siliciano that summarises recent evidence indicating ART can completely suppress viral replication, and mulls the implications for efforts to eradicate HIV infection.

Viral reservoirs, residual viremia, and the potential of highly active antiretroviral therapy to eradicate HIV infection

Lin Shen, MD, Robert F. Siliciano, MD, PhD

Journal of Allergy & Clinical ImmunologyVolume 122, Issue 1, Pages 22-28 (July 2008)

http://www.jacionline.org/article/PIIS0091674908010038/fulltext

Abstract: Although highly active antiretroviral therapy (HAART) can reduce HIV-1 viremia to levels that are below the limit of detection of clinical assays, the virus persists in reservoirs, and trace levels of free virions can be found in the plasma. Whether this residual viremia represents ongoing cycles of replication continuing despite HAART or simply the release of virus from stable reservoirs has been controversial. Here we summarize the evidence that HAART can stop ongoing

cycles of replication. The evidence comes from a detailed analysis of the residual viremia, which shows it to be archival and nonevolving in character. In addition, new pharmacodynamic measures incorporating a previously ignored slope parameter have provided the first real indication of how well HAART actually suppresses viral replication in vivo. Together, these results argue that the ultimate theoretical potential of HAART to control viral replication has already been reached. Progress toward eradication of the infection will require novel approaches to target the stable reservoirs that persist even when viral replication is completely halted.

New resources from HIV InSite

HPV Infection in HIV-Seropositive Men and Women

Dr. Joel Palefsky reviews human papillomavirus and HIV, including both cervical and anal disease, and vaccine development.

http://hivinsite.ucsf.edu/InSite?page=cfphp-palefsky2008

FUTURE MEETINGS

2008 conference listing

The following meetings are taking place during the next year.

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

1 - 2 August 2008, 3rd International workshop on HIV Transmission, Mexico City

http://www.virology-education.com

3-8 August 2008, 17th International AIDS Conference, Mexico City

http://www.aids2008.org/

25-28 October 2008, Washington, DC, ICAAC and IDSA joint meeting

http://www.icaac.org/

October 2008, 3rd International workshop on Hepatitis C, Resistance and New Compounds, Washington DC

http://www.virology-education.com

6-8 November 2008, 10th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, London, UK

http://www.intmedpress.com

9-13 November 2008, 8th Congress on Drug Therapy in HIV Infection, Glasgow

http://www.hiv8.com

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

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

http://www.i-base.info

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

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

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

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

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

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

NEW publications

- English edition of Introduction to combination Therapy (June 2008)

http://www.i-base.info/guides/starting/index.html

- English edition of Guide to avoiding & managing side effects (May 2008)

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

- Spanish online edition of the Guide to HIV and Hepatitis C (all web pages are now simultaneously available in both English and Spanish)

http://www.i-base.info/guides/hepc/es/index.html

- Czech issue of the Guide to HIV and Hepatits C (PDF file)

http://www.i-base.info/pdf/guides/nonuk/2008/hepchiv-czech08.pdf

i-Base announcements list

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

To subscribe please fill out the form at this link:

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

Training manual – revised, updated and now fully online

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

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

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

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

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

Sections include:

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

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

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

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

Generic clinic forms

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

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

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

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

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

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

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

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

Photography by Wolfgang Tillmans

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

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

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

UK CAB: reports and presentations

The UK Community Advisory Board (UK CAB) is a network for community treatment workers across the UK that has been meeting for three years. Each meeting includes two training lectures and a meeting with a pharmaceutical company or specialist researcher.

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

http://www.ukcab.net

World CAB - reports on international drug pricing

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

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

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

Introduction to combination therapy

June 2008 edition

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

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

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

May 2007 edition

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

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

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

April 2007 edition

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

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

Guide to HIV, pregnancy & women's health

July 2007 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 avoiding & managing side effects

May 2008 edition

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

Translations of i-Base guides

Original material published by i-Base can be translated and reprinted, and has so far been produced in over 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 form earlier editions of the treatment guides, and check the publication date before relying on all information.

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

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

Treatment 'Passports'

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

HIV Treatment Bulletin (HTB)

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

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

Treatment information request service - 0808 800 6013

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

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

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

Online Q&A service

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

Recent questions include:

- Do you believe Dr Fauci's claim for a cure from early treatment?
- Where can I get support in Singapore?
- Government, confidentiality, volunteering for trials…
- Why was I not infected after first exposure?
- Shall I avoid ritonavir?
- Do I really need to take my medications with/without food?
- Shall I have another test?
- Should I start treatment now?
- What are my treatment options after my viral load rebound?
- Can Hep tests detect my HIV status?
- Shall I start medications, as I have serious skin problems?
- Do I need to test my baby again?
- Have the Australians discovered a cure for HIV?
- Can I drink alcohol with ARVs?
- Should I take medication for a bladder problem?
- My CD4 cell count is 122. How do I boost them to get a higher count?
- Could you comment on the possible routes of infection?
- How often can I miss a dose?
- Can my HIV-positive partner come to live in the UK?
- Feeling tired on Atripla/Sustiva and CD4 increases after restarting treatment

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.

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Putting you in control of your HIV treatment with the most up to date information explained in non-technical language.

Calls are answered by HIV-positive advocates.

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treatment information phoneline

Or go online: www.i-Base.info

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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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If your employer operates a Give-As-You-Earn scheme please consider giving to I-Base under this scheme. Our Give-As-You-Earn registration number is **000455013**. Our Charity registration number is 1081905

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.

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NEW: Introduction to Combination Therapy *(June 2008)*

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Changing Treatment - Guide to Second-line and Salvage Therapy *(April 2007)*

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Translations of earlier treatment guides into other languages are available as PDF files on our website

Phoneline support material *(pls specify required number of each)*

A3 posters _____ *A5 leaflets* _____ *A6 postcards* _____ *Small cards* _____

Adherence planners and side effect diary sheets - In pads of 50 sheets for adherence support

1 Sheet ☐ **1 pad** ☐ **5 pads** ☐ **10 pads** ☐ **Other** ☐ _____ _____

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