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July/August 2010

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EDITORIAL

In this issue we lead with reports from the 18th International AIDS Conference, which took place in Vienna in July.

As we explain in our introduction, access to treatment, to which there are many barriers - including unjust legislation, donor funding and lack of commitment from local governments - is always the focus of this meeting.

We will look at some of the aspects of treatment access in our next issue, together with side effects and other complications.

In this issue we report the headline grabbing results from the CAPRISA 004 trial, which proved the principle that an antiretroviral microbicide can protect against HIV transmission. Although there is a lot more work to be done, this was an important finding in a field with little success to date.

We also report on new drug development, antiretroviral strategies and maternal and child health.

Additionally at IAS the Treatment Action Group (TAG) in New York launched their 2010 Pipeline Report, which reviews all the latest developments in the treatment pipeline for HIV, tuberculosis, hepatitis C, and this year, hepatitis B. This year i-Base collaborated with TAG on the report. Simon Collins contributed an in-depth analysis of the antiretroviral pipeline and Polly Clayden wrote new chapters for the report on paediatric antiretrovirals and HIV diagnostics.

We have worked with TAG on several projects including our hepatitis guide with Tracy Swan and include many of Richard Jefferys' basic science articles from his blog in HTB. We have always been fans of the Pipeline Report so were delighted to work with TAG on this one!

We include a selection of the articles from the report as a supplement to this issue of HTB.

The full report is at:

<http://i-base.info/home/pipeline-report-2010>

Find out more about TAG at:

<http://www.treatmentactiongroup.org>

CONFERENCE REPORTS

XVIII International AIDS Conference

18–23 July 2010, Vienna

Introduction

Treatment access will always dominate the programme of World AIDS Conferences. Since the Durban conference in 2000, every scientific advance at this meeting is rightly seen in the context of which populations, in a global health emergency, will have the opportunity to benefit.

This is one of the strengths of this meeting, which now has over 20,000 delegates, and many of the access-related sessions are online as webcasts and transcripts produced by the Kaiser Foundation.

A joint report from UNAIDS and Kaiser launched prior to the conference clearly and disturbingly showed that international donor funding, which now supports close to five million people on treatment, has leveled. This threatens to overturn the accumulated health benefits from the last ten years. Flat-lined funding means treatment programmes will be closed to new patients and this will have a disastrous impact on HIV prevention.

Without treatment, not only is there little incentive to test, and an increase in AIDS and death, but also the beneficial impact that antiretroviral therapy has on the risk of transmission will be reduced. And treatment is still likely to be more effective in preventing HIV than any other intervention.

This global crisis demands international support, and this involves funding. So while the US leads funding initiative, as the world's richest country, it is just as important that other wealthy nations meet, for example, the commitments made at the G8 summit. The expense and investment in the conference itself, did not sit easily with the decision to hold the meeting in country that has not supported the Global Fund since 2002. Currently the Global Fund to Fight AIDS, TB and Malaria (GFATM) is faced with a \$3 billion shortfall for 2010. Similarly, very few African nations have met their pledge in the Abuja Declaration 2001 to target at least 15% of GDP on healthcare.

The global demand for treatment challenges the concept of universal access using today's medications. Research into ARV drug delivery using nanotechnology is proceeding extremely slowly with only one abstract at this meeting, and yet this has the potential to address many obstacles to wider access. The volume of active ingredient is dramatically reduced with a nanoformulation requiring perhaps monthly dosing, both of which dramatically reduce costs.

This was a conference that highlighted access issues from a human rights perspective:

- The Vienna Declaration - is the official conference statement seeking to improve community health and safety by calling for the incorporation of scientific evidence into illicit drug policies (viennadeclaration.com).
- Many sessions addressed access to evidence-based harm reduction strategies including opioid substitution therapy (OST) and needle exchange programmes.
- Access to treatment to prevent mother-to-child transmission (PMTCT) – currently only 10–20% of HIV-positive women worldwide are able to access testing and treatment during pregnancy.
- The criminalisation of same sex relationships and discrimination against men and women whose sleep with partners of the same sex, highlighted most recently by extreme cases in Uganda, Malawi and Iran, was the focus of several sessions.

We will cover treatment access in the next issue.

In terms of medical and scientific research, there were a few important headline-grabbing studies and a good selection of interesting but preliminary research findings.

As with all meeting reports we include links to original abstracts and webcasts when available, and for this meeting we also start with a guide on how to navigate the conference website for other material.

Abstracts from the conference are published on the conference website:

<http://www.aids2010.org/>

Reports in this issue include:

- Navigating the conference online
- Results from the Caprisa 004 tenofovir microbicide trial
- Quadrivalent HPV vaccine reduces genital lesions and HPV acquisition in men
- Rilpivirine (TMC-278) vs efavirenz in treatment-naïve patients: phase 3 results
- Once-daily nevirapine extended release (XR) is non-inferior to current formulation
- GSK572: second-generation integrase inhibitor
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- Maraviroc vs atazanavir/r in treatment-naïve patients
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- CASCADE analysis of when to start treatment
- Impact of antiretroviral PMTCT prophylaxis regimens on subsequent maternal disease progression in Kesho Bora
- Birth outcomes with antiretroviral exposure
- Introduction to paediatric studies at IAS
- New WHO guidelines for children
- Early treatment for infants is cost-effective
- No difference in outcomes for children initiating treatment with a protease inhibitor or an NNRTI nor with viral load switching strategies in PENPACT-1
- Tablets more acceptable than syrups in the ARROW trial
- Paediatric formulation of TMC 278
- Smoking and atazanavir levels
- Darunavir/ritonavir and rosuvastatin
- Lime juice is not a microbicide: do not try at home

IAS: ON THE WEB

Navigating the conference online

Simon Collins, HIV i-Base

As with previous IAS conferences, much of the conference material is available online and HTB reports include appropriate hyperlinks.

Locating the appropriate files, presentations, webcasts, transcriptions or even the basic abstracts is more challenging. Access is routed through the 'Programme at a glance' link on the conference homepage. This requires a free software plug-in called Silverlight, but an automatic download button should come up if you do not already have this installed.

The search facility requires selecting one of the seven options directly under the search bar ie to search the abstracts, you need to first click 'abstract' which when selected has the tiny white triangle in the red block turn to face down. Then search as you would normally by entering a keyword in the search box and clicking search. Results come up listed below.

The abstract books are available to download as free PDF files, but only for each day, so searching the whole conference requires repeating each search four times.

Although you can browse sessions by day and time, this is not so easy if you are looking for a specific session but don't know when it was presented because there is not a programme that just shows the sessions. For example a search for 'late breaker' brings up no results whether searching 'programme at a glance', 'abstracts', or 'oral sessions'.

If you find a session page, you then have to find and click the yellow 'more info' button at the bottom right of an empty box, and then you finally get to a page that makes sense. Don't be entirely fooled. The 'abstract' links seems to work, but 'slides with audio' are not always available and the 'powerpoint' link doesn't work at all. For presentation slides, scroll further down the page where slides that are available are listed under the 'powerpoint presentations' heading.

The audio works but you need to manually download the powerpoint slides to really follow the presentation.

To make things more confusing, some webcast presentations are provided by Kaiser Foundation on a different website.

<http://globalhealth.kff.org/AIDS2010>

These webcasts only show the presenter, with no slides and no easy links to slides. Although you often hear two different presentations simultaneously, this accurately captures the conference experience. Only a cloth curtain divided most session rooms, so the webcasts accurately reflect the conference atmosphere, including this difficulty.

Kaiser provide rough transcripts of the sessions that can be more useful with the slide set, than the webcast, though they are draft transcripts only.

Web access should be a leading priority for these conferences. The interface used by the Retrovirus (CROI) conference would be a much more useful model to use and would make this aspect of the meeting far more accessible, whether provided by IAS or Kaiser.

IAS: PREVENTION

Results from the Caprisa 004 tenofovir microbicide trial

Simon Collins, HIV i-Base

In terms of conference headlines, the biggest news came from the results of a prevention study called Caprisa 004. This study reported that a microbicide gel containing 1% tenofovir reduced the risk of infection to women when used before sex to protect against HIV by 39%. [1, 2] Previous microbicides (not using HIV drugs) have not shown a benefit, so a positive result, no matter how slight, was likely to be greeted enthusiastically. When the results were presented, the audience gave the presenters a standing ovation.

Importantly, the presenters stressed that these preliminary results justified further research. This study was based on 98 endpoints for the primary analysis and the sample size ensured that they could be 90% confident of detecting a doubling/halving in the risk (ie an OR of 2 or 0.5). However, because the endpoints are by definition fewer in subgroup analyses, the study is not powered to analyse some of those interesting results. One of the most helpful aspects of the study is that the detailed results were published in a free-access article in Science Express. [3]

The theoretical benefit from an antiretroviral microbicide is similar to the use of pre- and post-exposure prophylaxis (PrEP and PEP) but instead of taking oral drugs, applying a gel enables the active drug to be absorbed in the tissues that are first exposed to the virus. If the cells in the genital tissues have antiretroviral activity, the hope is that this will reduce the risk of infection.

As with all studies, the complexity of the results is in the details, and the presenters themselves cautioned that their results primarily signaled the urgency of running additional studies.

Women were advised to use the microbicide 'up to 12 hours before sex' and 'as soon after as possible', using a maximum of two doses in any single 24 hour period. The gel was applied with a special pre-filled applicator, similar to a tampon container.

This phase 2b study was in around 900 women aged 18–40 years, living in two districts in South Africa where the risk of HIV for women reaches 50% by the age of 24. One trial site was in urban Durban (n=278) and the second was in a rural location 90 miles from Durban (n=611). This was a double-blind study with women randomised 1:1 to either the active gel or a placebo gel. Free condoms and counselling on the importance of safe sex were provided to all women, with monthly HIV testing and monitoring.

There were significant differences between the rural and urban women. Rural women were younger (mean 23.3 vs 25.1), poorer (86% vs 69% monthly income <R1000), less likely to have a stable partner (77% vs 93%), had fewer lifetime partners (mean 2 vs 6), used condoms less consistently (22% vs 42%) and had lower HSV-2 prevalence (48% vs 60%), see Table 1. However, randomisation ensured that there was no difference in these baseline characteristics between the active and placebo group.

Table 1: Demographic differences between rural and urban sites

	Rural site n=611	Urban site n=278	p-value
Mean age (years)	23.3	25.1	<0.001
Monthly income <R1000	86.1%	69.1%	<0.001
Married	6.5%	3.6%	0.085 *NS
Stable partner	77.0%	93.1%	<0.001
Mean age sexual debut	17.3	17.7	0.014
Mean no. sexual partners (lifetime)	2.1	6.0	<0.001
Mean age of oldest partner (past 30 days)	26.4	29.6	<0.001
Sex in the past 7 days	58.9%	68.3%	0.007
Always use condom	22.9%	42.8%	<0.001
New partner (past 30 days)	0.5%	2.5%	0.014
Anal sex (past 30 days)	0.5%	0.4%	1.000 *NS
HSV-2 prevalence	47.6%	59.6%	0.001

* NS = non significant differences

The predetermined endpoint of 98 events was reached after a mean 18 months with 1341 person years (PY) of follow-up, with a low drop-out rate (~5%).

Of the 98 women who became HIV-positive over 12–30 months, 38 were in the active gel group and 60 were in the placebo group. The HIV incidence rate per 100 PY was 5.6 (CI: 4.0, 7.7) in the tenofovir gel arm compared to 9.1 (CI: 6.9, 11.7) in the placebo gel arm (incidence ratio rate [IRR]=0.61; CI: 0.40, 0.94; p=0.017). After adjusting for baseline covariates including, age, site, anal sex history, contraceptive method, HSV-2 antibody status, and condom use, the hazard ratio was 0.63 (CI: 0.42, 0.94; p=0.025). Sensitivity analysis produced similar results. Although this fell just short of the predetermine OR of 0.50, the results remained statistically significant.

The combined rural/urban analysis produced a protection rate of 39% from using the active compared to placebo gel. However, the 95% confidence intervals are 6% and 60%. Further studies are likely to focus on dosing, adherence and other factors in order to see whether higher protection rates can be seen. Although the results were presented by site, showing effectiveness at the rural site of 43% (95%CI 5, 57; p=0.023) but not at the urban site (26%; 95%CI –59, 67; p=0.380), see Table 2. However, as the study was not designed to compare efficacy by site, while interesting, it was not powered for this comparison to be meaningful.

Table 2: Effectiveness results in Caprisa 004 study

	n	HIV infections/PY		HIV incidence		IRR	Efficacy	95%CI	p-value
		Tenofovir	Placebo	Tenofovir	Placebo				
Overall effectiveness of tenofovir gel (n=889)									
HIV endpoints	98	38/680.6	60/660.7	5.6 (4.0, 7.7)	9.1 (6.9, 11.7)	0.61	39%	6, 60	0.017
Site-specific effectiveness (n=889)									
Rural	611	25/484.7	42/461.2	5.2 (3.3, 7.6)	9.1 (6.6, 12.3)	0.57	43%	5, 67	0.023
Urban	278	13/195.9	18/199.5	6.6 (3.5, 11.3)	9.0 (5.3, 14.3)	0.74	26%	–59, 67	0.380 NS
HIV endpoints by levels of adherence (n=884) †									
Adherence >80%	336	11/259.2	25/269.4	4.2 (2.1, 7.6)	9.3 (6.0, 13.7)	0.46	54%	4, 80	0.025
Adherence 50-80%	181	10/159.8	10/99.7	6.3(3.0,11.5)	10.0 (4.8, 18.4)	0.62	38%	–67, 77	0.343 NS
Adherence <50%	367	16/258.5	25/290.6	6.2 (3.5, 10.1)	8.6 (5.6, 12.7)	0.72	28%	–40, 64	0.303 NS

NOTE: Study was not powered for the subgroup analyses by site and adherence.

† Adherence could not be calculated for the 5 women who reported no sex during their follow-up in the study. NS=non significant

Adherence is essential to monitor in any intervention study, see Table 2. In Caprisa 004, the researchers determined that two applications of the gel were used for over 70% of occasions when participants had sex. While approximately 40% women reported >80% adherence, a similar proportion reported that they used the gel less than half the time. When adherence was 80% or higher (n=336), the protection increased from 39% to 54% (95%CI 4, 80; p=0.025). There appeared to be a trend between adherence and efficacy, and this is clearly plausible, though again the study was not powered for this comparison. The Science Express paper reported 38% protection (95%CI -67, 77; p=0.343) at 50–80% adherence (n=181) dropping to 28% (95%CI -40, 64; p=0.303), when less than 50% (n=367).

The mean number of sex acts in the high, intermediate and low adherence groups was 3.2, 5.0 and 6.7 per month respectively. Median adherence in the women who become HIV-positive was similar throughout the study at approximately 60%, whereas in the HIV-negative women this started at 55% and increased to 75% in the first and last six months respectively. Even with an intensive education and support programme, only a minority of women achieved >80% adherence, and these were the women who had less sex (3 times a month). Condoms were reportedly used 80% of the time, though this may have been over-reported given the rough per-exposure risk this generates for the study, which is not uncommon in prevention studies.

No serious or significant safety issues (from the 4692 reported events) were associated to using the gel in terms of side effects, including renal toxicity or in the 54 unplanned pregnancies that occurred. Mild diarrhoea was reported in 16% people using the active gel compared to 11% of the placebo group. No safety concerns in terms of flares in liver enzymes were seen relating to the use of tenofovir in the small numbers of women who entered the study with active hepatitis B (19 in the active and 15 in the placebo group) or who acquired HBV during the study (22 women, 19 or who cleared the virus without additional treatment). The concern that continued exposure to tenofovir prior to HIV being diagnosed might exert sufficient pressure to generate drug resistance was not supported in genotypic results from 35 women (no K65R, K70E or RTI-associated mutations). Of interest, the use of the active gel had no impact of viral set point after infection (4.65 vs 4.30 log; p=0.15) and participation in the study did not lead to any increase in risk behaviour.

The study also reported an impact on transmission of HSV-2, the virus responsible for genital herpes. Of the 434 women who tested negative for HSV-2 at the beginning of the study, 29 became infected in the active gel group compared to 58 in the placebo group (IR/100PY 9.9 (6.6, 14.2) vs 20.2 (15.3, 26.1)). This was reported as tenofovir providing 51% protection against HSV-2 (95%CI: 22%–70%; p = 0.003). Because genital herpes increases the risk of catching HIV, these results are complicated to understand. Although tenofovir has not shown protective effects against HSV-2 in mouse and test-tube studies, drugs with a similar structure to tenofovir such as cidofovir have activity against HSV-2.

Results from the pharmacology substudy of CAPRISA 004 were presented in the same session by Angela Kashuba from the University of North Carolina. [5]

For the HIV analysis, 90 samples were available (37 active and 13 placebo in the HIV-positive women plus 24 active and 16 placebo from women who remained HIV-negative). Tenofovir levels were measured in blood plasma (BP), and cervicovaginal fluid (CVF) for all samples and additionally in vaginal and cervical tissue biopsy samples in the HIV-positive women. Plasma concentrations were minimal (<1 ng/mL), with detectable levels in only 12% of the HIV-positive women (median 0, range 0–0.1 ng/mL) a median 6 days (range 1–25) after application vs 50% of the HIV-negative women (median 0.1, range 0–0.8 ng/mL) after a median of 4.5 days (range 2–28), indicating very low systemic uptake even given the delay in sampling.

Tenofovir was more frequently detected and at higher CVF levels in the HIV-negative compared to HIV-positive women at 45% (median 1 ng/mL range 0–300,000) vs 96% (median 520 ng/mL (range 0–1,340,000), both at 4.5 days. CVF concentrations correlated well with infections and also importantly with intracellular levels of tenofovir diphosphate. This will help establish the target dose in future formulations. A separate PK study of 250 samples from 172 highly adherent HIV-negative women showed a mean half-life of about two days with most concentrations over the first few days of ~1000 ng/mL. It is important to note that there are currently no data on appropriate target levels of either tenofovir or tenofovir diphosphate and that data, as for early absorption (ie how soon before sex would you get protection?) will be the focus of the next studies. These results suggest that drug levels are a marker for adherence rather than poor absorption potentially due to interpatient variability of cellular transporters such as MRPs.

A similar relationship was observed between drug levels and acquisition of HSV-2. While oral tenofovir is not able to achieve sufficient drug levels to suppress HSV-2 (EC50 ~10,000 ng/mL), this is possible with a topical gel. 24% of the women with levels below this became HSV-2 positive compared to only 6% of women who had levels above.

Very low levels of tenofovir found in two women in the placebo arm was explained by possible shared sexual partners.

C O M M E N T

The proof of principal that an antiretroviral microbicide can protect against HIV and HSV infection is clearly important news.

The discussion in the published paper suggests that many of the infections may be due to infrequent but very high risk exposures with migrant workers and the investigators noted that the HIV incidence rate was similar in the low frequency placebo group to women who reported much more frequent sex.

In this high-risk setting, infection rates remained high in the women using the active gel (>5/100PY) and protection dropped significantly after 18 months for reasons that are unclear.

The differences in the urban/rural results may just be an issue of overall sample size (as opposed to something connected to the difference in lifetime sex partners or other factors). A good precedent for caution over the adherence analysis however comes from an earlier microbicide study. A similar adherence analysis in the phase 2b PRO2000 HPTN 035 study showed protection rates of 9%, 44% and 78% in low gel users, high gel users, and low condom/high gel users, respectively. Yet this microbicide was subsequently shown not to work.

Of note, the findings on prevention of HSV-2 transmission were more significant and robust than protection against HIV, and this will clearly be the focus for further research study.

References

Unless otherwise stated, all references are to the Programme and Abstracts of the 17th International AIDS Conference, 18-23 July 2010, Vienna.

1. Karim QA et al. Effectiveness of 1% tenofovir vaginal microbicide gel in South African women: results of the CAPRISA 004 trial. Oral abstract TUSS0502.
<http://pag.aids2010.org/session.aspx?s=13>
2. Karim SA et al. Safety of 1% tenofovir vaginal microbicide gel in South African women: results of the CAPRISA 004 trial. Oral abstract TUSS0502.
<http://pag.aids2010.org/Abstracts.aspx?SID=13&AID=17761>
3. Karim QA et al. Effectiveness and safety of tenofovir gel, an antiretroviral microbicide, for the prevention of HIV infection in women. *Science Express*. Published Online 19 July 2010. *Science* DOI: 10.1126/science.1193748.
<http://www.sciencemag.org/cgi/content/abstract/science.1193748>
4. Kashuba ADM et al. Do systemic and genital tract tenofovir concentrations predict HIV seroconversion in the CAPRISA 004 tenofovir gel trial? Oral abstract TUSS0503.

Further information: www.caprissa.org

Quadrivalent HPV vaccine reduces genital lesions and HPV acquisition in men

Simon Collins, HIV i-Base

Heiko Jensen from Praxis presented the results of a large randomised placebo-controlled study in over 4000 men in 18 countries of the Merck quadrivalent HPV vaccine (active against types 6/11/16/18) that was initially studied and approved for use in women. Participants needed to be HIV-negative, HPV seronegative, HPV PCR negative, without genital lesions and to have had fewer than seven sexual partners.

The primary efficacy objective was to demonstrate whether the vaccine reduces the incidence of external genital lesions (EGL) related to HPV6/11/16 or 18.

After approximately two years follow-up, in a per protocol analysis, there were 3 cases of lesions in the active arm vs 31 in the placebo group. This produced efficacy rates of 65.5% (95% CI: 45.8, 78.6) in the ITT and 90.4% (95% CI: 69.2, 98.1) in the per protocol analyses.

The majority of EGL observed were condylomata acuminata; no cases of penile/perianal/perineal intraepithelial neoplasia were observed, though this was a period, follow-up in the study will extend to ten years.

For other endpoints, the rapporteur report noted 89% efficacy in preventing condyloma, 75% efficacy in preventing high grade anal intra-epithelial neoplasia (AIN 2 or more), 78% efficacy in preventing a combined endpoint of AIN or anal cancer over all, and 86% efficacy against "persistent infection" (defined by positive DNA PCR on 2 samples 4 months apart).

References

1. Jessen H et al. Quadrivalent HPV vaccine efficacy against HPV 6/11/16/18 infection and disease in men. 18th IAS Conference, 18–23 July 2010, Vienna. Late breaker oral abstract THLBB0101.
<http://pag.aids2010.org/Abstracts.aspx?AID=17491>
2. Garland et al. Quadrivalent vaccine against Human Papillomavirus to prevent anogenital diseases. *N Engl J Med* 2007; 356:1928-1943
<http://www.nejm.org/doi/full/10.1056/NEJMoa061741>

IAS: ANTIRETROVIRALS

Rilpivirine (TMC-278) vs efavirenz in treatment-naïve patients: phase 3 results

Simon Collins, HIV i-Base

Results from two large international randomised phase 3 studies (ECHO and THRIVE) comparing rilpivirine to efavirenz were combined in one late-breaker presentation. Rilpivirine was developed with a 25mg dose due to phase 2 studies showing similar efficacy at 25mg, 50mg and 75mg and a caution over cardiovascular toxicity (QTc interval) at higher doses.

The two studies differed only in the use of nucleosides with ECHO using tenofovir/FTC in all patients and THRIVE allowing investigator choice. Each study randomised just under 700 treatment-naïve patients with no NNRTI resistance and sensitivity

to RTIs. The primary endpoint was viral load suppression <50 copies/mL at week 48 (ITT-TLOVR analysis) to demonstrate non-inferiority to efavirenz (lower margin -12%), with follow-up continuing to week 96.

Baseline characteristics of the 1368 patients included approximate median CD4 count 250 cells/mm³ (range 1–1,140), median viral load 5 log copies/mL (range 2–7), with just over 25% having a previous AIDS diagnosis, Gender ratio was 75% male: 25% female and mean age 36 years. Racial demographics were roughly 60% Caucasian, 24% Black and 12% Asian. Between 7–9% patients were coinfecting with hepatitis B or C. Nucleoside choice in THRIVE was 60% tenofovir/FTC, 30% AZT/3TC and 10% abacavir/3TC.

At week 48, suppression to <50 copies/mL was achieved in 84% vs 82% patients in the rilpivirine vs efavirenz groups (pooled results difference +1.6; 95%CI -1.7 to +8.8, p<0.0001). This lower bound for the confidence interval was significantly above the -12% lower limit pre-specified for non-inferiority studies. CD4 increases were +192 vs +176 cells/mm³ respectively.

Differences in the rilpivirine vs efavirenz arms were more apparent when looking at reasons for treatment failure, with 9% vs 5% reporting virological failure and approximately 2% vs 7% discontinuing due to side effects, respectively. Around 5% patients discontinued from each arm for other reasons.

In the rilpivirine vs efavirenz groups, 5.5% vs 2.6% of people who never suppressed <50 copies/mL and 3.5% vs 2.2% patients suppressed and then rebounded.

No differences in virological response were reported by gender, race or geographical region, or by nucleoside backbone. However, by baseline viral load the pooled response rates were 90% vs 84% (difference +6.6; 95%CI +1.6, +11.5) in favour of rilpivirine in the <100,000 group and 77% vs 81% (difference -3.6; 95%CI -9.8, +2.5) in favour of efavirenz in the >100,000 group.

People whose treatment failed on rilpivirine developed higher rates of both NNRTI- (63% vs 54%) and NRTI-associated (68% vs 32%) mutations. Rilpivirine was associated with E138K, with 90% of these patients showing phenotypic cross-resistance to etravirine, essentially losing the NNRTI class. People experiencing virological failure on efavirenz commonly developed K103N, which should retain sensitivity to etravirine.

Tolerability results favoured rilpivirine with comparisons below for rilpivirine vs efavirenz. While >90% of patients in each arm reported at least one side effect, grade 2–4 events related to study drug occurred in 16% vs 31%, p<0.0001) and discontinuations due to toxicity occurred in 3% vs 8%, p=0.0005. Neurological side effects occurred in 17% vs 38% (p<0.0001), psychiatric side effects in 15% vs 23% (p=0.0002), abnormal dreams in 8% vs 13% (p=0.0061) and rash in 3% vs 14% (p<0.0001).

Grade 3/4 laboratory abnormalities occurred in 11% vs 18% patients (p<0.001), with higher rates of ALT (1.5% vs 3.4%, p<0.05) and increases in LDL (0.7% vs 4.1%, p<0.0001), triglycerides 0.3% vs 2.2%, p<0.001) and total cholesterol (0.1 vs 2.5%, p<0.0001), all favouring rilpivirine.

Minimal change in mean serum creatinine in both groups with no grade 3/4 creatinine increases and no discontinuations due to renal side effects or cases of acute renal failure. No difference was seen in changes in QTc interval between TMC278 and efavirenz groups.

A one-pill once-daily fixed dose combination of rilpivirine plus tenofovir/FTC is already in development and bioequivalence to the separately dosed compounds were presented as a late breaker. [2]

This study from Gilead was an eight-day, randomised, single-dose, open-label, phase 1 study in 36 HIV-negative adults in fed conditions. Formulation bioequivalence was met based on 90% confidence intervals (CI) for the ratio of geometric least square means (GMR) for C_{max} and AUC. All treatments were generally well tolerated with most adverse events mild in severity. Two participants did not complete the study.

Results from a granule formulation for paediatric dosing were also presented. [3]

C O M M E N T

Rilpivirine data were submitted to the FDA in July and if approved then both the single and 3-in-1 formulations could be available early in 2011.

While the low dose (25mg) makes it easier to develop as a fixed dose combination the lower rates of virological suppression seen when baseline viral load is >100,000 copies/mL may be related to drug exposure levels in some patients. While no clear relationship to dose and response were seen in the smaller phase 2 studies for rilpivirine, the low dose must increase the risk of suboptimal dosing in at least a small percentage of patients with either poorer absorption or higher clearance. The option of dose escalation might be useful to study in this specific patient group.

The option of an alternative to Atripla that has fewer CNS toxicities will clearly be welcomed, though potentially as a switch drug, given the cross-resistance to etravirine and higher risk of virological failure at higher CD4 counts.

References

1. Cohen C et al. Pooled week 48 efficacy and safety results from ECHO and THRIVE, two double-blind, randomised phase III trials comparing TMC278 versus efavirenz in treatment-naïve, HIV-1-infected patients. 18th IAS Conference, 18–23 July 2010, Vienna. Oral abstract late breaker THLB206.
<http://pag.aids2010.org/Abstracts.aspx?SID=1990&AID=17280>
Webcast:
<http://pag.aids2010.org/flash/?pid=113137>

2. Mathias A et al. Bioequivalence of the co-formulation of emtricitabine/rilpivirine/tenofovir DF. 18th IAS Conference, 18–23 July 2010, Vienna. Oral abstract late breaker LBPE17.
<http://pag.aids2010.org/Abstracts.aspx?AID=17780>
3. Crauwels H et al. Relative bioavailability of a concept paediatric formulation of TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI). 18th IAS Conference, 2010, Vienna. Poster abstract THPE0158.
<http://pag.aids2010.org/Abstracts.aspx?AID=12590>

Once-daily nevirapine extended release (XR) is non-inferior to current formulation

Simon Collins, HIV i-Base

First-line nevirapine is rarely used in developed countries and yet still widely used in resource-limited settings. The short-term risk of serious rash and hepatic toxicity, especially during the first two months, make the risk vs benefit less favourable when alternative drugs are easily available. After the initial two months, long-term tolerability is rarely problematic and includes a favourable lipid profile. Although originally approved as a twice-daily combination, the current formulation is commonly used once-daily, especially once viral load has been successfully suppressed to <50 copies/mL.

In this study, a new extended release (XR) formulation was compared to the currently approved 'immediate release' (IR) formulation. Both formulations require two weeks initial treatment with 200 mg once-daily IR.

The VERxVE study was a double-blind, placebo-controlled study run by Boehringer Ingelheim predominantly in North America, Australia and Western Europe, with approximately 10% participants from Latin American (Argentina) and 10% from Africa (South Africa and Botswana). From 1068 patients starting the lead-dose, 55 discontinued, leaving 1013 who were stratified by viral load (< and > 100,000 copies/mL) and randomised 1:1 to XR (n=505) or IR (n=508). All patients used background tenofovir/FTC.

Baseline characteristics included mean CD4 count 228 cells/mm³, median viral load 4.7 log copies/mL, with just over 25% having a previous AIDS diagnosis, Gender ratio was 75% male: 25% female and mean age 38 years.

The primary endpoint of viral suppression to <50 copies/mL at week 48 (TLOVR criteria) was achieved by 81% and 76% of the XR and IR arms respectively (adjusted difference 4.92%: 95%CI -0.11, +9.96), meeting the pre-specified margin for non-inferiority of -10%. Virologic response was reported as being independent of age, gender, race or geographic region. Results were not presented by baseline viral load.

Approximately 20% patients discontinued prior to week 48, primarily due to side effects (7%) or virological failure (5%). Other reasons included loss to follow up, withdrawn consent and poor adherence (all approximately 1.5%). Six patients died (5 IR, 1 XR) none judged related to study drug (atherosclerosis, TB meningitis, 2 x sepsis, myocardial infarction, respiratory alkalosis).

Around 90% of patients reported at least one side effect, but this only led to discontinuation in 6% and 9% of the XR and IR groups. Serious side effects were reported in 11% of patients in each group, with grade 3/4 events in 14% vs 18% and grade 4 events in 3.2% vs 4.5% of the XR and IR groups respectively.

However, there were five cases of Steven's Johnson Syndrome, three prior to randomisation and two in the IR arm afterwards. Discontinuations due to hepatic toxicity occurred in 5 vs 9 patients, and due to rash in 9 vs 12 cases, in the XR vs the IR arms respectively.

The lipid profile of XR was similar to IR formulation: triglycerides reduced by -7%, cholesterol increased by +11%, LDL-cholesterol increased by 7% and HDL-cholesterol by 27%. This resulted in a similar reduction in the TC/HDL ratio of -12% in the XR vs -14% in the IR formulations respectively.

The 24-hour PK sub study in 50 patients at day 28 showed a flat profile, with lower C_{max} and C_{min} and target levels of 3 ug/mL. From the limited results presented, individual patient variability was wide and approximately 50% patients had trough levels below this target. However, reduced response rates only correlated with C_{trough} levels that were less than 1 ug/mL (3/9 patients, 33% response). Rates at 1–2 ug/mL, 2–3 ug/mL, 3–4 ug/mL and >4 ug/mL were all >80%, which lead investigators to state that therapeutic levels were achieved by most patients.

C O M M E N T

Even for a late-breaker, this presentation was data-lite, which was disappointing given the significant size of the study: no range for baseline demographics, VL, CD4 etc; no results by viral load stratification +/- 100,000 copies/mL, or for CD4 response; no laboratory markers results ALT, AST etc; no range or IQR was given for the PK sub study, with half the patients achieving a C_{trough} below the target of 3 ug/mL.

More critically, no details were included about the discontinuations during the lead period, there was no accounting for these in an overall ITT analysis (even though the randomisation occurred after this), and the most important safety issues were edited out.

A question from the audience had to specifically ask about incidence of Stevens-Johnson Syndrome, rash-associated discontinuations and hepatotoxicity and the presenter laughed when she had to answer, as if she had been caught out. Even though this was a non-inferiority study, it provided little understanding of whether the improved PK profile has an impact on reducing serious adverse events.

Reference

1. Gathe J et al. Comparison of 48 week efficacy and safety of 400 mg QD nevirapine extended release formulation (Viramune XR) versus 200 mg BID nevirapine immediate release formulation (Viramune IR) in combination with Truvada in antiretroviral (ARV) naive HIV-1 infected patients (VERxVE). 18th IAS Conference, 18–23 July 2010, Vienna. Oral abstract late breaker THLBB202.
<http://pag.aids2010.org/Abstracts.aspx?SID=1990&AID=17270>
Webcast:
<http://pag.aids2010.org/flash/?pid=113133>

GSK572: second-generation integrase inhibitor

Simon Collins, HIV i-Base

Results from a phase 2b dose finding study of the Shionogi/GSK(ViiV) integrase compound S/GSK1349572 (GSK572) were also presented as a late breaker. [1]

Approximately 200 HIV-positive people were randomised 1:1:1:1 to 10mg, 25mg or 50mg of GSK572 or efavirenz 600mg once-daily, plus either tenofovir/FTC or abacavir/3TC.

As with other integrase inhibitors, GSK572 produced more rapid viral load reductions compared to efavirenz (66% vs 18% at week 4, $p < 0.001$ and $>90\%$ vs 60% by week 16) though baseline viral load was originally very low (approximately 30,000 copies/mL) with only 26% participants $>100,000$ copies/mL. Other baseline characteristics included being largely male (86%) and white (80%), with mean CD4 count of 324 cells/mm³.

There were more side effects reported in the efavirenz arm, including more discontinuations, with GSK572 no safety concerns over this short period. One patient in each arm was defined as a virologic failure at week 16. No integrase mutations were seen in the GSK572 patient and the efavirenz patient suppressed by week 24. The only defined serious drug-related adverse event was an attempted suicide on the efavirenz arm. Median CD4 (IQR) increases from baseline to week 16 were similar, in favour of GSK572 +165 (88–242) vs +116 (66–226) cells/mm³. Grade 3/4 laboratory abnormalities were $<10\%$ in all arms with no relationship to dose. Efavirenz had a greater negative impact on lipids (increases in triglycerides, total and LDL cholesterol).

The degree to which people who already have resistance to raltegravir could benefit from GSK572 was addressed in results from an ongoing 24-week phase 2b study in 27 patients with resistance to raltegravir, presented by Joe Eron. [2]

Raltegravir is associated with three primary resistance pathways: Y143, N155 and Q148H (>10 -fold) with the accumulation of mutations associated with higher resistance and reduced impact of impaired fitness. For inclusion in the study, integrase resistance required Q148H/K/R alone or with one or more Q148-associated mutation, N155H and/or Y143H with or without additional mutations. Participants discontinued raltegravir and substituted GSK572 50mg once-daily while continuing their failing regimen to Day 11 when the background regimen was optimised, and 572 continued. Phenotypic susceptibility to GSK572 was then compared to virological responses. The primary endpoint was suppression to <400 copies/mL or a >0.7 log reduction in viral load at day 11 with change in viral load as a secondary endpoint.

By day 11, 21/27 participants either reduced viral load to <400 copies/mL or had a >0.7 log drop in viral load. Response rates differed by baseline genotype: 16/16 with N155H or Y143H or Q148 single mutant pathways; 3/4 with Q148 plus one mutation; 0/5 with Q148 plus ≥ 2 mutations; 2/2 other. See Table 1.

Table 1: Viral load response by baseline genotypic mutations

	Primary endpoint n/N (%)	Secondary endpoint Mean (SD)
All participants	21/27 (78%)	-1.45 (SD 0.76)
Q148H/K/R + \geq Q148-associated mutation at L74, E138 or G140 (n=9)	3/9 (33%)	-0.72 (SD 0.63)
All other genotypes from N155H and Y143H pathways (n=18)	18/18 (100%)	-1.82 (SD 0.53)

There was a positive correlation between baseline sensitivity to GSK572 and change in viral load at day 11 (correlation $r=0.79$, $p < 0.001$). GSK572 was well tolerated: the most frequent side effects were diarrhoea (n=3) and insomnia (n=3), two subjects experienced an SAE considered unrelated to study drug.

Details of phenotypic and genotypic changes during this study were presented in a separate poster by Bonaventura Clotet. [3]

Over the short study period, there was little evidence of new integrase-associated mutations or a reduction in sensitivity to GSK572. However, one person with mixed Y143+Q148 mutations at baseline had a susceptibility to GSK572 change from $FC=6.49$ at baseline to $FC=38$ at day 11. The day 11 genotypic changes included both wild-type to mutant L74I/M, E138E/A and mutant Y143H to Y143Y. Another patient without genotypic resistance changes had susceptibility increase from $FC=21$ to $FC=40$. Full details are included in the poster, also available online. [4]

C O M M E N T

These early results highlight the promise of integrase inhibitors as a class both for naive and experienced patients. Picking an early time point and a patient group with low baseline viral load will produce promising results if the study endpoint is percentage of patients below 50 copies/mL.

While GSK572 retained activity in many of these patients with low-level resistance, integrase mutations have the potential to rapidly accumulate and this was most significant for the 148 pathway. [5] People currently unsuppressed on raltegravir-containing regimens may want to switch to a combination that with not jeopardise their option to use this pipeline compound.

While the 50mg dose has apparently been selected for further development, it would be important to know whether higher doses would be able to overcome more extensive integrase resistance.

Reference

Unless otherwise stated, all references are to the Programme and Abstracts of the 17th International AIDS Conference, 18-23 July 2010, Vienna.

1. Nichols G et al. Once-daily S/GSK1349572 as part of combination therapy in antiretroviral naïve adults: rapid and potent antiviral responses in the interim 16-week analysis from SPRING-1 (ING112276). Oral late breaker THLBB205.
<http://pag.aids2010.org/Abstracts.aspx?SID=1990&AID=17600>
2. Eron J et al. Activity of a next generation integrase inhibitor (INI), S/GSK1349572, in subjects with HIV exhibiting raltegravir resistance: initial results of VIKING study (ING112961). Oral abstract MOAB0105.
<http://pag.aids2010.org/Abstracts.aspx?SID=631&AID=12762>
3. Clotet B et al. HIV integrase genotypic and phenotypic changes between Day1 and Day11 in subjects with raltegravir (RAL) resistant HIV treated with S/GSK1349572: results of VIKING study (ING112961). Poster abstract TUPE0130.
<http://pag.aids2010.org/Abstracts.aspx?AID=15484>
4. <http://pag.aids2010.org/PDF/15484.pdf>
5. Integrase inhibitor resistance and cross-resistance: weighing viral fitness and the option to benefit from second-generation compounds. HTB August 2008.
<http://i-base.info/htb/602>

TBR-652: early results for CCR5 inhibitor

Simon Collins, HIV i-Base

David Martin from Tobira therapeutics presented results for TBR-652, a CCR5 inhibitor with CCR2 activity. CCR2 is associated with and studied in association with diseases related to immune activation.

In this 10-day dose-ranging monotherapy study, 54 treatment-experienced but CCR5-naïve patients were randomised to 25, 50, 75, 100, or 150 mg TBR-652, all once-daily, or to a placebo group. Inflammatory markers (MCP-1, hsCRP and IL-6) were measured at day 1 and 10.

Baseline median viral load was 4.5 log (range 3.1–6.0), approximately 30,000 copies/mL, but this presumably limited the ability to detect maximum changes for patents starting with low viraemia.

At day 10 viral load reductions of 1.4–1.8 log were seen in the 50–150 mg groups. Side effects were generally mild but were dose-related, and were higher in the 100 mg and 150 mg groups.

Although MCP-1 increased in all groups except placebo (significantly compared to placebo in the 50, 100 and 150 mg groups) this was markedly higher for the 150mg arm (by approximately 350pg/mL).

Phase 2b studies of the compound are expected to start early in 2011.

Reference

Martin DE et al. TBR-652, a potent dual chemokine receptor 5/chemokine receptor 2 (CCR5/CCR2) antagonist in phase 2 development for treatment of HIV infection. 18th IAS Conference, 18–23 July 2010, Vienna. Oral abstract MOAB0104.

<http://pag.aids2010.org/Abstracts.aspx?SID=631&AID=8023>

Maraviroc vs atazanavir/r in treatment-naïve patients

Simon Collins, HIV i-Base

Maraviroc, was not approved for first line therapy when it failed to meet non-inferiority criteria compared to efavirenz. The results from phase 3 studies were complicated by the dependence on early less sensitive tropism test and an unexplained difference between responses in northern compared to southern hemisphere countries. This has limited the potential to use maraviroc earlier in treatment.

In Vienna, interim 24-week results were presented from a pilot phase 2b study of boosted atazanavir plus either maraviroc (n=60) or tenofovir/FTC (n=61). [1] A larger phase 3 study with the same design is also ongoing. This is an international study with over 30 sites in the US, Germany and Spain, although it recruited mainly from US sites.

Baseline demographics included 85-93% male, 75% white, 20% black, median age 37 years (range 18-68) with median (range) CD4 and viral load of 350 cells/mm³ (110-900) and 4.6 log copies/mL (3.4-5.9), respectively.

The study was not powered for treatment effect. Lower virological response (80 vs 89% <50 copies/mL) and increased side effects (ie 33% vs 23% grade 3/4 including 26% vs 13% hyperbilirubinaemia), were reported in the maraviroc vs atazanavir/r arms respectively. Virological response by baseline viral load was 80% vs 95% and 81% vs 77% for the <100,000 and >100,000 copies/mL maraviroc and tenofovir/FTC groups respectively. The PK sub-study in 15 patients – important because a positive interaction supports maraviroc 150mg once-daily with some boosted PIs – reported that all patients exceeded the Cave target of ≥ 75 ng/mL at week 2

Reference

1. Portsmouth S et al. Safety and immunovirological activity of once daily maraviroc (MVC) in combination with ritonavir-boosted atazanavir (ATV/r) compared to emtricitabine 200mg/tenofovir 300mg QD (TDF/FTC) + ATV/r in treatment-naïve patients infected with CCR5-tropic HIV-1 (Study A4001078): A week 24 planned interim analysis. 18th IAS Conference, 18-23 July 2010, Vienna. Late breaker abstract THLB203. <http://pag.aids2010.org/Abstracts.aspx?SID=1990&AID=17280>

Unboosted twice-daily atazanavir plus raltegravir

Simon Collins, HIV i-Base

A phase 2b comparison study compared an experimental unboosted combination of atazanavir (ATZ) 300mg plus 400mg raltegravir (RAL), both twice-daily, to boosted atazanavir/r (300/100mg) plus tenofovir/FTC, both once-daily (the SPARTAN study). The results were presented as a late breaker.

This small study randomised 94 people 2:1 to atazanavir/raltegravir (n=63) or the control group (n=31). The primary analysis at week 24 (percentage of patients with viral load < 50 copies/mL) used confirmed virologic response (CVR NC=F). The study was not powered to detect differences between the groups.

Baseline characteristics included 90% male, 85% white, mean CD4 250 cells/mm³ and mean viral log of 4.9 logs with approximately 50% patient having viral load >100,000 copies/mL.

About 10% patients in each arm discontinued treatment, all of who were undetectable in the atazanavir/raltegravir and they remained suppressed to week 24. The raltegravir arm produced a more rapid virological response, with 75% vs 63% undetectable at week 24, with higher CD4 increases in the experimental arm +166 vs +127 cells/mm³. Viral response rates were slightly higher using less stringent analyses. Of the 11 patients with virological failure in the raltegravir arm (>50 copies/mL; 6/11 were >400 copies/mL), eight had baseline viral load >250,000 copies/mL. Four patients had resistance testing, with 3/4 showing integrase mutations and the fourth phenotypic resistance. In the control group there were eight failures >50 copies/mL (4/8 with baseline viral load >250,000 copies/mL) but only one at >400 copies/mL. No resistance was identified to atazanavir in either arm.

A PK substudy showed approximately 39% increased AUC and 30% increased C_{min} for atazanavir twice-daily compared to levels seen with ritonavir boosted plus tenofovir.

Side effects were broadly similar, except significantly higher bilirubin levels in the raltegravir arm (60% vs 43% grade 3/4; and 20% vs 0% grade 4). Lipid differences included higher HDL cholesterol and lower triglycerides in the raltegravir arm. LDL and total cholesterol were similar.

These differences, together with no virological benefits compared to standard of care regimens, and the twice-daily regimen, were sufficient for BMS to close the study early.

C O M M E N T

For UK patients at least, the cost of double-dose atazanavir plus raltegravir would limit the use of this combination, even if the results had been more successful.

Reference

1. Kozal MJ et al. The SPARTAN study: a pilot study to assess the safety and efficacy of an investigational NRTI- and RTV-sparing regimen of atazanavir (ATV) experimental dose of 300mg BID plus raltegravir (RAL) 400mg BID (ATV+RAL) in treatment-naïve HIV-infected subjects. 18th IAS Conference, 18-23 July 2010, Vienna. Vienna. Late breaker abstract THLB204. <http://pag.aids2010.org/Abstracts.aspx?SID=1990&AID=17423>

CASCADE analysis of when to start treatment

Simon Collins, HIV i-Base

Joe Eron from University of North Carolina, presented an analysis from the CASCADE seroconverter study, looking at rates of AIDS events and deaths for treatment by baseline CD4 count. The presentation was given in the context of the debate about when to start treatment. [1]

The summary results supported current guidelines to start after CD4 count drops below 350 cells/mm³. The group also reported a significant benefit from starting at 350-500, but still emphasised that due to the difficulties of interpreting cohort data, the randomised START study was still essential to address this question. Of note, the analysis found no benefit from starting at CD4 counts over 500 cells/mm³.

CASCADE is an international collaboration of cohorts that includes people who have been diagnosed in primary HIV infection, with recent diagnoses confirmed by a recent (<1 year) negative test or PCR-positive. The cohort includes 52,268 person years of follow up (PYFU), median 4.7 years, from 9,455 people: 78% male. 56% MSM, 25% MSW, median age at diagnosis 30 years (IQR 25–37). From this group, 8.6% (n=812) developed AIDS and 5.8% died (n=544).

In this analysis, the group pooled observations from 161 monthly sub-cohorts from January 1996–May 2009, based on whether 3-drug HAART was started in each month or deferred. Primary endpoints included time to first AIDS diagnosis, all-cause mortality and last time alive, with secondary endpoints including time to death. Covariates with each monthly update included age, gender, CD4, viral load, injecting drug use, viral hepatitis, seroconversion illness and calendar year. The methodology including complicated weighting analyses to reduce lead-time bias included looking at the probability of starting or deferring as a factor of patient characteristics using these covariates.

The study was more strongly weighted in terms of both patient numbers and events to higher CD4 strata (see Table 1).

Table 1: Patients and events by CD4 strata

CD4 count	n	Initiated	Events / deaths	PYFU
0-49	183	107	102	664
50-199	1,521	832	353	6,934
200-349	4,459	1,792	732	22,106
350-499	5,527	1,005	815	29,653
500-799	5,162	615	696	28,631

Note: n, events and PYFU are not unique across CD4 strata

Adjusted hazard ratios (aHR), 3-year cumulative risk differences (RD), and numbers needed to treat (NNT) for 3 years to prevent one additional outcome were calculated. As with other studies, HAART was strongly associated with better outcomes for CD4 counts <200 cells/mm³. However, the study found no benefit to starting at 500-799 cells/mm³ and a relatively small decrease in risk among those with CD4 counts of 350-499 cells/mm³, see Table 2.

The absolute differences between the <350 and 350-500 groups were low over one year. The NNT at CD4 350-499 was 34 to prevent one AIDS event or death within three years and was 74 to prevent one death over the same period.

The presenter emphasised the importance of the data from the randomised START trial to be able to exclude confounders associated with cohort data (including non-AIDS events, comorbidity, concurrent medications, current IDU, depressions and social support). Similarly, viral response and treatment interruptions were not analysed to determine relative and absolute risk in patients on successful treatment.

Table 2: Adjusted relative and absolute effects of starting vs deferring HAART

CD4 cells/mm ³	aHR AIDS/death (95%CI)	3-Yr RD AIDS/death (95%CI)	3-Yr NNT AIDS/death (95%CI)	aHR death alone (95%CI)	3-Yr RD death alone (95%CI)	3-Yr NNT death alone (95%CI)
0-49	0.32 (0.17, 0.59)	-30.0 (-45.1, -15.0)	3 (2, 7)	0.37 (0.14, 0.95)	-18.2% (-32.0, -4.4)	6 (3, 23)
50-199	0.48 (0.31, 0.74)	-15.0 (-19.7, -10.3)	7 (5, 10)	0.55 (0.28, 1.07)	-7.2% (-10.1, -4.4)	14 (10,23)
200-349	0.59 (0.43, 0.81)	-4.8% (-7.0, -2.6)	21 (14, 38)	0.71 (0.44, 1.15)	-1.4% (-3.0, 0.3)	74 (33, ∞)
350-499	0.75 (0.49, 1.14)	-2.9% (-5.0, -0.9)	34 (20, 115)	0.51 (0.33, 0.80)	-1.4% (-2.2, -0.6)	71 (45, 165)
500-799	1.10 (0.67, 1.79)	0.3% (-3.7, 4.2)	∞ (n/a)	1.02 (0.49, 2.12)	-0.4% (-2.0, 1.2)	239 (49, ∞)

C O M M E N T

This study was less powered than both the ART-CC and NA-ACCORD cohort studies that have reported conflicting results when looking at cohort data to inform the question of optimal CD4 count to start treatment. However the advantage of this study is that the group looked at absolute events rather than relative estimates. At 350-499 there is seems to be a low incidence of events anyway and the benefits don't

appear till 3 years after initiation- which all needs to go into the decision weighing the risk:benefit ratio.

This is complicated in the CASCADE analysis as non-AIDS events are not recorded and there is sometimes incomplete information on the cause of death.

It was notable that the presentation referred to the need for data from the randomised START study to answer the question of when to start treatment at higher CD4 counts. [2]

References

1. Eron J et al. HAART initiation and clinical outcomes: insights from the CASCADE cohort of HIV-1 seroconverters on 'When to Start'. 18th IAS Conference, 18–23 July 2010, Vienna. Oral abstract late breaker THLBB201.
<http://pag.aids2010.org/Abstracts.aspx?SID=1990&AID=16875>
<http://pag.aids2010.org/session.aspx?s=1990>
2. Strategic Timing of AntiRetroviral Treatment (START) study.
<http://insight.cabr.umn.edu/start/>

IAS: PREGNANCY & MTCT

Impact of antiretroviral PMTCT prophylaxis regimens on subsequent maternal disease progression in Kesho Bora

Polly Clayden, HIV i-Base

HAART regimens used as prophylaxis during pregnancy and breastfeeding are effective in reducing mother to child transmission and are standard of care in industrialised countries.

There are some concerns, particularly since the results from the SMART study, that stopping HAART prophylaxis at the end of breastfeeding may have adverse effects on maternal health and survival.

The Kesho Bora study randomised pregnant women with CD4 counts 200-500 cells/mm³ at 28-36 weeks of pregnancy, to receive either maternal HAART (zidovudine + lamivudine + lopinavir/ritonavir to six months after delivery or breastfeeding cessation if earlier) or short- course zidovudine plus single-dose nevirapine in labour. All infants received single-dose nevirapine post partum. The results, presented at the IAS conference last year (and reported in the August 2009 edition of HTB) showed HIV transmission rates to be almost identical. [1, 2]

These data also contributed to the evidence that enabled the WHO to recommend that HIV-positive mothers or their infants take antiretrovirals while breastfeeding to prevent mother-to child transmission.

In an oral late breaker, Tim Farley presented findings from an evaluation of maternal HIV disease progression at 18-24 months post delivery. [3]

Disease progression endpoints were stage 4 or CD4 <200 cells/mm³ and stage 3 or CD4 <350 cells/mm³. These represent previous and current WHO thresholds for initiating antiretroviral treatment.

There were 412 women in each arm, who had received prophylaxis for a median of 6 weeks before delivery. Women receiving HAART received it for a median of 19 additional weeks during breastfeeding.

The investigators found lower rates of progression to stage 4 or CD4 200 cells/mm³ among women receiving HAART at all time points from delivery when all women were included in the analysis, p=0.003. See Table 1. But rates were similar after stopping antiretroviral prophylaxis, p=0.159. See Table 2.

Table 1: Progression rates from delivery to stage 4/CD4<200 – all women

Regimen	6 months	12 months	18 months
Short course	(408) 6.4%	(362) 11.8%	(303) 19.6%
HAART	(405) 2.8%	(376) 6.1%	(332) 12.4%

Table 2: Progression rates from stopping prophylaxis to stage 4/CD4<200 – all women

Regimen	6 months	12 months	18 months
Short course	6.4%	11.8%	19.6%
HAART	(386) 2.6%	(358) 7.9%	(213) 14.7%

They performed the same analysis censoring women with CD4 >350 cells/mm³ and there was a significant difference in progression rate from delivery, p=0.002, and no difference from stopping prophylaxis, p=0.107. See Tables 3 and 4.

Table 3: Progression rates from delivery to stage 4/CD4<200 – women CD4 <350 at entry

Regimen	6 months	12 months	18 months
Short course	(226) 10.6%	(192) 20.0%	(152) 32.4%
HAART	(226) 4.9%	(209) 10.1%	(186) 20.4%

Table 4: Progression rates from stopping prophylaxis to stage 4/CD4<200 – women CD4 <350 at entry

Regimen	6 months	12 months	18 months
Short course	(226) 10.6%	(192) 20.0%	(152) 32.4%
HAART	(217) 4.7%	(199) 12.0%	(107) 25.9%

A further analysis was performed looking at rates of progression to stage 3 or CD4 <350 cells/mm³ among women with CD4 ≥350 cells at entry. This gave differences of p=0.002 and p=0.013 from delivery and stopping prophylaxis respectively. See Tables 5 and 6.

Table 5: Progression rates from delivery to stage 3/CD4<350 – women CD4 ≥350 at entry

Regimen	6 months	12 months	18 months
Short course	(182) 12.0%	(151) 15.7%	(129) 24.1%
HAART	(179) 2.9%	(162) 6.1%	(138) 10.4%

Table 6: Progression rates from delivery to stage 4/CD4<200 – women CD4 <350 at entry

Regimen	6 months	12 months	18 months
Short course	(182) 12.0%	(151) 15.7%	(129) 24.1%
HAART	(168) 3.7%	(152) 8.2%	(98) 9.5%

Overall the investigators concluded that receiving maternal HAART as prophylaxis and stopping after breastfeeding did no harm compared to short course zidovudine plus single dose nevirapine. In the discussion following the presentation it was suggested that the conclusion that this strategy did “no harm” was difficult to make without having included an arm in which treatment was continued. Dr Farley agreed that this was also an important question but the study design reflects an era when even using HAART and continuing it through breastfeeding in healthier women was considered quite radical in resource limited settings.

The other important conclusion from the analysis is that the high rate of progression to CD4 <200 cells/mm³ in both arms among women with <350 cells/mm³ at entry, reinforces WHO guidance to treat from 350 cells/mm³ and emphasises the importance of early treatment initiation in pregnant women or women desiring pregnancy.

References

1. Farley T and The Kesho Bora Study Group. Impact of triple ARV prophylaxis during pregnancy and breastfeeding compared with short-ARV prophylaxis for MTCT prevention on maternal disease progression. 18th IAS Conference, 18–23 July 2010, Vienna. Oral abstract ThLBB105. <http://pag.aids2010.org/Abstracts.aspx?SID=644&AID=17446>
2. Clayden P. Reducing HIV transmission during breastfeeding. HIV Treatment Bulletin, August 2009. <http://i-base.info/htb/4466>

Birth outcomes with antiretroviral exposure

Polly Clayden, HIV i-Base

In a session at the IAS 2010 conference entitled Antiretrovirals during pregnancy and breastfeeding: Importance of surveillance, data were presented describing what we know (or don't know) about outcomes among infants exposed to antiretrovirals in utero. [1]

New data from the US was shown by George Siberry that evaluated growth parameters in tenofovir exposed infants. [2]

Lynne Mofenson provided a useful overview of the implications for women and children in developing countries. Nathan Ford presented findings from a meta-analysis looking at the safety of efavirenz in the first trimester of pregnancy (which we reported in the June 2010 edition of HTB) [3, 4, 5]. And Karen Beckerman showed data from the Antiretroviral Pregnancy Registry (APR) that looked at preterm delivery (PTD) and low birth weight (LBW) in this cohort. [6]

There was agreement among the presenters on the importance of surveillance, both from industrialised and resource-limited settings. Nathan Ford rightly pointed out that, although the largest data set contributing to their review was from the APR, the second largest set came from one centre, the Frere Hospital in South Africa. It is very likely that much important pregnancy outcome data is simply not being captured.

During discussions with the audience, Graham Taylor emphasised the role of reporting bias, particularly with respect to efavirenz. This is the only antiretroviral with preclinical primate data and in turn has the strongest FDA category and the most scrutiny in pregnancy. The point was made that the only report of myelomeningocele in the prospective reports section of the APR was of a child exposed to efavirenz during the first trimester. However, the absence of other reports of myelomeningocele in the registry, that

might be expected given a general background rate in the order of 1 per 1000 births, despite almost 12,000 evaluable prospective case reports was also commented upon.

There was agreement that when a mother needs treatment for her own health the benefits of antiretrovirals in pregnancy hugely outweigh any theoretical risks.

Tenofovir exposure and low birth weight and infant growth

Preclinical studies showed that tenofovir crosses the placenta. There have been concerns that undermineralisation of foetal bones was observed in animal studies. Tenofovir use in pregnancy is on the increase but there are limited human data describing infant outcomes.

George Siberry presented data on behalf of the Pediatric HIV/AIDS Cohort Study (PHACS) Surveillance Monitoring of Antiretroviral Toxicity (SMARTT) study. SMARTT enrolls antiretroviral exposed uninfected children in the US at two weeks of age (dynamic cohort) and at one year to 12 years of age (static cohort).

This study was conducted to evaluate the association of maternal tenofovir use and growth measures (weight, length, head circumference) at birth and at one year of age.

Maternal information is collected prospectively for dynamic cohort and retrospectively for static cohort.

In this study, LBW was defined as <2.5kg. Z-score < -1.5 was used to define small-for-age for length and HC at birth and length, weight and HC at one year.

Logistic regression models for LBW and growth outcomes were fit, controlling for potential confounders, including demographic and socioeconomic characteristics, maternal health status (CD4< 250, viral load>1000 copies/mL, genital infections) and substance use during pregnancy.

The evaluation revealed 1887 children with birth weight data for which birth length and HC measurements were available from 739 children from the dynamic cohort. Growth measurements at one year were recorded for 532 children (weight length and HC), of which 356 were from the dynamic and 176 from the static cohorts.

The investigators found that maternal tenofovir use increased from 15% in 2003 to 39% in 2009. Overall 21% of the cohort was exposed to tenofovir including 12% receiving it from the first trimester.

Among the 20% of infants with LBW, there was no difference in those exposed to tenofovir (20.7 vs 19.5%). After adjusting for confounders there remained no effect (aOR: 1.03, 95% CI 0.75-1.40, p=0.87). Neither was there an association between tenofovir use and short length or small HC at birth.

However, at one year of age children exposed in utero to tenofovir in this cohort had a marginally increased risk of low weight (aOR:1.76, 95% CI 1.01-3.05).

The investigators suggested that this observation requires confirmation in further studies.

Preterm birth in the Antiretroviral Pregnancy Registry

Some reports suggest increase prevalence of PTD and LBW associated with protease inhibitor (PI) exposure, while reports from other cohorts do not.

Karen Beckerman presented data from an evaluation from the Antiretroviral Pregnancy Registry (APR) of birth weight and estimated gestational age of live births reported to this registry.

We have reported findings from the APR in previous issues of HTB. It is a prospective registry with which providers register pregnant women with antiretroviral exposure during their pregnancy and in turn provide outcome data.

In this analysis the investigators compared the prevalence of PTD at <37 and <32 weeks gestation, and LBW <2.5kg and very LBW <1.5kg among infants exposed to one antiretroviral or regimens of two or more antiretrovirals that either included a protease or did not.

Since 1989 and as of January 31st 2009 the APR had enrolled 12451 pregnancies; 426 (3.4%) had outcomes pending and 1082 (8.7%) were lost to follow up. There were 9513/10022 (95%) singleton live births with evaluable data.

Dr Beckerman reported that, in this analysis, the investigators found no differences in the prevalence of either PTD <37 weeks, 14.7% vs 13.0%, or LBW <2.5kg, 15.4% vs 16.1%, between the 1404 infants exposed to one antiretroviral compared to 8109 infants exposed to combination antiretroviral regimens.

Of those exposed to combination antiretroviral regimens, PTD <37 weeks was higher among those receiving PI-containing regimens (n=4658) compared to non PI-containing regimens (n=3451), 14.1% vs 11.8%, p=0.003, as was LBW <2.5kg p=0.001.

But PTD <32 weeks was no different between those exposed to regimens containing a PI compared to regimens without a PI, 2.3% vs 1.8%, p=0.16.

They also found that very LBW <1.5kg was more prevalent in infants exposed to PI-containing regimes compared to those without a PI, 17.4% vs 14.0%. But after controlling for race very LBW <1.5kg, for each exposure group, overlapped prevalence in the background population.

They found that there was no difference in very LBW <1.5kg in infants exposed to PI containing regimens compared to those exposed to one antiretroviral. They also found exposure to PI-containing regimens was protective against PTD <32 weeks, p=0.05.

They noted that very LBW <1.5kg was lower in all groups exposed to combination antiretroviral regimens than published reports of cohorts of HIV-exposed infants not exposed to antiretrovirals.

They concluded that optimised combination antiretroviral regimens offer profound benefit to maternal survival and vertical transmission prevention.

They added: "We hypothesise that exposure to PI could be a surrogate marker for immunologic and other factors contributing to preterm parturition and low birth weight syndromes in HIV-exposed neonates."

C O M M E N T

The debate on whether combination therapies, particularly PI-based HAART are associated with PTD continues.

Given that most of the data suggesting that there is no association has come from the US and that most of the data (85%) in the APR is also from the US, it should perhaps come as no surprise that no strong link with HAART was found.

The data suggesting a link with PTD is mostly from Europe, however in her presentation Lynne Mofenson drew attention to the recent RCT from Botswana investigating HAART during pregnancy and breastfeeding to reduce HIV transmission in which an increased rate of PTD was found in the PI-based arm compared with the triple NRTI.

References

Unless otherwise stated, all references are to the Programme and Abstracts of the 17th International AIDS Conference, 18-23 July 2010, Vienna.

1. Antiretrovirals during pregnancy and breastfeeding: Importance of surveillance. Session WEAX01
<http://pag.aids2010.org/session.aspx?s=181>
2. Siberry G et al. Safety of tenofovir use during pregnancy: associations with low birth weight and early growth in HIV-exposed uninfected infants. Oral abstract WEAX0103.
<http://pag.aids2010.org/Abstracts.aspx?SID=181&AID=5375>
3. Mofenson L. Overview on antiretrovirals during pregnancy and breastfeeding: importance of surveillance and implications for developing countries. Session introduction WEAX0101.
4. Ford N et al. Safety of efavirenz in the first trimester of pregnancy: a systematic review and meta-analysis of outcomes from observational cohorts. Oral abstract WEAX0102.
<http://pag.aids2010.org/Abstracts.aspx?SID=181&AID=8350>
5. Clayden P. Pregnancy outcomes with efavirenz. HTB. Volume Volume 11 Number 5/6 May/June 2010.
6. Beckerman K et al. Preterm Birth (PTB), low birth weight (LBW) and fetal antiretroviral (ARV) exposure: Gestational age (EGA) and birth weight data from 10022 singleton live births (LB) reported to the Antiretroviral Pregnancy Registry (APR) 1989 through 31 January 2009. Oral abstract WEAX0105.
<http://pag.aids2010.org/Abstracts.aspx?SID=181&AID=1161>

IAS: PAEDIATRIC CARE

New WHO guidelines for children

Polly Clayden, HIV i-Base

The new WHO 2010 paediatric guidelines – Antiretroviral Therapy for HIV Infection in Infants and Children: Towards Universal Access - also summarised on their website in a preliminary version for programme planning in June, were released at IAS 2010.

Lynne Mofenson provided an excellent summary of the new guidelines at the paediatric meeting and Shaffiq Essajee in the Early Infant Diagnostics (EID) session at IAS. [1,2] We will review developments in diagnostics including EID in the next issue of HTB.

When to start

Universal treatment is recommended for all infants and young children under two years irrespective of CD4 or clinical indication. The recommendation is strong for less than 12 months and conditional for 12-24 months.

Data to guide when to start for children one to five years old are scant and this is reflected in differences in recommendations between guidelines (see statement from PENTA in the comment below). After five years of age, guidance is similar to that for adults (see Table 1). Table 2 shows a comparison between the 2006 and 2010 WHO guidelines.

Table 1: WHO 2010 Guidelines When to Start Children on ART

Age	WHO 2010 Guidelines
Less than 24 months	
	All
24–59 months	
Clinical	Stage 3 or 4
Immunological*	< 25% or < 750
5 years and older	
Clinical	Stage 3 or 4
Immunological	< 350

*CD4 percentage/absolute CD4 count mm³

Table 2: Comparing WHO guidelines 2006 and 2010

2006	Immune marker	Age specific recommendations to initiate ART				Clinical criteria
		<12 months	12-35 months	36-59 months	≥ 5 years	
	CD4 percent	All	<20%	<20%	<15%	Stage 4 disease Stage 3 disease (ART initiation may be delayed in some cases)
	CD4 count/mm ³	All	<750 cells	<350 cells	<200 cells	
	TLC/mm ³	All	<3000 cells	<2500 cells	<2000 cells	
2010	Immune marker	Age specific recommendations to initiate ART			Clinical criteria	
		<24 months	24-59 months	>5 years	Stage 3 and 4 disease	
	CD4 percentage	All	<25%			
	CD4 count mm ³	All	<750 cells	<350 cells		

Adapted from WHO 2010 revision. Essajee S.

C O M M E N T

PENTA have published a letter in support of the new guidance for resource limited settings and are continuing to recommend PENTA guidance ie universal treatment for infants less than 12 months and immunological and clinical criteria for those above for treating children in Europe. In the letter they write:

“Both PENTA 2009 and WHO 2010 guidelines considered the same body of evidence, and several experts took part in the drafting of both sets of recommendations. The universal treatment of infants is based on evidence from the CHER study, children over five are treated at adult thresholds in both guidelines, based on comparisons between the HPPMCS child cohort and CASCADE adult seroconverter cohort. The recommendations for children aged between 2 and 5 are based on cohort data, largely from the HPPMCS study.

The new recommendations in the WHO guidance for children between age one and five are based on programmatic considerations, in particular the ability to closely monitor a child clinically and by repeat CD4 count measurement if they are not started on ART. Such monitoring is available in Europe, and in many settings outside Europe. It is also noted that the evidence basis for these recommendations is weak or very weak, and that studies expected to publish results soon may shed more light on the subject. We endorse WHO’s recommendation to treat early where the ability to provide monitoring is limited, as well as the call for more research to provide RCT evidence for treatment initiation thresholds after infancy. We continue to recommend PENTA 2009 guidance as appropriate for European and other settings with the facility to monitor closely children in whom treatment is deferred.”

<http://www.pentatrials.org/PENTA%20letter%20re%20WHO%20jul%202010.pdf>

What to start with

Recommended regimens are:

- For children less than two not exposed to maternal or infant nevirapine or whose exposure status is unknown: nevirapine plus two NRTIs.
- For children exposed to maternal or infant nevirapine or other NNRTIs used for maternal treatment or PMTCT: lopinavir/ritonavir plus two NNRTIs (with the caveat that nevirapine is better than nothing).
- For children over two but under three: nevirapine plus two NRTIs.
- All others (irrespective of nevirapine exposure): nevirapine or efavirenz (efavirenz preferred for TB treatment)
- Under three and needs TB treatment: nevirapine plus two NRTIs or abacavir plus lamivudine plus zidovudine/stavudine.

- Adolescents over 12 with hepatitis B: tenofovir plus lamivudine/emtricitabine plus efavirenz/nevirapine (can take FDC of lamivudine/emtricitabine plus efavirenz if this is available).
- Adolescents with hepatitis C: preferred regimen is efavirenz plus two NRTIs.

The guidelines also recommend a preferential order of NRTIs (zidovudine/lamivudine > abacavir/lamivudine > stavudine/lamivudine).

They recommend that any child with active TB begin TB treatment immediately and start ART in the first eight weeks of TB treatment.

For children already on ART who develop TB, they recommend that ART regimens may need to be adjusted to decrease the potential for toxicities and interactions: if on nevirapine substitute for efavirenz if over three years; if under three ensure nevirapine is at high dose (2 mg/m²) and if on lopinavir/ritonavir consider adding ritonavir to a 1:1 ratio lopinavir/ritonavir to achieve the full therapeutic dose of ritonavir.

The guidelines recommend solid in preference to liquid formulations, use of heat stable FDCs or co-packaged formulations wherever possible and dosing in accordance with WHO weight band tables.

When to switch

Switching to second line treatment is recommended when clinical, immunological or virological failures occur.

- Clinical failure is defined as the appearance (or reappearance) of WHO clinical stage 3 or 4 events at least 24 weeks on ART and child is adherent.
- Immunological failure is defined as returning to age related thresholds in a treatment adherent child: CD4 count of ≤ 200 cells/mm³ or CD4 percentage $\leq 10\%$ for a child over two and less than five years of age; CD4 count of ≤ 100 cells/mm³ for a child of five years or more.
- Virological failure is defined as a persistent viral load above 5000 copies/mL after at least 24 weeks on ART for a treatment adherent child.

What to switch to

Choice of second line ART is dependent on the first line regimen received:

- After failure on an NNRTI: boosted PI plus 2NRTIs. Lopinavir/r is preferred.
- After failure on zidovudine or stavudine plus lamivudine: abacavir plus lamivudine is the preferred NRTI backbone, abacavir plus didanosine is an alternative.
- After failure on abacavir plus lamivudine, zidovudine plus lamivudine is the preferred NRTI backbone; zidovudine plus didanosine is an alternative.

C O M M E N T

These guidelines represent a liberalisation of criteria and if they are followed should ensure that many more children are identified and treated.

They are available on the WHO website. [3]

Annexe E has updated weightband dosing tables and formulations that are needed. We also look at paediatric formulations in the TAG/i-Base Pipeline Report. [4]

References

1. Mofenson L. What's new in WHO Pediatric Treatment Guidelines? 2nd International Workshop on HIV Pediatrics. July 2010, Vienna, Austria. http://regist2.virology-education.com/2ndHIVPed/docs/I_04Mofenson.pdf
2. Essajee S. Scaling up early infant diagnosis of HIV as the bridge between prevention, care and treatment: successes, challenges and potential solutions. Special session SUSS03. <http://pag.aids2010.org/session.aspx?s=150>
3. World Health Organisation. Antiretroviral therapy for HIV infection in infants and children: Recommendations for a public health approach (2010 revision) <http://www.who.int/hiv/pub/paediatric/infants2010/en/index.html>
4. Clayden P. Paediatric antiretroviral pipeline. TAG 2010 Pipeline Report. July 2010. <http://i-base.info/htb/13436>

Early treatment for infants is cost-effective

Polly Clayden, HIV i-Base

In 2008, the CHER trial demonstrated the effectiveness of universal early antiretroviral treatment for all infants regardless of CD4 or clinical stage.

This in turn influenced paediatric guidance worldwide.

For resource limited countries one of the main obstacles to the implementation of this strategy is cost.

In an oral late breaker, Gesine Meyer-Rath, showed findings from a cost comparison of early (from 6-12 weeks of age) vs deferred (based on CD4 percentage threshold or clinical criteria in accordance with previous WHO guidelines) initiation of antiretrovirals in young infants. The study also included a third arm that used a cost analysis of children in routine care in a standard HIV clinic.

The investigators used data describing outpatient/inpatient resource use during the first 12 months of life from 411 children in the CHER trial randomised to early (n=252) or deferred (n=125) treatment, and 130 infants initiating treatment at the Empilweni Clinic in Johannesburg between 2005 and 2007.

Patient level resource data was accessed from patient files and included information on: antiretroviral drugs, laboratory tests, clinic consultations and inpatient days.

Other costs were obtained from multiple sources: the government drug depot provided drug costs; the National Health Laboratory Service the cost of tests; staff salaries, equipment and overheads were accessed from clinic/hospital accounts and inpatient days calculated on a hospital cost per- patient day equivalent. Cost data was from 2009.

The evaluation revealed that early treatment for children was cost saving.

The cost of early treatment per child for a mean time in care of 10 months was \$1349 compared to \$2432 for deferred treatment (mean time in care 9 months) and \$2908 for routine care (mean time in care 3 months). Dr Meyer-Rath explained that the difference in time in care across the three scenarios was due to higher loss to follow up in the deferred arm and higher loss to follow up and later presentation in the routine care arm.

The differences in cost were largely due to differences in frequency of hospitalisation, which was an average of 2, 7 and 13 days and a maximum of 68, 84 and 121 days per child in the early, deferred and routine care arms respectively.

The proportion of the total cost spent on inpatient care rose from 26% in the early therapy arm to 84% in the routine care arm.

Details of the cost per child are shown in Table one.

Table one: Cost per child (2009 US dollars)

Scenario	Early treatment		Deferred treatment		Routine care	
Mean time in care	10 months		9 months		3 months	
Cost item	Cost \$	%	Cost \$	%	Cost \$	%
Anti-retrovirals	245	18	127	5	35	1
Diagnostics	243	18	341	14	56	2
Staff/overheads	515	38	726	30	266	9
Total out-patient cost	1004	74	1195	49	359	12
Total in-patient cost	346	26	1237	51	2523	84
Total cost	1349		2432		2908	
95% CI	1244-1464		1982-2889		2273-3743	

The investigators estimated that in South Africa the cost of 90% coverage early treatment for 103,000 infants in 2010/11 would be \$67 million, and for 202,000 infants in 2012/13 would be \$133 million. This represents 6-7% of the total cost of the national antiretroviral treatment programme and 1% of the public health service budget.

Dr Math-Reyer remarked that the cost of the paediatric programme, "will always be dwarfed by the cost of the adult programme, regardless of eligibility criteria."

Among the limitations of the analysis she noted that the cost of screening HIV-exposed children was not included and would add about \$300 per child.

Reference: Meyer-Rath G et al. The cost of early vs. deferred paediatric antiretroviral treatment in South Africa - a comparative economic analysis of the first year of the CHER trial. 18th IAS Conference, 18-23 July 2010, Vienna. Oral abstract THLB103.
<http://pag.aids2010.org/Abstracts.aspx?SID=644&AID=17823>

No difference in outcomes for children initiating treatment with a protease inhibitor or an NNRTI nor with viral load switching strategies in PENPACT-1

Polly Clayden, HIV i-Base

In an oral late breaker, Ann Melvin presented data on behalf of the PENPACT 1 study (a collaboration between PENTA and PACTG/IMPAACT). This was a long-term comparison of antiretroviral naïve children initiating treatment on PI or NNRTI based regimens as well as two different viral load criteria for switching from first to second line treatment (>1000 vs 30,000 copies/mL).

This was a randomised study with a 2x2 factorial design. Children in PENPACT 1 received an initial regimen of two NRTIs plus either an NNRTI or a PI and the second randomisation compared switch to second-line at the two different viral load measurements. The primary outcome was viral load change between baseline and 4 years. The minimum follow up was 4 years.

Children were randomised between September 2002 and September 2005 and 263/266 included in the analysis. At the end of the study in August 2009, 218 (83%) children were still in follow up. The median length was 5 years (IQR 4.2-6.0 years).

At baseline, the children were a median age of 6.5 years (IQR 2.8-12.9), CD4 17% (IQR 10-25%), viral load 5.1 (4.5-5.7) log₁₀copies/mL. Only 15% had received antiretrovirals for prevention of mother to child transmission and 4% (10/239) had one or more major mutation.

Choice of antiretrovirals within the randomised arm was open label. Lopinavir/r (49%) and nelfinavir (48%) were the most common PIs and efavirenz (61%) the most common NNRTI.

At the end of follow up the majority of children (188/263, 71%) were on their first line regimen. There was no difference between PI (73%) and NNRTI (70%). The median viral load at switch was 6720 copies/mL (IQR 1,380-26,100) compared to 35,712 copies/mL (IQR 8,060-72,800), $p < 0.01$ in the 1000 copies/mL and 30,000 copies/mL switch groups respectively. Children with the higher viral load criterion switched approximately one year later ($p = 0.04$).

The investigators observed no significant differences in change in viral load between baseline and 4 years between children initiating treatment on a PI or NNRTI: -3.16 vs -3.31 log₁₀ copies/mL, giving a difference of -0.15 (95% CI, 0.41-0.11), $p = 0.26$; or children switching earlier or later: -3.26 vs -3.20, difference 0.06 (95% CI, 0.2-0.32), $p = 0.56$.

Similar proportions of children (>70% all groups) had viral load <50 copies/mL and CD4 percentage increase of approximately 16%.

Overall, one child died at week 277 from a malignancy and there were 14 new CDC stage C events in 9 children (3 PI/1000; 3 PI/30,000; 1 NNRTI/1000; 2 NNRTI/30,000). Grade 3 or 4 adverse events occurred in 60 children (28 PI; 32 NNRTI. 30 1000; 30 30,000) of which 17 had their regimen modified.

There were a low number of children for which resistance testing could be performed but preliminary results showed more children with 3 NRTI mutations or more in the NNRTI/30,000 copies/mL group. The most frequent being the M184V.

Dr Melvin suggested that these results are reassuring for paediatric treatment scale up worldwide and, in the absence of nevirapine exposure through PMTCT, either PI or NNRTI are equally good options for first line regimens. She added that although routine viral load testing may help identify children at risk of developing NRTI resistance it is unlikely to have an impact on the acquisition of NNRTI resistance as this occurs soon after viral rebound.

C O M M E N T

As Dr Melvin remarked, these data are extremely useful for paediatric treatment programmes worldwide.

Ref: Melvin A et al. PENPACT-1 (PENTA 9/PACTG 390): a randomised trial of protease inhibitor (PI) vs non-nucleoside reverse transcriptase inhibitor (NNRTI) combination antiretroviral (ART) regimens and viral load (VL) treatment switching strategies in HIV-1-infected ART-naïve children age >30 days and < 18 years. 18th IAS Conference, 18–23 July 2010, Vienna. Oral abstract. THLBB104

<http://pag.aids2010.org/Abstracts.aspx?SID=644&AID=17536>

Tablets more acceptable than syrups in the ARROW trial

Polly Clayden, HIV i-Base

Provided accurate dosing is possible, tablets are usually more feasible than syrups for treating children in resource limited settings.

A substudy of the ARROW trial - an ongoing randomised paediatric trial of antiretroviral monitoring and treatment strategies conducted in Uganda and Zimbabwe - looked at the acceptability of syrup and scored tablets among children substituting syrups with tablets. The children were dosed in accordance with WHO weight band tables, which recommend substitution of liquids with tablets at around three years of age.

A poster authored by P Nahirya Ntege and colleagues showed findings from questionnaires given to the children's carers to discover their experiences with syrups and with tablets.

A total of 1207 children, aged 3 months to 17 years, were enrolled during 2007/2008. At enrollment, 34% (406/1207) of children received the antiretrovirals in their regimen (NNRTI + two or three of zidovudine, abacavir and lamivudine) as syrups.

Just over half (236/406, 58%) of this group substituted scored tablets for syrups between May 2008 and December 2009. The first questionnaires were given at baseline (time of substitution) and follow up questionnaires eight weeks later.

The investigators found, among the 186/236 (79%) of questionnaires included in the analysis, the median age of the children at time of substitution was 2.9 years (IQR 2.4-3.4).

Over three quarters (77%) of carers reported problems with the number and weight of the bottles as they were difficult to transport. About half (53%) expected difficulties with the tablets at baseline but only 27% of carers reported problems at 8 weeks.

Most tablets were dissolved/crushed in liquid. The most frequent problems were with taste, swallowing and vomiting.

Overall 69% of carers at baseline and 93% at eight weeks reported a preference for tablets. They also reported that 24% of children at baseline and 56% at eight weeks preferred tablets to syrups.

At eight weeks none had switched back to syrups. The investigators are evaluating longer-term information after the children have received tablets for 24 weeks. They will also evaluate the affect of tablet acceptability on adherence.

C O M M E N T

These data reinforce the WHO recommendation of solid formulations as the preferred regimens for children. They should also act as an incentive to manufacturers (particularly generic) to produce more innovative solid formulations including fixed dose combinations.

Liquid formulations have been a barrier to more rapid scale up and are less convenient and more costly for all involved in treating children with HIV.

Ref: Nahirya Ntege P et al. Tablets are more acceptable and give fewer problems than syrups among young HIV-infected children in resource-limited settings in the ARROW trial. 18th IAS Conference, 18–23 July 2010, Vienna. Poster abstract TUPDB206.

<http://pag.aids2010.org/Abstracts.aspx?AID=13055>

Paediatric formulation of TMC 278

Polly Clayden, HIV i-Base

TMC 278 or rilpivirine is currently being evaluated for adults in a tablet formulation at a once daily dose of 25mg.

A poster at IAS2010 authored by Herta M Crauwels and colleagues showed bioavailability data from a Phase 1 trial looking at a new granule formulation intended for use in paediatric patients compared to the adult tablet formulation.

This was an open label, randomised, three way crossover trial in 12 HIV-negative adults, under both fed and fasted conditions.

Volunteers were randomised to receive:

- Treatment A: granule formulation within 10 minutes of a standardised breakfast.
- Treatment B: granule formulation after 10-hour overnight fast.
- Treatment C: Tablet formulation within 10 minutes of a standardised breakfast.

The granules were dispersed in water.

Volunteers were in six groups of two and received Treatments A, B and C in six different sequences with a washout period of at least 14 days in between.

Plasma samples from a full pharmacokinetic (PK) profile were analysed for TMC278 using a validated liquid chromatography-mass spectrometry/mass spectrometry method with a lower limit of 1.0ng/mL.

Evaluable PK parameters were available for 11 volunteers. Comparisons were made between Treatments A and B with C (reference 1), and between A (reference 2) and B for food effects on the granule formulation.

The investigators noted that plasma concentrations were quantifiable from 30 minutes post dose for the granule formulations compared to one to two hours for the tablet formulation. However the time to achieve the maximum plasma concentrations were similar between the three treatments.

They reported increases in the PK parameters with the granule formulation under both fed and fasted conditions of 18%, 28% and 26% in C_{max}, AUC_{last} and AUC_{inf} respectively. The granule formulation under fasted conditions achieved similar exposure to tablets taken with food.

There was a decrease of 30%, 29% and 28% in exposure for the granules taken under fasted conditions compared to with food in the Cmax, AUClast and AUCinf respectively. See Table 1.

Table1: Comparing TMC 278 granules and tablet formulations LSM (95% CI)

	Test	Reference 1	n/n	Cmax	AUClast	AUCinf
Relative bioavailability	Granules fasted	Tablet fed	11/11	1.18 (1.09-1.40)	1.28 (1.11-1.48)	1.26 (1.09-1.46)
	Granules fed	Tablet fed	11/11	0.87 (0.76-0.96)	0.93 (0.85-1.00)	0.93 (0.86-1.00)
	Test	Reference 2	n/n	Cmax	AUClast	AUCinf
Food effect	Granules fasted	Granules fed	11/11	0.70 (0.59-0.83)	0.71 (0.63-0.80)	0.72 (0.64-0.81)

In a taste questionnaire 10/12 volunteers rated the granules “acceptable” or “good”. The investigators noted that all treatments were generally well tolerated and no new safety signals were observed.

They concluded that the TMC 278 granule formulation has good oral bioavailability and palatability and will be developed further for use in paediatric trials.

Reference

Crauwels HM et al. Relative bioavailability of a concept paediatric formulation of TMC278, an investigational NNRTI. 18th IAS Conference, 18–23 July 2010, Vienna. Abstract THPE0158.
<http://pag.aids2010.org/Abstracts.aspx?AID=12590>

IAS: DRUG INTERACTIONS

Smoking and atazanavir levels

www.hiv-druginteractions.org

The effect of tobacco smoking on atazanavir trough concentrations was assessed in a cohort of 416 patients, of which 246 were smokers and 170 were non-smokers or ex smokers. No association was found between smoking history and atazanavir trough concentration: median (IQR) trough concentrations were 571 (329-960) ng/mL for smokers and 536.5 (323-1030) ng/mL for non/ex-smokers (p=0.85).

In multivariate analysis there were no significant variables associated to atazanavir trough concentration and smoking history.

Source: IAS report (20 July 2010)

www.hiv-druginteractions.org

Ref: Guillemi S et al. Does smoking tobacco affect atazanavir exposure in HIV-infected individuals? 18th IAS Conference, 18–23 July 2010, Vienna. Poster abstract WEPE0095.

Darunavir/ritonavir and rosuvastatin

www.hiv-druginteractions.org

Coadministration of darunavir/ritonavir (600/100 mg twice daily) and rosuvastatin (10 mg once daily) was studied in 12 HIV- subjects. The geometric mean AUC for rosuvastatin increased by 48% in the presence of darunavir/ritonavir and Cmax increased by 2.44-fold. There were no significant changes in darunavir or ritonavir AUC or Cmax. Lipid lowering effects of rosuvastatin were not significantly altered, despite higher concentrations of rosuvastatin. There were no adverse events attributable to the interaction.

Source: IAS report (20 July 2010)

www.hiv-druginteractions.org

Ref: Fichtenbaum C et al. Darunavir/ritonavir increases rosuvastatin concentrations but does not alter lipid-lowering effect in healthy volunteers. 18th IAS Conference, 18–23 July 2010, Vienna. Poster abstract WEPE0101.

IAS: OTHER STUDIES

Lime juice is not a microbicide: do not try at home

Simon Collins, HIV i-Base

Every few years an abstract reports anecdotal use of lemon or lime juice as a douche prior to sex to reduce the risk of HIV transmission. The risk associated with this has been demonstrated by many groups, even when lime/lemon diluted, as the acidity causes tissue damage that is more likely to increase the risk of HIV transmission. [1, 2] It was worrying to see this presented again at an IAS meeting in 2010.

This small in vitro data reported that lime juice negatively impacts on healthy, potentially protective, bacteria. The conclusion that "future research should proceed with caution" should instead have reported the currently known risks that obviate the need for additional research. [3]

Of interest, another in vitro study in the Jul 2010 edition of AIDS Research and Therapy using lime, lemon and vinegar similarly concluded "The data from this study and previous reports clearly demonstrate that the use of citrus juices as topical microbicides is potentially more toxic than nonoxynol-9 and thus not recommended for vaginal application." [4]

References

1. TheBody.com. Why women should NOT use lemon or lime juice as a microbicide. (June 2008)
<http://www.thebody.com/content/treat/art48598.html>
2. Shattock R et al. Preclinical evaluation of lime juice as a topical microbicide candidate. *Retrovirology* 11 January 2008. doi: 10.1186/1742-4690-5-3.
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2259360/>
3. Onyejebu N et al. Assessing the mutagenicity of lime juice: a potential microbicide. 18th IAS Conference, 18–23 July 2010, Vienna. <http://pag.aids2010.org/Abstracts.aspx?AID=13260>
4. Lackman-Smith CS et al. Safety and anti-HIV assessments of natural vaginal cleansing products in an established topical microbicides in vitro testing algorithm. *AIDS Research and Therapy* 2010, 7:22doi:10.1186/1742-6405-7-22.
<http://www.aidsrestherapy.com/content/7/1/22>

ANTIRETROVIRALS

FDA safety updates to antiretroviral labels

The following summaries cover revisions to the US drug labels that were recently approved by the FDA in the US. Please check the full update for details.

Revised label are posted to the FDA website:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory

Maraviroc in patients with renal impairment

On 27 May 2010, the FDA approved changes to the labeling for maraviroc (Celsentri/Selzentry) 150 mg and 300 mg tablets to include:

- Dosing recommendations for patients with renal impairment,
- A contraindication for patients with severe renal impairment or end-stage renal disease,
- A warning regarding postural hypotension for renal impaired patients,
- New pharmacokinetics information related to renal impairment.

Saquinavir increases QT interval prolongation

Recently the FDA-mandated all manufacturers of protease inhibitors to investigate whether there were any signals for concern for QT interval prolongation with the licensed drugs in this class. The safety study by Roche in HIV-negative volunteers that showed that ritonavir-boosted saquinavir (Invirase) had a greater effect on QT interval prolongation than a control group.

This will results in a label change in both the US and Europe.

Roche will issue a "Dear Healthcare Provider" letter to inform healthcare professionals that:

- Saquinavir is contraindicated in patients with congenital or acquired QT prolongation or other predisposing conditions for cardiac arrhythmias, including concurrent therapy with other drugs that prolong the QT and/or PR interval.

- The combination of saquinavir with drugs known to increase the plasma level of saquinavir is not recommended and should be avoided when alternative treatment options are available.
- Saquinavir should be discontinued in case of arrhythmias, QT or PR prolongation.

Raltegravir approved in Scotland

On 10 May 2010, the Scottish Medicines Consortium (SMC) announced that raltegravir (Isentress) had been accepted for restricted use within NHS Scotland for using in combination for adult patients.

The indication included not only in the context of drug resistance to other classes, but for patients where drug interactions to other medications is problematic, and most important for patients who are intolerant to protease inhibitors and NNRTIs due to difficult side effects.

C O M M E N T

Despite the delay in this decision (raltegravir was approved in Europe in January 2008) patients in Scotland have been able to access the drug if it was needed to treat multidrug resistant virus.

The indication for tolerability is important, as this option that could improve quality of life for many patients is unlikely to be available in England, and certainly not in London, while the price differential remains so significantly compared to every other antiretroviral (apart from tipranavir and T-20, both of which are rarely used).

Source: MSD press release. Scottish Medicines Consortium approves expanded use of first-in-class integrase inhibitor, 'Isentress' (raltegravir), for the treatment of HIV in appropriate patients. (10 May 2010).
http://www.pharmiweb.com/pressreleases/pressrel.asp?ROW_ID=21506

Atazanavir/r approved in Europe for children aged 6 to 18 years

On 7 July 2010, the use of boosted atazanavir was extended in Europe to include children aged 6–18 years old, weighing >15kg. [1]
This was based on results from the open label multicentre PACTG 1020A study. [2]

The study included 182 naïve and experienced paediatric patients aged 6 to 18 years old, using once daily atazanavir, with (n=141) or without (n=41) ritonavir, in combination with two NRTIs. The data from the 41 patients using ritonavir-boosting (n=16 naïve and 25) supported this new paediatric indication.

The recommended atazanavir/ritonavir doses by body weight are 150 mg/100 mg (15kg–less than 20 kg) and 200 mg/100 mg (20 kg–less than 40 kg); with children weighing over 40 kg recommended to use the standard adult dose of 300 mg/100 mg.

Source: BMS press release (07 July 2010).
http://www.pharmiweb.com/pressreleases/pressrel.asp?ROW_ID=24756

FDA finally approves 4th generation HIV Ag/Ab test in the US

On 18 June 2010, the FDA approved a new, "4th generation" HIV diagnostic assay.

The ARCHITECT HIV Ag/Ab Combo Assay is the first HIV diagnostic assay to be approved in the US that detects both antigen and antibodies for HIV.

The new test is also the first diagnostic test approved by FDA for use in children as young as 2 years of age, and pregnant women. It is specific for the detection of the HIV-1 p24 antigen (the substance found on the virus that triggers the production of antibodies), as well as antibodies to HIV-1 groups M and O, and as antibodies to HIV-2.

Levels of p24 antigen increase early after initial infection, before HIV antibody is produced and extends diagnosis to earlier, acute phase (recent) infection with HIV, reducing the window period (that period after initial infection and before the detection of infection based on formation of detectable antibodies).

The median detection time was demonstrated to be 7 days earlier (range 0 to 20 days) compared to 3rd generation enzyme immunoassay antibody tests.

C O M M E N T

Fourth generation tests have been widely used in Europe for many years, although a handful of clinics, still use third generation despite current guidelines.

Although these tests reduce the window period between potential exposure and the opportunity to test down to 2–3 weeks, from a public health perspective, 28 days/4weeks is now possible.

Testing guidelines still refer to a six-week window by which time p-24 which peaks before 3 weeks and disappears after 2–3 months, is already fading.

Despite the widespread use of fourth generation testing, it is difficult to understand why many clinics in the UK still routinely refer to a three-month window period. This not only prolongs the anxiety for anyone who is concerned about recent exposure, but also undoubtedly misses the opportunity to diagnose some people during early infection. Many people who are concerned enough to test early, may be less likely to test three months later once their initial anxiety has abated, especially give the sometimes difficult access to walk-in, same day and out-of-hours testing services.

The British Association for Sexual Health and HIV (BASHH) guidelines on HIV testing state: [2]

“Fourth generation tests will detect the great majority of individuals who have been infected with HIV at one month (4 weeks) after specific exposure.”

“Patients attending for HIV testing who identify a specific risk occurring more that 4 weeks previously, should not be made to wait three months (12 weeks) before HIV testing. They should be offered a 4th generation laboratory HIV test and advised that a negative result at 4 weeks post exposure is very reassuring/highly likely to exclude HIV infection. An additional HIV test should be offered to all persons at three months (12 weeks) to definitively exclude HIV infection. Patients at lower risk may opt to wait until three months to avoid the need for HIV testing twice.”

References

1. FDA list serve announcement. (18 June 2010).
2. The British Association for Sexual Health and HIV (BASHH) statement on HIV window period (15 March 2010).
<http://www.bashh.org/guidelines>

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
Atazanavir sulfate capsules, 300 mg	Emcur, India	19 August 2010
3TC/d4T FDC 150/30mg	Macleods, India	05 August 2010
AZT/3TC/nevirapine tablets for Oral Solution, 60 mg/30 mg/50 mg	Matrix Laboratories, India	08 July 2010

“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 programme for use outside the United States.

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

<http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>

C O M M E N T

This brings the total of FDA approved generic drugs and formulations to 114 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/InternationalPrograms/FDABeyondOurBordersForeignOffices/AsiaandAfrica/ucm119231.htm>

PREGNANCY & PMTCT

Potential impact of new WHO pregnancy guidance

Polly Clayden, HIV i-Base

A research letter in the June 1 2010 issue of AIDS, authored by Louise Kuhn and colleagues described an evaluation of the potential impact of the WHO 2010 guidelines for initiating antiretroviral treatment in pregnant women.

The guidelines now recommend treatment for adults with stage 3 or 4 (irrespective of CD4 count), or with CD4 count of 350 cells/mm³ and below (irrespective of clinical stage). Previously WHO guidelines required stage 3 if CD4 count was 200-350 cells/mm³.

The study was performed using data from 1025 HIV-positive women and infants followed for 24 months in Lusaka Zambia before the widespread use of ART. Children were breast fed for 4 months after which some women weaned their infants as randomised and some continued to breastfeed. Overall the median duration of breastfeeding was 12 months.

The investigators evaluated the associations between maternal characteristics measured during pregnancy, including CD4 count, viral load, clinical stage, and the old and new WHO treatment criteria. They looked at the capacity of these factors to predict: maternal mortality between delivery and 24 months, and perinatal (detected before 6 weeks) and postnatal (detected after 6 weeks) transmission. They show a detailed analysis of the percentage of the pregnant population who would require treatment, rates and relative risks of maternal mortality and perinatal/postnatal transmission. Assuming a fully effective intervention, they estimated the preventable proportion according to various criteria for initiating antiretroviral treatment.

They reported that in their cohort 54% of women had CD4 counts below 350 cells/mm³ and the majority of maternal deaths (88%) occurred in this group, RR 7.2 (95% CI, 3.6-14.5). Sixty-eight percent were eligible for treatment using the new criteria, which includes clinical stage 3 as well as CD4 count below 350 cells/mm³, and 92% deaths occurred in this group, RR 6.2 (2.7-14.2).

They explained that if the new criteria were applied, 10.1 women would need to be treated per death averted, using only CD4 criteria of less than 350 cells/mm³ the number of women needed to be treated would be 8.4. When they looked at the effect of viral load criteria they found having a viral load of 48,428 copies/mL classified the same proportion of women needing treatment as a CD4 threshold of 350 cells/mm³ and below but only identified 76% of deaths. If viral load was added to CD4 count they found this performed similarly to the new WHO criteria. Adding viral load to the new criteria would identify the maximum number of deaths (96%) but 76% of women would need to be treated.

They noted that although it has suggested that lower CD4 thresholds could be used in pregnancy to accommodate the effects of haemodilution, their data suggest that CD4 of 200, 250 and 350 cells/mm³ would only identify 59%, 72% and 79% of deaths respectively. Therefore they recommend that, "making this adjustment is unwise".

Additionally the new criteria would detect 88% of perinatal and post natal HIV transmissions. Using CD4 criteria alone would detect almost as many postnatal transmissions (83%) but fewer perinatal (76%).

Viral load and CD4 are independent predictors of transmission. Multivariate analysis revealed viral load, RR 3.1 (95% CI, 2.0-4.6) to be a stronger predictor for perinatal transmission controlling for CD4, RR 2.0 (95% CI 1.3-3.0). For postnatal transmission they were similarly predictive: viral load RR 3.8 (95% CI 2.2-6.3) and CD4 RR 3.8 (95% CI 2.1-6.8). The investigators suggested: "Combining viral load and CD4 count as either/or criteria for initiating therapy would lead to better results than the new WHO criteria while treating slightly fewer women."

If they adjust for ART to reduce transmissions effectively, treating women according to the new WHO criteria could prevent 82% of all infections even if no extended postnatal interventions are used among women not indicated for ART. They suggest that although it is desirable that these interventions are implemented they will be more costly per infection prevented, as the transmission rate among healthier women is lower.

The investigators write that their data suggest that the inclusion of clinical staging in the new criteria increases the number of women treated but with only marginal increase in coverage of women and children at risk. Although they acknowledge that it is useful in settings where laboratory testing cannot be done or is unreliable. They acknowledge that estimates of the proportion of deaths and transmissions averted will vary across settings but note that the characteristics they observed are similar to those in a large multisite dataset from women participating in the MTCTPlus programme. They concluded that their data provide evidence-based support for the thresholds in the revised treatment guidelines. They write: "Our analysis also provides estimates of the large positive impact these guidelines could have if widely implemented on reducing mortality among women and HIV transmission to children."

C O M M E N T

This elegant analysis once again makes the case for treatment of pregnant women at 350 cells/mm³ both for their own health and prevention of transmission.

Kesho Bora data at IAS this year also supports this.

Ref: Kuhn L et al. Potential impact of new WHO criteria for antiretroviral treatment for prevention of mother to child HIV transmission. AIDS. Volume 24. Number 9. June 2010.

DRUG INTERACTIONS

Darunavir/ritonavir and hepatic impairment

www.hiv-druginteractions.org

This study assessed the steady state pharmacokinetics and safety of darunavir/ritonavir (600 mg/100 mg twice daily) in HIV-negative subjects with mild (n=8) or moderate (n=8) hepatic impairment (Child-Pugh classification A [mild] or B [moderate]) compared with matched, HIV-negative, healthy subjects (n=16). Pharmacokinetic profiles were obtained up to 72 hours post-dose for darunavir and 12 hours post-dose for ritonavir on day 7.

Darunavir pharmacokinetics in subjects with mild and moderate hepatic impairment were comparable to those in matched healthy control subjects. In those with mild hepatic impairment, the least square mean ratios relative to healthy subjects for darunavir AUC, C_{max} and C_{min} were 0.94 (90% CI 0.75, 1.17), 0.88 (90% CI 0.73, 1.07) and 0.83 (90% CI 0.63, 1.10), respectively. In those with moderate hepatic impairment, these values were 1.20 (90% CI 0.90, 1.60), 1.22 (90% CI 0.95, 1.56) and 1.27 (90% CI 0.87, 1.85), respectively. Ritonavir pharmacokinetics were comparable between healthy subjects and those with mild hepatic impairment, but mean exposure was 50% higher in subjects with moderate hepatic impairment. Darunavir/ritonavir was generally well tolerated, regardless of hepatic impairment.

The results of this study show that the pharmacokinetics of darunavir/ritonavir are not affected by mild or moderate hepatic impairment (although there is a trend to increased exposure in moderate impairment). Therefore, dose adjustments of darunavir/ritonavir are not required in patients with mild or moderate hepatic impairment.

Source: www.hiv-druginteractions.org (17 June 2010).

Reference:

Sekar V et al. Pharmacokinetics of multiple-dose darunavir in combination with low-dose ritonavir in individuals with mild-to-moderate hepatic impairment. *Clin Pharmacokinet*, 2010, 49 (5): 343-350.

<http://www.ncbi.nlm.nih.gov/pubmed/20384396>

Case report – lack of PK interaction between bosentan and nevirapine

www.hiv-druginteractions.org

This case report describes the successful treatment of pulmonary arterial hypertension using bosentan in a woman receiving nevirapine, lamivudine and zidovudine. Due to concerns about a potential drug interaction with nevirapine (bosentan is a substrate of OATP, CYP3A4 and CYP2C9 and is also an inducer of these cytochrome P450s), nevirapine plasma concentrations, CD4 count and viral were extensively monitored.

Throughout the four-year follow up, no effect of bosentan on nevirapine was observed. Nevirapine trough concentrations were maintained between approximately 5.0 and 6.5 ug/mL, despite a doubling of bosentan dose (from 62.5 mg to 125 mg twice daily, although the authors do not indicate if this increase was related to nevirapine induction). Viral load remained below 75 copies/mL and significant clinical and haemodynamic improvement was noted.

Source: www.hiv-druginteractions.org (15 July 2010).

Reference

Hardy H et al. Successful bosentan and NNRTI-based therapy in a patient with AIDS and pulmonary arterial hypertension. *Pharmacotherapy*, 2010, 30(4): 139e-144e.

<http://www.ncbi.nlm.nih.gov/pubmed/20334465>

Pharmacokinetics of once daily darunavir/ritonavir and efavirenz

www.hiv-druginteractions.org

A two-way interaction exists between efavirenz and darunavir/ritonavir where coadministration decreased darunavir AUC (13%) and C_{trough} (31%) and increased efavirenz AUC (21%) and C_{trough} (17%). However these data were obtained with a lower than licensed twice-daily dose of darunavir/ritonavir and no data exist for once daily darunavir/ritonavir.

This study looked at the effect of efavirenz on the pharmacokinetics of once daily darunavir/ritonavir in healthy volunteers (n=12). Subjects received darunavir/ritonavir (900/100 mg once daily) for 10 days and then efavirenz (600 mg once daily) was added for 14 days. Darunavir-ritonavir was then stopped and efavirenz alone was given for 14 days. At the end of each period, samples were taken for pharmacokinetic analysis (AUC 0-24h)

Coadministration decreased darunavir C_{trough} by 57% (from 2137±1034 to 1180±1138 ng/ml, mean±sd) and decreased AUC by 14%. Ritonavir C_{trough} and AUC decreased by 54% and 26%, respectively, when given with efavirenz. The half-life of efavirenz was increased significantly in the presence of darunavir/ritonavir, but there was no change in efavirenz C_{trough} and only a 9% decrease in AUC.

Although efavirenz reduced the trough concentrations of darunavir significantly, all trough concentrations remained above the EC₅₀ for darunavir for the wild-type virus (55 ng/mL). However, there was considerable variability in trough darunavir concentration which, in a larger study, may result in some patients not achieving plasma concentrations 1.5 times that of the EC₅₀ (a value that equates to an inhibitory quotient of more than 1.5 and predicted antiviral efficacy in previous studies). The clinical efficacy and durability of this regimen needs to be validated with a larger sample of treatment-naïve patients.

Source: www.hiv-druginteractions.org (15 July 2010).

Reference

Soon GH et al. Pharmacokinetics of darunavir at 900 milligrams and ritonavir at 100 milligrams once daily when coadministered with efavirenz at 600 milligrams once daily in healthy volunteers. *Antimicrob Agents Chemother*, 2010, 54(7): 2775-2780.

<http://www.ncbi.nlm.nih.gov/pubmed/20385850>

BASIC SCIENCE

HIV infection, inflammation and premature ageing

Webcasts from a symposium on this topic, held on 18 May 2010 by the Center for AIDS Research at the University of California at San Francisco, are available online.

<http://cfar.ucsf.edu/cfar?page=symposia-10-home>

Five talks addressing the intersection of HIV and aging have been posted, with more presentations from the afternoon session coming soon.

The intersection of HIV and aging development and reversion of immunosenescence in HIV-1 infection - Victor Appay

How Might HIV Infection and Therapy Drive Aging and Age-Related Disease? - Judith Campisi

The Role of HIV-Associated Inflammation in Aging - Russell P. Tracy

Polarised Immune Responses Regulate Cancer Development - Lisa Coussens

The HIV Tat Protein Regulates Immune Activation via SIRT1 - Melanie Ott

Meeting summary notes

Bob Munk, New Mexico AIDS Infonet

- Senescence is amazingly complicated at the cellular level and involves the accumulation of cells that are in many ways non-functional. Senescence is thought to increase our susceptibility to autoimmune disorders and cancers.
- Inflammation is a complex and poorly defined process.
- Cancer is a hyperproliferative process, in some ways the opposite of immune decline; both occur in aging. Aging is distinct from disease. It makes people susceptible to disease and degrades quality of life. Cancers appear to be a separate process; some are related to habits or genetic factors; others are the result of mutations accumulated through cellular division.
- Environmental factors can “shift the curve” of onset of age-related disease. The use of antiretroviral therapies, particularly the nucleoside analogs, may be an important “environmental” factor.
- Carl Grunfeld made a provocative main point that HIV does not “accelerate” aging. He argued that we need to identify the specific disease processes. Maybe hepatitis co-infection accelerates aging when it occurs together with HIV; maybe CMV infection does; maybe metabolic syndrome does. To lump all of these together as “HIV-accelerated aging” might cut off needed research into specific disease processes.
- The cancers with a viral cause (Kaposi’s Sarcoma and non-Hodgkins Lymphoma) appear to occur earlier in people with HIV. But Hodgkin’s Lymphoma appears later. How can we explain this?
- Geriatric medicine is not far advanced. Additional research on HIV and associated illnesses could help advance our general knowledge of aging. Atherosclerosis is considered a model for aging. A parallel process may occur with all other organ systems.
- We need to develop measurements for the manifestations of aging. These include comorbidities and functional problems, which constitute frailty. There is a scale in common use but it does not include a component on clarity of thought or memory.
- We need better markers of immune function. The CD4 count is too blunt a tool, and at higher levels, more CD4s do not correlate with improved immune responses.

- With highly refined viral load measurements, virus can be found in up to 80% of people with HIV. We don't know if this residual viremia is the result of new production of virus or the release of virus from infected cells. This residual viremia may be a cause of ongoing inflammation.
- There was also discussion of "leaky gut" and microbial translocation. This topic is getting more and more attention and is clearly a source of generalized immune and inflammatory responses throughout the body. My original naïve understanding of this was an almost "physical" leakage from the gut rather than bad bugs that should be killed by an effective immune system in the gut (the Peyer's patches, which are wiped out by HIV very early in infection.)
- Osteoporosis: vitamin D is currently seen as affecting a huge range of body processes, and deficiency causes problems. Vitamin D deficiency is not an HIV phenomenon, but is prevalent in the general population. Unfortunately, there is no agreement on what levels of supplementation to use, and as yet, no evidence that supplementation leads to any clinical improvements in any population.
- Bone remodeling is a very slow, continuous process; increases due to calcium supplementation or other therapies take a long time to show up as increased bone mineral density. However, studies of bisphosphonates such as alendronate (Fosamax) have shown very rapid decreases in fracture rates even in the absence of increases in bone mineral density.

Antiretroviral therapy dramatically reduces HIV transmission

Richard Jefferys, TAG

A recent posting linked to the abstract of a study evaluating the impact of ART on HIV transmission that was presented at CROI earlier this year.

The full results have now been published in the Lancet. [2] The paper is generating considerable press coverage because the effect of ART was dramatic, equating to a 92% reduction in risk of transmission.

The study involved 3,381 couples in which one partner was HIV positive and the other negative. Out of 103 cases of transmission that were documented, 102 occurred in couples where the positive partner was not using ART. In the remaining case, ART had only very recently been initiated. Although the results represent the most compelling evidence to date that ART can reduce the risk of sexual transmission of HIV infection, it's worth noting that the main purpose of the trial was to investigate the impact of suppressing herpes simplex virus infection with acyclovir on HIV transmission (these primary results have <<http://content.nejm.org/cgi/content/abstract/NEJMoa0904849>>already been published). The analysis of the effect of ART was thus "post hoc" meaning it was not pre-specified in the protocol (there is an ongoing trial called <http://www.hptn.org/research_studies/HPTN052.asp>HPTN 052 in which the primary endpoint is the impact of ART on transmission but results are not anticipated until 2014).

In an accompanying commentary in the Lancet, several scientists argue that these results call for rapid development of trials of a "test and treat" approach to reducing HIV incidence in which the main goal will be preventing transmission. [3] However the paper also makes it clear that transmission risk is highest among people who need ART for their individual health; given the stalling in funding to support treatment access globally, arguably the most important implication of the study is that this shortfall needs to urgently be addressed for reasons of public health, as well as to ensure the wellbeing of people with HIV who are currently being turned away from treatment programs due to lack of resources.

References

1. Treatment reduces infections by over 90%: a theme that is here to stay. HIV Treatment Bulletin, April 2010.
<http://i-base.info/htb/10266>
2. Donnell D et al. The Lancet, Volume 375, Issue 9731, Pages 2092 - 2098, 12 June 2010. doi:10.1016/S0140-6736(10)60705-2.
[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(10\)60705-2/abstract](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60705-2/abstract)
3. Dabis F, Newell M-L, Hirschel B. HIV drugs for treatment, and for prevention. Editorial comment. The Lancet.
[http://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(10\)60838-0/fulltext](http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(10)60838-0/fulltext)

Source: TAG basic science blog. (27 May 2010).

http://tagbasicscienceproject.typepad.com/tags_basic_science_vaccin/2010/05/the-impact-of-antiretroviral-treatment-on-hiv-transmission-risk.html

BHIVA NEWS

Access to formula milk for HIV-positive mothers in the UK

The British HIV Association (BHIVA) is aware that new mothers leave their birth hospital with a starter pack including a supply of formula milk.

However HIV positive mothers seem mostly to fall on their own resources thereafter, although there is funding available from some trusts, charities and groups.

BHIVA are interested to hear whether accessing resources for formula milk is a problem in your area and for any suggestions that you may have as to how this situation could be improved or solved.

In addition, we are trying to find out whether it is possible know if you are able to apply for such support through your clinical management path to the trust in your area and, if BHIVA were to recommend this, would it be helpful?

BHIVA would like to collect comments to the BHIV secretariat. If you have any queries, or require any further information, please do not hesitate to contact me through the Secretariat.

Dr Ian G Williams,

Chair, British HIV Association (BHIVA)

<http://www.bhiva.org/>

Secretariat: Mediscript Ltd, 1 Mountview Court, 310 Friern Barnet Lane, London N20 0LD

T: +44 (0)20 8369 5380

ON THE WEB

Conference reports and online abstracts:

International HIV & hepatitis virus drug resistance workshop & curative strategies

8–12 June 2010, Dubrovnik

Abstracts from the recent International HIV & Hepatitis Virus Drug Resistance Workshop & Curative Strategies meeting have been published in the journal *Antiviral Therapy*. The abstract book is available to download free from the conference website:

<http://www.intmedpress.com/journals/avt/abstract.cfm?id=1575&pid=88>

‘Towards a cure’: HIV reservoirs and strategies to control them

16–17 July 2010, Vienna

Immediately prior to the XVIII International AIDS Conference, the International AIDS Society held a workshop entitled “Towards a cure: HIV reservoirs and strategies to control them” that focused on the moving beyond antiretroviral therapy and addressing HIV persistence.

Powerpoint presentations and abstracts along with rapporteur summaries of each session have now been posted to the workshop website:

<http://www.iasociety.org/Default.aspx?pagelid=349>

Reports and journals:

PLoS Medicine

HIV in Maternal and Child Health: Concurrent Crises Demand Cooperation

The *PLoS Medicine* editors argue that the time has come to integrate prevention and treatment of HIV into maternal and child health care programs.

<http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000311>

Antiretroviral Treatment of Adult HIV Infection 2010: Recommendations of the International AIDS Society–USA Panel - Thompson MA et al.

JAMA. 2010;304(3):321-333. doi:10.1001/jama.2010.1004

<http://jama.ama-assn.org/cgi/content/full/304/3/321#AUTHINFO>

Community resources and publications:

HIV, TB and hepatitis pipeline report 2010

Treatment Action Group, now in collaboration with HIV i-Base has produced the the sixth edition of their Pipeline Report.

The 2010 report reviews the current clinical pipeline for new drugs and vaccines for HIV, hepatitis C virus, and tuberculosis, along with new sections on the hepatitis B virus pipeline and diagnostics for TB and HIV.

<http://i-base.info/home/pipeline-report-2010/>

AIDS cure research for everyone: a beginner's guide to how it's going and who's paying for it.

A review from US treatment activists who 'have written this simple report to share what we have learned about the search for a cure for AIDS'.

Section one analyses the scientific and cultural landscape that affects this research and makes recommendations. The second part surveys current US research.

The report is available free online in PDF format:

<http://www.aidspolicyproject.org/documents/The%20Cure%20Final.pdf>

RITA: Non-AIDS diagnoses and aging in people with HIV

Mark Mascolini

A report on HIV and Ageing by Mark Mascolini in this issue of RITA from the Center for AIDS in Houston.

The article includes three related interviews with Steven Grinspoon (Harvard), Carl Grunfeld (UCSF), and David Vance (UAB).

PDF:

<http://www.centerforaids.org/pdfs/mar2010ritagm.pdf>

Medical resources:

Launch of new EMA website

The European Medicines Agency has launched a new website, accessible at the same address:

<http://www.ema.europa.eu>

New features include:

- Quick medicine searches: Allows you to search for human and veterinary medicines by name and active substance and for herbal medicinal substances by name.
- An online library: Enables you to search for all Agency documents currently online through a search on title and date published online.
- Improved navigation: More intuitive labelling and improved organisation of content so that browsing is quicker for all audience groups.
- Audience landing pages: Flags information of specific value to different key users.
- Online calendar and news search: Allows you to keep up to date with the latest news and events at the Agency.
- RSS feeds: Brings information straight to you as soon as it is published online.

Hepatitis C drug resistance slide set

The Forum for Collaborative HIV Research's HCV Drug Development Advisory Group (academicians, clinicians, researchers and patient advocates) have contributed to a slide deck explaining resistance in HCV, its consequences as well as its mitigation. The slide deck explains important drug resistance concepts in HCV, including:

- How resistance can arise before, during and after stopping therapy;
- The mechanism of action of direct acting antivirals (DAAs) and their effects on viral kinetics and the possibility of cure;
- How mutations lead to changes which makes the virus resistant to DAAs;

- Viral, drug and patient factors that influence treatment outcomes.

http://www.hivforum.org/index.php?option=com_content&task=view&id=285&Itemid=113

Paediatric HIV studies: collected reports

The Southern African Journal of HIV Medicine (Vol 10, No 4; 2009) has published a collection of articles on paediatric care including by Polly Clayden, HIV i-Base. The article is available in PDF format and like all journal contents is available free online.

<http://www.sajhivmed.org.za/index.php/sajhivmed/article/viewFile/594/464>

FUTURE MEETINGS

2010/11 conference listing

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

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

50th ICAAC

12–15 September 2010, Boston

<http://www.icaac.org>

3rd Intl Workshop on Clinical PK of TB Drugs

11 September 2010, Boston

<http://www.virology-education.com>

14th Annual UK Resistance Meeting

22 September 2010, London

<http://www.mediscript.ltd.uk/conference.htm>

1st International Workshop on HIV & Aging

4–5 October 2010, Baltimore

<http://www.virology-education.com>

3rd BHIVA Conference on HIV and Hepatitis Co-infection

6 October 2010, London

<http://www.bhiva.org>

BHIVA Autumn Conference

7–8 October 2010, London

<http://www.bhiva.org>

12th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV

4–6 November 2010, London

<http://www.intmedpress.com/lipodystrophy>

10th International Congress on Drug Therapy in HIV Infection

7–11 November 2010, Glasgow

<http://www.hiv10.com>

41st Union World Conference on Lung Health City

11–15 November 2010, Berlin

<http://www.worldlunghealth.org/confBerlin/>

18th Conference on Retroviruses and Opportunistic Infections (CROI)

27 February–3 March 2011, Boston

<http://www.retroconference.org>

15th International Workshop on HIV Observational Databases

24–26 March 2011, Prague

<http://www.hivcohorts.com>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website

The i-Base website has been completely redesigned with new portals for healthcare professionals, HIV-positive people and community advocates.

It is even faster and easier to access, use and 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/qa>

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.

Training manual – revised, updated and now fully online

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

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

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

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

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

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

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://i-base.info/category/publications/clinic-forms>

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://i-base.info/home/africans-and-treatment-information/>

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

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

UK CAB: reports and presentations

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

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

<http://www.ukcab.net>

World CAB - reports on international drug pricing

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

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

i-Base treatment guides

i-Base produce five booklets that comprehensively cover five important aspects of treatment. Each guide is written in clear non-technical language. All guides are free to order individually or in bulk for use in clinics and are available online in web-page and PDF format.

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

- Introduction to combination therapy (June 2009)
- Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support (March 2009)
- Guide to changing treatment: what to do when your treatment fails (September 2008)
- Guide to HIV, pregnancy & women’s health (January 2009)
- Guide to avoiding & managing side effects (May 2008)

Translations of i-Base publications

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

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

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

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

<http://i-base.info/category/translations/>

Languages currently include:

Bosnian, Bulgarian, Chinese, Czech/Slovak, Croatian, French, Greek, Hindi, Indonesian, Italian, Kosovo, Macedonian, Nepali, HIV i-Base publication

Polish, Portuguese, Romanian, Russian, Serbian and Spanish.

Treatment 'Passports'

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

HIV Treatment Bulletin (HTB)

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

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

HTB South

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

ARV4IDUs

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

Treatment information request service - 0808 800 6013

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

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

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

Online Q&A service

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

<http://www.i-base.info/qa>

Recent questions include:

- How do they get a HIV test result from blood on a piece of paper?
- Where can I buy a home testing kit for HIV?
- We want to start a family, what are the risks?
- Can HIV be transmitted through biting/being bitten? Has this ever happened?
- I am really angry with the NHS treatment I received...
- Why do NHS and private clinics have different recommendations?
- I have multi-drug resistant HIV, can I stop the T-20?
- What are the chances of getting HIV from this one time unprotected oral sex?
- How do I officially complain about my GUM clinic?
- I would like to know what does the rash which appears during seroconversion look like?
- Which malaria prophylaxis should I take?
- What are the lumps in my arm-pits, are they cancer?
- Can I get HIV from kicking a needle?
- How easy is it to get HIV?
- Is there a cure for HIV?
- Will I get the same HIV test if I go to my GP?

- Are GUM clinics infecting people with HIV?
- Is it better to test at a GUM clinic or when I give blood?
- Where can I get fertility treatment?
- If my friend is sharing needles is the test accurate at 31 days?
- Can I do body-building if I have HIV?
- Can I ask questions when I go for a test?
- My viral load is 10,000,000 in seroconversion...
- I have lost my sex drive – what is the cause of this?
- Can I take supplements when I'm HIV positive?
- Do seroconversion symptoms all come together and go together and how long can they last?
- Do PCR tests look for all types of HIV?
- Can I take steroids (Deca-durabolin and Sustanon) if I am on HIV medication (Sustiva and Truvada)? Many thanks
- Am I cured of hepatitis B and is it possible to still infect my partner?
- When should I take cotrimoxazole?
- How accurate is a fourth generation test at 23 days?
- Is CMV present in saliva?
- How can I use raltegravir as first treatment in the UK?

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>

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://i-base.info/order>

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

h-tb

HIV Treatment Bulletin

HTB is a monthly journal published in print and electronic format by HIV i-Base. As with all i-Base publications, subscriptions are free and can be ordered directly from the i-Base website:

<http://www.i-base.info>; by fax or post using the form on the back page by sending an email to: subscriptions@i-base.org.uk

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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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Guide To HIV, Pregnancy and Women's Health (January 2009)

1 5 10 25 50 100 Other

NEW: Introduction to Combination Therapy (June 2008)

1 5 10 25 50 100 Other

Changing Treatment - Guide to Second-line and Salvage Therapy (September 2008)

1 5 10 25 50 100 Other

Guide To Avoiding and Managing Side Effects (May 2008)

1 5 10 25 50 100 Other

Guide To HIV and hepatitis C coinfection (May 2007)

1 5 10 25 50 100 Other

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

Please fax this form back, post to the above address, or email a request to HIV i-Base:

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