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## November/December 2007

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## EDITORIAL

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### New i-Base resources

#### Introduction to Combination Therapy, November 2007

The latest edition of the i-Base Introduction to Combination Therapy is included as a supplement to this issue of HTB.

The November 2007 edition has been updated to include recent changes to the European and US guidelines. We have reduced the size, rewritten the section on choice of treatment, included several new graphs and tables, including a pull-out colour chart of ARVs, and added pages to record CD4, viral load, and other test results.

We hope this is a useful new resource and welcome any feedback.

As with all publications, the guide is free, including bulk orders for use in clinics.

We have also added several new online resources to the i-Base website.

#### Training manual for advocates, December 2007

The training manual for advocates – made up of 8 modules for learning about basic aspects of HIV care has been updated and published online as an interactive resource:

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

Sections include:

1. Immune system and CD4 count
2. Virology, HIV and viral load
3. Introduction to anti-retrovirals (ARVs)
4. Side effects of ARVs
5. Opportunistic infections and coinfections
6. HIV and pregnancy
7. Drug users and HIV
8. How to read science

Each section includes online test questions and answers. 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.

#### Generic clinic forms, December 2007

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

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

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

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

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## CONFERENCE REPORTS

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### 11th European AIDS conference (EACS)

#### 24-27 October 2007, Madrid

We include several reports from this recent European conference, held this year in Madrid.

These include:

- New European Guidelines launched
- Saquinavir/r non-inferior to Kaletra at week 48 (Gemini Study)
- Darunavir once-daily is non-inferior to lopinavir/r in treatment-naïve patients at 48 weeks (Artemis Study)
- Tesamorelin (TH9507) reduces abdominal fat in patients with HIV-related lipodystrophy: 52 week results
- Drug interaction studies presented at EACS

Abstracts are posted online to the conference website and it is very encouraging to see that web casts of the oral presentations, including late-breakers, are also online for the first time:

<http://www.multiwebcast.com/eacs/2007/11th>

Presentations from the excellent pre-conference educational course, together with some of the pharmaceutical satellite sessions, are also posted from links to the conference home page:

<http://www.eacs-conference2007.com/>

## New European guidelines launched

The conference saw the launch of three sets of very useful summary guidelines, produced by the European AIDS Clinical Society.

These excellent guidelines use comprehensive summary tables for clinical management and treatment, metabolic complications and hepatitis coinfection.

<http://www.eacs.eu/guide/index.htm>

### Guidelines for the clinical management and treatment of HIV-infected adults in Europe

[http://www.eacs.eu/guide/1\\_Treatment\\_of\\_HIV\\_Infected\\_Adults.pdf](http://www.eacs.eu/guide/1_Treatment_of_HIV_Infected_Adults.pdf)

### Guidelines on the prevention and management of metabolic diseases in HIV

[http://www.eacs.eu/guide/2\\_Prevention\\_and\\_Management\\_of\\_Metabolic\\_diseases\\_in\\_HIV.pdf](http://www.eacs.eu/guide/2_Prevention_and_Management_of_Metabolic_diseases_in_HIV.pdf)

### Guidelines for the clinical management and treatment of chronic hepatitis B and C co-infection in HIV-infected adults

[http://www.eacs.eu/guide/3\\_Treatment\\_chronic\\_hepatitis\\_coinfection.pdf](http://www.eacs.eu/guide/3_Treatment_chronic_hepatitis_coinfection.pdf)

Presentations on each of these guidelines, including case studies, are available online:

<http://www.multiwebcast.com/eacs/2007/11th>

## C O M M E N T

Many of the recommendations in these summary tables are more appropriate than the recently published 2007 WHO European guidelines. It would be useful if EACS doctors were also involved into the WHO guidelines, for consistency and a better standard of clinical care.

## Saquinavir/r non-inferior to Kaletra at week 48 (Gemini study)

Simon Collins, HIV i-Base

The Gemini Study was a 48-week prospective, open-label trial that randomised 337 treatment-naïve patients to either saquinavir/r or lopinavir/r, using tenofovir and FTC as background nukes.

Interim 24-week and full 24-week results were presented at the Glasgow 2006 and IAS 2007 conferences respectively, showed very little difference between the two groups. 48-week results were presented at EACS by Sharon Walmsley from the University of Toronto.

337 treatment-naïve patients from the US, Canada, France and Thailand were randomised to either saquinavir/ritonavir 1000mg/100mg BID (n=167) or lopinavir/r 400mg/100mg BID, Kaletra capsule formulation (n=170), with tenofovir/FTC as background nucleosides.

39 of these patients were excluded in the 'per protocol analysis' due to not meeting entry criteria (mainly having baseline CD4 counts >350 cells/mm<sup>3</sup> or viral load <10,000 copies/mL). Further discontinuations and loss to follow-up in the trial, detailed in Table 1, resulted in only 128 and 135 patients in the saquinavir/r (SQV/r) and lopinavir/r (LPV/r) arms respectively, reaching the week 48 endpoint,

**Table 1: Subject discontinuations in Gemini by week 48**

Reason for withdrawal	SQV/r (n = 167)	LPV/r (n = 170)
Overall discontinuations, n (%)	39 (23)	35 (21)
Safety, n (%)	8 (5)	13 (8)
Adverse event ≥ 1%, n (%)	5 (3)	12 (7)

Death [a] n	3 [b]	1 [c]
Non-safety, n (%)	22 (13)	19 (11)
Violation of selection criteria at entry	0	2
Other protocol violations	1	0
Refused treatment	6	4
Failed to return	12	12
Other	3	1
Insufficient therapeutic response, n (%)	9 (5)	3 (2)

[a] 7 total: 3 deaths occurred outside of treatment period in LPV/r group (after withdrawal or during follow-up period): hepatic failure (possibly related to study drug), Burkitt's lymphoma, PML

[b] Cause of death: victim of crime (remotely related to study drug), drowning, sepsis

[c] Cause of death: suicide

This was a non-inferiority study (defined with lower CI threshold of -12%). The primary efficacy endpoint was the percentage of patients with HIV-1 RNA <50 copies/mL at week 48. Secondary efficacy and tolerability endpoints included time course of viral load and CD4 changes and clinical and laboratory side effects, serious side effects and deaths.

Study groups were balanced at baseline: approximately 80% male, median age 37 (range 28-66). Although the median weight 69kg this ranged from 34-131kg, which was reported as reflecting the geographic differences (and presumably HIV-related wasting in some patients). This was an advanced group of patients. Mean viral load was 5.2 log ( $\pm 0.5$  log), with >63% starting at over 100,000 copies/mL. Mean CD4 count was reported as approximately 160 cells/mm<sup>3</sup> ( $\pm$ SD 125), with 40% starting with <100 cells/mm<sup>3</sup>. 24% of the SQV/r arm and 29% of the LPV/r arm had experienced a prior AIDS defining event. Just under 10% of patients were coinfecting with hepatitis C.

At week 48, by ITT analysis (missing data=non-response), 64.7% patients in the SQV/r and 63.5% in the LPV/r arm had viral load <50 copies/mL (estimated difference 1.14% [95% CI -9.6-11.9]  $p < 0.0119$ ), meeting the predefined definition of non-inferiority for saquinavir/r. There was a similar difference in the per-protocol analysis (3.5% (95% CI -8.1-15.0),  $p < 0.0058$ ).

Both groups reported viral load reductions of -3.3 logs at week 48 ( $p=0.62$ , NS). Median CD4 increases were similar: +178 (SQV/r) vs +204 (LPV/r), ( $p=0.33$ , NS).

More patients failed virologically in the SQV/r arm: 11 (7%) vs 5 (3%),  $p=0.13$  NS, with more patients also having documented poor adherence (6/11 vs 2/5). 5 of the patients in the SQV/r arm compared to 0 in the LPV/r arm were subsequently found to have had undocumented resistance at baseline. The only case of new PI resistance was in a patient using SQV/r.

Side effects, detailed in Table 2, were broadly similar in each group, with slightly less GI disorder reported with SQV/r.

The only statistical difference in lipid changes at week 48, favouring the SQV/r arm, were lower increases in triglycerides: +0.16 vs +0.62 mmol/L, ( $p=0.0022$ ), with no differences for TC, LDL and HDL. However, the SQV/r benefit in TC/HDL ratio seen at week 24 (-0.40 vs -0.07,  $p=0.02$ ) lost statistical significance by week 48 (-0.27 vs -0.13,  $p=0.47$ ).

Interventions with lipid lowering drugs (based on NCEP and ACTG guidelines), were warranted for higher number of patients in the SQV/r arm due to increases in LDL, and for more patients in the LPV/r arm due to increases in triglycerides. Lipid lowering drugs were not widely used during the study ( $n=4$  patients in the SQV/r arm and 7 patients in the LPV/r arm).

#### C O M M E N T

**These results provide support for use of boosted saquinavir in first-line treatment, when a PI is indicated.**

**It is unclear how the newer Kaletra tablet formulation would effect these results. After the study was enrolled, Kaletra was reformulated to require fewer pills, no refrigeration or diet restrictions, to have better pharmacokinetics and possibly an easier GI side effect profile.**

**It is disappointing that the improvement in TC:HDL ratio in favour of saquinavir seen at week 24, lost statistical significance by week 48. It will be important to see additional analysis by baseline viral load and CD4 count, and details about incidence of lipodystrophy, and it is disappointing that extended follow-up will not be presented.**

Ref: Walmsley S, Ruxrungtham K, Slim J et al. The Gemini Study: Saquinavir/r (SQV/r) vs lopinavir/r (LPV/r) plus emtricitabine/tenofovir (FTC/TDF) as initial therapy in HIV-1 infected patients. Abstract PS1/4.

This presentation is available online:

<http://www.multiwebcast.com/eacs/2007/11th>

**Table 2: Summary of adverse events (all grades)**

	SQV/r (n = 163)	LPV/r (n = 168)
Total pts with ≥ 1 AE, n (%)*	83 (51)	106 (63)
Total number of AEs	231	247
Total number of SAEs	32	24
Individual AEs reported in ≥3% of participants in either group	Individual AEs reported in ≥3% of participants in either group	Individual AEs reported in ≥3% of participants in either group
Infections:		
Total pts with ≥ 1 AE	39 (24)	47 (28)
Bronchitis	9 (6)	2 (1)
Upper respiratory tract	4 (2)	8 (5)
Gastrointestinal disorders:		
Total pts with ≥ 1 AE	27 (17)	45 (27)
Nausea	10 (6)	15 (9)
Vomiting	10 (6)	10 (6)
Diarrhea	11 (7)	24 (14)
Abdominal pain	3 (2)	5 (3)
General disorders:		
Total pts with ≥ 1 AE	20 (12)	16 (10)
Fatigue	8 (5)	6 (4)
Metabolism/nutrition disorders:		
Total pts with ≥ 1 AE	13 (8)	13 (8)
Hypertriglyceridemia	0	5 (3)
Anorexia	5 (3)	4 (2)
Nervous system disorders:		
Total pts with ≥ 1 AE	13 (8)	12 (7)
Headache	4 (2)	7 (4)
Psychiatric disorders:		
Total pts with ≥ 1 AE	10 (6)	13 (8)
Depression	4 (2)	5 (3)
Musculoskeletal/ connective disorders: Total pts with ≥ 1 AE	9 (6)	13 (8)
Respiratory/thoracic/mediastinal disorders: Total pts with ≥ 1 AE	8 (5)	6 (4)
Renal/urinary disorders: Total pts with ≥ 1 AE	7 (4)	2 (1)
Skin/Subcutaneous Tissue disorders: Total pts with ≥ 1 AE	6 (4)	5 (3)
Vascular disorders: Total pts with ≥ 1 AE	1 (<1)	5 (3)

### **Darunavir once-daily is non-inferior to lopinavir/r in treatment-naïve patients at 48 weeks (Artemis study)**

**Simon Collins, HIV i-Base**

In an oral late breaker presentation, Nathan Clumeck presented results from a randomised, multinational (26 country) study, comparing darunavir once-daily to lopinavir/r (once- or twice-daily) in almost 700 treatment-naïve patients. Use of lopinavir/r once-daily by some US patients was a patient/doctor choice and not subject to randomisation.

Darunavir is approved as a twice-daily protease inhibitor at 600mg/100mg twice daily, for use in combination with other active drugs as a treatment for PI-experienced patients. In this study, darunavir was dosed at 800mg with 100mg ritonavir once-daily (n=343) and lopinavir/r was dosed at 400/100mg twice-daily or 800/200mg once-daily (n=346). Truvada (tenofovir+FTC) once-daily was included as background nucleosides in both arms. Viral load needed to be >5,000 copies/mL at screening but there were no CD4 entry restrictions.

The study was designed as a non-inferiority study based on the primary endpoint of the percentage of patients with viral suppression <50 copies/mL at week 48. Secondary endpoints include safety, efficacy and tolerability results over 192 weeks.

All demographics were balanced at baseline: 70% of patients were men and 30% women, mean age 35 (SD±9), and just over 40% of patients were Caucasian. While the group as a whole was not advanced – with a median CD4 of around 220 cells/mm<sup>3</sup> and viral load of 60,000 copies/mL – the ranges for these characteristics were broad: CD4 ranged from 2 to 750 cells/mm<sup>3</sup> and viral load from 600 – 5.5 million copies/mL. It is unclear why some of these patients were entered into the study; some patients had CD4 counts far higher than guidelines recommend starting treatment and others had such advanced HIV, that they, arguably, should not be relying on an unproven treatment.

Approximately 14% patients were coinfecting with hepatitis C and 10% were CDC class C.

Stratification at screening showed 40% patients had CD4 count <200 cells/mm<sup>3</sup> and 36% had viral load >100,000 copies/mL.

At week 48, by Intent-To-Treat TLOVR (Time to Loss of Virologic Response) analysis, 84% of patients using DRV/r vs 78% of LPV/r patients reached <50 copies/mL. The estimated difference in response compared to LPV/r for non-inferiority per-protocol analysis was 5.6% (95% CI -0.1;11.3) p<0.001; and for superiority by ITT was 5.5% (95% CI -0.3;11.2) p=0.062. Assessed by primary endpoint, darunavir once-daily was found to be non-inferior to lopinavir/r, and results showed a trend towards superiority.

71% of the subset of 52 mainly US patients who used lopinavir/r once daily (who as a group had similar baseline characteristics to the DRV/r and LPV/r BID groups) achieved suppression to <50 copies/mL. This 13% difference showed darunavir/r to be superior to once-daily lopinavir/r (95% CI 1; 24; p<0.05). Differences between the LPV/r once- vs twice daily [9%\* (95% CI -3; 21)] and DRV/r once-daily vs LPV/r twice daily [(3% (95% CI -3; 9)] were not significant.

Results in patients with baseline viral load >100,000 copies/mL saw an even greater difference between DRV/r and once-daily LPV/r with 79% vs 56% achieving <50 copies/mL (P<0.05). The significance remained when comparing DRV/r to the overall LPV/r group (67%, p<0.05) but not when comparing to LPV/r twice-daily (71%).

Grade 2-4 side effects, summarised in Table 1, showed a higher rate of diarrhoea in the LPV/r arm overall (4% vs 10%). These rates were 8% in the LPV/r twice daily and 17% in the LPV/r once-daily groups. Nausea was similar at 2-3% in both arms and rash was slightly higher in the DRV/r (3% vs 1% LPV/r overall).

The majority of LPV/r QD use was in the US. The proportion of US patients who used LPV/r QD was 66% (45 of 68 patients). Only 7 patients outside of the US used LPV/r QD. 27 (8%) patient used both once- and twice-daily LPV/r dosing during the study, and were excluded from the QD vs BID LPV/r analyses.

**Table 1: Grade 2-4 side effects and lipid changes (seen in >2% patients)**

	<i>DRV/r QD</i> <i>n=343</i>	<i>LPV/r overall</i> <i>n=346</i>	<i>LPV/r BID</i> <i>n=267</i>	<i>LPV/r QD</i> <i>n=52</i>
<i>Diarrhoea</i>	<b>14 (4%)</b>	<b>34 (10%)</b>	<b>22 (8%)</b>	<b>9 (17%)</b>
<i>Nausea</i>	<b>6 (2%)</b>	<b>10 (3%)</b>	<b>8 (3%)</b>	<b>0</b>
<i>Rash</i>	<b>9 (3%)</b>	<b>4 (1%)</b>	<b>3 (1%)</b>	<b>1 (2%)</b>
<i>TChol</i>	<b>44 (13%)</b>	<b>78 (23%)</b>	<b>69 (26%)</b>	<b>8 (15%)</b>
<i>LDL</i>	<b>44 (13%)</b>	<b>36 (11%)</b>	<b>31 (12%)</b>	<b>9 (17%)</b>
<i>TG</i>	<b>10 (3%)</b>	<b>38 (11%)</b>	<b>27 (10%)</b>	<b>9 (17%)</b>

C O M M E N T

This study supports the use of darunavir/r as a once-daily option in naïve patients, especially when viral load is >100,000 copies/mL, although it would be interesting to know whether twice-daily darunavir/r would improve on these rates or suppression in this group.

The results of the LPV/r once-daily analysis should be interpreted cautiously as this is a small non-randomised subset of US patients.

Several studies have previously shown lopinavir/r once daily to be inferior to twice-daily, with poorer trough concentrations, and although licensed as a once-daily option in the US for naïve patients, Abbott no longer appear to be actively pursuing once-daily registration in Europe.

Ref: Clumeck N et al. ARTEMIS: Efficacy and safety of lopinavir (BID vs QD) and darunavir (QD) in antiretroviral-naïve patients. Late breaker abstract LBPS7/5.

<http://www.multiwebcast.com/eacs/2007/11th>

## Tesamorelin (TH9507) reduces abdominal fat in patients with HIV-related lipodystrophy: 52 week results

Simon Collins, HIV i-Base

In another late breaker at the meeting, Steve Grinspoon from Massachusetts Medical School, presented 52-week results from the use of the investigational growth hormone releasing factor (GHRF) tesamorelin (2mg/day) to reduce visceral adipose tissue (VAT). [1]

At the Retrovirus conference in February this year, 26 week results were presented from 412 patients randomised to either GHRF or placebo, that showed an approximate reduction in VAT of 20% in the GHRF arm with little negative impact on limb fat. The beneficial lipids profile included reductions in TG, TC and TC:HDL ratio and an increase in HDL. [2]

In the extended study, patients who completed the initial study and had been randomised to the GHRF arm (n=211), were re-randomised to either continue using the active compound (TT, n=154) or switch to placebo (TP, n=50). Patients who completed the original study who had received placebo were switched to GHRF for the following 26 weeks (PT, n=111).

Baseline characteristics in these three group were similar and included 12% women. 90% patients had either undetectable or low level viral load <400 copies/mL. Entry criteria selected patients with high waist circumference (~105 ±10cm), with waist:hip ratio 1.1 ±0.1 and BMI ~30 ± 4.5. visceral fat was increased at ~180 ± 80 cm<sup>2</sup>.

At week 52, patients who continued on GHRF (TT) maintained the benefits seen at week 26, but did not see any additional change. Patients who received GHRF from week 26 (PT) showed a similar response by week 52 seen in the TT group. Patients who switched from GHRF to placebo (TP) lost the benefits seen at week 26 and returned close to baseline. Changes in VAT using GHRF compared to baseline were statistically significant (p < 0.001) as were changes in waist circumference (p<0.05), which approximated to reduction by 3-4 cms.

Safety data was generally good and not significantly different to placebo, and are summarised in Tables 1 and 2.

**Table 1: Summary of adverse events**

% patients	Week 26		Week 52		
	T	P	TT	TP	PT
n	273	137	154	50	111
Any a/e	83	75	58	66	75
Related a/e (generally injection site)	54	37	14	18	36
A/e discontinuation	12	3	3	6	12
Serious a/e	4	2	3	4	3

**Table 2: Selected adverse events in >5% patients**

% patients	Week 26		Week 52		
	T	P	TT	TP	PT
n	273	137	154	50	111
Headache	16.1	18.2	2.6	4.0	2.7
Arthralgia	13.6	10.9	3.9	4.0	14.4
Injection site bruising	9.2	9.5	0	4.0	1.8
Diarrhoea	8.1	9.5	2.6	6.0	2.7
Peripheal edema	8.4	5.1	1.3	0	2.7
Myalgia	7.7	2.2	1.3	0	2.7
Extremity pain	6.2	6.6	1.9	0	5.4

There were no significant differences between groups or compared to baseline in glucose parameters or immune responses.

IGF levels increased in response to GHRF treatment and dropped if discontinued, explaining the increase in VAT seen in the TP group.

Approximately 50% of patients exposed to GHRF developed antibodies to tesamorelin which was not unexpected but this was not related to the treatment response.

C O M M E N T

**These results are very encouraging. Central fat accumulation is not only a distressing side effect, but is an independent predictor of coronary artery disease. GHRF is more tolerable than recombinant HGH, which, apart from diet and exercise, is the only other treatment that has convincingly reduced VAT.**

**The disappointing aspect of these results is that GHRF appears to require maintenance treatment.**

**The study prompted many questions, including interest in using GHRF together with treatment switching to newer ARVs (integrase inhibitors and entry inhibitors) together with diet and exercise, cost, and to identify a suitable maintenance dose.**

References

1. Grinspoon S et al. Long-term safety and efficacy of tesamorelin (TH9507), a Growth Hormone-Releasing Factor (GRF) Analogue, in HIV-infected patients with abdominal fat accumulation. Late breaker abstract LBPS7/3.
2. See HTB March/April 2007  
<http://www.i-base.info/htb/v8/htb8-3-4/Growth.html>

### Drug interaction studies presented at EACS

The following summary of drug interaction studies was produced by HIV-druginteractions.org

#### Interactions between two or more anti-HIV drugs

##### No interaction between TDF/FTC and nevirapine

The effect of tenofovir/emtricitabine on the pharmacokinetics of nevirapine (200 mg twice daily) was studied in seven HIV-positive, African-American subjects.

The mean  $\pm$  sd steady state nevirapine C<sub>min</sub> was 4971  $\pm$  1985 ng/ml and was comparable to historical values. The mean nevirapine C<sub>min</sub> after the 200 mg once daily 2 week lead-in phase was also determined and was 2876 ng/ml.

Ref: Davis JrC, Gillam B, Amoroso A, et al. Lack of pharmacokinetic interaction of tenofovir and emtricitabine on nevirapine. Abstract P4.1/03.

##### Etravirine reduces maraviroc levels requiring maraviroc dose increase to 600mg BID

The pharmacokinetics of maraviroc and etravirine were determined in HIV-negative subjects following coadministration of etravirine (200 mg twice daily) and maraviroc (300 mg twice daily) or coadministration of etravirine (200 mg twice daily, maraviroc (150 mg twice daily) and darunavir/ritonavir (600/100 mg twice daily).

Coadministration of etravirine decreased maraviroc AUC and C<sub>max</sub> by 53% and 60% respectively; coadministration of etravirine, darunavir and ritonavir increased maraviroc AUC and C<sub>max</sub> by 210% and 77% respectively.

Maraviroc had no significant effect on etravirine, darunavir or ritonavir pharmacokinetics. When maraviroc is coadministered with etravirine, in the absence of a potent CYP3A4 inhibitor, the recommended dose of maraviroc is 600 mg twice daily.

Ref: Davis J, Scholler-Gyure M, Kakuda TN, et al. An open randomised two period crossover study in 2 cohorts to investigate the effect of steady state TMC125 and the combination of TMC125/DRV/r on the steady state pharmacokinetics of oral maraviroc in healthy subjects. Abstract P4.3/02.

##### Atazanavir levels not significantly reduced by tenofovir, but higher in Caucasians

Factors affecting atazanavir trough concentrations were determined in a cohort of 128 HIV-positive subjects receiving atazanavir/ritonavir (300/100mg once daily) with two nucleos(t)ide inhibitors. Tenofovir was administered to approximately half of the cohort and was found not to influence atazanavir C<sub>min</sub> (525 vs 402 ng/ml, alone vs with tenofovir; p=0.2).

There was no impact of age, gender, weight or BMI on atazanavir concentrations; however, concentrations were significantly higher (p=0.04) in non-Caucasians (562 ng/ml) than in Caucasians (418 ng/ml).

Ref: Lescure F-X, Poirier J-M, Meynard J-L, et al. Impact of demographic factors and tenofovir coadministration on atazanavir trough plasma concentration in HIV infected patients treated with boosted atazanavir. Abstract P4.3/06.

#### Interactions between anti-HIV drugs and other drugs

##### No significant interaction between NucleomaxX and AZT/3TC

NucleomaxX is an oral uridine supplement which may be given to prevent and revert mitochondrial toxicities. The effect of a single dose of NucleomaxX (36 g) on the pharmacokinetics of a single dose of zidovudine/lamivudine (300/150 mg) was studied in eight HIV-negative subjects.

Coadministration of NucleomaxX had no effect on the pharmacokinetics of zidovudine; however, lamivudine C<sub>max</sub> and T<sub>max</sub> were significantly higher, but there was no effect on AUC or half life. No adverse events were observed and the pharmacokinetics of zidovudine and lamivudine were consistent with historical data from HIV-negative subjects.

Ref: Venhoff N, Venhoff AC, Jayewardene A, et al. Pharmacokinetics of zidovudine and lamivudine under oral uridine supplementation with NucleomaxX. Abstract P4.1/12.

### **Dose adjustments necessary for immunosuppressants following liver transplant**

Plasma trough concentrations of ciclosporin, tacrolimus and rapamycin (sirolimus) were studied in 12 HIV-positive subjects undergoing liver transplants. Following the addition of protease inhibitor therapy, the fold changes required to maintain therapeutic immunosuppressant concentrations were determined.

After initiating a boosted protease inhibitor regimen (n=4), the mean fold decrease in immunosuppressant dose was 8.75 (range 6-14). The mean fold decrease required after initiating an unboosted protease inhibitor regimen (n=8) was 3 (range 2-4).

Ref: Guaraldi G, Cocchi S, Ciaffi S, et al. Different dose adjustments of immunosuppressants are necessary after initiating boosted or unboosted first protease inhibitor regimen post liver transplantation. Abstract P4.2/04.

### **No interaction between etravirine and paroxetine**

Coadministration of etravirine (125 mg twice daily, phase II formulation) and paroxetine (20 mg once daily) was investigated in 16 HIV-negative subjects. Etravirine increased paroxetine AUC, and C<sub>max</sub> by 3% and 6%, respectively, and decreased C<sub>min</sub> by 13%. AUC, C<sub>max</sub> and C<sub>min</sub> of etravirine increased by 1%, 5% and 7%, respectively. No dose adjustments are required when etravirine and paroxetine are coadministered.

Ref: Scholler-Gyure M, Kakuda TN, Bollen S, et al. No pharmacokinetic interaction between TMC125 and paroxetine in HIV-negative volunteers. Abstract P4.3/01

### **Tipranavir/r significantly reduces levels of bupropion**

The effect of tipranavir/ritonavir (500/200 mg twice daily) on the pharmacokinetics of bupropion (150 mg twice daily) was studied in 16 HIV-negative subjects. Coadministration decreased bupropion by ~50% with decreases (mean ± sd) observed for AUC (from 619 ± 248 to 337 ± 208 ug.h/L), C<sub>max</sub> (from 88.6 ± 38.5 to 51.4 ± 32.2 ug/L) and C<sub>min</sub> (from 27.0 ± 17.1 to 12.2 ± 8.4 ug/L). Exposure of the active metabolite (4-hydroxybupropion) decreased by ~25%.

Increased ALT was observed in 6/16 subjects after 1 week of tipranavir/ritonavir, but returned to baseline by the end of the study in 5/6 subjects. Coadministration resulted in significant decreases in exposure to both bupropion and its active metabolite.

Patients should be closely monitored for the therapeutic effect on depression.

Ref: Lavrut T, Garraffo R, Ferrando S, et al. Effect of tipranavir/ritonavir treatment on the steady-state pharmacokinetics of bupropion in healthy volunteers. Abstract P4.3/03.

### **No dose adjustment required when using TMC-278 and atorvastatin**

Coadministration of the NNRTI TMC278 (150 mg once daily) and atorvastatin (40 mg once daily) was studied in 16 HIV-negative subjects. Atorvastatin had no significant effect on the pharmacokinetics of TMC278. Atorvastatin C<sub>max</sub> increased by 35% in the presence of TMC278, but there were no changes in AUC or C<sub>min</sub>. AUCs of the 2-OH and 4-OH metabolites of atorvastatin increased by 39% and 23% respectively. The AUC of total HMG-CoA reductase activity (as determined by the sum of atorvastatin, 2-OH and 4-OH atorvastatin) increased by 20%. No dosage adjustment is required when TMC278 and atorvastatin are coadministered.

Ref: Van Heeswijk RPG, Hoetelmans, RMW, Aharchi F, et al. The pharmacokinetic interaction between atorvastatin and TMC278, a next generation NNRTI in HIV-negative volunteers. Abstract P4.3/04.

### **Efavirenz significantly reduces levels of posaconazole**

Coadministration of efavirenz (400 mg once daily) and posaconazole (400 mg twice daily) was studied in HIV-negative subjects. Data from 10 subjects showed there was no effect on efavirenz AUC and a 13% increase in C<sub>max</sub>. However, data from 11 subjects showed that efavirenz decreased posaconazole exposure with AUC decreasing by 50% and C<sub>max</sub> by 45%.

Based on these data, the authors suggest that concomitant use should be avoided unless the benefit outweighs the risk.

Ref: Moton A, Ma L, Krishna G, et al. Pharmacokinetics of the antifungal triazole posaconazole and the NRTI [sic] efavirenz when coadministered in healthy adult volunteers. Abstract P4.3/05.

### **Efavirenz dose may not need increasing in low-body weight patients treated with rifampicin**

When given with rifampicin, the recommendation is to increase efavirenz from 600 to 800 mg once daily. However, as the results of this safety and efficacy study show, this dose increase may not be necessary in all patients.

A retrospective cohort study was conducted in 77 HIV/TB coinfecting Thai subjects who received efavirenz 600 mg once daily and rifampicin. At 48 weeks, 78% of subjects achieved viral loads <50 copies/mL and CD4 counts had risen to 253 cells/mm<sup>3</sup>. No subjects discontinued therapy due to adverse events.

Ref: Manosuthi W, Tansuphaswadikul S, Mankathitham W, et al. Efavirenz-based versus nevirapine-based antiretroviral therapy among HIV-infected patients with tuberculosis and receiving rifampicin. Abstract P7.3/29.

## **TREATMENT ACCESS**

The following round-up of articles and links relates to treatment access news over the last month.

### **HIV and TB co-infection and treatment charges in the UK**

**Joe Murray, National AIDS Trust**

Treatment for tuberculosis (TB) remains free of charge for all in the UK, irrespective of residency status.

While treatment for TB remains free of charge for all in the UK, the situation for HIV care is different. Since 2004, new NHS regulations mean some of the most vulnerable people living with HIV in the UK – refused asylum seekers and other undocumented migrants – cannot access free HIV treatment.

The National AIDS Trust believes these charging regulations are damaging people's health. HIV organisations like the National AIDS Trust are hearing stories of people living with HIV, who have not been provided with HIV treatment because of misunderstandings over entitlement, or who disappear from care for fear of HIV-related bills. It is often the most vulnerable who suffer from delayed, denied, interrupted or withdrawn care because they are unable to pay such HIV-related bills for treatment. And many have been pursued aggressively by debt collectors. The consequences for the health and well-being of those affected are grave, and could well result in serious illness and sometimes death.

Even though an individual may be chargeable for their HIV treatment, if that care is needed, they should not be denied it. Clinicians have an obligation to treat all with a serious communicable disease like HIV, irrespective of residency status, if that treatment is 'immediately necessary'. Where HIV treatment is deemed by a clinician to be necessary, either to save life or to prevent a condition from becoming life-threatening, then Government guidance stipulates that treatment must be given without delay, regardless of whether the patient is, or may be, chargeable for their HIV care. The guidance is explicit on this.

Sadly it is often those most vulnerable that are not entitled to free HIV care. Refused asylum seekers and other undocumented individuals are unable to work legally and, as a result, are often destitute – certainly unable to pay any bill for hospital care or medication. If an individual is charged for their HIV treatment and are unable to pay such a bill, hospitals have the ability to write off debt if they realise that someone simply cannot pay. Support organisations such as the Terrence Higgins Trust can help people negotiate debt write-off – clinicians should have no doubt about providing access to vital treatment. Although the charging regulations can be confusing, treating clinicians have a duty to provide the best possible care for their patients, and at the right time, whether or not they are eligible for free HIV treatment.

Nearly nine million new cases of TB, and nearly two million deaths from TB, are estimated to occur around the world every year. About 8000 new cases of TB are reported each year in the UK, where it is the most common AIDS defining illness among migrant communities.

With these alarming statistics in mind, it is imperative that TB, a serious communicable infection, is diagnosed and treated as early as possible. This is particularly important for patients living with HIV, as co-infection can be a deadly duo. TB does not need to be one of the leading causes of death for people living with HIV. With adequate and timely treatment, patients may fully recover from TB.

'Will I have to pay?' by the National AIDS Trust and Terrence Higgins Trust provides further information and advice on getting NHS sexual health and HIV services for recent migrants and those of uncertain residency status. You can download a PDF of the leaflet at:

[www.nat.org.uk/document/253](http://www.nat.org.uk/document/253)

## 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
Tenofovir DF (300mg)	Matrix, India	30 November 2007
AZT/3TC (300/150 mg)	Matrix, India	29 November 2007
d4T/3TC (40/150mg and 30/150mg)	Matrix, India	2 November 2007
d4T oral solution	Cipla, India	29 October 2007

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

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

[http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl\\_No=3D021360&TABLE1=3DOB\\_Rx](http://www.accessdata.fda.gov/scripts/cder/ob/docs/obdetail.cfm?Appl_No=3D021360&TABLE1=3DOB_Rx)

### C O M M E N T

**Of this expanding list, this is the first approval of tenofovir, which will enable both more tolerable first-line and more effective second-line options. This brings the total of FDA approved generic drugs and formulations to 51 since the programme started.**

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

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

Source: FDA list serve:

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

A list of FDA approved generic antiretroviral drugs for the treatment of HIV is available on the web at

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

## ANTIRETROVIRALS

### US adult treatment guidelines updated

An update of the US Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents were released on 1 December 2007.

These guidelines very usefully highlight changes from the last edition with a yellow background for easy comparison.

These include:

- Adding the recommendation for resistance testing for all patients either on diagnosis or before starting treatment
- Starting treatment when CD4 count is <350 cells/mm<sup>3</sup>
- Use of HLA B\*5701 testing prior to using abacavir
- Starting HIV treatment for people coinfecting with HBV who need to treat their hepatitis B
- Preferred first line dual nucleosides: tenofovir/FTC or AZT/3TC. This is the first time that the guidelines have even mentioned lipodystrophy, and although they recognise it occurred more frequently with AZT compared to tenofovir, AZT is still a preferred first line choice. Abacavir/3TC is only an alternative option, despite being the backbone nucleosides in the trials used to recommend fosamprenavir.
- Preferred NNRTI is efavirenz; alternative is nevirapine.
- Preferred boosted PIs for first-line therapy are atazanavir/r, fosamprenavir/r, lopinavir/r. Alternative PI-regimens

are unboosted atazanavir (but not with tenofovir), fosamprenavir twice daily, boosted fosamprenavir once-daily and lopinavir/r once-daily. Lowest recommendations are for nelfinavir, and boosted saquinavir.

- Nelfinavir is now contraindicated in pregnancy because of the unknown risk of small amounts of a byproduct (ethyl methanesulfonate or EMS).
- Changes to management of treatment-experienced patients stress for the need for two, or preferably three, active drugs and includes recently developed drugs (maraviroc, raltegravir, etravirine). They also recognise that there is 'no consensus on the optimal time to switch a failing regimen'.
- A new discussion on immunological failure that quantifies chances of reaching over 500 cells/mm<sup>3</sup>.

"The proportion of patients experiencing immunologic failure depends on how failure is defined, the observation period, and the CD4 T-cell count when treatment was started. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 T-cell count >500 cells/mm<sup>3</sup> through 6 years of treatment was 42% (starting treatment with a CD4 <200 cells/mm<sup>3</sup>), 66% (starting with CD4 200–350 cells/mm<sup>3</sup>) and 85% (starting with CD4 >350 cells/mm<sup>3</sup>) increases in CD4 T-cell counts in treatment-naïve patients with initial antiretroviral regimens are approximately 150 cells/mm<sup>3</sup> over the first year. A CD4 T-cell count plateau may occur after 4–6 years of treatment with suppressed viremia."

"A persistently low CD4 T-cell count while on suppressive antiretroviral therapy is associated with a small, but appreciable, risk of AIDS- and non- AIDS-related morbidity and mortality. For example, in the FIRST study, a low CD4 T-cell count on therapy was associated with an increased risk for AIDS-related complications (adjusted hazard ratio of 0.57 for CD4 T-cell count 100 cells/mm<sup>3</sup> higher). Similarly, a low CD4 T-cell count was associated with an increased risk for non-AIDS events, including cardiovascular, hepatic, renal and cancer events. Other studies support these associations."

Unlike French guidelines, use of IL-2 to boost CD4 counts to above 200 cells/mm<sup>3</sup> in immunological non-responders is only recommended within a clinical trial setting.

The guidelines are available online and in PDF format:

<http://www.hivatis.org>

<http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentCL.pdf>

## Half-dose Kaletra tablet approved for paediatric use in the US

On 9 November 2007, the FDA approved a new half-strength lopinavir/r (Kaletra) tablet formulation, manufactured by Abbott Laboratories.

Each film-coated tablet of this new formulation contains 100 mg lopinavir and 25 mg ritonavir. The major changes to the label include clear instructions regarding the importance of accurate calculation of the dose of Kaletra to minimise the risk for medication errors and overdose or under dose, and the addition of tablet dosing to section 2.2 Pediatric Patients.

In a press release, Abbott announced that it would make the lower strength formulation available in resource-poor countries, where Kaletra is marketed under the brand name Aluvia.

This wider access programme is dependent on European approval. The timeline for the EMEA decision is unclear.

Sources: FDA list serve and Abbott press release (12 Nov 07)

## SIDE EFFECTS

### Case report of efavirenz-associated nephrolithiasis

Simon Collins, HIV i-Base

Hassane Izzendine and colleagues from Hôpital Pitié-Salpêtrière reported a case of efavirenz-associated nephrolithiasis in a letter to the September 2007 issue of AIDS. [1]

Nephrolithiasis has been widely associated with indinavir, and more recently with atazanavir. This case reported a stone analysed by infrared spectrometry, liquid chromatography and mass spectrometry that comprised 60% efavirenz metabolites and 40% unspecified proteins.

The patient, a 47 year old HIV-positive man, presented with a six-week history of left flank pain. He had no history of indinavir use, but had a history of renal colic of unknown cause between the age of 16 and 27 years. He had been successful

responding to his current regimen of efavirenz 600mg, atazanavir 300mg and ritonavir 100mg, all taken once-daily, for over two years.

No calculi were seen by plain radiography, as would be expected with other ARV-related stones, and identified by computed tomography.

A 3mm non-crystalline beige stone was subsequently spontaneously cleared.

Although efavirenz is principally metabolised by CYP P-450 liver enzymes to hydroxylated metabolites, which are subsequently clear by glucuronidation. Approximately 14-34% of efavirenz in this case was recovered in urine, with less than 1% excreted as unchanged efavirenz.

The researchers suggested that atazanavir/ritonavir may have increased efavirenz exposure. Plasma levels of efavirenz were slightly raised at 3400 ng/mL at 24-hours post dose (vs a normal target of 3000 ng/mL).

A previous case of efavirenz-associated nephrolithiasis has been reported. [2]

#### References

1. Izzendine H et al. Efavirenz urolithiasis. AIDS. Volume 21 (4) September 2007, p1992.
2. Wirth GJ et al. Efavirenz-induced urolithiasis. Urol Res 2006. 34 288-289.

## Yellow card reporting scheme for doctors and patients in the UK

The MHRA and the Commission on Human Medicines (CHM) run the UK's spontaneous adverse drug reaction reporting scheme - called the Yellow Card Scheme. This receives reports of suspected adverse drug reactions (ADRs) from healthcare professionals. More recently the scheme was extended to include direct reporting by patients.

The MHRA and its predecessor organisations have collected reports of suspected adverse drug reactions through the Yellow Card Scheme for over 40 years. Since the establishment of the Yellow Card Scheme over 500,000 UK reports have been collected.

The scheme collects Yellow Card reports from both health professionals and members of the public on:

- prescription medicines;
- herbal remedies; and
- over-the-counter (OTC) medicines.

The MHRA and CHM also have five Yellow Card Centres whose role focuses on follow-up of reports in their areas as this has been shown to improve follow-up rates.

### Patient reporting

Patients are now welcome to directly report suspected adverse drug reactions to the MHRA through the Yellow Card Scheme. Until recently, only health professionals were able to make Yellow Card reports.

[http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodeId=276](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=276)

Patient reporting of suspected adverse drug reactions:

[http://www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&nodeId=755](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=755)

### A side effect from your medicine? Report it through the Yellow Card Scheme

#### What to report

If you think a medicine or herbal remedy has caused an unwanted side effect (an adverse drug reaction), please report the problem on a Yellow Card.

The Medicines and Healthcare products Regulatory Agency (MHRA) is the medicines safety watchdog. The Yellow Card scheme has been used for over 40 years to collect information on suspected side effects from all types of medicines. These include prescription medicines, medicines you can buy without a prescription, and herbal and other complementary remedies.

The MHRA welcomes Yellow Card reports on any suspected side effect. It is especially useful to know about:

- a suspected side effect that is not mentioned in the patient information leaflet that came with the medicine; or
- a suspected side effect that has caused problems bad enough to interfere with everyday activities.

Sometimes it is difficult to tell whether a possible side effect is due to a medicine or something else. Even if you are not sure whether a medicine or combination of medicines has caused a side effect, but suspect it has, please complete a Yellow Card.

**If you are worried about a suspected side effect, contact a doctor or pharmacist, or call NHS Direct in England and Wales on 0845 46 47 or NHS24 in Scotland on 08454 24 24 24.**

### **How to report a suspected side effect**

You can report a suspected side effect on the schemes website, on a Yellow Card form, which you can find at pharmacies, GP surgeries or from the Yellow Card hotline by calling freephone 0808 100 3352 during business hours.

The Yellow Card hotline is contactable on freephone **0808 100 3352** (available weekdays 10:00 - 14:00)

[Source: MHRA website](#)

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## **PREGNANCY AND MTCT**

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### **US updates guidelines on use of ARVs during pregnancy**

The Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States have undergone a complete revision and reorganisation to reflect important new information, and to make them more user-friendly.

The guidelines have been restructured into principles for medical management of the woman and her infant during the antepartum, intrapartum, and postpartum period, including panel recommendations for each section.

Changes to the report include the following:

- Due to contamination with ethyl methane sulfonate (EMS), nelfinavir is no longer recommended for use in pregnant HIV-infected women
- New sections on antepartum management of HIV-infected pregnant women in special situations, including HBV and HCV coinfection
- New information on ARV drug choice and continuation during labor, and management of women not receiving antepartum ARVs
- New sections on choice and management of infant ARV prophylaxis
- Two new tables: "Results of Major Studies on ARV Prophylaxis to Prevent Mother-to-Child HIV Transmission" and "Clinical Scenario Summary Recommendations for ARV Use by Pregnant HIV-Infected Women and Prevention of Perinatal HIV-1 Transmission in the U.S."
- Updated information for emtricitabine, tenofovir, amprenavir, atazanavir, lopinavir/ritonavir, nelfinavir, maraviroc, and raltegravir in Table 2, "Preclinical & Clinical Data Relevant to the Use of ARVs in Pregnancy"
- Updated information for tenofovir, saquinavir-HGC, atazanavir, nelfinavir, maraviroc, and raltegravir in Table 3, "ARV Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy"

The updated guidelines are available in the "Guidelines" section of the AIDSinfo Web site under 'Perinatal Guidelines':

<http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=3DGuide=lines&Search=3DOff&GuidelineID=3D9&ClassID=3D2>

You can download the guidelines or can request to receive them by e-mail or regular mail on the AIDSinfo website:

<http://aidsinfo.nih.gov>

### **Perinatal transmission of HIV in England 2002-2005**

**Polly Clayden, HIV i-Base**

A report published by the NHS Audit, Information and Analysis Unit (AIAU) in collaboration with the National Study of HIV in Pregnancy and Childhood (NSHPC), and the Children's HIV Association of the UK and Ireland (CHIVA), describes the circumstances in which infants are born HIV-positive, despite well documented interventions that can reduce mother to child transmission to almost zero in this country.

The authors write, "Across the UK more than 30 infants are still being infected annually, and each carries a substantial human and economic cost."

The audit looked at children who were born in England during the four year period between January 2002 and December 2005 and who were reported to the NSHPC as HIV-positive by April 2006.

The audit identified 87 children; 33/87 infants were born to women who were diagnosed before or within 48 hours of delivery.

The audit identified “failure of communication, between health care professionals and the mother, and between themselves, and failure to ascertain or act upon suboptimal virological responses” as issues.

The audit also found the problem of preterm delivery reducing the time for antiretroviral therapy to be given during pregnancy. The authors suggest, “in some cases, the obstetric history would have identified the risk of premature delivery, highlighting the need for individualised management.”

Among the 54 infants born to undiagnosed women, at least 20% were born following maternal seroconversion during pregnancy.

In some cases, care was not accessed because health workers or the women themselves were not sure if HIV in pregnancy is an emergency condition and therefore eligible for free NHS treatment.

No transmissions occurred in mothers and infants receiving optimal care (according to the BHIVA guidelines) and with an undetectable maternal viral load at delivery.

The audit makes a number of recommendations including:

- All pregnant women should be recommended an HIV test at time of booking. Any woman who declines a test, should be recommended one on at least one more occasion by a health worker with specialist training.
- Any woman receiving a test after 20 weeks should have her blood samples marked for rapid testing.
- Women tested at 28 weeks or later should have point of care testing (or rapid testing within 24 hours).
- Rapid/same day tests should be recommended to women who present in labour with unknown HIV status.
- Potentially mitigating adverse social circumstances should be well documented. Women with complex social needs should receive appropriate referrals and support from a multidisciplinary team.
- A woman’s circumstances should be considered so ART can be started at the appropriate time. For example if a woman has previously delivered at 28 weeks ART ideally needs to be initiated at 20 weeks.
- BHIVA guidelines for active management for all modes of delivery should be followed.
- There should be no delay in provision of neonatal ART. In cases where there is an increased risk of transmission triple therapy should be considered.
- HIV care and treatment for a woman in pregnancy, and for the infant should be considered emergency care. Care should be free regardless of immigration, asylum or residence status.

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#### C O M M E N T

**This audit is quite revealing. There needs to be some clarification about point of care testing, especially in relation to women in labour. In this setting POCT is the test of choice and the result must be acted upon.**

**A ‘rapid’ or same day test with a result several hours later simply isn’t good enough especially as the majority of presentations will be out of hours, simply because there are only 40 ‘in hours’ a week compared to 124 ‘out of hours’ hours. Therefore, all units need to have this facility in place.**

**It’s good that they give really clear recommendations for women who may have been dissuaded from attending because of fears that they are not eligible for treatment.**

**The other significant question is of course what to do about seroconversions in pregnancy and as yet there is no simple answer.**

Ref: Perinatal transmission of HIV in England 2002-2005. October 2007. Download from CHIVA website:  
<http://www.chiva.org.uk/publications/PDF/2007/perinatal.pdf>

### **Risk factors for *in utero* or *intrapartum* mother-to-child transmission in Thailand**

The risk factors for mother-to-child transmission (MTCT) of HIV have been well documented: high maternal viral load, low CD4, sexually transmitted infections during pregnancy, prolonged ruptured membranes and vaginal delivery.

A paper authored by Gonzague Jourdain and coworkers, published in the December 1 2007 edition of Journal of Infectious Diseases, reported findings from an analysis of data from the Perinatal HIV Prevention Trial-1 (PHPT-1) from 24 June 1997 to 3 December 1999 performed to look at the role these factors play in relation to the timing of transmission.

PHPT-1 was a randomised, controlled, double-blind, two factorial trial of short (from 35 weeks gestation) versus long (from

28 weeks gestation) course AZT MTCT prophylaxis, conducted in 27 hospitals in Thailand. Infants received oral AZT for either three days or for 6 weeks (following the first interim analysis enrolment in the “short-short” arm was stopped). All infants were formula fed.

1437 antiretroviral-naive women were enrolled in the trial. Of 97 transmissions, 35 were *in utero* and 49 *intrapartum*.

In multivariate analysis, risk factors independently associated with *in utero* transmission were baseline maternal viral load of 35,000 copies/mL (AOR, 4.2) and delayed maternal AZT prophylaxis until >31.4 weeks gestation (AOR, 3.0).

Risk factors independently associated with intrapartum transmission were baseline HIV-1 load 10,000 copies/mL (AOR, 3.8 for 10,000–35,000 copies/mL and 7.1 for 35,000 copies/mL), induction of labour, and premature labour (AOR, 2.6) with tocolysis (AOR, 15.1).

Risk factors independently associated with transmission overall were high baseline maternal viral load, high baseline maternal serum creatine level, premature labour with tocolysis, prematurity and low birth weight.

However, when the analysis was restricted to full-term infants, the association between low birth weight and transmission was not significant. The authors noted that only 10 women had creatinine levels 1.5 mg/dL so they were unable to investigate this observation further.

They wrote: “To prevent *in utero* transmission, initiation of antiretroviral prophylaxis at 28 weeks gestation appears to be crucial. The fact that *intrapartum* transmission was found to occur at relatively low levels of maternal HIV-1 load suggests that minimising exposure to HIV and/or ensuring efficient pre-/postexposure antiretroviral prophylaxis is of paramount importance at the time of labour and delivery.”

Ref: Jourdain G, Mary JY, Le Coeur S et al. Risk factors for in utero or intrapartum mother-to-child transmission of Human Immunodeficiency Virus Type 1 in Thailand. JID 2007;196: 1629.

## DRUG INTERACTIONS

### New drug interaction summary tables

HIV-druginteractions.org has compiled three new summary tables relating to interactions with the latest and most developed pipeline drugs and a similar chart for oral contraceptives.

#### Maraviroc

Maraviroc, the CCR5 antagonist that blocks the entry of HIV-1 into cells, is now licensed in Europe and the USA as Celsentri and Selzentry, respectively.

The Summary of Product Characteristics and the Prescribing Information contain details of drug interactions with maraviroc. Some of the dosing recommendations in these documents differ from those submitted to the FDA and on which the June 2007 chart was based.

Two key differences are that a dose increase of maraviroc to 600 mg is no longer recommended when coadministered with rifabutin or nevirapine; instead maraviroc is to be dosed at 300 mg twice daily with either of these drugs. Dosing recommendations are now given for coadministration of maraviroc and efavirenz with the boosted PIs atazanavir, darunavir and fosamprenavir (in addition to saquinavir and lopinavir which appeared previously). The combinations of St John’s wort and maraviroc and rifampicin + efavirenz and maraviroc are not recommended for coadministration.

A new chart (October 2007) of drug interactions has been prepared and is available in pdf format via the link below. Links to the Summary of Product Characteristics and Prescribing Information can be found in the Links/antiretrovirals section of this website.

[http://www.hiv-druginteractions.org/new/Uploaded\\_Attachment/52\\_Maraviroc%20Oct07.pdf](http://www.hiv-druginteractions.org/new/Uploaded_Attachment/52_Maraviroc%20Oct07.pdf)

#### Integrase inhibitors: raltegravir and elvitegravir

The first of the integrase inhibitors, raltegravir, has received accelerated approval by the U.S. Food and Drug Administration (FDA). Interaction Charts have been produced for raltegravir and a second integrase inhibitor, elvitegravir, which is currently in Phase III trials.

Raltegravir (Isentress®, MK-0518) has been approved for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents.

Raltegravir is not a substrate of cytochrome P450 (CYP) enzymes and does not inhibit (IC<sub>50</sub> >100 μM) CYP3A or induce CYP3A4. Further in vitro studies have shown it not to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6. Similarly, raltegravir is not an inhibitor (IC<sub>50</sub> >50 μM) of the UDP glucuronosyltransferases UGT1A1 or UGT2B7, and does

not inhibit P-glycoprotein-mediated transport. Based on in vivo and in vitro data, raltegravir is eliminated mainly by metabolism via a UGT1A1-mediated glucuronidation pathway. Caution should be used when coadministering raltegravir with strong inducers of UGT1A1, especially in patients with different UGT1A1 genotypes as plasma concentrations of raltegravir may be reduced.

Elvitegravir is being developed for once daily dosing with low dose ritonavir. Ritonavir doses as low as 20 mg have been shown to substantially increase elvitegravir concentrations, but the coadministered dose is likely to be higher. Interactions with elvitegravir are likely to be driven by the co-dosing with ritonavir.

When elvitegravir is added to a boosted protease inhibitor regimen, the ritonavir dose is that specified by the protease inhibitor (e.g., if given with tipranavir/ritonavir, the ritonavir dose would be 200 mg twice daily). Thus, plasma concentrations of elvitegravir may be affected by the "additional" ritonavir doses.

[http://www.hiv-druginteractions.org/new/Uploaded\\_Attachment/55\\_Integrase\\_Oct07.pdf](http://www.hiv-druginteractions.org/new/Uploaded_Attachment/55_Integrase_Oct07.pdf)

### **Etravirine**

A chart of interactions with etravirine (TMC125) is now available.

Etravirine is a next generation NNRTI that shows high intrinsic activity against both wild-type HIV-1 and strains with resistance-inducing mutations. Etravirine is metabolised by CYP3A4, CYP2C19 and UDP-glucuronyl transferase, and has been shown to induce CYP3A and inhibit CYP2C19 *in vivo*.

A substantial improvement in the oral bioavailability was achieved by means of reformulation, with the licensed phase III formulation (F060) showing a 9-fold increase in AUC when compared to a phase II formulation (TF035). As a result of the reformulation, several phase II formulations (TF002, TF034, TF035) and doses have been used in interaction studies as well as the phase III formulation (F060, 200 mg twice daily). However, interactions are expected to be independent of formulation (Kakuda T et al, 8th congress on HIV Therapy, November 2006, Glasgow. Abstract PL5.2).

An interaction chart has been produced to summarise all the studies performed to date – this is available in PDF format via the link below. Interactions between etravirine and the other anti-HIV drugs (i.e. as rows) have been added to the interactive charts. Interactions between etravirine and other drugs (i.e. a column) will be added once etravirine is licensed in Europe and/or the US.

[http://www.hiv-druginteractions.org/new/Uploaded\\_Attachment/51\\_Etravirine\\_Chart.pdf](http://www.hiv-druginteractions.org/new/Uploaded_Attachment/51_Etravirine_Chart.pdf)

### **Hormonal contraceptives**

Information on hormonal contraceptives is listed on the charts in the steroid section under ethinylestradiol and progesterone/progestogens. The information available is predominantly for daily oral contraceptives, but other routes and frequencies of administration are now available.

The site has produced a chart which details the various forms of hormonal contraception and, for the newer forms, any interactions or contraceptive failures that have been reported. A link to this chart has been added to the relevant interaction descriptions in the interactive charts.

[http://www.hiv-druginteractions.org/new/Uploaded\\_Attachment/57\\_Hormonal%20Contraceptives.pdf](http://www.hiv-druginteractions.org/new/Uploaded_Attachment/57_Hormonal%20Contraceptives.pdf)

## **Recent reviews from HIV-druginteractions.org**

### **The effect of lopinavir/r on the renal clearance of tenofovir**

The findings of this study add weight to an underlying concern of an association between tenofovir-induced nephrotoxicity and concomitant boosted protease inhibitor treatment.

After adjusting for renal function, tenofovir renal clearance was 17.5% slower in HIV+ patients taking lopinavir/ritonavir versus those not taking a protease inhibitor; this is consistent with a renal interaction between the drugs. Additional studies are required to determine the exact mechanism of the interaction with the most obvious focus being on renal transporters.

Here the authors have shown that tenofovir renal clearance was 15% lower in ABCC4 3463G variants compared with wild type and this decreased renal clearance translates into a 32% increased AUC in the subjects with the variant ABCC4. However the authors clearly point out that this was a small cohort of patients and the evaluation of the relationship between genotype and phenotype was retrospective.

A prospective study will be necessary to fully evaluate the contribution of genetics to tenofovir disposition. Also, since the basis of nephrotoxicity is likely to be multifactorial the drug interaction described may just be one factor and prospective studies are clearly needed to identify patients at risk.

<http://www.hiv-druginteractions.org/new/Content.asp?ID=330&TDM=>

Ref: Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. Clin Pharmacol Ther, 2007, (e-pub ahead of print).

### **T-20 increases tipranavir levels but not hepatotoxicity**

In 2006, Gonzalez de Requena et al. reported an unexpected drug interaction between tipranavir/ritonavir and enfuvirtide (AIDS, 2006, 20:1977-1979).

The present paper documents a sub-analysis from RESIST and shows that among 661 patients for whom tipranavir C<sub>min</sub> data were available, tipranavir/ritonavir/enfuvirtide patients had a 31% higher median tipranavir C<sub>min</sub> than patients not on enfuvirtide. Of importance, higher median lopinavir (+19%) and saquinavir (+39%) C<sub>min</sub> values were also observed in lopinavir/ritonavir/enfuvirtide and saquinavir/ritonavir/enfuvirtide recipients compared with lopinavir/ritonavir or saquinavir/ritonavir without enfuvirtide.

The authors make several important points. First, the observed increase in C<sub>min</sub> among RESIST patients receiving enfuvirtide was not associated with increased risk of hepatotoxicity. Secondly, the authors discourage any recommendation to change tipranavir or ritonavir dosing in patients receiving enfuvirtide. Finally, the mechanism of the interaction is unknown.

<http://www.hiv-druginteractions.org/new/Content.asp?ID=347&TDM=>

Ref: Raffi F, Battegay M, Rusconi S, et al. Combined tipranavir and enfuvirtide use associated with higher plasma tipranavir concentrations but not with increased hepatotoxicity: sub-analysis from RESIST. AIDS, 2007, 21(14): 1977-1980.

### **Atazanavir, with or without ritonavir, may increase buprenorphine and buprenorphine metabolites, requiring dose adjustment**

This study examined the interaction between buprenorphine and atazanavir (400 mg once daily) or atazanavir/ritonavir (300/100 mg once daily) in opioid-dependent, buprenorphine/naloxone-maintained, HIV-negative volunteers. Pharmacokinetics of atazanavir and atazanavir/ritonavir were compared in subjects and matched, healthy controls (n=10 per group) to determine effects of buprenorphine. Objective opiate withdrawal scale scores and mini-mental state examination were determined prior to and following antiretroviral administration to examine pharmacodynamic effects.

When coadministered with atazanavir, buprenorphine AUC increased from 39.5 to 76.3 ng.h/ml; a similar increase was observed when coadministered with atazanavir/ritonavir (46.2 to 77.0 ng.h/ml). Concentrations of norbuprenorphine, buprenorphine glucuronide, and norbuprenorphine glucuronide also increased with both atazanavir and atazanavir/ritonavir. The likely complex mechanism is discussed. Buprenorphine did not significantly alter atazanavir or ritonavir concentrations. Three buprenorphine/naloxone-maintained participants reported increased sedation with atazanavir/ritonavir.

Atazanavir or atazanavir/ritonavir may increase buprenorphine and buprenorphine metabolite concentrations and might require a decreased buprenorphine dose.

<http://www.hiv-druginteractions.org/new/Content.asp?ID=345&TDM=>

Ref: McCance-Katz EF, Moody DE, Morse GD et al. Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. Drug Alcohol Depend, 2007, 91(2-3): 269-278.

### **Acid reducing agents and protease inhibitors**

There have been two publications in October's HIV Medicine on this important topic.

Beique et al have provided a systematic review of all the available pharmacokinetic and clinical data on drug interactions between protease inhibitors and acid-reducing agents and their clinical consequences. The table documenting the interactions is a particularly valuable resource. [1]

However, new data are constantly emerging and Luber et al have documented their findings on once daily fosamprenavir/ritonavir and atazanavir/ritonavir alone and in combination with 20 mg omeprazole in healthy volunteers.

This paper is an update of reference 12 cited by Beique et al – data initially presented at the Lisbon HIV Pharmacology Workshop in 2006. The major findings were:

- No impact of omeprazole on amprenavir exposure.
- Atazanavir AUC and C<sub>min</sub> reduced by 27%.
- 4/19 subjects experienced greater than 50% decline in both AUC and C<sub>min</sub>.

#### References

1. Beique L, Giguere P, la Porte C, Angel J. Interactions between protease inhibitors and acid-reducing agents: a systematic review. HIV Med, 2007, 8(6):335-345.

- Luber A, Brower R, Kim D, et al. Steady-state pharmacokinetics of once-daily fosamprenavir/ritonavir and atazanavir/ritonavir alone and in combination with 20 mg omeprazole in healthy volunteers. *HIV Med*, 2007, 8(7):457-464.

## VACCINE RESEARCH

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Round up of news posted to Treatment Action Group (TAG) basic science blog.

### **Merck HIV vaccine trial is unblinded**

It was announced on 13 November that the STEP trial will be unblinded; all 3,000 participants will be told whether they received vaccine or placebo and informed of their anti-adenovirus antibody titer.

One of the unexplained results from this study is the higher rate of infections reported in patients receiving the active vaccine, and the disappointing lack of impact on viral load post infection.

### **Merck HIV Vaccine Trial: Data Presentations from the HVTN Meeting**

The HVTN has quickly made data presentations regarding the Merck HIV vaccine efficacy trial results available online:

<http://www.hvtn.org/science/1107.html>

#### **Introduction to the 502 Protocol**

[http://www.hvtn.org/fgm/1107slides/ANN\\_FGMStepintro.pdf](http://www.hvtn.org/fgm/1107slides/ANN_FGMStepintro.pdf)

#### **Baseline characteristics of participants in the STEP trial**

[http://www.hvtn.org/fgm/1107slides/DAN\\_Demographics11\\_2.pdf](http://www.hvtn.org/fgm/1107slides/DAN_Demographics11_2.pdf)

#### **STEP trial: efficacy analyses**

<http://www.hvtn.org/fgm/1107slides/Robertsonfinal.pdf>

#### **Hypotheses for differential HIV acquisition rates**

<http://www.hvtn.org/fgm/1107slides/Buchbinder.pdf>

#### **STEP study: summary of results**

[http://www.hvtn.org/fgm/1107slides/STEVESELF\\_FINAL\\_502\\_Summary\\_12NOV07.pdf](http://www.hvtn.org/fgm/1107slides/STEVESELF_FINAL_502_Summary_12NOV07.pdf)

#### **A pathway toward understanding the biological basis for the vaccine efficacy results**

<http://www.hvtn.org/fgm/1107slides/McElrath.pdf>

#### **Roundtable intro: follow-up of participants in STEP**

<http://www.hvtn.org/fgm/1107slides/Roundtableintro.pdf>

#### **Longer-term follow-Up for STEP/HVTN 502**

<http://www.hvtn.org/fgm/1107slides/FGM502LongertermfupGilbert.pdf>

#### **Why we unblinded**

<http://www.hvtn.org/fgm/1107slides/Gray.pdf>

Source: Richard Jeffreys Vaccine Prevention Blog

<http://tagbasicscienceproject.typepad.com/>

Related links:

[A Step Back? by Kristen Jill Kresge \(IAVI report\)](#)

<http://www.iavireport.org/Issues/Issue11-4/Step.asp>

HIV vaccine may have made people more vulnerable to HIV by Gus Cairns, from AIDSmap.

<http://aidsmap.com/en/news/CCC37BDD-D724-41BD-8097-D880FACAA12F.asp>

Merck/HVTN Press Release

<http://www.medadnews.com/News/index.cfm?articleid=492370>

## OTHER NEWS

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### **IAS statement on US policy for HIV-positive visitors**

The International AIDS Society (IAS) would like to express concern over the proposed United States Department of Homeland Security (DHS) ruling, docket number USCBP-2007-0084, "Issuance of Visa and Authorisation for Temporary Admission

into the United States for Certain Nonimmigrant Aliens Infected with HIV.” Public comment on this proposed ruling is due on December 6, 2007, and we attach our comments with this statement.

IAS believes this ruling:

1. Undermines United States Government’s current efforts in providing global leadership on the response to HIV/AIDS;
2. Promotes a discriminatory bias in selecting waivers for short-term visitors to the United States who are living with HIV; and,
3. Promotes a policy that has no plausible basis in science, public health and medicine.

As a network of more than 10,000 professionals from around the world working in research, treatment, care, support and prevention services on HIV/AIDS, the IAS is the world’s largest network of HIV professionals. Our members hail from around the world, including more than 2,500 members in the United States.

We were encouraged in December 2006, when President George W. Bush announced on World AIDS Day that the White House would issue an executive order allowing HIV-positive people to enter the U.S. on short-term visas without seeking a special waiver. That executive order never materialised.

From our perspective, the latest proposal from the Department of Homeland Security to “streamline” the visa waiver process for HIV-positive persons wishing to enter the United States, only serves to reinforce a bad policy that is clearly discriminatory and has no public health basis.

Furthermore, this new “streamlined” policy, (please see our attached comments on the specifics of the ruling) undermines the United States Government’s credibility as the global leader in resource-provision for HIV prevention, treatment, care and disease mitigation. Because the United States’ leadership has made HIV prevention, treatment and care services more available around the world, this policy says to people living with HIV in those most affected countries, “here is your funding for HIV services, now stay away from our borders.”

We firmly believe there is no sound public health reason to single out HIV as a basis for inadmissibility to the United States or any other country. The majority of nations in the world do not have this type of discriminatory statute in their visa laws, because they have found that allowing HIV-positive persons to enter their borders poses no imminent threat to their population.

Holding on to, and “streamlining” this antiquated policy, puts the United States in line with only 13 other countries that “ban” HIV-positive persons from entering their borders on a short-term visitor basis - Iraq, China, Saudi Arabia, Libya, Sudan, Qatar, Brunei, Oman, Moldova, Russia, Armenia, and South Korea.

Because there is no public health rationale for this policy, the only plain effect could be to target men, women and children from countries most affected by HIV (who are predominantly persons of color), gay men, and people who are from other socially marginalized groups, from entrance into the United States.

This is deplorable. The International AIDS Society urges the United States Government, through the Department of Homeland Security, to table this proposed ruling and to hold a rigorous and evidence-based public review of this statute instead of advancing a bad policy that undermines the United States leadership and credibility.

For more information on the IAS, please visit:

<http://www.iasociety.org>

Source: IAS press statement “Statement on United States Department of Homeland Security proposed ruling to “Streamline” temporary visa provision for people living with HIV/AIDS”. December 4, 2007

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## ON THE WEB

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*Free full text articles:*

### PLoS Medicine

**HCV–HIV Coinfection: simple messages from a complex disease.** Paul Klenerman and Arthur Kim

<http://lists.plos.org/lt.php?id=ekIQBw1RUQBbVUJFB1sARQQEV1ENDA%3D%3D>

**Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies.** Erik von Elm et al.

<http://lists.plos.org/lt.php?id=ekIQBw1RUQBbVUJFB1sARQQEV1ENDA%3D%3D>

**Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. Jan P. Vandembroucke et al.**

<http://lists.plos.org/lt.php?id=eklQBw1RUQBbVEUFB1sARQQEV1ENDA%3D%3D>

**Patient retention in antiretroviral therapy programs in Sub-Saharan Africa: a systematic review. Sydney Rosen et al.**

<http://lists.plos.org/lt.php?id=eklQBw1RUQBbVkuFB1sARQQEV1ENDA%3D%3D>

**The ongoing regulation of generic drugs. R.G. Frank**

<http://content.nejm.org/cgi/content/full/357/20/1993?query=TOC>

### *Online reports:*

## **Forum for Collaborative Research**

The "HIV/TB Co-Infection: Meeting the Challenge" report and the accompanying press release are now available online:

<http://www.hivforum.org/uploads/TB/Final%20HIV-TB%20Report.pdf>

HIV-TB Fact sheet:

[http://www.hivforum.org/uploads/TB/HIV\\_TB\\_Fact%20Sheet.pdf](http://www.hivforum.org/uploads/TB/HIV_TB_Fact%20Sheet.pdf)

The report is based on the symposium and roundtable discussion held in conjunction with the 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention in Sydney, Australia. These two events were sponsored by the Forum and the TB/HIV Working Group of the STOP TB Partnership in collaboration with ANRS, Bill & Melinda Gates Foundation, CREATE, EDCTP, IAS, NIH, Tibotec, and the WHO TB-HIV Working Group.

In collaboration with the Public Health Agency of Canada, the European Centre for Disease Prevention and Control and UNAIDS, the Forum is also pleased to announce the release of another report, "HIV Testing and Counselling: Polices in Transition?" which was prepared for the International Public Health Dialogue on HIV Testing and Counselling. A link to this report can be found on the Forum's website at:

[http://www.hivforum.org/uploads/PHAC%20hivtest\\_e.pdf](http://www.hivforum.org/uploads/PHAC%20hivtest_e.pdf)

Links to other reports and current activities can be found on:

[www.hivforum.org](http://www.hivforum.org)

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## **FUTURE MEETINGS**

### **2007/2008 conference listing**

The following meetings are taking place during the next year.

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

**7-8 December - 3rd International Workshop on Targeting HIV Entry, Washington**

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

**3-6 February 2008, 15th Conference on Retroviruses and Opportunistic Infections. Boston**

<http://www.retroconference.org/2008/>

**26 - 28 March 2008, 6th European HIV Drug Resistance Workshop, Budapest**

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

**7-9 April 2008, 9th International workshop on Clinical Pharmacology of HIV Therapy, New Orleans**

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

**9 - 11 April 2008, 3rd International workshop on Clinical Pharmacology of Hepatitis Therapy, New Orleans**

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

**23-25 April 2008, 14th BHIVA Annual Conference, Belfast**

<http://www.bhiva.org>

**10-14 June 2008, 17th International HIV Drug Resistance Workshop, Sitges**

<http://www.informedhorizons.com>

**19-21 June 2008 ( dates tbc), 4th International workshop on HIV and Hepatitis Coinfection, Madrid**

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

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

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

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

<http://www.aids2008.org/>

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

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

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

<http://www.hiv8.com>

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## **PUBLICATIONS & SERVICES FROM i-BASE**

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### **i-Base website**

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

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

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

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

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

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

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.

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).

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

### **i-Base Book: “Why we must provide HIV treatment information”**

#### **Photography by Wolfgang Tillmans**

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

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

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

We are asking for minimum donation price of £10.00 plus £2.50 p&p. Please contact the i-Base office for more details: T: 020 7407 8488 or email: [bookoffer@i-Base.org.uk](mailto:bookoffer@i-Base.org.uk) or post the donation form on the inside back page of this issue of HTB, using either ‘standing order’ or ‘one-off donation’ as appropriate.

Thank you for your support.

### **NEW: Treatment training for advocates, December 2007**

The Training Manual for Advocates – made up of 8 modules for learning about aspects of HIV care has been updated and published online as an interactive resource. It provides a basic entry-level curriculum relating to HIV and treatment.

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

Sections include:

1. Immune system and CD4 count
2. Virology, HIV and viral load
3. Introduction to anti-retrovirals (ARVs)
4. Side effects of ARVs
5. Opportunistic infections and coinfections
6. HIV and pregnancy
7. Drug users and HIV
8. How to read science

Each module includes 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.

Earlier editions are available in Russian, Portuguese, Hindi and Nepalese as are available as PDF files.

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

### **NEW: Generic clinic forms, December 2007**

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

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

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

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

### **UK CAB: reports and presentations**

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

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted. The 23rd meeting was on Friday 20 April, and focused on treatment for people in the UK facing deportation, and feedback from the EACS conference.

<http://www.ukcab.net>

<http://www.ukcab.net/apr07>

### **World CAB - reports on international drug pricing**

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

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

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

### **NEW: Introduction to combination therapy November 2007 edition**

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

The November 2007 edition has been updated to include recent changes to the European and US guidelines. We have reduced the size, rewritten the section on choice of treatment, included several new graphs and tables, including a pull-out

colour chart of ARVs, and added pages to record CD4, viral load, and other test results.

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

### **Guide to hepatitis C for people living with HIV: testing, coinfection, treatment and support** May 2007 edition

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

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

### **Guide to changing treatment: what to do when your treatment fails** April 2007 edition

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

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

### **Guide to HIV, pregnancy & women's health** July 2007 edition

Updated and revised in April 2005, this patient guide helps women get the most out of HIV treatment and care before, during and after pregnancy. It should help whether on therapy or not and includes information for the mothers health and for the health of the baby.

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

### **Guide to avoiding & managing side effects** February 2005 edition

This is a comprehensive 44-page guide that is aimed at helping anyone using HIV drugs to get the most out of their treatment, the most out of their relationships with their doctor and other health professionals, to get better medical care to improve their health and, most importantly, to enjoy a better quality of life.

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

### **Translations of i-Base guides**

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

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

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

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

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

#### **Bosnia Herzogovenia**

Introduction to combination therapy May 07 PDF File [452 Kb]

#### **Bulgarian**

HIV, pregnancy & women's health - Mar 06

Introduction to combination therapy - May 06

**Chinese**

Avoiding & managing side effects - Aug 02

Changing treatment: second line & salvage therapy - Aug 02

Introduction to combination therapy - Aug 02

**Croatian**

Introduction to combination therapy May 07

**Czech/Slovak**

Introduction to combination therapy - Jun 07

Changing treatment: second line & salvage therapy - Jun 05

**French**

HIV, pregnancy & women's health - April 06

Avoiding & managing side effects - Jun 06

Introduction to combination therapy - Jun 01

**Greek**

Changing treatment: second line & salvage therapy - Mar 03

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**Hindi**

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## **Treatment 'Passports'**

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

## **HIV Treatment Bulletin (HTB)**

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

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

Treatment information request service - 0808 800 6013

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

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

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

## **New online Q&A service**

A new 'question and answer' service has been added to the i-Base website. Questions can either be answered privately, or if you give permission, we will post the answers online (omitting any personally identifying information).

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

Recent questions include:

- Do I need the pneumococcal vaccine?
- How long does one have before developing AIDS?
- I need to tell I am positive, what shall I do?
- Can ARVs protect me from HPV?
- Is the test reliable?
- Which clinics are in Dublin?
- Will my CD4 count and VL change?

- Can I use valciclovir to treat HIV?
- Do I need an HIV test after oral sex?
- Can stress cause similar symptoms to HIV seroconversion?
- Is it important to get a resistance test after being diagnosed?
- Can you go from having AIDS to just having HIV?
- What do these other lab results mean?
- Where can I find some additional general information?
- What does HIV-negative mean?
- My viral load went up from 58 to 102...
- What are the treatment guidelines for HIV-2 Infection?
- Does my neurologist need to know that I am HIV-positive?
- Does Prozac interact with PIs and could this cause hair loss?
- Can I find out when I was infected?
- Where can I test for HIV in the UK?
- When Atripla is approved, can I still take efavirenz and Truvada separately?
- Do my lab results show that I am a fast or slow progressor?
- What treatment can I use if my CD4 count is over 800?
- Is having a cold a symptom of HIV?
- Is my negative HIV test accurate?
- Why am I HIV-negative if my boyfriend is HIV-positive?
- Will marijuana use affect results of an HIV test?
- Symptoms after an HIV-negative test
- Is taking nevirapine a risk factor for heart disease?
- Will a test for recreational drug use show that I am HIV-positive?

### **Find HTB on AEGiS**

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

<http://www.aegis.org/pubs/i-base/2006>

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

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

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

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

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

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## **treatment information phonenumber**

**Or go online: [www.i-Base.info](http://www.i-Base.info)**

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### *h-tb*

HIV Treatment Bulletin

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

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**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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