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## EDITORIAL

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This issue leads with a treatment alert relating to the European recall of nelfinavir. As we went to press, the EMEA are working with Roche to formulate a patient registry to follow patients exposed to any level of contaminated drug. Further details will be announced as soon as they are available.

We also include first reports from the XVI International Resistance Workshop that focus on the first chance to look at issue of resistance relating to integrase inhibitors.

This issue includes the last of our reports from the Retrovirus conference and a selection of studies from the PK Workshop held in April.

### **i-Base update**

The new Guide to HIV, Pregnancy and Women's Health is included as a supplement to this issue of HTB. For additional copies of this guide (additional bulk print copies are free to UK clinics), please order these online:

<http://www.i-base.info/forms/order.php?women=true>

This month other new translations of the Introduction to Combination Therapy have been produced (in Czech, Croatian, Bosnian and Macedonian) and the Treatment Training for Advocates manual has been produced in Portuguese.

All these publications are available as PDF files to download from the i-Base website.

i-Base have also launched an online general treatment Q&A service:

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

Later this month, i-Base will produce the first issue of a new electronic publication called ARVs4IDUs. This will be a quarterly summary of research relating to injecting drug users and HIV, with the first issue available for the IAS conference in Sydney in July.

HTB readers who currently receive HTB by email will receive this automatically as a supplement to the next issue of HTB. Print readers will need to subscribe for this new service online:

<http://www.i-base.info/forms/esub.php>

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## TREATMENT ALERT

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### **Roche recalls nelfinavir (Viracept) due to chemical impurity**

**Patients are requested to contact their doctors as soon as possible to start alternative therapies.**

On 6th June 2007, Roche, in agreement and cooperation with Health Authorities (EMEA, Swissmedic and MHRA), recalled in Europe and some other world regions all batches of nelfinavir (Viracept) powder and tablets. [1] The US, Canada and Japan were not affected by this recall, as nelfinavir is manufactured by Pfizer in those countries.

The recall was triggered by the presence of a contaminant called methane sulfonic acid ethyl ester in the active substance, after market reports related to a bad smell of the tablets, and of nausea and vomiting.

Patients are requested to contact their doctors **as soon as possible to start alternative therapies.**

Methane sulfonic ethylester is a normal byproduct of the manufacturing process but is only present in very small amounts. The normal tolerated levels are 3 parts per million (ppm). Due to human error in the maintenance of the production line it would appear levels of this compound increased. This molecule is classed as a carcinogen.

This problem does not affect any other Roche products.

Information from Roche has suggested that in the worst-case scenario, some batches seem to have contained 2,300 ppm.

The effects of methane sulfonic acid ethyl ester in humans have not been studied. Animal studies show that the class of chemicals called 'alkyl mesylates' which includes methane sulfonic acid ethyl ester are genotoxic carcinogens. The potential long-term consequences to patients are currently unknown. Roche in association with Health Authorities is looking into the measures to be taken in order to monitor patients.

Studies in which rats were given water containing methane sulfonic ethylester for 3 months at a dose of 10mg/kg/day developed tumours.

If a patient has taken contaminated nelfinavir with the 'worst case scenario' – 2300ppm, then their dose would have been 0.1mg/kg/day. This is 100-fold less exposure than that known to cause tumours in rats. There is insufficient data to estimate the level of risk at the exposed dose in humans.

There are references below with regards to data we have on methane sulfonic ethylester. [2, 3, 4]

#### References

1. EMEA announces recall of Viracept (6 June 2007):  
<http://www.emea.europa.eu/pdfs/general/direct/pr/25128307en.pdf>
2. Sega GA. A review of the genetic effects of ethyl methanesulfonate. *Mutation Res.* 1984 134: 113-42.
3. Op het Veld CV et al. Effect of nucleotide excision repair on hprt gene mutations in rodent cells exposed to DNA ethylating agents. *Mutagenesis* 1997 Nov;12(6):417-24.
4. IARC monographs on the evaluation of carcinogenic risks to humans. Overall Evaluations of Carcinogenicity: An updating of IARC monographs volume 1 to 42. supplement 7, 1987.

## European Medicines Agency press release on the nelfinavir recall

### European Medicines Agency agrees on action plan following the recall of Viracept and recommends suspension of the Marketing Authorisation

The European Medicines Agency today agreed on an action plan to follow-up patients who were exposed to contaminated Viracept (nelfinavir). Viracept, from Roche Registration Limited, is an antiretroviral medicine used to treat HIV-1 infected adults, adolescents and children of 3 years of age and older. It was recalled from the European market in early June 2007 because during the manufacturing process some batches had become contaminated with ethyl mesilate, a known genotoxic substance (harmful to DNA).

A meeting of toxicology experts held at the EMEA on 13 June 2007 concluded that there are currently insufficient data to establish which doses of ethyl mesilate may be toxic in humans. The CHMP has therefore requested the company to carry out studies in animals in order to calculate toxic levels of ethyl mesilate more precisely. Preliminary results from these studies should be available by the end of this year.

While awaiting the above results, the Agency's Committee for Medicinal Products for Human Use (CHMP) has asked the company to identify the group of patients who have been exposed to contaminated batches of Viracept, with a view to establishing appropriate follow-up and monitoring. The current view of the CHMP is to follow patients exposed to high levels of contaminant in the batches of Viracept released since March 2007, all pregnant women who have ever been exposed to Viracept and all children who have ever been exposed to Viracept, including those exposed *in utero*. The situation will be reviewed as data become available.

Furthermore, the European Medicines Agency today recommended to the European Commission to suspend the marketing authorisation for Viracept (nelfinavir), because it had concerns that the quality and therefore the safety of Viracept could not be ensured at this time. As a consequence of the recommended suspension, Viracept will continue to be unavailable for patients until corrective measures have been implemented to resolve the manufacturing issues identified by the CHMP.

Further updates will be provided as more information becomes available.

Source: EMEA Press office, London, 21 June 2007

<http://www.emea.europa.eu/pdfs/general/direct/pr/27536707en.pdf>

#### NOTES

1. The CHMP reviewed the marketing authorisation of Viracept on the request of the European Commission under Article 20 of Regulation (EC) No 726/2004. This type of procedure is initiated in cases where there are public health concerns with a centrally authorised medicine.
2. The recall was initiated on 6 June 2007. It affected the 27 EU Member States and Iceland, Liechtenstein and Norway. A press release was published and can be found here.
3. Viracept had been authorised as an oral powder 50 mg/g, 250 mg tablets and 250 mg film-coated tablets. The marketing authorisation holder is Roche Registration Limited. More information can be found in the European Public Assessment Report for Viracept:  
<http://www.emea.europa.eu/humandocs/Humans/EPAR/viracept/viracept.htm>.

## EMEA questions and answers on the nelfinavir recall [1]

The European Medicines Agency (EMA) and the European Commission have now taken further steps following the recall of Viracept by Roche Registration Limited, because of a contamination with a harmful substance. Patients who may have been exposed will be closely monitored while more information on the harmful potential of the contaminant is gathered. The EMA has recommended to the European Commission that Viracept's marketing authorisation be suspended.

## **What is Viracept?**

Viracept is an antiviral medicine used in combination with other antiviral medicines to treat adults, adolescents and children over 3 years of age who are infected with human immunodeficiency virus (HIV-1), the virus that causes acquired immune deficiency syndrome (AIDS). Viracept contains nelfinavir mesilate.

## **What has been happening with Viracept?**

Recent batches of nelfinavir mesilate have been contaminated with high level of ethyl mesilate, a known genotoxic substance (harmful to DNA, the genetic material in cells). The medicine has been recalled and all packs are being returned to the manufacturer.

## **What is the level of risk for patients?**

Genotoxic substances such as ethyl mesilate may increase the risk of developing cancer. Is it difficult at present to assess the risk to patients because there are insufficient data to establish which doses of ethyl mesilate may be toxic in humans.

## **What are the consequences for patients?**

Patients who were receiving Viracept should have been 'switched' by their doctors to another anti-HIV medication.

Patients who have been taking Viracept may have been exposed to ethyl mesilate, and the EMEA has requested the company to establish ways to follow them up. Patients who will be closely followed and monitored are all those who have been exposed to the medicine made from highly contaminated batches, as well as women who took the medicine during pregnancy and children who have taken Viracept at any time or were exposed to it in the womb.

## **How will patients know if they have been exposed?**

The level of exposure to ethyl mesilate will depend on the level of contamination in the Viracept they have taken. When looking into the contamination, the company have already found out that the higher level of contamination was seen in the batches of Viracept that have been released on the market since March 2007. However, they have also looked at earlier batches, and found that some contamination, but at lower levels, had also happened in the past. At the moment, the company is actively identifying which batches were affected, so that, in each country, patients who have taken potentially contaminated Viracept can be traced, identified and followed up.

## **What is happening now?**

The CHMP has recommended that the marketing authorisation for Viracept be suspended [2], because it has concerns that the quality and therefore the safety of the medicine cannot be guaranteed at present. The Committee's opinion has now been forwarded to the European Commission in order to issue a decision.

## **What is going to happen in the next few months?**

A group of experts met at the EMEA on 13 June 2007 to look at the information available on the toxicity of ethyl mesilate. They have now requested that the company carry out specific animal studies with ethyl mesilate, with the aim of identifying more precisely what level of exposure is harmful. The protocols for the studies, which describe how they will be carried out, will be checked by the CHMP before the studies start, to ensure that they are adequate for their purpose. Preliminary results will be available by the end of the year.

Until then, the CHMP has proposed that a level for ethyl mesilate in nelfinavir mesilate be set, in line with currently available animal study results and scientific consensus on genotoxic impurities [3]. In practice, this would correspond to a maximum daily intake of around one and a half micrograms of ethyl mesilate for an adult patient taking the recommended daily dose of Viracept.

The EMEA is also working with Roche to put in place a full Risk Management Plan, a set of measures to ensure that the risk associated with contaminated Viracept is handled in an appropriate manner. In addition to finding ways of following up patients exposed to contaminated Viracept, other measures will also be introduced, such as closer monitoring of side effects reported in patients who have taken Viracept.

## **What measures are being taken to prevent similar problems occurring in the future?**

The manufacturing site in Switzerland where the contamination happened has been inspected. The report from the inspectors highlights areas of concern and the company has prepared an action plan to address the reasons why the contamination occurred, and to prevent it from happening again. The CHMP has recommended a set of corrective measures that must be put in place by Roche.

## **Will the action in Europe have an impact on other countries outside the EU?**

The suspension of the marketing authorisation for Viracept will have an impact on the supply of this medicine to other countries outside the EU who rely on Viracept's EU authorisation to allow it onto their markets. In case of concern, patients and healthcare providers outside the EU are advised to refer to the World Health Organization website. Canadian, Japanese

and United States markets are not affected as they use a different source of nelfinavir mesilate.

The EMEA will update this document as new information becomes available.

Source: EMEA, London, 21 June 2007.

#### References

1. The previous question and answer document on the recall of Viracept was published on 6 June 2007:  
<http://www.emea.europa.eu/humandocs/PDFs/EPAR/Viracept/25171807en.pdf>
2. This was carried out as a review procedure under Article 20 of Regulation (EC) 726/2004 initiated by the European Commission.
3. This is set at 0.6 parts per million (ppm).

### **IMPORTANT – Notification of product recall due to Class 1 drug alert**

Dear Healthcare Professional

Further to the recent announcement regarding the recall of Viracept® (nelfinavir) we are writing to advise you of the actions you now need to take to ensure that all stocks of the following products are removed from the marketplace.

PRODUCT	PACK SIZE	PRODUCT LICENCE NO.	EAN CODE	PIP CODE
VIRACEPT FC Tablets 250mg	300	EU/1/97/ 054/004-005	50 00471 00593 6	286- 3264
VIRACEPT Paediatric Oral Powder 50mg/g	144g	EU/1/97 /054/001	50 00471 00502 8	247- 9434

Please ensure that all stock (all batches) of the above product presentations is quarantined and returned to your point of purchase. This recall does not affect the US, Canada or Japan. If supplied by Roche directly, please use the attached Stock Return Form to arrange for stock to be returned to Roche for full credit.

If your organisation has supplied product on, you should contact all your customers/patients who have been supplied with Viracept®. This includes all patients who may have stock within shelf life and this is applicable to stock issued since 2004.

#### **Further information on recommendations to Healthcare Professionals**

1. When switching patients to an alternative, treatment choices should be individualised. Please see guidelines below as an aide to this medication switch.
2. Please inform your Health Authority and local Roche Drug Safety Department immediately of any unexpected adverse events from patients taking Viracept.
3. Please thoroughly check all stock of Viracept formulations in your practice and any inventory under your control. If you do have any Viracept formulation stock, contact your local Roche Company to arrange collection. Please see attachment 2 for UK arrangements.

Additionally several treatment guidelines are available to assist you in building medication combinations that help a patient achieve undetectable viral loads. These include:

1. Hammer S, et al. Treatment for adult HIV infection: 2006 recommendations of the International AIDS Society – USA panel. JAMA, 2006;296:827-843
2. The Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS). Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. May 4, 2006  
<http://AIDSinfo.nih.gov> (accessed August 10 2006).
3. Recommandations du groupe d'experts sous la direction du Professeur Patrick Yeni réalisé avec le soutien du Ministère de la Santé et des Solidarités. Prise en charge médicale des personnes infectées par le VIH. 2006: 46.
4. British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy. British HIV Association HIV Medicine (2006) 7, 494.  
<http://www.bhiva.org>

#### **Communication Information**

For further information, please contact your local Roche Office in the UK: Freephone 0800 3281 629 or the official Roche web site:

<http://www.roche.com/med-cor-2007-06-06b>

Please be assured that Roche is using its best efforts to resume the supply of Viracept on your market as soon as possible. We will continue to keep you informed as appropriate.

We apologise for any inconvenience that this recall causes you. We wish to confirm that Roche has the safety of all our patients as our outmost concern, and is fully engaged at the highest level to ensure continuity of supply of validated stock.

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C O M M E N T

Roche urges patients taking nelfinavir to seek immediate advice from their healthcare professional about alternative therapies. If it is not possible for patients to contact their doctor, patients should contact their local HIV clinic for further advice.

Further information is likely to be released by Roche and the EMEA when available. A programme that identifies batches that contained higher doses and closely monitoring patients who received these batches is expected. Although the short-term risk is expected to be low, further animal studies to determine the relationship between exposure and toxicity have been requested, with preliminary results from these studies due by the end of the year.

Clearly these are very unusual circumstances and Roche are working closely with the EMEA to understand any potential risks.

Patients in the UK have many alternative options to nelfinavir. This may not be the case in other countries where access to second-line therapies is more restricted.

As we went to press, discussions about patient registries for all patients potentially exposed to nelfinavir containing ethyl methansulphate from March 2007, and a separate registry for pregnant patients, children (under 18 years), and children who may have been exposed in utero who took nelfinavir since the product was first granted in 1998 (in all countries in the EU).

At this stage Roche do not recommend contacting patients for these registries yet. "However if you do see any patients who fall into these categories then please keep a record of these patients' details."

Roche ask doctors to NOT send any data/patient information to Roche until asked to do so.

Roche has already found out that the higher level of EMS was seen in the batches of Viracept that have been released on the market since March 2007. "However, we have also looked at earlier batches, and found that some impurity, but at lower levels, had also happened in the past. At the moment, Roche is actively identifying which batches were affected, so that, in each country, patients who have taken these Viracept batches can be traced, identified and followed up. Since the recall, the toxicology data available have not changed and hence, with this current knowledge, Roche believe the risk from the impurity is low."

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## CONFERENCE REPORTS

### XVI International HIV Drug Resistance Workshop

12-16 June 2007, Barbados

Although this workshop has a wealth of studies focussing on basic science and more obscure aspects of resistance, research with the most important impact on clinical management is always presented to this meeting first.

We held back distribution of the June/July issue in order to include the first reports from this workshop. More will follow in the next issue of HTB.

Studies reported include:

- Integrase inhibitors and resistance
- Treatment failure and tropism changes in maraviroc trial related to previously undetected CXCR4 rather than a mutational shift from CCR5
- Mechanisms of failure to CCR5 inhibitors is not explained by mutation in the V3 loop, cross-resistance between CCR5 inhibitors is likely
- Higher risk of resistance using lopinavir/r monotherapy
- Macaque study shows similar protection from rectal exposure using 2-hour pre- and 24-hour post exposure prophylaxis with tenofovir plus FTC compared to daily regimen
- Thirteen NNRTI mutations linked to resistance to etravirine (TMC-125)

The abstract book from the Workshop is available to download: (PDF file 1.2MB)

[http://www.informedhorizons.com/resistance2007/pdf/AbstractBook\\_RW2007\\_final.pdf](http://www.informedhorizons.com/resistance2007/pdf/AbstractBook_RW2007_final.pdf)

## Integrase inhibitors and resistance

Simon Collins, HIV i-Base

The workshop provided the first forum with numerous early studies addressing the issue of resistance to integrase inhibitors (INIs): Which key mutations develop and impact on drug sensitivity? How quickly do they develop? What is the role of polymorphisms in naïve and treated patients? What is the impact of cross class resistance? The relationship between integrase mutations and those in RT and protease genome; and the activity in HIV-1 subtypes and HIV-2.

With raltegravir already available on named patient programmes, these presentations probably had the greatest clinical significance. As with every other class, the risk of cross-resistance to other INIs should be expected until proved otherwise.

10 abstracts at the resistance workshop addressed this subject, with the two most important studies providing the first *in vivo* data from Merck and Gilead compounds.

While these are the first important pool of studies, more are sure to follow at the IAS meeting in Sydney later in July.

### Raltegravir resistance in experienced patients

One caution from the otherwise impressive results available on raltegravir, is that it appears to have a low genetic barrier to resistance. Michael Miller from Merck presented results from their Phase 2 dose-finding study that randomised patients to either 200mg, 400mg or 600mg raltegravir or placebo, all in addition to optimised background therapy. [1]

Approximately 70% of these three-class experienced patients achieved viral suppression to <400 copies/mL by week 16. 38 non-responders either failed to reduce viral load by > 1 log or reach and maintain levels <400 copies/mL. Mutations in integrase were found in 35/38 of these patients.

Two distinct pathways were also identified in *in vitro* studies – either via N155H (n=14) or Q148H/R/K (n=20) – which reduced raltegravir susceptibility by 10 and 25-fold respectively. One patient developed Y143R.

Secondary mutations found with N155H included L74M, E92Q, T97A, Y143H, V515I, G163R and D232N; and with Q148H/R/K included L74M, E138A/K, and G140S/A. All secondary mutations led to increased resistance. Fold changes in IC50 were greatest in patients whose virus developed the 148 pathway with secondary mutations increasing from 10-fold (Q148H) to over 500-fold (Q148H+G140S and Q148K+E138A+G140A).

There was no dose-related relationship with the pattern of these mutations. A higher percentage of virological failures had baseline viral load >100,000 copies/mL (53% vs 47% <100,000), baseline CD4 <200 cells/mm<sup>3</sup> (58%, vs 42% >200), and genotypic sensitivity score of 0 (68%, vs 32% when GSS>/=1).

Time to developing resistance was not clear, although no resistance was seen in the 10 day monotherapy study, but some patients failed by week 8 and accumulated multiple mutations by week 16. Longitudinal analysis presented on four patients showed detection of the primary N155H mutation from 50 to 300 days on study.

Impact on fold-change of other integrase inhibitors indicated cross-resistance to the Gilead GS-9137 compound. Merck has a pipeline compound MK-2048 which retained sensitivity to at least some of these mutations.

Vincent Calvez and colleagues from Hôpital Pitié-Salpêtrière reported resistance patterns from four highly treatment experienced patients who received raltegravir as part of a rescue therapy. [2]

Baseline viral load ranged from 4.3-5.5 logs. Two patients had a genotypic sensitivity score (GSS) of 0 and two patients had a GSS of 1.

Two patients achieved suppression to <50 copies/mL and then rebounded, one suppressed to 2.8 log and one only had a -0.5 log reduction (this patient had a GSS of 1 at baseline). Resistance mutations at failure included Q140S+Q148H, which occurred at the same time; N155H; E92Q and E157Q with viral load returning to pre-treatment levels by week 8-24 as these mutations were detected, with a loss of 7-14 fold drug sensitivity.

The researchers concluded that selection of only one mutation that led to failure in these patients emphasised the low genetic barrier to resistance, and highlights that this drug should only be used with other active drugs in the regimen.

### Elvitegravir resistance in experienced patients

Damian McColl presented the first analysis of resistance found in the Gilead Phase 2 dose-ranging (20mg, 50mg, 125mg) study of elvitegravir (EVG) in treatment-experienced patients. [3]

The control arm in the Gilead study was investigator chosen boosted-PI. All patients had optimised nucleoside background regimens (OBR), T-20 could also be used (but not NNRTIs), and a protocol amendment allowed use of darunavir and tipranavir in the EVG/r arms after 8 weeks.

30/73 patients in the 125mg EVG/100mg ritonavir arm had virological failure (with higher failure rates in the lower dose arms

which were stopped early) and results were presented for 28/30 patients with integrase genotype results.

Although mean viral load responses of approximately -2.0 logs from baseline were seen in the 125mg arm at week 2, this rebounded in patients with no active drugs in their OBR to -0.7 log by week 24, compared to maintaining -2.1 log reductions when one or more active drugs were included in the OBT or who were using T-20 for the first time.

The first observed mutations included T66I/A/K, E92Q, E138K, S147G, Q148R/H/K and N155H.

The most common mutation patterns by week 24 as detailed in Table 1.

**Table 1: Most common EVG-related mutations**

Integrase resistance mutations	N (%)
Any E92Q	11 (39%)
E92Q + N155H (+/- others)	4 (14%)
E92Q + T66A (+/- others, no N155H)	3 (11%)
E92Q (+/- others, no T66A or N155H)	4 (14%)
Any N155H	11 (39%)
N155H + other mutations (No E92Q)	7 (25%)
N155H + T66I (+/- others, no E92Q)	1 (4%)
N155H + E138K (+/- others, no T66I, no E92Q)	3 (11%)
N155H + others (no E138K, T66I, or E92Q)	3 (11%)
E138K + S147G + Q148R (+/- others)	6 (21%)
G140C/S + Q148R/H/K (+/- others inc T66I)	3 (11%)

Again, resistance not reported in the 10-day monotherapy studies but developed by week 4 in some patients who had no other active drugs. Analysis of longitudinal data is ongoing.

Mean phenotypic changes in sensitivity to elvitegravir were >150-fold at viral failure (median 152, range 1.02-301-fold). Cross resistance to raltegravir was indicated by mean changes in phenotypic sensitivity of 28-fold (median 10-fold, range 0.78->256-fold).

There was a close correlation between reduced susceptibility to both EVG/r and raltegravir in isolates with most common mutation patterns ( $R^2=0.66$ ).

### Polymorphisms in integrase

Several studies also analysed the importance of pre-existing integrase mutations in integrase-naïve patients. While the range of natural polymorphisms seems very extensive, they do not seem to be related to reduced susceptibility to diketo acid compounds or to a higher risk of treatment failure, in either naïve or treatment experienced patients. [4, 5, 6]

However, early data was presented that tentatively suggested that the relationship between changes in integrase may be linked to shifts in other parts of the genome – reverse transcriptase, protease and perhaps other regions – and that this might have an impact in treatment sequencing for experienced patients. [6]

Richard Myers from the Health Protection Agency in the UK and Deenan Pillay from UCL presented an analysis from 1,250 INI-naïve isolates from the Los Alamos database, where they identified 41 mutations at 30 positions in integrase. [4]

The most prevalent variants were V201I (in 80%) and V72I (46%). 15 mutations occurred at >5% frequency in different HIV sub-types. Other common mutations were identified at codons 74, 97, 125, 154, 163 and 206. However some of the between-clade differences led the researchers to conclude that susceptible to integrase inhibitors may vary by sub-types and that this should be examined in future in vitro models.

Kurt van Baelan and colleagues from Virco also presented data looking at the prevalence of naturally occurring integrase polymorphisms amplified from the RT-RNase-H-IN region in 47 patient samples and 89 clones. [5]

The most common polymorphisms were V72I (in 41 patients and 77 isolates) and V201I (in 33 patients and 48 clones), and included L74M/I, T97A, V151I, K156N, 165I, I203M, T206S and S230R/N, though none were associated with significant fold-changes. They also reported no differences between HIV sub-type, or between RTI sensitive and resistant isolates.

Carlo Perno and colleagues from Universities of Rome and Milan, looked at gene sequences for the whole sequence of RT and IN (1-320 residues) from 448 patient with HIV-1 sub-type B (134 naïve and 314 experienced). [6]

Protein sequences in integrase were unaltered at 62% and 67% of codons in naïve and experienced patients respectively. However 24/37 integrase mutations were not found in either naïve or RTI-treated patients. The eight position changes showing >5% variability were I72V, T125A/V, M154I, K156N, V165I, V201I, T206S and S230N.

Some mutations were present significantly more frequently in treated compared to naïve patients: M154I (21% vs 6%,  $p < 0.001$ ), V165I (13% vs 6%,  $p = 0.022$ ), M185L (6% vs 0%,  $p = 0.003$ ). M185L was significantly positively associated with V165I in integrase and F227L and T215Y in RT.

I72V occurred more frequently in untreated patients, and was positively associated with the protective R83K mutation in RT, and negatively associated with D67G and M184V in RT ( $p < 0.03$ ).

The authors concluded that the association found between selected INI and RT mutations supports the hypothesis of a tight interaction of these two proteins, and suggest the importance of IN-sequencing for RT-experienced patients prior to starting integrase-based regimens.

### **Integrase inhibitors sensitivity to HIV-2**

Dianne Descamps and colleagues from Bichat-Claude Bernard Hôpital Paris presented a paper on the phenotypic sensitivity of raltegravir and elvitegravir in isolates from 19 integrase-naïve patients infected with HIV-2 (9 with subtype A, 9 with subtype B, 1 with sub-type H). [7]

The HIV-2 integrase gene differed from HIV-1 at 133/288 codons, including some that have been described as integrase resistant sites for HIV-1. However, mean IC50 was similar between HIV-2 and HIV-1 reference strains, including two isolates with MDR Q151M in RT. Despite overall amino acid polymorphism of 31% this didn't alter phenotypic susceptibility of HIV-2 to either integrase inhibitor.

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All references are to the Programme and Abstracts of the XVI International HIV Drug Resistance Workshop, 12-16 June 2007, Barbados. Published as part of Antiviral Therapy (Volume 12 Issue 5).

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## **Treatment failure and tropism changes in maraviroc trial related to previously undetected CXCR4, rather than a mutational shift from CCR5**

**Simon Collins, HIV i-Base**

Understanding the mechanism behind treatment failure with CCR5 inhibitors is as important as the new data provided on integrase: maraviroc is also already available in an expanded access programme and both maraviroc and vicriviroc are in Phase III studies.

Understanding CCR5 inhibitor resistance is still unclear though, as are the implications for receptor tropism changes from CCR5 to CXCR4. The tropism question is complicated by limitations of current assays to detect minority X4 virus. The clinical significance for potentially changing the natural course of infection – X4 is associated with later stage infection – has led to arguably tougher regulation than for developers of drugs in existing classes – and rightly so according to many of the debates at the meeting.

Marilyn Lewis from Pfizer presented results from a phylogenetic sub-study using *env* clones sequenced from 20 patients from the Phase 3 MOTIVATE 1&2 studies, in whom X4 virus was detected on-study (using the Monogram Trofile test).

Four of these patients were in the placebo arm and 16 were receiving maraviroc.

In 14 patients (11 maraviroc, 3 placebo), the X4 virus that emerged during the study was identical to X4 detected in baseline sample: 4 patients with >10% X4 populations were identified as dual/mixed tropism at baseline and ten patients were found to have had X4 at 1-6%, below the 10% threshold for detecting X4 at baseline.

X4 samples from the remaining six patients (5 maraviroc, 1 placebo) were too phylogenetically different from both baseline and on-treatment R5 tropic virus (with 7-15 differences in the 35-amino acid V3 loop alone) to have evolved from the R5 virus.

The authors concluded that this showed that maraviroc did not cause viral evolution from R5 to X4 virus and that X4 virus emerging as a response to CCR5 inhibition was entirely from pre-existing X4 populations, generally below the limit of detection for the Trofile tropism assay.

The limited clinical data from people who subsequently stop maraviroc is that majority (detectable) tropism returns to R5 virus. This increases the importance of understanding the sensitivity of the current tropism test and natural history of tropism changes, especially given that 4/20 patients with detectable X4 virus were in the placebo arm and that 5 patients classified as R5 when screened for these studies were later found to have dual/mixed tropism at study entry (day 1).

50% of patients screened for the MOTIVATE studies were not eligible for entry due to dual/mixed or X4 virus at screening.

### Testing for viral tropism

Currently the Monogram Trofile tropism assay has been used in CCR5 registrational trials and is recognised as the gold standard, but this is expensive and requires sample to be shipped to the US. Several other labs are looking at whether genotype-based systems are able to provide similar results for use in clinical practice.

In the MOTIVATE sub-study of tropism changes reported above, there was a 90% concordance between tropism for individual clones assignment using the Trofile test and Position Specific Mutation Scoring (PSMS) algorithm (see Table 1).

However, Marilyn Lewis and colleagues from Pfizer reported that the sensitivity of both the 11/25 rule and PSMS to detect X4 usage was lower than for detecting R5 tropism. (see Table 1) [1]

Although several other tropism assays are in development (see reports from the European resistance workshop in the May issue of HTB [2, 3]), none of these tests are commercially available yet.

**Table 1: Concordance between tropism assays in MOTIVATE study**

Trofile assignment	11/25 rule		PSMS	
	R5-tropic	X4-using	R5-tropic	X4-using
R5 tropic (n=72)	96% (n=69)	4% (n=3)	99% (n=71)	1% (n=1)
X4-using (n=74)	34% (n=25)	66% (n=49)	19% (n=14)	81% (n=16)
Overall concordance	81%		90%	

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## **Mechanisms of failure to CCR5 inhibitors is not explained by mutation in the V3 loop, cross-resistance between CCR5 inhibitors is likely**

**Simon Collins, HIV i-Base**

In vivo resistance to CCR5 inhibitors is not clearly understood. It does not seem to follow loss of sensitivity predicted by in vitro changes in the V3 loop and is limited by the small number of patient with clinical failure. Studies at the conference provided data on both maraviroc and vicriviroc.

Julie Mori and colleagues from Pfizer maraviroc looked at phenotypic and genotypic markers in paired baseline and on-treatment samples from 37 patients (12 clones from each patients) with virological failure in the MOTIVATE studies. [1]

Criteria for further investigation were based on IC50 fold changes compared to either reference or baseline virus, or a plateau (<95%) in maximal percentage inhibition (MPI) – one of the new methods to investigate lack of CCR5-inhibitor response (and which had characterised in vitro resistance over changes in IC50).

No changes in MPI were found at baseline, though this was found on study in 4/12 failures patients in maraviroc arms and in one placebo patient. In general, patients failing maraviroc showed no increase in IC50, except for one patient who showed a 3-fold shift from baseline.

Changes in the V3 loop were shown in 6/12 patients with virological failure (including one patient on placebo). Mutation patterns were distinct for each patient although mutations at position 13 or 26 in the V3 loop were present in 5/6 patients.

Site-directed mutagenesis presented for four patients suggested that V3 mutations were sufficient at baseline and necessary at treatment failure for resistance to CCR5 antagonists.

In randomly selected samples from 8 patients with virological failure in the dose-finding Phase II ACTG 5211 vicriviroc study (2 patients from each of the placebo, 5mg, 10mg and 15mg VVC arms), V3 loop mutations were found in 5 patients. [2]

However, those mutations did not show any consistent reduction in viral susceptibility to the vicriviroc (shown by changes in IC50 through to week 24) with a maximum increase compared to control of 2.8 fold. V3 loop changes in 4/4 patients in the 5mg and 10mg arms were not found in the placebo or 15mg arms.

Additional sampling on one patients from the 10mg arm of the study, who showed reduced susceptibility to vicriviroc (and progressive loss of CCR5 inhibition) showed emergence of V3 loop mutations. Five months after discontinuing vicriviroc, this patient showed a return to R5 virus, baseline V3 sequences and phenotypic sensitivity.

Finally, Wei Huang and colleagues from Monogram, manufacturers of the Trofile tropism assay used in current CCR5 inhibitor studies, presented results from resistance to vicriviroc derived from in vitro passaging that suggested high-level resistance may be dependent on mutations that occur outside of V3. [3]

In this case, escape viruses with high level resistance contained 15-16 amino acid changes in gp120 and 2-3 changes in gp41, with only minor changes in the V3 loop.

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## Higher risk of resistance using lopinavir/r monotherapy

Simon Collins, HIV i-Base

In the last presentation at the workshop, Constance Delaugerre presented an analysis of resistance results from the MONARK trial (Kaltera monotherapy).

In the study, 136 treatment naïve patients were randomised to either lopinavir/r monotherapy (n=83) or lopinavir/r + AZT/3TC (n=53). Baseline genotypes were available for 131 patients, 36% of which were non-B (CRF02 was most common).

As previously reported, low level viremia occurred significantly more frequently in patients on lopinavir/r monotherapy arm. This was to a level that required genotyping in 32/83 and 7/53 of the monotherapy and triple therapy arms respectively.

18/32 monotherapy sequences showed protease changes compared to baseline, including 5/18 with major PI-associated mutations: 46I+63P at week 40, 76V at week 44. 13V+46I+76V at week 62, 10F+82A at week 76, and 76V at week 90.

These changes were detected at low levels of viremia, with latest median viral load (within 4 weeks of the test) of 2.9 logs (2.8-3.1). There was no relationship between baseline viral load and risk of viral rebound or of particular mutations. However, all patients who developed 76V had CRF02 virus.

Mean fold change in sensitivity to lopinavir in 4/5 samples available for phenotyping showed mean increase in IC50 of 1.64-fold (1.13 – 2.69).

4/7 patients in the triple therapy arm showed changes in protease but none of these included major PI mutations.

All patients who developed major PI mutations added AZT+3TC and resuppressed virus. It will be important to know whether these patients maintain suppression in the long-term.

Ref: Delaugerre c, Flandre P, Chaix MI et al. Protease gene mutations in a trials comparing first-line lopinavir/ritonavir monotherapy to lopinavir/ritonavir + zidovudine/lamivudine (MONARK Trial). *Antiviral Therapy*. 2007;12:S84. Abstract 75.

## **Macaque study shows similar protection from rectal exposure using 2-hour pre- and 24-hour post exposure prophylaxis with tenofovir plus FTC compared to daily regimen**

**Simon Collins, HIV i-Base**

Results in macaque studies showing protection from HIV infection using daily tenofovir, and similar protection with reduced risk of resistance from using tenofovir plus FTC, provided sufficient confidence for large scale studies in humans to proceed, even though most of these studies have run into practical difficulties.

Results from another important macaque study adds further supportive evidence for this concept, with perhaps additional implications for drug exposure.

J. Geraldo Garcia-Lerma and colleagues from the US DAIDS Centres for Disease Control (CDC) presented results from two different PrEP regimens. [1]

They first exposed six macaques by rectal administration on a once-weekly basis for 14 weeks. Dosing of TDF (22mg/kg) and FTC (20mg/kg) was given sub-cutaneously 2 hours prior and 24 hours after exposure, and results were compared to 21 control animals (9 real-time and 12 historical) and to previous study results using daily dosing. A second approach looked at using only 2-hour pre-dosing in another 6 animals.

20/21 untreated macaques became infected after a median of 2.5 exposures, with the majority infected during the first four challenges.

All animals receiving either daily dosing or the reduced pre- and post-only dosing were protected for the full 14 weeks. The 2-hour pre-exposure only dose for which only limited results were available reported infection in 1/6 animals.

### References

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## **Thirteen NNRTI mutations linked to resistance to etravirine (TMC-125)**

**Mark Mascolini, for natap.org**

Tibotec researchers identified 13 non-nucleoside (NNRTI)-related mutations that blunted response to etravirine (TMC125) in the phase 3 DUET trials [1]. The most harmful mutations were among the rarest; and the worst responses to etravirine occurred in people with three or more of these mutations before beginning the new NNRTI. Several resistance experts at the workshop questioned the method Tibotec used to gauge the impact of various mutations on response to etravirine.

This analysis involved 406 antiretroviral-experienced (PI & NNRTI) people taking 200 mg of etravirine twice daily with other antiretrovirals - but without enfuvirtide - in DUET 1 and 2, two double-blind, placebo-controlled trials. Tibotec investigators reckoned the impact of baseline NNRTI mutations by comparing virologic responses in people with mutations and responses in people with no detectable NNRTI mutations when they started etravirine. The final analysis included 26 of 44 potential NNRTI mutations (59%) that appeared in 5 or more people when the study began.

Univariate analysis earmarked 13 mutations that muted response to etravirine in the DUET trials--V90I, A98G, L100I, K101E, K101P, V106I, V179D, V179F, Y181C, Y181I, Y181V, G190A, and G190S. Notably, this list does not include K103N, which causes high-level resistance to both efavirenz and nevirapine. Virus housing the mutation A98G, K101E, Y181C, V179F, or G190A had more additional mutations than virus without those changes. Four mutations - V179F, Y181V, V106I, and V179D - appeared in people with the worst responses to etravirine, but they were among the least common mutations, detected in 7, 14, 5, and 24 people respectively. V179F always appeared with Y181C, another critical efavirenz and nevirapine mutation.

Tibotec used a novel yardstick to compare virologic response in people with these mutations to response in people with no detectable mutations when the study began. They set the response at 1.0 for people with no detectable entry mutations and figured inferior responses as a fraction of 1.0. For example, people whose virus carried the V179F mutation had a response of about 0.3 compared with the no-mutation group, and people with Y181C had a response of about 0.7.

Study participants whose virus harbored just one of the 13 identified mutations had a response of about 0.9 compared with the no-mutation group, as did people whose virus carried two of the 13 mutation. But people with three of the identified mutations had a relative response of about 0.6 and people with four of those mutations had a relative response of about 0.4. In other words, according to this type of calculation, people with one or two of the identified 13 etravirine mutations can expect some response from the drug, but people with three or more of those mutations have significantly reduced response. And Tibotec figured that 85% of the people they studied had 0, 1, or 2 of the 13 critical mutations.

But several workshop attendees had qualms about the reliability of this method, including Charles Boucher (University Hospital Utrecht), Daniel Kuritzkes (Brigham and Women's Hospital Boston), and Jonathan Schapiro (National Hemophilia

Center, Israel). Schapiro observed that one entry criterion for the trial was at least one NNRTI mutation at screening for the trial or in an earlier resistance test. In other words, the comparison group of people with undetectable NNRTI mutations at screening had such mutations at some point and possibly had one or more NNRTI mutations at low levels in blood or cells when they were screened for the trial. Thus it becomes difficult to figure out what a relative response of 0.9 or 0.5, for example, actually means.

Susceptibility to etravirine - measured as fold change in 50% effective concentration (EC50) - decreased in a stepwise fashion as the number of mutations in a baseline sample rose. As one would expect, virologic response to etravirine also fell as the number of mutations mounted.

Efficacy results in the DUET trials, which will clarify the importance of these 'relative responses' will be unveiled at the July IAS meeting in Sydney.

Barcelona clinicians determined that mutations linked to poor response to etravirine in earlier studies appear relatively rarely after failure of efavirenz or nevirapine [2]. Bonaventura Clotet (IrsiCaixa Foundation, Barcelona) and colleagues predicted that "complete resistance to etravirine will be very rare, but low-to-intermediate resistance will be fairly common."

The mutations used in this analysis did not mesh precisely with those in the latest Tibotec study, described above [1]. The Barcelona team considered viral samples sent for resistance testing from 1998 through 2006 and including the hallmark NNRTI mutations K103N, Y181C, G190A, or V108I. Then they tallied the number of etravirine-related mutations in those viral samples. On the basis of earlier reports, they defined high-level resistant virus (more than a 10-fold change in susceptibility) as virus containing F277C, Y181I, or V179F alone--or K101P, V179E/I, Y181I/V, G190S, or M230L plus two additional mutations. The Barcelona team considered Y181C, V179D, K101E, and Y188L plus two additional mutations as changes that confer intermediate (5- to 10-fold) resistance to etravirine.

Overall, 56% of the 1586 viral samples studied contained one or more mutations from this list. But many of these mutations or groups of mutations were considered to confer intermediate resistance to etravirine. The critical mutations F227C, V179F, or Y181I alone appeared in only 0.1%, 0.3%, and 4% of the viruses studied. The researchers saw K101P plus two other mutations in no viral isolates, Y181V plus two other mutations in 0.1%, V179E plus two other mutations in 0.2%, M230L plus two other mutations in 0.4%, G190S plus two other mutations in 0.9%, Y181I plus two other mutations in 1%, and V179I plus two other mutations in 5.8%. No viral samples harbored these mutations with four other NNRTI mutations.

Among mutation sets judged to confer intermediate resistance to etravirine, V179D plus two other mutations appeared in 1% of viral isolates, Y188L plus two others in 6%, K101E plus two others in 10%, and Y181C plus two others in 13.4%. The mutations V179E/F/I/D, or Y181I/V/C, or K101P/E, or G190S, or M230L, or F227C, or Y188L showed up in only four viral samples (0.2%).

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## CONFERENCE REPORTS

### 14th Conference on Retroviruses and Opportunistic Infections

25-28 February 2007, Los Angeles

Our final reports from this meeting include:

- Protease inhibitors in pregnancy
- IDU-related studies at CROI:
  - Low Rates of HCV treatment among eligible injection drug users;
  - Effect of HCV and HIV on mortality among injecting drug users;
  - HCV/HIV-co-infected IDUs are at increased risk of death from hepatitis-related death in the HAART era, compared with HCV-mono-IDUs;
  - Long-term effectiveness of isoniazid prophylaxis on TB incidence in a cohort of IDUs;
  - The dynamics of HCV transmission among injection drug users in St. Petersburg;
  - "Founder effect" among HIV-positive IDUs in Karachi, Pakistan;

## Protease inhibitors in pregnancy

### Poly Clayden, HIV i-Base

Since the report of hepatotoxicity risk in women with CD4 counts above 250 cells/mm<sup>3</sup> receiving nevirapine, the need has increased for more information on use of protease inhibitors in pregnancy.

Two posters from the Perinatal Pregnancy Group London and The University of Nijmegen, Netherlands showed data on use of atazanavir and saquinavir (500mg formulation) respectively.

#### Atazanavir

Macky Natha and co-workers presented findings from a report of 33 pregnancies among women receiving atazanavir (ATV) [1]. ATV is labelled pregnancy category B but there have been concerns about infant hyperbilirubinaemia with use of this drug in pregnancy. Nevertheless, ATV is increasingly used by pregnant women, both already on treatment and those for whom it is initiated in pregnancy.

This was a case note review of all women attending 9 HIV units in London to February 2007, who were receiving ATV in pregnancy. Data were collected on maternal CD4 count, viral load, toxicity, and plasma ATV concentrations. Infant data included serum bilirubin, use of phototherapy, and, where available, HIV status at 3 months. Adverse events were also recorded in both mothers and infants.

The investigators identified 31 women with a total of 33 pregnancies. All but two women received the 300mg/100mg ATV/RTV dose.

There were 2 miscarriages at 12 and 16 weeks and 1 woman was still pregnant at the time of review.

20 women had conceived when on ATV. Their median viral load at their first antenatal visit was 98 copies/mL (range <50-101454 copies/mL) and median CD4 count 262 cells/mm<sup>3</sup> (range 61-660 cels/mm<sup>3</sup>). 10 women initiated treatment at 22 weeks gestation. All had viral load <50 copies/mL and a median CD4 count of 270 cells/mm<sup>3</sup> (range 151-930 cells/mm<sup>3</sup>) at baseline.

At delivery median viral load and CD4 counts were <50 copies/mL (range 50-28189 copies/mL) and 269 cells/mm<sup>3</sup> (range 67-910 cells/mm<sup>3</sup>) respectively. 23/30 women had an undetectable viral load. Median maternal bilirubin level was 30 (range 4 to 76) umol/l [1.8 (range 0.2-4.4) mg/dL] and 23/26 mothers had a raised bilirubin (>17umo/L [>1 mg/dL]).

ATV concentration measurements were available for 19 mothers (performed at a median of 30 weeks' gestation). 16 were taken in the third trimester and the mean trough ATV concentration was 373 mg/L and all but two were above the recommended therapeutic concentration of 100 mg/L.

29 infants were born at a median of 38 weeks gestation (19 planned cesarian sections, 9 emergency cesarian sections, 2 planned spontaneous vaginal delivery). Mean birth weight was 2894g (range 1080-4050g) and median infant bilirubin levels were 71 umol/L (range 10 to 191) (4.2 mg/dL, range 0.6 to 11.2).

No infants required phototherapy and no birth defects were detected. The investigators reported the median time since delivery was 12 months (range 1-26 months) and all infants were uninfected at time of review.

The investigators wrote: "To our knowledge, this is the largest reported case series of the use of ATV in pregnancy. Atazanavir was well tolerated in our cohort and most women had good immunological and virological responses. Maternal plasma levels, where measured, were adequate. No early infant morbidity as a result of in utero exposure to ATV was demonstrated."

#### Saquinavir

David Burger and co-workers presented findings from a pharmacokinetic (PK) study of saquinavir new formulation (500mg tablet) and ritonavir dosed at 1000/100mg BID in pregnancy. [2] SQV is also labelled pregnancy category B.

This was a prospective multicentre study of 14 HIV-positive women initiating SQV-containing treatment in pregnancy. At week 33 (+/-2 weeks), a 12-hour pharmacokinetic curve was recorded. Blood was sampled prior to dosing with a standardised breakfast and at t = 1, 2, 3, 4, 6, 8, 10, and 12 hours post-dosing.

The investigators reported that mean (+/- standard deviation [SD]) values for SQV AUC<sub>0-12h</sub>, C<sub>max</sub> and C<sub>min</sub> were 19.3 (7.4) mg/L.h, 3.8 (1.5) mg/L, and 1.4 (0.78) mg/L, respectively. For RTV mean values for AUC<sub>0-12h</sub>, C<sub>max</sub> and C<sub>min</sub> were 5.8 (2.5) mg/L.h, 1.1 (0.51) mg/L, and 0.44 (0.22) mg/L, respectively.

They noted that SQV PK parameters were comparable to those reported in a previous study using the same formulation in non-pregnant healthy volunteers at the licensed dose of 1000/100 mg BID. None of the 14 women showed a subtherapeutic C<sub>min</sub> of SQV (defined as <0.10 mg/L. For 2 women a 12-hour PK curve was also recorded during the second trimester (week 20) or 4 to 6 weeks post-partum. SQV PK parameters in these women were not different from those reported during third trimester.

The investigators concluded: "Saquinavir pharmacokinetics when taken as the new 500-mg tablet formulation and boosted

with RTV at a dose of 1000/100 mg twice daily were adequate in all 14 women investigated. No difference was observed in pharmacokinetics of saquinavir between 2<sup>nd</sup> and 3<sup>rd</sup> trimester. In contrast to observations with other PI (ie, NFV, lopinavir/RTV), saquinavir pharmacokinetics appear not to be influenced by pregnancy.”

#### References

1. Natha M, Hay P, Taylor G et al. Atazanavir use in pregnancy: A report of 33 cases. Abstract 750.
2. Burger D, A Eggink A, van der Ende ME et al. The pharmacokinetics of saquinavir in new tablet formulation + ritonavir (1000/100 mg twice daily) in HIV-1-infected Pregnant Women. 14 CROI, Los Angeles 2007. Poster abstract 741.

## IDU-related studies at CROI

### Polly Clayden, HIV i-Base

These reports will be included in a new electronic publication produced by i-Base called ARVs4IDUs. This will be a quarterly summary of research relating to injecting drug users and HIV, with the first issue available for the IAS conference in Sydney in July.

HTB readers who currently receive HTB by email will receive this automatically as a supplement to the next issue of HTB. Print readers will need to subscribe for this new service online:

<http://www.i-base.info/forms/esub.php>

### Low Rates of HCV treatment among eligible injection drug users

Most HCV-positive IDUs do not receive HCV treatment. M Sulkowski and co-workers from Johns Hopkins in the US presented findings from a study to determine the proportion of HIV-positive and HIV-negative IDUs (former and active) in their programme who are eligible for and initiate HCV therapy with pegylated interferon (pegINF) + ribavirin (RBV) in the absence of geographic and financial barriers (treatment was offered free and on-site).

The study enrolled 332 subjects (172 HIV/HCV co-infected; 158 HCV mono-infected). HIV-co-infected IDUs were younger (41 to <44 years) and were more likely to be African American (90% to >74%), have a monthly income >\$500 (52% to >23%) than those with HCV alone. The investigators reported no difference in the prevalence of mental illness (~64%), alcohol use (~20%), or interest in receiving HCV treatment (~93%).

HIV-co-infected IDUs were more likely to have detectable HCV RNA (20/172 HIV/HCV co-infected, 11%; 29/143 of HCV mono-infected, 20%;  $p < 0.001$ ) and less likely to be eligible for HCV treatment (75/152 of HIV/HCV, 49%; 78 /114 HCV, 68%;  $p = 0.002$ ). Reasons given for ineligibility were: severe depression (HIV/HCV 12%; HCV 30%); life expectancy <2 years (HIV/HCV 40%; HCV 30%); hematologic abnormality (HIV/HCV 49%; HCV 22%); renal insufficiency (HIV/HCV 10%; HCV 8%). Of the treatment-eligible IDUs, ~40% initiated HCV therapy, defined as at least pegINF injection (31/75 HIV/HCV, 41%; 27/80 HCV, 36%).

The investigators concluded: “While ~50% of HIV/HCV-co-infected IDUs were ineligible for HCV treatment, most (~80%) of HCV-mono-infected IDUs were treatment-eligible. Despite the removal of financial and geographic barriers, only ~40% of treatment-eligible IDUs initiated HCV treatment. Strategies are needed to increase HCV treatment uptake among IDUs.”

Ref: Sulkowski M, S Mehta S, Moore R et al. Low rates of HCV therapy among treatment-eligible injection drug users with and without HIV Co-infection. 14<sup>th</sup> CROI, 2007, Los Angeles. Poster abstract 947.

### Effect of HCV and HIV on mortality among injecting drug users

Jason Grebely and co-workers from CHASE (a cohort study of Vancouver inner city residents recruited from January 2003 to June 2004) presented mortality data from this cohort.

The investigators found, of 2069 participants identified, 721 were both HCV and HIV-negative (HCV-/HIV-), 962 were HCV-positive and HIV-negative (HCV+/HIV-), 33 were HCV negative and HIV-positive (HCV-/HIV+), and 353 were HCV and HIV-positive (HCV+/HIV+).

Among the 82 reported deaths, they found common causes of death were HIV (25.6%) and unnatural causes (19.5%). The natural cause mortality rate was 15.5 deaths/1000 person-years overall ( $n = 66$ ), 9.6 deaths/1000 person-years for HCV-/HIV- ( $n = 15$ ), 11.0 deaths/1000 person-years for HCV+/HIV- ( $n = 28$ ), 30.4 deaths/1000 person-years for HCV-/HIV+ ( $n = 2$ ), and 37.8 deaths/1000 person-years for HCV+/HIV+ subjects ( $n = 37$ ).

For HCV-/HIV+ and HCV+/HIV- subjects, mortality attributed to HIV and HCV was 15.2 and 2.0 deaths/1000 person-years. In HCV+/HIV+ subjects, mortality attributed to HIV and HCV were 25.6 and 1.3 deaths/1000 person-years. Overall, natural cause mortality was associated with HIV infection (adjusted HR 5.3, 3.0 to 9.7,  $p < 0.001$ ), age (HR 1.8/10-year increase, 1.3 to 2.4,  $p < 0.001$ ) and aboriginal ethnicity (HR 1.7, 0.96 to 3.0,  $p = 0.07$ ), and not associated with HCV infection (HR 1.0, 0.50 to 2.0,  $p = 0.99$ ).

The investigators concluded that mortality rates in IDUs were high in this analysis, and HIV infection gave a 5-fold increase in risk of mortality. They noted that due to the timing of the HCV epidemic in this population, there has been little impact of HCV on mortality to date. "They wrote "Without programmes to treat HCV in this group, we expect a significant increase in mortality attributable to HCV infection."

Ref: Grebely J, Raffa J, Conway B et al. Effect of hepatitis C virus and HIV infections on mortality among illicit drug users. 14th CROI, 2007, Los Angeles. Poster Abstract 922.

### **HCV/HIV-co-infected IDUs are at increased risk of death from hepatitis-related death in the HAART era, compared with HCV-mono-IDUs**

Maria Prins and coworkers from the Amsterdam Cohort Studies compared mortality from specific causes of death in HCV/HIV-co-infected IDUs with that of HCV-mono-infected IDUs and IDU without HCV and HIV, before and after the widespread use of HAART.

The study population consisted of 1276 IDUs from the cohort that started in 1985. Blood samples collected for HIV testing at 4- to 6-monthly visits was retrospectively tested for HCV.

The investigators found serological groups at study entry were: 19% HCV+/HIV+, 43% HCV+/HIV-, 1% HCV-/HIV+, 36% HCV-/HIV-. During follow-up, 272 IDU died. Overall, mortality risk decreased for most causes of death in the HAART era (defined as after 1997), but the risk was not the same across the groups. For the HIV+/HCV+ IDU group, the risk of death from AIDS decreased significantly (CHR 0.37, 95%CI 0.19 to 0.72), whereas the risk of hepatitis or liver-related death did not change over time (CHR 0.87, 95%CI 0.21 to 3.58). In the HCV+/HIV- and HCV-/HIV- IDU groups, no significant changes in the risks of death were observed.

When comparing the risks of death among serologic groups, they found in the HAART era that the HCV+/HIV+ IDU group had a significantly higher risk of hepatitis or liver-related death than the HCV+/HIV- IDU group (CHR 7.15, 95%CI 1.98 to 25.8). Increased risks of dying from non-natural and natural causes of death were also found. No major differences were observed between the HCV-/HIV- and HCV+/HIV- IDU groups.

The investigators concluded that the risk of dying from HCV-related causes among HCV/HIV-co-infected IDU, has not increased after the introduction of HAART. But they found that compared to the HCV+/HIV- IDU group, HCV/HIV-co-infected IDU remained at increased risk of hepatitis and liver-related death after 1997, suggesting that HIV co-infection continues to accelerate HCV disease progression. They wrote: "Efforts should be made to establish effective HCV treatment in HCV/HIV-co-infected persons."

Ref: Prins M, Smit C, van den Berg C et al. HCV/HIV-co-infected drug users are at increased risk of dying from hepatitis-related death in the HAART era, compared with HCV-mono-infected drug users. 14th CROI, 2007, Los Angeles. Poster Abstract 923.

### **Long-term effectiveness of isoniazid prophylaxis on TB incidence in a cohort of IDUs**

Jonathan Golub and co-workers from the AIDS Linked to Intravenous Experience (ALIVE), cohort in Baltimore USA assessed long-term effectiveness of an 8-year tuberculin skin testing (TST)/isoniazid (IPT) programme among a cohort of HIV-positive and HIV-negative IDUs.

This cohort includes >2000 IDUs in Baltimore, 35% of whom were HIV-positive at baseline. TST and IPT were offered to all ALIVE participants from 1990 to 1998. TB incidence was measured in 3 periods: pre-purified protein derivative (PPD) era (1988-1990), PPD era (1990-1998), and post-PPD era (1998-2004). Incidence rate ratios compared TB incidences among eras.

The investigators found out of a group of 753 HIV-positive participants, 651 (86%) had a TST ; 103 (16%) had a positive result (>5 mm); 65 (60%) started IPT; and 40 (62%) completed 6 months. Of the 1264 HIV-negative participants, 1105 (87%) had a TST; 435 (39%) had a positive result (>10 mm); 246 (56%) started IPT; and 133 (54%) completed 6 months. In total, 32% of those with a positive TST completed 6 months of IPT.

In this study 30 TB cases were diagnosed over 28,750 person-years: IR = 1.04/1000 person-years in HIV-negative; IR = 2.66/1000 person-years among the HIV-positive population. The investigators reported TB incidence in the post-PPD-era for the overall cohort was half that seen in the PPD-era (IRR = 0.44, 95%CI 0.19 to 1.04), but they found no significant difference between eras in the HIV-positive population (2.04 vs 3.14/1000 person-years; IR = 0.64, 95%CI 0.27 to 1.58).

Both overall and amongst the HIV-positive participants, TB incidence among those who never received IPT was greater than those who started IPT; no cases were detected for those who received 6 months of IPT. Among the HIV-positive participants the investigators found body mass index <21 (RH = 3.1, p <0.01) and CD4 <200 (RH = 9.6, p <0.01) to be most predictive of TB. ART use had no association with risk of TB.

The investigators reported that a significant long-term reduction in TB incidence was observed in a cohort of IDU with a high HIV prevalence after an 8-year strategy of TST/IPT, but no change was seen in the HIV-positive subset. They noted that

IPT was highly effective for those who completed it, but only 32% of TST-positive patients completed. "Broader use of IPT in HIVIDUs could substantially decrease TB incidence" they wrote.

Ref: Jonathan Golub, J Astemborski, M Ahmed et al. Long-term effectiveness of isoniazid preventive therapy on TB Incidence in a cohort of injection drug users. 14th CROI, 2007. Los Angeles. Abstract 851.

### **The dynamics of HCV transmission among injection drug users in St. Petersburg**

Elijah Paintsil and co-workers from the Sexual Transmission and Acquisition of HIV Cooperative Agreement Program (SATH-CAP) project in St. Petersburg presented findings from a study in which they compared network linkages with linkages among the viral genomes among a group of people with HCV recruited by respondent-driven sampling in St. Petersburg.

The investigators reported that sequences from 77 people studied showed 3 main genotypes (3a, 1a, and 1b) circulating in the study population, with a majority of genotype 3a (62%). Genotypes 1b and 1a were 21% and 17%, respectively.

Of the total, 67/77 samples belonged to 11 recruitment chains of productive seeds or chains with more than 2 people; 4 chains with 6, 4, 2, and 3 people (excluding seeds) had a single genotype (3a); 4 chains with 7, 11, 5, and 4 members (excluding seeds) had multiple genotypes with >50% of them belonging to 3a; 3 chains with 13, 4, and 2 members (excluding seeds) contained discordant genotypes in variable amounts.

They concluded that these data suggest that molecular epidemiological tools could provide data to support or refute transmission within social networks that are exploited in assembling respondent-driven sampling study populations.

They wrote: "The ability of respondent-driven sampling to capture transmission patterns for prevalent infections appears limited, but the two data sets combined could provide a more robust exploration of incident transmissions of infectious diseases like HCV and HIV."

Ref: Paintsil E, Abdala N, Nicolai L et al. The dynamics of HCV transmission among injection drug users in St. Petersburg, Russia: Sexual Transmission and Acquisition of HIV Cooperative Agreement Program. 14th CROI, 2007, Los Angeles. Abstract 131.

### **"Founder effect" among HIV-positive IDU in Karachi, Pakistan**

Pakistan has >74,000 HIV-positive people out of a population of 162 million; with a recent shift in acquisition of HIV via IDU.

Mohammad Rai and co-workers reported findings from a study to determine whether an HIV outbreak among a community of 15 IDU in Karachi was from a single source.

Viral DNA was extracted from blood samples collected between January and December 2004. Sequence alignment of the nef gene from HIV-1-positive patients from Pakistan indicated that the HIV-1 strains differed from the strains circulating in neighbouring India, and were genetically closer to HIV-1 subtype A strains from Senegal, Uganda, and Kenya. Additionally, phylogenetic analysis of the complete nef gene sequence revealed highly congruent topologies, using the neighbour-joining method. The HIV-1 strains from Pakistan formed a monophyletic group.

The investigators wrote: "Our data suggest that the HIV-1 sequences circulating among IDU in Karachi, Pakistan, belong to only 1 HIV subtype, subtype A. Moreover, the intra-sequence identity of 98% indicates a founder effect."

They noted that these data contrast with a previous observation demonstrating presence of multiple HIV-1 subtypes among overseas contract workers.

They concluded: "The HIV-1 epidemic in Pakistan is shifting from imported cases, such as among the overseas contract workers, to the spread of HIV among local high-risk behavior populations. More prevention and control studies are urgently warranted to curtail the spread of HIV in Pakistan."

Ref: Rai M, Nerurkar V, Yanagihara R et al. Founder effect among HIV-1-infected Injection drug users in Karachi, Pakistan. 14th CROI, 2007, Los Angeles. Poster Abstract 241.

## **CONFERENCE REPORTS**

### **8th International Workshop on Clinical Pharmacology of HIV Therapy**

**April 2007, Budapest, Hungary**

**Jennifer J. Kiser, Courtney V. Fletcher, for NATAP.org**

#### **Introduction**

The 8th International Workshop on Clinical Pharmacology of HIV Therapy was held April 16-18, 2007 in Budapest, Hungary. 193 HIV clinical pharmacologists attended this year's Workshop and more than half were new attendees. This year's meeting included 80 posters, 30 platform presentations, six invited lectures, and a roundtable discussion on the optimal design of drug interaction studies.

The plenary lectures covered a variety of topics of relevance to clinical pharmacology and the therapeutics of treating HIV infection.

Dr. Kevin Park reminded the audience of the high frequency of drug-induced adverse reactions and their consequences including hospital admissions and drug withdrawals from the market, and discussed mechanisms of drug-induced hepatotoxicity.

Dr. Judith Currier gave a state of the art lecture on women's health topics in HIV focusing on virologic, pharmacologic and complication of treatment issues. Dr. Currier noted that to date most clinical trials are underpowered to detect differences with respect to safety and efficacy between men and women and the need for future studies to address this problem.

Dr. Daria Hazuda discussed the development of integrase inhibitors and illustrated the promise these agents hold for treatment of HIV infection.

Dr. Anton Pozniak's lecture focused on treatment and drug-drug interactions in the setting of HIV and tuberculosis co-infection. This lecture dealt with the sober statistics of infection with tuberculosis, noting one death from tuberculosis every 15-20 seconds, questions of when to start antiretroviral therapy in the co-infected person, and the management challenges of drug-drug interactions. There remain critical gaps in our understanding of the pharmacotherapy of HIV and tuberculosis coinfection that need urgent attention.

Dr. Terry Blaschke discussed a variety of issues related to the co-formulation of antiretroviral agents noting the usefulness of co-formulated drugs and the variety of challenges that must be addressed in their development.

The last lecture, given by Dr. Bruno Stieger discussed the role of membrane transporters in drug pharmacokinetics and pharmacodynamics. This is a topic of increasing importance for antiretroviral agents, with drug-drug interactions such as those between rosuvastatin and lopinavir/ritonavir, and pravastatin and darunavir/ritonavir (discussed later) likely being transporter mediated.

Drs. Thomas Kakuda and Courtney Fletcher led a roundtable discussion on the role of phenotyping cocktails to identify drug interactions, the optimal design of drug-drug interaction studies, and the importance of determining which drug-drug interactions may be of clinical significance for patients.

It is not possible to cover all of the abstracts presented at the Workshop, so we have chosen to focus on studies we felt were well designed and most clinically relevant. This report is divided into four sections:

- drug-drug interactions
- pharmacokinetic data with existing antiretrovirals
- antiretroviral pharmacokinetics in special patient populations, and
- pharmacology of investigational drugs.

## **Drug-drug interactions**

### **Rifampin interactions with saquinavir/r and lopinavir/r**

Previous studies have shown significant hepatotoxicity in healthy volunteers receiving rifampin in combination with saquinavir/ritonavir [1] and lopinavir/ritonavir [2]. At this year's Workshop, a study detailing adverse events in healthy volunteers receiving the combination of rifampin and lopinavir/ritonavir was presented. [3]

Volunteers received 600 mg of rifampin daily for 5 days; then either 600/150 mg or 800/200 mg of lopinavir/ritonavir was added to the rifampin. By the second day of the combination, 10/11 subjects suffered nausea and vomiting and all 11 had liver enzyme elevations and thus the study was terminated. Liver enzyme elevations peaked 2-3 days after discontinuing the combination (n=2 with grade 2, n=9 with grade 4 elevations). Liver enzymes returned to normal in all subjects during follow up and there were no signs of clinical hepatotoxicity.

The mechanism(s) for the development of severe hepatotoxicity with the combination of rifampin plus saquinavir/ritonavir or lopinavir/ritonavir in healthy volunteers is unclear. There remains a real unmet need for effective strategies for concomitant treatment of tuberculosis and HIV, and in particular whether rifampin can be given with any ritonavir-boosted protease inhibitor.

This latter question needs to be addressed in healthy volunteer studies because of the risk of suboptimal protease inhibitor concentrations; however, it is clear that the combination of ritonavir-boosted protease inhibitors and rifampin may pose significant risks to these subjects and a high degree of caution is warranted for any future studies.

### **Tipranavir pharmacokinetics**

A phenotyping cocktail study was conducted to evaluate the in vivo effects of tipranavir on various cytochrome (CYP) P450 enzymes. [4]

Sixteen healthy volunteers were given single doses of caffeine (CYP1A2 probe), warfarin (CYP2C9 probe), and dextromethorphan (CYP2D6 probe) at baseline and 10 hours after a first dose and a steady-state dose of tipranavir/ritonavir 500/200 mg twice daily.

At steady state, tipranavir/ritonavir was found to induce CYP1A2 and CYP2C9 because the ratios of caffeine and warfarin AUCs at steady state tipranavir/ritonavir vs. baseline were 0.57 and 0.88, respectively. The ratio of dextromethorphan AUC at steady state tipranavir/ritonavir vs. baseline was 6.24 suggesting tipranavir/ritonavir is a potent inhibitor of CYP2D6.

Data presented by the same group at the 2007 CROI demonstrated that tipranavir/ritonavir is a potent intestinal CYP3A inhibitor and has modest effects on P-glycoprotein [5].

Collectively, these data provide some insight into the complex mechanisms of previously identified interactions with tipranavir/ritonavir including the ability to inhibit and induce different drug elimination pathways simultaneously, and may assist in prediction of other interactions with this compound. Enzyme and transporter phenotyping studies are emerging as a new tool to aid in the prediction of drug-drug interactions. At this time, the greatest benefit of probe studies appears to be in identifying potential drug interactions that do not need further clinical evaluation.

#### **Tadalafil dose adjustments with tipranavir/r**

The Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents recommends starting with a 5 mg dose of tadalafil (not to exceed 10 mg in a 72 hour period) for the treatment of erectile dysfunction in persons with HIV on a protease inhibitor.

The results of a healthy volunteer study presented at the Workshop suggest that this lower 5 mg dose of tadalafil only needs to be used during the first few days of initiating a tipranavir/ritonavir-based regimen, but after 7-10 days on tipranavir/ritonavir, no tadalafil dose adjustment is necessary. [6]

#### **Unexpected interaction between darunavir/r and pravastatin**

Pravastatin is one of the most widely used HMG-CoA reductase inhibitors in persons with HIV because of its low propensity for CYP-mediated drug interactions. However, Vanitha Sekar presented data on an unexpected interaction between darunavir/ritonavir and pravastatin in 14 healthy volunteers. [7]

In this study, pravastatin AUC and C<sub>max</sub> were increased 81% and 63%, respectively (on average) when combined with darunavir/ritonavir 600/100 mg twice daily. Interestingly, there was substantial interindividual variability in the magnitude of this interaction, with not all volunteers having an increase in pravastatin exposure with the addition of darunavir/ritonavir and others having up to a 3 to 10 fold increase.

The mechanism for this interaction is speculative, but is likely mediated by darunavir and/or ritonavir's inhibition of organic anion transporting polypeptide 1B1 (OATP1B1) located on the basolateral side of the hepatocyte. Pravastatin is a high affinity substrate for OATP1B1. A previously presented study identified a similar unexpected interaction between another OATP1B1 substrate, rosuvastatin, and lopinavir/ritonavir. [8]

A study is ongoing to elucidate the purported mechanism for the interaction between darunavir/ritonavir and pravastatin. Clinicians may wish to avoid the combination of darunavir/ritonavir and pravastatin until more data are available.

#### **Pharmacokinetic data with existing antiretrovirals**

##### **Intracellular concentrations of once- and twice-daily abacavir**

Marta Boffito presented data on the plasma and intracellular concentrations of abacavir when given as either 600 mg once daily or 300 mg twice daily. [9]

27 subjects (9 females) completed the study. Plasma exposures of abacavir were similar between patients on 300 mg twice daily and 600 mg once daily, while C<sub>max</sub> was 109% higher and C<sub>trough</sub> 63% lower, as expected, following 600mg once daily vs. 300 mg twice daily. However, intracellular carbovir triphosphate AUC and C<sub>max</sub> were 32% and 99% higher in those on 600 mg once daily.

Plasma concentrations of abacavir were 38% higher in females even after adjusting for weight, and intracellular carbovir triphosphate AUCs were 2-fold higher in females.

##### **Gender effect on intracellular triphosphate concentrations**

The finding of a gender effect with regard to intracellular triphosphate concentrations of nucleosides was echoed in a study of tenofovir. [10]

This investigation found no difference in plasma tenofovir concentrations between men and women but did show that women had approximately 50% higher intracellular tenofovir concentrations than did men.

These studies, in conjunction with previous reports showing that women had higher intracellular triphosphate concentrations of zidovudine and lamivudine provide a pharmacokinetic basis to warrant further studies of gender-based differences in nucleoside phosphorylation that incorporate virologic, immunologic and safety evaluations. [11]

### **Dose reductions of d4T**

Stavudine (d4T) is part of generic, fixed dose antiretroviral combination products available in developing countries. However, its use has been associated with toxicities. Thus the pharmacokinetics, efficacy and safety of lower doses of d4T are being explored.

Gilles Peytavin presented data from 57 patients (median weight 72 kg), who had been on a stavudine-containing regimen for a median of 6 years, who decreased their stavudine dose from 40 mg twice daily to 30 mg twice daily. [12]

Eleven of the 57 subjects underwent intensive pharmacokinetic studies while on 40 mg and 30 mg twice daily. Despite d4T AUC and C<sub>max</sub> being reduced by 31% and 44%, respectively, with the dose reduction, 98% and 93% of subjects had viral loads of less than 400 copies/mL at 24 and 48 weeks after d4T dose reduction. Additionally, 6 of 17 patients who reported symptoms of neuropathy on 40 mg reported an improvement at week 48. These data are encouraging for the potential for d4T dose reduction in countries without access to other less-toxic nucleoside analogs.

### **Effects of different PIs on ritonavir**

Ritonavir is frequently used to “boost” the concentrations of other protease inhibitors. However these concomitant protease inhibitors have differing effects on ritonavir concentrations. Higher ritonavir concentrations may lead to rises in lipids and gastrointestinal adverse effects; thus, there may be differences in tolerability between ritonavir-boosted protease inhibitor regimens due to differences in ritonavir concentrations.

Marta Boffito presented data from 16 studies on the effects of eight protease inhibitors on ritonavir concentrations when used as a pharmacokinetic booster. [13]

Overall, atazanavir and indinavir were found to increase ritonavir concentrations by 62 and 72%, saquinavir showed no significant effect, while amprenavir, nelfinavir, darunavir and lopinavir lower ritonavir levels. Tipranavir showed the greatest reduction in ritonavir concentrations by 90% (hence the reason for using a 200 mg dose of ritonavir to boost this agent).

The question posed by these investigators of the differential effects of PIs on ritonavir is interesting and clinically relevant. This initial effort to present a comprehensive examination of the pharmacokinetic effects of protease inhibitors on ritonavir concentrations warrants additional study of these issues.

### **Food and antacid interactions with tipranavir**

Antacids decrease tipranavir exposure by about 25%, thus the potential for an interaction between omeprazole and tipranavir requires investigation.

Charles laPorte and colleagues reported the results of a drug-drug interaction study in 15 healthy volunteers between tipranavir/ritonavir and the proton-pump inhibitor omeprazole. [14]

This study was designed to evaluate the pharmacokinetics of single doses of tipranavir/ritonavir (500/200 mg) given with food alone and after 5 days of omeprazole 40 mg once daily. The geometric mean ratios (and 90% confidence interval) for the tipranavir AUC and C<sub>max</sub> were 1 (0.89, 1.12) and 1.05 (0.94, 1.17), respectively. These data indicate that omeprazole had no adverse affect on tipranavir bioavailability and concomitant therapy with food should be acceptable.

In addition, these authors investigated the effect of food on the pharmacokinetics of tipranavir/ritonavir, 500/200 mg twice daily in healthy volunteers. 32 of 35 participants completed this study. The geometric mean ratios (and 90% confidence interval) for the tipranavir pharmacokinetic characteristics given fasted versus fed were: AUC, 0.99 (0.88, 1.11); C<sub>max</sub>, 1.02 (0.91, 1.14); and C<sub>min</sub>, 1.02 (0.84, 1.23). These data would suggest that tipranavir can be given either with or without food.

However, these data are in contrast to data in the manufacturer’s product information that described an enhanced bioavailability of tipranavir when given with high-fat meals (868 kcal, 53% derived from fat, 31% derived from carbohydrates) with a 31% increase in AUC (1.23-1.39).

The most prudent recommendation until the complete data from this food effect study are available (and perhaps a regulatory agency review) is to continue with the recommendation to administer tipranavir/ritonavir with food.

## **Antiretroviral pharmacokinetics in special patient populations**

### **Hepatic impairment**

There are limited data on the appropriate dosing of antiretroviral drugs in patients with varying degrees of hepatic impairment.

Josep Mallolas presented a study evaluating fosamprenavir dosing and pharmacokinetics in HIV-infected subjects with mild and moderate hepatic impairment. [15]

Thirteen subjects with mild hepatic impairment (Child Pugh score 5-6) received fosamprenavir 700 mg twice daily plus ritonavir 100 mg once daily (Group A). Ten subjects with moderate hepatic impairment (Child Pugh score 7-9) received fosamprenavir 300 mg twice daily (as the oral suspension) plus 100 mg of ritonavir once daily (Group B). Eight subjects with moderate hepatic impairment received fosamprenavir/ritonavir 700/100 mg once daily (Group C). Ten patients with normal hepatic function received fosamprenavir/ritonavir 700/100 mg twice daily (Group D/controls). All subjects underwent intensive pharmacokinetic studies (including measurement of unbound amprenavir concentrations at two time points) two weeks after initiating fosamprenavir/ritonavir.

Patients in Group A had total amprenavir plasma AUCs 22% higher and Cmins that were similar to controls, but amprenavir unbound Cmin was 2-fold higher in patients in Group A vs. controls. Subjects in Group B had amprenavir AUC and Cmin 27% and 57% lower, respectively than controls, but the amprenavir unbound Cmin was similar for subjects in Groups B and D. Subjects in Group C had amprenavir AUC and Cmin 24% and 65% lower than controls, and unbound amprenavir Cmin that were 40% lower on average than controls.

The investigators concluded that the reduced ritonavir dose regimen of fosamprenavir 700 mg twice-daily plus ritonavir 100 mg once daily, is the appropriate dose for subjects with mild hepatic impairment. However, neither dosing strategy appeared adequate for subjects with moderate hepatic impairment. Thus, they speculate that fosamprenavir 450 mg twice daily plus ritonavir 100mg once daily would provide adequate exposures for patients with moderate hepatic impairment, though there are no pharmacokinetic or safety data with this dosing strategy.

The pharmacokinetics of maraviroc following a single 300 mg dose in subjects with mild and moderate hepatic impairment were compared to the pharmacokinetics in subjects with no hepatic impairment. [16]

Maraviroc AUC and Cmax were increased 25% and 11%, respectively in subjects with mild hepatic impairment relative to those with no hepatic impairment. Maraviroc AUC and Cmax were increased 46% and 32%, respectively in subjects with moderate hepatic impairment relative to those without hepatic impairment.

Further studies are necessary to determine if dose adjustments may be necessary for subjects with moderate hepatic impairment.

### **Renal impairment**

Sangeeta Agarwala presented a study evaluating the pharmacokinetics of unboosted atazanavir in persons with severe renal impairment including those on hemodialysis. [17]

This was an open-label, parallel design study with 3 groups (controls, severe renal impairment not on hemodialysis, and hemodialysis) of HIV negative subjects (n=10 per group). Subjects with severe renal impairment not receiving dialysis had atazanavir AUCs 19% higher than age, weight, and gender matched controls with normal renal function.

Subjects on hemodialysis had atazanavir AUCs 42% lower on dialysis days and 28% lower on non-dialysis days compared to controls. Though the mechanism for the reduction in atazanavir exposures in those on hemodialysis is not known, the investigators speculate that there may be decreased gastric acid production in hemodialysis patients.

These investigators (from Bristol Myers Squibb) commented that for patients receiving hemodialysis clinicians could consider using atazanavir/ritonavir to compensate for the reduction observed in this study in atazanavir concentrations. While the basis for this recommendation is understandable it is important to stress that no pharmacokinetic or safety data are available at this time to support this recommendation.

### **Pediatrics**

#### **Efavirenz pharmacokinetics in children**

David Burger described the pharmacokinetics, efficacy, and tolerability of efavirenz tablets and capsules when used in children ages 2-16 years and dosed per the weight-based manufacturer's guidelines. [18]

307 efavirenz plasma concentrations were obtained in 33 children. 8.8% of samples were less than 1000 ng/mL, while 14.7% of samples were greater than 4000 ng/mL. There was a trend towards a higher proportion of samples greater than 4000 ng/mL in the children who reported central nervous system adverse effects vs. those without these effects (p=0.23, 26 vs. 13%).

All 27 children who remained on efavirenz achieved viral loads of less than 50 copies/mL, despite the occasional presence of subtherapeutic concentrations in 12 of these children most likely due to sporadic non-adherence.

These data suggest that efavirenz tablets and capsules are effective in children who are able to tolerate the drug and provide some validation of the dosing guidelines for children contained in the manufacturer's dosing guidelines.

This study raises the question as to whether those children who had CNS adverse events and were found to also have efavirenz concentrations greater than 4000 ng/mL might have benefited from therapeutic drug monitoring and dose adjustment.

### **Ritonavir-boosted saquinavir formulations**

The United States Food and Drug Administration requested that Roche evaluate the pharmacokinetics of ritonavir-boosted saquinavir following opening the Invirase capsules and dissolving them in various vehicles in an attempt to find an acceptable means of administering the drug to children 4 months to 5 years of age.

Diane McKay presented an open-label, randomized, four period, crossover relative bioavailability study of this strategy in 27 healthy adult volunteers. [19]

Volunteers received ritonavir 100 mg as the oral solution plus Invirase® capsules either unopened (A), opened or suspended in simple syrup (B), baby formula (C), or jelly jam (D). The bioavailability of saquinavir was 10, 60 and 40% higher in simple syrup, baby formula, and jelly jam, respectively, relative to the unopened capsules. The next step is to evaluate this strategy in children. All three vehicles will be used in the studies with children.

### **Atazanavir/ritonavir and tenofovir in HIV-infected adolescents and young adults**

Children appear to have faster apparent oral clearances of tenofovir and atazanavir than adults. [20, 21] Additionally, there is a bidirectional interaction between these drugs. [22]

Jennifer Kiser presented data evaluating the interaction between atazanavir/ritonavir and tenofovir in HIV-infected adolescents and young adults. [23]

Atazanavir pharmacokinetics appeared similar to values observed in older adults on the combination (Taburet AM, AAC 2004;48(6):2091-6). Though a higher tenofovir AUC may have been expected based on a previous study in healthy volunteers receiving the combination, this was not observed in this study. Apparent oral clearance increased as weight increased for atazanavir, ritonavir, and tenofovir. Estimated creatinine clearance was also associated with tenofovir apparent oral clearance.

The geometric mean for intracellular tenofovir diphosphate concentrations in 22 subjects was 94 fmol/10<sup>6</sup> cells (63% CV) and were similar to that reported by Hawkins in a small number of patients (Hawkins T. JAIDS 2005;39(4):406-11).

### **Pharmacology of investigational drugs**

#### **Maraviroc and darunavir/r**

Maraviroc is a CYP3A4 and P-glycoprotein substrate, thus previous interaction studies have shown that a lower dose of maraviroc, 150 mg twice daily, should be used in combination with protease inhibitors (excluding tipranavir/ritonavir).

John Davis presented data on the interaction between maraviroc 150 mg twice daily and darunavir/ritonavir in 12 healthy volunteers. [24]

Maraviroc AUC and C<sub>max</sub> were increased 405% and 229%, respectively when combined with darunavir/ritonavir. This increase is consistent with other protease inhibitors and thus, the reduced 150 mg twice daily dose is recommended in combination with darunavir/ritonavir.

In this study, as has been the case with all maraviroc drug interaction studies, maraviroc is administered in the fasting state, approximately 1.5 hour prior to the dosing of the protease inhibitor in combination with food. Food decreases maraviroc concentrations by about 50%, however there are no data on the magnitude of these drug interactions when administered with food.

As more concentration-response data with this agent become available, it will be important to determine if the maraviroc concentrations achieved when taken in combination with other protease inhibitors and food fall within the therapeutic range for this drug. If so, that would eliminate the food incongruence between this agent and many other antiretroviral compounds.

#### **Vicriviroc**

Vicriviroc is an investigational CCR5 inhibitor. Charles Flexner presented data exploring the relationship between vicriviroc concentrations and antiretroviral effects. [25]

Two concentrations were obtained from 86 treatment experienced patients participating in a Phase II clinical trial of vicriviroc at doses of 5, 10, or 15 mg once daily in combination with ritonavir-boosted protease inhibitor regimens (Adult AIDS Clinical Trials Group study 5211). In this study, patients randomized to vicriviroc received the drug with their current failing antiretroviral regimens for two weeks, then patients continued on vicriviroc but their background regimen was optimized based on resistance test results.

The concentration data from these 86 patients were combined with intensive pharmacokinetic data from 110 healthy volunteers from five Phase I vicriviroc studies to develop a pharmacokinetic/pharmacodynamic model. At week 2, a C<sub>min</sub> above 54 ng/mL (the EC<sub>90</sub> for this drug is 56 ng/mL) and an AUC above 1460 ng\*hr/mL were associated with greater viral load decreases. This relationship was no longer apparent at weeks 16 or 24, most likely because treatment response at that point also depended on having other active drugs in the regimen.

Data were presented on the combination of vicriviroc and tipranavir/ritonavir in 8 healthy volunteers. [26]

Volunteers received vicriviroc 15 mg once daily plus ritonavir 200 mg twice daily for two weeks. Tipranavir 500 mg twice daily was then added for an additional two weeks. Vicriviroc AUC and C<sub>max</sub> were reduced 6% and 12%, respectively when combined with tipranavir/ritonavir, thus consistent with other ritonavir-boosted protease inhibitors, no vicriviroc dose adjustment is necessary.

### Apricitabine

Tipranavir/ritonavir reduces the concentrations of many nucleoside analogs. However, the AUC and C<sub>max</sub> of apricitabine, an investigational nucleoside analogue, are actually moderately increased by 40 and 25%, respectively by tipranavir/ritonavir. [27]

Adverse effects with the combination were mainly nausea, anorexia, headache, and elevated liver enzymes, which are consistent with the side effect profile of tipranavir/ritonavir. Additional studies of the safety of this combination and data on the intracellular concentrations of apricitabine (the active moiety of the nucleoside analogs) in combination with tipranavir/ritonavir are needed.

The pharmacophore of the HIV integrase inhibitors forms a complex with divalent cations (magnesium) at the active site of the integrase enzyme. This propensity for cation binding can result in an interaction with antacids at the level of drug absorption upon co-administration due to the high concentrations of di- and tri-valent cations in antacids.

### Antacids and elvitegravir

Thus the effect of simultaneous and staggered administration of antacids and elvitegravir (Gilead's investigational integrase inhibitor, also known as GS-9137) were presented. [28]

The effect of omeprazole 40 mg on elvitegravir absorption was also evaluated. The dose of elvitegravir used in this study was 50 mg with a 100 mg boosting dose of ritonavir administered once daily. Omeprazole did not alter elvitegravir absorption, thus this compound does not exhibit pH-dependent absorption. However, as expected, simultaneous administration of antacid reduced elvitegravir concentrations by about 50%. Separating the antacid by 2 hours only decreased elvitegravir concentrations by 10-20%, however elvitegravir concentrations were unchanged if separated by 4 hours.

Source: NATAP.org

Further coverage of the workshop is provided in additional reports posted to the NATAP website.

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## TREATMENT ACCESS

A round-up of articles related to treatment access news:

### G8 pledges to Africa are insufficient

Some HIV/AIDS advocates and other groups have criticized the recent pledges from the G8 industrialised nations to Africa as “insufficient” and “part of a pattern of unfulfilled promises”.

G8 leaders in the final communique issued at the close of their summit in Heiligendamm, Germany, agreed to provide more than \$60 billion to fight HIV/AIDS and address other issues in Africa. The document indicated the \$60 billion would be disbursed “over the coming years” but did not lay out a specific time frame.

Part of the funding includes \$6-8 billion for the Global Fund To Fight AIDS, Tuberculosis and Malaria. The communique also “recommits” to pledges made during the 2005 G8 summit in Gleneagles, Scotland, to increase aid to \$50 billion annually by 2010. Leaders also pledged to help reduce malaria prevalence and deaths in 30 African countries.

The \$60 billion will not be a “firm pledge” because “some countries are cautious about increased spending,” according to some diplomats. The final communique also includes the goal of providing five million HIV-positive people with drug access by 2010. Leaders announced a target of providing 10 million people with drug access by 2010 in the Gleneagles communique.

Some advocacy groups have said that G8 leaders have not fulfilled pledges made at Gleneagles concerning aid to Africa. Groups also said that the \$60 billion commitment is not enough to provide drug access in Africa, where 65% of the world’s HIV-positive people live. “The announcement of \$60 billion to tackle disease is not the increase promised in Gleneagles,” Kumi Naidoo, a member of the Global Call to Action Against Poverty, said, adding, “There is no time frame for delivery and a deliberate absence of detail. We are appalled by the lack of urgency they are showing”. Irish musician and HIV/AIDS advocate Bono said the communique was designed to hide the actual funding level, adding, “I understand if they think rock stars can’t add or subtract, or spell, or read. This maze is designed to lose us. But we are not lost; the G8 [is] lost”.

Aditi Sharma, head of the HIV/AIDS campaign for ActionAid, said, “Even this \$60 billion smoke screen can’t cover up for the abject failure of the G8 to move forward on [its] AIDS promises.” Kate Krauss, spokesperson for the U.S.-based Physicians for Human Rights, said that there “needs to be a plan for meeting the previous commits made at Gleneagles”.

German Chancellor Angela Merkel said that G8 leaders would meet their responsibilities to developing countries. According to Merkel, the \$60 billion is “not yet enough” because “Africa is not only a continent with many diseases, it is also a continent with many chances for the future”.

Source: kaisernetwork.org (11 June 2007)

[http://www.kaisernetwork.org/daily\\_reports/rep\\_index.cfm?DR\\_ID=45475](http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=45475)

For details of the G8 proposal and further links see:

[http://www.kaisernetwork.org/daily\\_reports/rep\\_index.cfm?DR\\_ID=45456](http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=45456)

### FDA approval of generic ARVs

Since the last issue of HTB, the US Food and Drug Administration (FDA) has granted approval for Zidovudine (AZT) 100mg caps Cipla Laboratories, India (23 May 2007).

This is a full approval and can be purchased and marketed in the US as AZT went off-patent in the US in 2006.

C O M M E N T

**This brings the total of FDA approved generic drugs and formulations to 42 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>

**Whilst generic approval has led to a wide range of NNRTI-based options for first-line therapy, including in paediatric formulations, the lack of protease inhibitors and second-line RTIs, or other drugs that would be effective in treatment experienced patients, is alarming.**

Source: FDA list serve:

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

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

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

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>

### **Abbott sues ACT-UP Paris**

Abbott laboratories, manufacturer of lopinavir/r (Kaletra) and ritonavir (Norvir) has filed a lawsuit against ACT-UP Paris for organising a web protest which encouraged other advocates to use software to repeatedly access the Abbott site.

This is part of the continuing issue of Kaletra pricing and the decision by to issue a compulsory license in order to produce generic lopinavir/r (see HTB 2007, issues 4 and 5). Abbott's decision not to register the new heat stable Kaletra in Thailand, or other new drugs, prompted widespread community criticism, including this web protest.

Abbotts already-dented community profile will not be improved by its decision to use its financial weight in the courts. This has prompted an even wider challenge from community organisations including those that generally do not support either ACT-UP's analysis or approach to global access or treatment issues.

The lawsuit is seen as bullying. Many peaceful demonstrations have the ability to reduce profits and they are chosen for this reason. The action should be withdrawn before more money is wasted in legal fees.

The Abbott website was affected for 'over 30 minutes' which clearly was a nuisance, but court costs alone could send ACT-UP into bankruptcy, irrespective of any claims for damages.

ACT-UP emphasise that websites are places for public access to information, and that any member of the public should be able to access any site, as often and as frequently as they want to.

[http://www.kaisernetwork.org/daily\\_reports/rep\\_index.cfm?DR\\_ID=45620](http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=45620)

### **UK's DFID support of Thailand**

In a letter to Sarah Walden of People and Planet, Gareth Thomas from the UK's Department for International Development (DfID) supported the decision by Thailand to issue a compulsory license for HIV medications.

The letter states "we continue to be a strong supporter of the right of developing countries, including Thailand, to implement the TRIPS agreement, and particularly of their right to use TRIPS flexibilities to ensure affordable access to medicines to meet public needs". It continued "we support Thailand's right to use compulsory licensing provisions in order to protect public health, and in particular to promote access to medicines for all" and added "we agree that Thailand's stated use of compulsory licensing provision has not broken any WTO rules...".

Source: letter from DfID to People and Planet (22 May 2007)

### **Roche's patent for hepatitis C drug challenged in India**

The Indian Patent Office has received a challenge against Hoffmann-La Roche's patent rights for the hepatitis C drug Pegasys.

Public interest groups have said that patent protection and the resultant high price of the drug is making it unaffordable for an estimated 12.5 million Hepatitis C infected people in India. The groups also argued that the product was not an innovation and hence not eligible for patent protection.

Sankalp, a Mumbai-based non-governmental organisation that provides treatment and rehabilitation support to injecting drug users, backed by a group of NGOs led by Lawyers Collective, filed the opposition with the Patent Office on May 18.

Absence of patent protection could help Indian pharmaceutical companies develop cheap reverse-engineered versions of Pegasys, it said.

Source: Business Standard (12 June, 2007)

[http://www.business-standard.com/search/storypage\\_new.php?leftnm=1&leftindx=1&subLeft=1&autono=287446](http://www.business-standard.com/search/storypage_new.php?leftnm=1&leftindx=1&subLeft=1&autono=287446)

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## SIDE EFFECTS

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### 30 cases of atazanavir-related kidney stones reported

Simon Collins, HIV i-Base

A review of atazanavir-related nephrolithiasis collected from case reports to an adverse events programme in the US was published as a research letter in the 31 July 2007 issue of the journal AIDS. [1]

Kirk Cahn-Tack and colleagues identified 30 cases of nephrolithiasis in HIV-infected patients taking an atazanavir-based regimen that had been reported to the Adverse Event Reporting System (AERS) of the US Food and Drug Administration (FDA) from December 2002 to January 2007. Many of these patients required hospitalisation for management, including lithotripsy, ureteral stent insertion, or endoscopic stone removal.

The AERS is a voluntary reporting system and the database contains spontaneous reports generated by health professionals, consumers, and manufacturers from the United States and other countries. [2]

The 30 cases (21 men, 5 women, 4 gender not reported) included two cases that have previously been published. [3, 4]

Five patients (17%) had underlying liver disease: four patients had hepatitis C (one with cirrhosis), and one patient had hepatitis B with cirrhosis. Three patients had pre-existing renal disease and five patients (17%) had a history of nephrolithiasis.

Of the 20 cases reporting complete antiretroviral information (medications and doses), 13 patients received concomitant tenofovir and 17 patients received 100 mg ritonavir. Among 14 cases reporting stone analysis, 12 had atazanavir confirmed by infrared spectrophotometry or other analysis. In six cases with available data, atazanavir concentrations in the stone ranged from 40 to 100%. In 17 cases with complete atazanavir treatment history, the median time between atazanavir initiation and the onset of nephrolithiasis was 1.7 years (range 5 weeks to 6 years).

Five patients developed renal insufficiency (four with acute renal insufficiency and one with a worsening of baseline chronic renal insufficiency) at the time of nephrolithiasis. In all four cases of acute renal insufficiency, renal function returned to baseline after stone removal and atazanavir discontinuation. In the patient who developed a worsening of baseline chronic renal insufficiency, renal function improved but had not returned to its previous baseline after stone removal. Only 9/30 patients discontinued atazanavir after nephrolithiasis was diagnosed.

The mechanism for the development of atazanavir-associated nephrolithiasis is unknown. Further information is needed to determine whether patients with pre-existing hepatic or renal impairment or a history of nephrolithiasis are at an increased risk of this event.

The researchers concluded that although the voluntary nature of these reports prevented an estimation of the likely prevalence or risk, healthcare professionals and patients should be informed that nephrolithiasis is a possible adverse event with atazanavir.

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### Tenofovir and indinavir associated with increased risk of chronic renal failure in EuroSIDA study

Simon Collins, HIV i-Base

Results from a cross-sectional analysis of chronic renal disease from a large European cohort were reported in the 13 May issue of AIDS. [1]

EuroSIDA is a prospective international study in patients from 24 European countries (plus Argentina and Israel) that has been running since 1994 and now includes over 14,000 patients and 51,000 years of follow-up. Routine collection of serum creatinine was only included in data collection from January 2004 and this analysis included all patients (n=4474) who had 2 or more serum creatinine measurements from January 2004.

Chronic renal failure (CRF) was defined as two consecutive glomerular filtration rate (GFR) < 60mL/min per 1.73sq using either Cockcroft-Gault (CG) or Modification of Diet in Renal Disease (MDRD), both adjusted for body surface area (BSA).

Using CG, the median GFR at baseline was 94.4 (IQR, 80.5-109.3).

158 patients (3.5%) had CRF using CG and 209 (4.7%) using MDRD. 101 (2.3%) had CRF using both measurements.

The researchers reported a high degree of correlation between CG and MDRD (0.773, p<0.0001) but this dropped to 0.518 if CG was not adjusted for BSA. CG generally gave higher readings, and the difference was greatest in the youngest patients. For patients aged <40 years the mean difference was 8.29 (95CI 7.33-9.25) and in patients aged over 50 years MDRD gave a higher value, mean difference 1.17 (95CI 0.27-2.07).

Patients with CRF were older (median 61.9 vs 43.1 years), had lower CD4 nadirs (median 80 vs 137 cells/mm<sup>3</sup>) and were more likely to be diagnosed with AIDS (44.3 vs 30.4%), diabetes (16.5 vs 4.3%) or hypertension (53.8 vs 26.4%), all p<0.001.

The relationship between CRF and use of antiretroviral and renal-toxic drugs was then examined.

Of 2118 patients never exposed to indinavir, 38 had CRF (1.8%) compared to 120/2356 (5.1%) of patients who had used indinavir. For tenofovir, these figures were 98/3213 (3.1%) and 60/1261 (4.8%) in the non-exposed and exposed patients respectively.

Details of antiretroviral drug use are included in Table 1.

**Table 1: Antiretroviral drug exposure in patients with CRF**

ARV	No. exposed	Approx % exposed with CRF	No. not exposed	Approx % not exposed with CRF
AZT	3977	2.0	497	3.7
ddC	1178	3.4	3296	3.8
ddl	2628	2.9	1846	4.0
d4t	4137	1.5	337	3.7
3TC	2923	2.6	1551	4.0
abacavir	1751	2.9	2723	4.5
tenofovir	1261	3.1	3213	4.8
nevirapine	1692	3.3	2782	4.0
efavirenz	2043	3.5	2431	3.6
saquinavir	1563	3.0	2911	4.5
indinavir	2356	1.8	2118	5.1
ritonavir	823	3.3	3651	4.1
RTV (any PI)	2457	2/8	2017	4.1
nelfinavir	1593	3.3	2881	4.0
fosamprenavir	373	3.4	4101	4.6
lopinavir	1332	3.5	3142	3.4
atazanavir	360	3.3	4114	6.1
tipranavir	65	3.5	4409	3.1
T-20	112	3.6	4362	1.8
Any TDF+RTV	804	3.2	3670	4.8

Any use of indinavir (OR, 2.49) or tenofovir (OR, 2.18) was associated with increased odds of CRF, and results are detailed below in Table 2. Similar results were found when the analysis was repeated looking at duration of exposure to ARVs. Each additional year of exposure to indinavir increased the risk of CRF at baseline by 15% (OR, 1.15; 95CI 1.05-2.24; p = 0.0013), and to tenofovir by 60% (OR, 1.60; 95CI 1.20-2.15; p=0.0015).

Use of ritonavir, as single or part of boosted PI regimen, including with tenofovir had no increased risk. T-20 use showed a decreased risk.

**Table 2: Multivariate analysis of factors associated with confirmed GFR< 60 (CG)**

	OR	95% CI	P
E Europe vs rest	2.45	1.35-4.45	0.0033
Prior AIDS vs none	1.34	0.88-2.02	0.17
Age (per 10 yrs older)	5.47	4.45-6.72	<0.0001
CD4 nadir (per 50% higher)	0.90	0.82-0.99	0.028
Viral load (above 500 vs lower)	1.54	0.98-2.41	0.062
Baseline (per 12 mo later)	1.65	1.04-2.62	0.033
Hypertension	1.34	0.92-1.95	0.12
Any TDF use	2.18	1.25-3.81	0.0061
Any IDV use	2.49	1.62-3.83	<0.0001
Any t-20 use	0.13	0.03-0.65	0.013
Any RTV use (single PI)	0.77	0.39-1.50	0.44
Any RTV (2 or more PI regimen)	0.89	0.56-1.43	0.64
Any TDF/RTV use	1.27	0.82-1.98	0.29
Any renal-toxic drug *	1.47	0.94-2.30	0.089

\* acyclovir, pentamidine, foscarnet, cidofovir or amphotericin B.

There was a significantly greater proportion of patients with CRF at baseline that had used renal-toxic drugs (pentamidine, cidofovir, foscarnet). These differences are detailed in Table 3.

**Table 3: Proportion of patients with baseline CRF by exposure to renally toxic drugs**

	% exposed	% not exposed	p
Any renal drug exposure	27.2%	15.9%	<0.0001
Pentamidine	15.8%	9.6%	0.010
Cidofovir	3.8%	0.5%	<0.0001
Foscarnet	26.0%	15.1%	0.063

The study provided important information on the use of CG and MDRD calculations and the importance of adjusting for BSA. For patients identified as being at higher risk, the use of more sensitive tests including estimating urinary clearance of IV-infused insulin or labeled tracers with timed urine collection is recommended.

The authors noted several limitations to cross-sectional analysis including the relatively recent decision to measure creatinine, the impossibility of showing whether CRF occurred before or after exposure to drugs, and whether it was a consequence of exposure to individual drugs, and the impact of other factors that cannot be adjusted for (such as use of NSAIDs, and that choice of ARV treatment was not randomised).

#### C O M M E N T

Future analysis are planned in order to provide longitudinal analyses from this database.

This should also include analyses for patients at highest risk, and with overlapping risk factors (previous AIDS, use of nephrotoxic drugs, age, and use of indinavir and tenofovir etc) in order to consider risk and impact of using nephrotoxic and renally cleared drugs in these patients.

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## PREGNANCY AND MTCT

### Antiretroviral therapy and premature delivery in the United Kingdom and Ireland

Polly Clayden, HIV i-Base

Prematurity has been associated with use of antiretroviral therapy in pregnancy in some studies, but not in others.

A paper, authored by Claire Townsend and co-workers, published in the 11 May 2007 edition of AIDS, explored the association between antiretroviral therapy in pregnancy and premature delivery, birthweight, stillbirth and neonatal mortality, in pregnancies in HIV-positive women delivering between 1990 and 2005 in the UK and Ireland. [1]

Surveillance of obstetric HIV infection in the UK and Ireland, is performed by the National Study of HIV in Pregnancy and Childhood (NSHPC).

Over the study period 5009 pregnancies were reported with an overall rate of prematurity of 13.3% (667/5009). 494 pregnancies were in untreated women and these were excluded from the analysis.

Of the 4445 pregnancies with antiretroviral exposure, most deliveries were by planned caesarean section and the median gestational age was 38 weeks (IQR, 38-39). Most women received HAART in pregnancy, (3384/4445; 76.1%) and this was more frequently NNRTI than PI containing regimens.

The overall prematurity rate (defined as <37 weeks gestation) was 13.1% (583/4445; 95% CI 12.1-14.2); 51.8% (302/583) were at <35 weeks including 23.3% (136/583) at <32 weeks.

The investigators reported a higher rate of prematurity in women receiving HAART, (14.1%, 476/3384) than in women on mono/dual therapy (10.1%, 107/1061), even after adjusting for ethnicity, maternal age, clinical status and injecting drug use as the route of HIV acquisition, AOR, 1.51 (95% CI, 1.19-1.93;  $p = 0.001$ ). Delivery at <35 weeks was even more strongly associated with HAART, AOR, 2.34 (95% CI, 1.64-3.37,  $p 0.001$ ). The effect was the same whether or not HAART included a PI.

In comparison with exposure to mono/dual therapy, exposure to HAART was associated with lower birthweight ( $p < 0.001$ ), and an increased but not significant risk of stillbirth, AOR, 2.27 (95% CI, 0.96-5.41,  $p = 0.063$ ).

The authors suggest that their findings raise important questions about the type of treatment used for pregnant women, and in particular, for those not needing HAART for their own health and they write: "Although the beneficial effects of antiretroviral therapy on mother-to-child transmission are indisputable, monitoring antiretroviral therapy in pregnancy remains a priority."

#### C O M M E N T

The evidence that suppressive antiretroviral therapy is associated with pre-term delivery (PTD) continues to accumulate. In this UK cohort, spanning 15 years and a variety of therapies, HAART is associated with a 1.5 times increased risk of PTD compared with mono or dual therapy. Recently a 1.8 fold increase in PTD with PI-containing HAART was reported from Miami [2], and an almost 2 fold risk with HAART from Holland [3] supporting the original reports from the European Collaborative and Swiss Studies. [4, 5]

Whilst for many, if not the majority of, mothers HAART is required either for maternal health or for the prevention of HIV mother to child transmission, especially when maternal viral load is high, the authors' conclusions suggest that the use of HAART in all pregnancies may be inappropriate.

It is important to note that in more than 50% the PTD occurred before 35 weeks and in more than 20% before 32 weeks. With increasingly early deliveries neonatal morbidity and mortality increases and survival becomes linked to the availability of resource intense facilities.

The subgroup of mothers for which less intense antiretroviral therapy is most appropriate is likely to vary according to local circumstances, but defining this group is important.

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## Early response to NNRTI-based antiretroviral therapy among women with prior exposure to single-dose nevirapine

Polly Clayden, HIV i-Base

A Zambian study authored by Benjamin Chi and co-workers, published in the 11 May 2007 edition of AIDS, evaluated outcomes for women receiving NNRTI-containing HAART after prior exposure to single dose nevirapine (NVP) from April 2004 to 31 July 2006. This was an open cohort evaluation in programme sites across Zambia.

In this study of 6740 women initiating NNRTI-containing ART, 751 (11%) reported prior use of NVP for PMTCT.

The investigators found of the 229 NVP-exposed and 1530 NVP-unexposed women for whom CD4 data were available at baseline and at 6 months, the mean increase was 202 cells/mm<sup>3</sup> and 182 cells/mm<sup>3</sup> respectively,  $p=0.20$ . At 12 months for the 110 NVP-exposed and 659 NVP-unexposed with data available, the mean increase was 201 cells/mm<sup>3</sup> and 211 cells/mm<sup>3</sup>,  $p=0.60$ .

Multivariable analyses showed no significant differences in mortality (adjusted HR, 1.2; 95% CI, 0.8-1.8) or clinical treatment failure (adjusted HR, 1.1; 95% CI, 0.8-1.5).

434 (58%) NVP-exposed women had timing data available from NVP-exposure to initiation of therapy. The median interval time was 15.6 months (IQR 7.5-29.9). Of this group, 81 (19%) were exposed within 6 months prior to initiation of therapy. The remaining 353 (81%) reported remote (defined as 6 months or greater) NVP exposure prior to initiation of therapy.

Comparison of recent NVP exposure with remote exposure suggested a less favorable CD4 cell response at 6 months (+150 versus +219 cells/mm<sup>3</sup>;  $p=0.06$ ) and 12 months (+149 versus +215 cells/mm<sup>3</sup>,  $p=0.39$ ) months. Women with recent NVP exposure also had a trend towards increased risk for clinical treatment failure (adjusted HR, 1.6; 95% CI, 0.9-2.7).

Exposure to maternal single-dose NVP was not associated with substantially different short-term treatment outcomes in this study. However, evidence was suggestive that exposure within 6 months of ART initiation may be a risk factor for poor treatment outcomes.

The investigators acknowledged the limitations of this study, including the short duration of follow up; they suggest longer periods (2 years or more) may be needed for comparisons to manifest. Additionally, viral load data would allow a more critical evaluation of this question and the study relies on self-report of NVP exposure. Finally, although this is one of the largest cohorts yet available to look at this question, the sample may still be too small to detect subtle differences in survival or treatment failure.

They write. "In the meantime, links between PMTCT and ART services should be strengthened so that women requiring ART start therapy prior to delivery and thus avoid treatment initiation following NVP exposure occurring less than 6 months previously."

### C O M M E N T

**The authors are absolutely right - the short follow up and lack of viral load and resistance data make it difficult to comment on what this means for those mothers who have already taken sdNVP alone for PMTCT and have deferred starting NVP based HAART for at least 6 months.**

**The recommendation is that links between PMTCT and ART services should be strengthened, so that women who require treatment for their own health receive it in pregnancy cannot be stressed more and is echoed in findings from many other cohorts.**

Ref: Chi B H, Sinkala M, Stringer E M et al. Early clinical and immune response to NNRTI-based antiretroviral therapy among women with prior exposure to single-dose nevirapine. AIDS. 21(8):957-964, May 11, 2007.

## Mother to child transmission during exclusive breastfeeding

Polly Clayden, HIV i-Base

Breastfeeding remains an important route of mother to child transmission.

A study by Coovadia and co-workers, published in the 31 March 2007 issue of the Lancet, assessed the HIV transmission risk and survival associated with exclusive breastfeeding, and mixed breastfeeding and formula feeding among a cohort of women and infants attending antenatal clinics in Kwazulu Natal, South Africa.

This was a non-randomised intervention cohort study in which 2722 HIV-positive and HIV-negative women were enrolled. Infant feeding data were obtained weekly from mothers and samples taken monthly from infants for HIV testing. Of the infants born to HIV-positive mothers, complete feeding data were available for 1276.

The median duration of exclusive breastfeeding for women who initiated breastfeeding and whose infants had HIV diagnosis

results available (n=1034) was 159 days (IQR, 122-174 days). 847 women (82%) reported exclusively breastfeeding for at least six weeks, 688 (67%) for at least 3 months and 415 (40%) for 6 months.

The investigators reported, of the exclusively breastfed infants, 175 had been diagnosed with HIV before 6 months of age. Kaplan-Meier survival analysis, conditional on exclusive breastfeeding, found cumulative infection rates were 14.1% (12.0-16.4) at 6 weeks of age, 18.1% (15.8-20.8) by 4 months, 18.6% (16.2-21.4) by 5 months and 19.5% (17.0- 22.4) by 6 months.

Of 723 exclusively breastfed infants who were uninfected at or after 6 weeks the estimated risk of infection was 1.1% (0.28-1.84) after 1 month, 2.2% (1.05-3.34) after 2 months, 2.7% (1.44-4.02) after 3 months, 3.3% (1.88-4.77) after 4 months and 4.0% (2.29-5.76) after 5 months (ie at about 6 months of age).

For infants who were HIV-negative at or after 6 weeks the overall transmission rate per 100 child-days, including infants who were replacement fed and those with missing data excluded was 0.032 (0.0222-0.0455). This rate varied from 0.0290 (0.0195-0.442) for 100 days of exclusive breastfeeding and 0.0436 (0.0208-0.0915) for breastmilk plus other foods or fluids. The investigators noted that this result equates to an estimated risk of 10.72 per 100 child-years of exposure to exclusive breastfeeding (or 0.89% per child month). With exclusive breastfeeding as reference they found the hazard ratio for breastmilk plus other fluids was, HR 1.56 (0.66-3.69, p=0.308). Infants who were breastfed but also received solid foods at any time were nearly 11 times more likely to become HIV infected than exclusively breast fed children, HR,10.87, 1.51-78.00, p=0.018. Numbers in non-exclusive breastfeeding categories however were small. The proportions of infants with HIV test results available who were fed a mixture of breastmilk and other fluids at 6 weeks, 3 months and 6 months were 3.8%, 5.75 and 15.4% respectively.

Transmission risk was strongly associated with maternal CD4 count <200 cells/mm<sup>3</sup>, HR 3.79 (2.35-6.12), p=<0.001 (and less strongly with maternal age, birthweight below 2500g, vaginal delivery and long duration of ruptured membranes). Estimated transmission at 6 months in exclusively breastfed women born to women with <200 cells/mm<sup>3</sup> and >200 cells/mm<sup>3</sup> were 34% and 17% respectively. Data for single dose nevirapine were inconsistent and not included in the analysis.

In multivariate analysis only infant HIV status was significantly associated with greater infant mortality risk. HIV positive infants were 15 times more likely to die than HIV negative children (HR, 15.28, 9.20-25.40, p<0.0001). In multivariate analysis, in a model that included infant HIV status, the only significant factor was maternal CD4 count. Infants born to mothers with CD4 count 200-500 cells/mm<sup>3</sup> were almost twice as likely to have died, HR 1.89, 1.16-3.08, p=0.011, than those born to mothers with CD4 count >500 cells/mm<sup>3</sup>. Those born to mothers with a CD4 counts <200 cells/mm<sup>3</sup> were more than three times likely to have died, HR, 3.19, 1.73-5.88, p=0.0001.

Infants born to mothers with CD4 counts <200 cells/mm<sup>3</sup> were nearly four times more likely to be HIV positive or die than those born to mothers with CD4 cell counts >500 cells/mm<sup>3</sup>. Those born to mothers with CD4 counts between 200 and 500 cells/mm<sup>3</sup> were 2.2 times more likely to acquire HIV or die.

#### C O M M E N T

Important lessons from this study are that 1) high rates of exclusive breast feeding can be achieved with adequate support, 2) mixed feeding with early introduction of solids greatly increases the risk of HIV transmission (HR 10.87) and 3) HIV-infected babies were 15 times more likely to die than uninfected infants.

Additionally, the study found increased early mortality associated with exclusive replacement feeding at 3 months in a small group (15% vs 6%) but that the gap narrowed by 6 months if HIV-free survival is the goal.

An important limitation of the study is the lack of data beyond 6 months, when, as reported in HTB (May 2007), a number of studies have shown high morbidity rates after weaning which seem also to be associated with the increased mobility of the infant. Additionally the effect of HIV-related infant mortality and morbidity will be clearer. Hopefully, further data from this cohort will cover this period. The study supports both the use of exclusive formula feeding (replacement feeding) where resources allow this to be conducted safely as well as exclusive breast feeding rather than mixed breast-feeding in other settings and identifies the need to target resources at the most vulnerable mother-infant pairs ie those with maternal CD4 counts less than 200.

Ref: Coovadia HM, Rollins NC, Bland RM et al. Mother- to-child-transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life; an intervention cohort study. The Lancet, Vol 369; 31 March 2007.

## **Surveillance of mother-to-child-transmission programmes: the case for universal screening**

**Polly Clayden, HIV i-Base**

A paper in June AIDS authored by Nigel Rollins and coworkers shows data first presented at World AIDS Conference in Toronto describing mother-to-child transmission in Kwazulu Natal, South Africa. [1, 2]

In the introduction, the authors write: "In spite of substantial financial and human resource investments in prevention of mother-to-child transmission of HIV (PMTCT), it remains unclear to what extent these programmes have reduced the number of children becoming infected or dying with HIV each year."

In this study, routine, anonymous, unlinked, HIV prevalence testing was performed on infants with consenting parents or guardians, attending 6-week immunisation clinics at seven primary health care clinics offering PMTCT services. Dried blood spot (DBS) samples were collected on filter paper and tested for HIV antibodies (maternal) using a commercial ELISA. DBS samples of infants that were antibody positive were then tested for HIV RNA by PCR. The mothers also answered questions about any previous pregnancies and whether the child was alive or dead.

There were 2489 infants aged 4-8 weeks in the transmission analyses.

The investigators reported the detection of HIV antibodies, in 931 infants (37.4%; 95% CI, 35.5–39.4%). Maternal prevalence rates varied with maternal age: 20.8% (95% CI, 17.7–24.2%) in mothers aged 16–20 years, which was significantly lower than that in women aged 20–29 years (45.5%; 95% CI, 42.7–48.3%),  $p < 0.001$ , or women more than 30 years (38.0%; 95% CI, 33.9–42.2%); the higher prevalence in 20–29 year old women compared with women  $> 30$  years was also statistically significant,  $p = 0.003$ .

Overall, 931 infants were HIV-exposed and 188 were HIV-positive, giving a transmission rate of 20.2% (95% CI, 17.8–23.1).

Of the mothers who reported being HIV-positive, 93% also reported taking nevirapine (NVP).

Amongst mothers reporting NVP use the transmission rate was 15% (95% CI, 11.9–18.6) compared to 26.0% (95% CI, 21.9–30.3%) in mothers who did not report having taken NVP. The transmission rate among women who reported themselves HIV-positive was 15.6% (95% CI, 12.5–19.1%); among mothers who reported themselves as HIV-negative but whose infants were antibody positive the transmission rate was 30.5% (95% CI, 24.0–37.6%).

In univariate analysis, reported NVP use was significantly associated with lower transmission rates (OR, 0.50; 95% CI, 0.36–0.70,  $p < 0.001$ ). Home delivery was associated with twice the transmission risk compared with clinic delivery (OR, 1.97; 1.04–3.71),  $p = 0.037$ , but the difference between home and hospital delivery was not significant (OR, 0.86; 95% CI, 0.57–1.29),  $p = 0.466$ . HIV-positive mothers who attended antenatal clinic on more than three visits had less transmission (OR, 0.67; 95% CI, 0.43–1.02), although this did not reach statistical significance,  $p = 0.064$ .

In multivariate analysis, reported non-use of NVP and home deliveries remained significantly associated with increased MTCT risk.

There were also 172 mothers (6.9% of the total) who reported themselves as HIV-negative but whose infants were found to be antibody positive.

In the discussion the authors make the case for universal screening of infants at immunisation clinics. They write: "Conventional monitoring and evaluation of PMTCT programmes usually report on process indicators such as the quality of counselling or intermediate outcomes such as the number of mothers or children receiving prophylaxis."

However, these are no guarantee of decreased transmissions or improved survival." And they suggest that, "Linked HIV testing of all 6-week-old infants at immunisation clinics could identify infected infants at an early stage and give maximum opportunity for protecting their health. It would also offer the mother another chance to learn her own status and gain access to care and treatment."

#### References

1. Rollins N, Mzolo S, Little K et al. HIV prevalence rates amongst 6 week old infants in South Africa: the case for universal screening at immunization clinics. XVI International AIDS Conference, Toronto, Canada. 13-18 August 2006. Oral abstract THAC0104.
2. HIV prevalence rates amongst 6 week old infants in South Africa: the case for universal screening at immunisation clinic. HTB October 2006.
3. Rollins N, Little K, Similo Mzoloa S et al. Surveillance of mother-to-child transmission prevention programmes at immunisation clinics: the case for universal screening. AIDS 2007, 21:1341–1347.

## **Rapid progression in infants infected with HIV despite single dose nevirapine prophylaxis**

**Polly Clayden, HIV i-Base**

A paper in AIDS authored by Wendy Mphatswe and coworkers reported findings from a study conducted in KwaZulu Natal, South Africa, to evaluate MTCT in a cohort of mothers and infants receiving single-dose NVP and disease progression in a subset of infants that were HIV-positive despite the NVP prophylaxis.

The infants form part of a study designed to assess the feasibility of ART delivery and to compare immediate versus delayed ART in early infancy.

In the study HIV-positive infants were randomised at enrolment (2:1) to immediate versus delayed ART (the results will be reported upon completion of the study). This report looks at transmission across the whole cohort and also the natural history of disease progression in the 20 infants randomised to delayed ART.

Infants were tested (whole blood) on days 1 and 28 to establish intrauterine (IU) and intrapartum (IP) infection. Follow up included monthly viral load and CD4 cell measurement. ART was initiated at infant CD4% of 20% in infants randomised to deferred treatment.

A total of 740 babies born to 719 HIV-positive mothers between July 2003 and September 2005 were included in the MTCT analysis. The investigators reported 75 transmissions at time of analysis, giving an overall MTCT rate of 10.3% (69% IU, 31% IP). The calculated IU MTCT rate was 7.1% and the IP MTCT rate 3.2%.

They found the median viral load in mothers of HIV-positive infants was higher than in mothers of HIV-negative infants (99,650 vs 26,750 copies/mL,  $p < 0.001$ ). Median viral load was higher in mothers of IP-infected than IU-infected infants (279,000 versus 86,600 copies/mL,  $p = 0.039$ ). Viral loads in mothers of both groups of infected infants were significantly higher than in mothers of uninfected infants (IU vs no transmission,  $p = 0.002$ ; IP vs no transmission,  $p < 0.001$ ).

Additionally median CD4 cell counts in mothers of IP-infected infants were significantly lower than in mothers of uninfected infants (200 vs 394 cells/mm<sup>3</sup>,  $p < 0.001$ ). Those in mothers of IU-infected infants were lower than those in mothers of uninfected infants (327 versus 394 cells/mm<sup>3</sup>,  $p = 0.05$ ).

Viral load data were analysed from both the 20 infants randomised to deferred ART and from the 43 randomised to immediate ART before treatment was initiated. The median viral load of IU-infected infants on day 0–1 was 155,000 copies/mL and 6,510 copies/mL at confirmatory testing (median day 5).

Where the timing of infant NVP administration was recorded (59/61 IU infected infants), this was a median 5 days before the confirmatory test and was, likely to have caused the fall in viral load in the first week of life. The investigators noted that in 13/34 (38%) infants, this day 5 viral load was beneath the limit of detection (3.6 log<sub>10</sub> or 4000 copies/mL) that would have been measured had the analysis used dried blood spots (50mL whole blood) and in one infant was undetectable (<50 copies/mL).

Concerning this the investigators wrote: "The NVP-induced 25-fold reduction of viral load in IU-infected infants in the first days of life is of significance where filter paper methods of HIV diagnosis using dried blood spots are employed." They suggest that, "Collection of dried blood spots should, therefore, either be undertaken prior to infant NVP administration or delayed until the potential effects of NVP have passed in order to reduce under diagnosing of IU-infected infants. Use of dried blood spots testing to diagnose IP infection at day 28 does not suffer from the same limitation."

In IP-infected infants the first median viral load (day 28) was higher than in IU-infected infants (585,000 vs 155,000 copies/mL). The highest viral load in the first 6 months of life, was significantly higher in IP-infected infants than in IU-infected infants (5,160,000 vs 984,000 copies/mL,  $p < 0.001$ ).

In the group of 20 infants randomised to deferred treatment the median CD4 cell% at birth was 47% and 7 infants (35%) had progressed to a CD4% of 20% by 3 months; this increased to 14 (70%) by 6 months and 16 (80%) by 1 year. Time to CD4% 20% was directly related to maternal CD4 cell count,  $r = 0.51$ ,  $p = 0.02$ , Spearman.

The investigators wrote: "It is critical, therefore, that women have access to CD4 cell count testing in pregnancy and that ART is made available for women with advanced disease, both to improve their own health and to prevent transmission more effectively than current perinatal regimens."

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C O M M E N T

**Again these authors are absolutely right!**

Ref: Mphatswea W, Blanckenberg N, Gareth Tudor-Williams G et al. High frequency of rapid immunological progression in African infants infected in the era of perinatal HIV prophylaxis. *AIDS* 2007, 21:1253–1261.

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## HEPATITIS COINFECTION

### Schering's pegylated interferon approved for treating hepatitis C in HIV coinfecting patients

On 25 June 25, 2007, Schering-Plough announced that the European Commission has approved combination therapy with Pegintron (peginterferon alfa-2b, 1.5 mcg/kg once weekly) and Rebetol (ribavirin, 800 – 1,200 mg daily) for the treatment of previously untreated adult patients with chronic hepatitis C who are coinfecting with clinically stable HIV.

The European Commission approval results in Marketing Authorization with unified labeling that is valid in the current European Union (EU) 27 member states as well as in Iceland and Norway.

Although already widely used in coinfecting patients earlier EU approval in March 2001 was for treating adult patients with chronic hepatitis C alone.

Approval was based on the results of two published clinical studies in previously HCV untreated adult patients. [1, 2] Duration of treatment in HCV/HIV coinfecting patients is 48 weeks, regardless of HCV genotype.

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C O M M E N T

**For approval in coinfecting patients to come more than 5 years after the original indication highlights the delay that coinfecting patients face in access to new treatments for hepatitis C, which was recognised in a recent EU concept paper. [3]**

Source: Schering-Plough press release (06/25/07). Pegintron and Rebetol combination therapy approved in European Union for treating hepatitis C in patients coinfecting with HIV.

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

References:

1. Carrat F, Bani-Sadir F, Pol S et al. JAMA 2004; 292(23): 2839-2848.
2. Laguno M, Murillas J, Blanco J et al. AIDS 2004; 18(13): F27-F36.
3. Concept paper for clinical development of medicinal products for the treatment of hepatitis C infection (26 April). Ref: EMEA/CHMP/EWP/156308/2007

### **i-Base guide to HIV and hepatitis C coinfection in English and Russian**

HIV i-Base have produced a new non-technical guide for people living with HIV and hepatitis C.

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.

A Russian translation of this guide is also available to download from the i-Base website.

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## **OTHER NEWS**

### **Campaign launched for HIV-positive people denied access to stay in the UK**

The African HIV Policy Network (AHPN) has launched a new campaign to highlight the situation of HIV-positive people in the UK who are being deported to countries where they have little or no chance of accessing HIV treatment.

There is a clear contradiction between this policy and the UK's policy aim of universal access to HIV treatment for all those who need it by 2010. The withdrawal of treatment increases the body's vulnerability to opportunistic infection and will result in drastically shortened life expectancy.

The AHPN believes that there are strong public health arguments for allowing a concession. Those awaiting removal may go underground and fail to keep appointments resulting in an increased risk of opportunistic infection with the need for emergency treatment and an increased risk of onward transmission. The Department of Health has valued the prevention of one single onward transmission as between £500,000 and £1 million in terms of individual health benefits and treatment costs.

The AHPN's 'Destination Unknown' Campaign is calling on the Home Office to delay the deportation of people living with HIV from the United Kingdom until antiretroviral treatment becomes more widely available.

The AHPN is also asking MPs to support the campaign by endorsing Early Day Motion 1556.

Please write to your local MP and encourage others (friends, colleagues, service users) to do likewise. If you are not sure who your local MP is, you can access this information at:

<http://www.parliament.uk/people/index.cfm>

You can then check if they have already signed the EDM by going to the EDM website:

<http://edmi.parliament.uk/EDMi/EDMDetails.aspx?EDMID=33357&SESSION=885>

For further information see the AHPN website:

[http://www.ahpn.org/campaigns/index.php?camp\\_id=7](http://www.ahpn.org/campaigns/index.php?camp_id=7)

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## ON THE WEB

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### *Meeting abstracts and reports:*

#### **XVI International Workshop on HIV Drug Resistance**

The abstract book from this important meeting is now online:

[http://www.informedhorizons.com/resistance2007/pdf/AbstractBook\\_RW2007\\_final.pdf](http://www.informedhorizons.com/resistance2007/pdf/AbstractBook_RW2007_final.pdf)

#### **Statistical and Epidemiological Issues in HIV Research Workshop**

Posters and presentations from the 2007 Statistical and Epidemiological Issues in HIV Research Workshop are available on the Forum for Collaborative HIV Research website:

<http://www.hivforum.org/projects/Statistical%20Epi.htm>

#### **Report on Expanded Access Programmes**

The Forum for Collaborative HIV Research have published a new report: Re-thinking approaches to Expanded Access Programmes. This report is available to download in PDF format:

<http://www.hivforum.org/uploads/EAP/EAP%20Final%20Report.pdf>

Presentations and other information associated with this project are available at:

<http://www.hivforum.org/projects/Expanded%20Access.htm>

### *Journal articles and online resources:*

#### **PLoS medicine**

##### **Scales of CD4+ T cell depletion in HIV infection**

<http://medicine.plosjournals.org/perlserv/?request=getdocument&doi=10.1371/journal.pmed.0040193>

##### **Understanding the slow depletion of memory CD4+ T cells in HIV infection**

<http://medicine.plosjournals.org/perlserv/?request=getdocument&doi=10.1371/journal.pmed.0040177>

#### **HIV inSite Knowledge Base**

Resources updated in June 2007

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

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

##### **Policy issues in AIDS vaccine development**

<http://hivinsite.ucsf.edu/InSite?page=kbr-08-01-11>

##### **Voluntary counseling & testing (VCT) for HIV**

<http://hivinsite.ucsf.edu/InSite?page=kbr-07-01-04>

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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.

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

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.

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

### **Photography by Wolfgang Tillmans**

A meeting organised by i-Base 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.

## **Treatment training for advocates**

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

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

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

<http://www.nkplus.org>

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

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

The CAB has a separate website, where reading material, reports and presentations from these meetings are posted. The 21st meeting was on Friday 20 April, and focused on two subjects: integrase inhibitors, and African-specific treatment issues.

<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: 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.

## **NEW: 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.

## **Introduction to combination therapy** June 2006 edition

This non-technical patient guide to treatment is available in 12 languages. It explains what combination therapy is, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and how to avoid drug resistance.

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

## **NEW: Guide to HIV, pregnancy & women's health** June 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**

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

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

In addition, pdf files of some of the translated publications are available on the i-Base site. Please be aware that some of these translations are from earlier editions of the treatment guides, and check the publication date before relying on all information.

<http://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 PDF File [360 Kb]

### **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

Introduction to combination therapy - Nov 01

### **Hindi**

Treatment training for advocates: a manual - 2006

Introduction to combination therapy - 2006

Guide to Changing treatment - 2006

Avoiding & managing side effects - 2006

HIV, pregnancy & women's health - 2006

### **Indonesian**

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Further treatment information in Indonesian

<http://www.spiritia.or.id>

### **Italian**

Introduction to combination therapy - Jun 06

Avoiding & managing side effects - Oct 03

Changing treatment - Oct 03

HIV, pregnancy and women's health – Jun 04

### **Macedonian**

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### **Nepali**

Treatment training for advocates: a manual - 2006

Guide to Starting Treatment - 2006

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Introduction to combination therapy - 2007

### **Spanish**

HIV, pregnancy and women's health - May 06

Avoiding & managing side effects - Nov 02

Introduction to combination therapy - Nov 00

## **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 we need to have an abortion?
- Should I get treatment in Manchester or London?
- Can people with Black skin use New-Fill?
- What does a viral load of 2.8 mean?
  - Is general weakness and other symptoms related to HIV or starting meds?
  - I'm HIV-positive and want to know how often should I have sex with my girlfriend?
  - I'm worried that a reaction to antibiotics are symptoms of HIV
  - Can switching to Atripla from Sustiva + Truvada explain a drop in my CD4 count?
  - Is it possible to have sex with someone with HIV and not catch the virus?
  - Can I safely keep chickens?
  - Can I wait 2 weeks to see my doc? My first CD4 count came back at 266.
  - Question about travel vaccinations to Egypt
  - How reliable is the DUO HIV test?
  - Is it mandatory to take prophylaxis against PCP?
  - Why does my CD4 count vary on treatment? Can I do anything to keep it higher?
  - Newly diagnosed in Ireland
  - My CD4 count is 568. Can I increase it without treatment?
  - Do Truvada and Sustiva cause weight loss?
  - What is the safe window period to take HIV drugs? How can I help my partner adhere?

- I still have severe side effects after 6 months on efavirenz (Sustiva) - should I switch?
- What is the outlook for my girlfriend who has a CD4 count of 101?

## 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.

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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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## *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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