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EDITORIAL

This issue of HTB includes reports from the 7th International Workshop on Clinical Pharmacology of HIV Therapy that was held in April in Lisbon.

This meeting included important data with clinical implications both for practice in the UK and other industrialised countries, and for resource limited settings. We also report findings from children's studies, as PK data of antiretroviral drugs in children are generally scant.

This issue also includes a special report on the use of autologous stem cell transfer (ASCT) in HIV-positive patients, and treatment access coverage on the opposition to Gilead's patent application on tenofovir in India by organisations representing people living with HIV/AIDS.

Included with the distribution of this issue is a copy of the June 2006 edition of i-Base 'Introduction to Combination Therapy'. This is a non-technical guide and is available free in bulk to organisations and clinics in the UK.

Main changes to this edition include updated information on recently approved ARVs and an updated section on Treatment Interruptions following the early SMART study results.

Please order using the fax-back form on the back page of HTB or directly from our website.

CONFERENCE REPORTS

7th International Workshop on Clinical Pharmacology of HIV Therapy

20-22 April 2006, Lisbon

Introduction

The following articles are included in our coverage of this year's PK meeting held this year in Lisbon from 20-22 April.

- Efavirenz levels above recommended upper target in 20% of African patients in Senegal
- Lower dose of AZT provides adequate exposure in patients with low body weight
- Pharmacokinetics for generic fixed dose combinations for children are comparable to the branded products
- Caution against dividing adult FDCs (Triomune) for young children
- University of Liverpool audit of paediatric TDM
- Age-dependent pharmacokinetics of 3TC in children
- Use of small sample drug level monitoring for paediatric PI concentrations
- Intracellular and plasma measurements of AZT and 3TC and their metabolites in neonates
- Effect of pregnancy on PK of protease inhibitors
- Using enzyme inducers to reduce the half-life of nevirapine (Viramune)
- Relationship between nevirapine concentrations and virological failure in a clinical setting
- Summary of drug interaction studies
- Effects of ketoconazole and rifampin on TMC278
- Brexnavir interaction study with ritonavir and atazanavir
- Fixed-dose formulation of efavirenz/tenofovir/FTC bioequivalent to separate dosing
- Saquinavir/r (1000/100mg) levels reduced when taken fasted and should be taken with food
- Lack of food effect with Meltrex formulation of lopinavir/r
- Food interaction reduces ddl intracellular absorption and supports requirement to take fasted
- Conflicting results on how T-20 affects tipranavir

Unless stated otherwise, references are to the Programme and Abstracts of the 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon.

Abstracts and presentations from the meeting are already available online at:

<http://www.hiv-presentation.com>

Efavirenz levels above recommended upper target in 20% of African patients in Senegal

Simon Collins, HIV i-Base

Gilles Peytavin and colleagues from Bichat-Claude Hospital, Paris, presented data on efavirenz plasma concentrations from two pilot studies involving 80 African patients from Senegal. [1]

Previous research has shown higher plasma levels of efavirenz in African patients and linked clearance rates to single nucleoside polymorphisms in CYP2B6, 3A4, 3A5 and MDR1 enzymes. [2, 3, 4] With these mutations being more common in African compared to Caucasian populations, and efavirenz being a key component of first-line regimens in ARV roll-out programmes, PK data in these populations is important,

Patients initiated regimens using efavirenz/3TC plus either ddI/EC or d4T; and efavirenz plasma levels were measured at month 1 and 6 using HPLC and referenced to the standard range of 1,000-4,000 ng/mL. This was a largely male study (86%), with baseline characteristics including median age 35, CD4 count 143 cells/mm³ (93-213) and viral load 5.6 log copies/mL (5.2-5.8).

Patients responded immunologically and virologically to treatment (~ CD4 increase +113 cells/mm³; 67% < 50 copies/mL), and treatment was reported as well tolerated.

However, plasma concentrations were found to be below minimum target in 12% and 4% of patients, and above the maximum target in 21% and 23%, at months 1 and 6 respectively. Inter-patient variability was approximately 100% and there was a statistically significant relationship between patients levels at each time point ($p < 0.0001$).

Although the study reported no difference in efavirenz levels by gender, and that despite the higher levels treatment was 'well tolerated', further detail on the relationship between efficacy, tolerability and drug levels was not provided.

C O M M E N T

Unusually for an African cohort, there was a majority of male participants in this study (86% male). Earlier studies (Taylor et al) have suggested that higher efavirenz levels are more likely in African women than men, but this group did not report a gender difference.

One remark from the floor following the presentation, was that these data were hard to interpret, given that patients weight were not recorded, making it impossible to evaluate any effect of weight change on drug levels.

Additional studies are required to understand whether the reduced efavirenz clearance in some patients may affect current recommendations for dose adjustment when using rifampicin-based TB medication.

References

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2. Taylor S, Allen S, Fidler S et al. Stop study: after discontinuation of efavirenz, plasma concentrations may persist for two weeks or longer. 11th CROI 2004, Abstract 131.
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<http://www.i-base.info/pub/htb/v5/htb5-3/Race.html>

Lower dose of AZT provides adequate exposure in patients with low body weight

Polly Clayden, HIV i-Base

In Thailand, the standard AZT dose of 300 mg BD has frequently been linked with gastrointestinal intolerance and anaemia. Based on this observation, Thai National Guidelines recommend prescribing AZT at a dose of 200 mg BD in patients less than 60 kg. However, although some studies support AZT administration adjusted for body weight, 200 mg twice daily in patients less than 60 kg has never been formally evaluated.

A poster from Tim Cressey, from the Institut de Recherche pour le Développement, Program for HIV, Chiang Mai, Thailand, reported findings from an intensive PK study of AZT 200mg BD in HIV positive Thai patients initiating a highly active antiretroviral therapy (HAART) regimen.

Antiretroviral naive patients less than 60 kg initiated a regimen of AZT 200 mg lamivudine 150mg, indinavir 600 mg and ritonavir 100 mg BD. At one month from initiation of therapy, blood samples were taken pre-dose, and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12 hours after drug intake. Three men and five women were evaluated in this study. Their median age was 38 years (range: 29-41years); weight 54kg (range: 46-59 kg); CD4 count 162 cells/mm³ (range: 88-268 cells/mm³), plasma HIV-1 RNA log₁₀ 3.83 copies (range: 2.86-5.59 copies), hemoglobin 12.0 g/dl (10.5-12.3g/dl) and absolute neutrophil 1845 cells/mm³ (1280- 3710 cells/mm³).

At one month, the investigators found the median AZT AUC, C_{max}, T_{max} and T_{1/2} were 1.27 mg.h/L (range:1.0-1.88 mg.h/L), 0.56 mg/L (range: 0.34-1.26 mg.h/L), 0.59 hours (range: 0.25-2.1 hours) and 1.11 hours (range: 0.93-3.80 hours), respectively. AZT was undetectable (<25 ng/mL) 8 hours post dose in all patients.

The inter-patient variability (%CV) for AUC, C_{max} and T_{max} was 21%, 52% and 75%, respectively. There were no differences in AZT PK parameters in blood samples drawn one week later. The investigators found no correlation between weight and PK parameters. Two patients experienced mild anaemia early during the 48 weeks of study follow-up. This resolved without intervention.

AZT 200 mg BD in patients less than 60 kg achieved a plasma exposure only slightly lower than that previously reported for 300 mg BD in non-Asian populations, but a considerable reduction in C_{max} was observed. The investigators wrote: "This indicates that lower zidovudine dosing can likely provide adequate exposure in patients with low body weight thus possibly reducing the risk of anemia and neutropenia."

C O M M E N T

It is unclear whether toxicity is related to plasma levels, C_{max} or accumulation of intracellular metabolites of AZT.

Ref: Cressey T, Leenasirimakul, Jourdain G et al. Intensive pharmacokinetics of zidovudine 200 mg twice daily in HIV-1 infected patients less than 60 kg on highly active antiretroviral therapy. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 24.

Pharmacokinetics for generic fixed dose combinations for children are comparable to the branded products

Polly Clayden, HIV i-Base

Cipla Pharmaceuticals in India have developed two generic fixed dose combinations (FDC) for children, Pedimune Baby (d4T 6mg; 3TC 30mg; nevirapine 50mg) and Pedimune Junior (d4T 12mg; 3TC 60mg; nevirapine 100mg).

A poster from Raffaella L'homme and co-workers from the Radboud University Medical Centre, Nijmegen, The Netherlands, reported findings from a pilot study to determine the pharmacokinetic (PK) profile of d4T, 3TC and nevirapine in Pedimune and compare this with the individual branded products.

This was a phase I, comparative, open-label, three-period, single-dose study designed, not as a formal bioequivalence study, but to exclude large differences in bioavailability. Cipla is currently conducting a formal bioequivalence study.

Six HIV-negative adult males were randomised to one of the following regimen sequences: ABC; ACB; BCA; BAC; CAB; CBA. (A = reference, B = Pedimune Baby, C = Pedimune Junior) Single doses of medication (200mg of nevirapine), were administered in three cycles of four weeks each.

An 8-hour PK curve was recorded on day 1 of every cycle post dose. Additionally, blood was sampled on days 2, 3, 4, 8 and 15. Drug levels were measured by validated high performance liquid chromatography.

The authors found that in Pedimune Baby, geometric mean ratios of log-transformed parameters (GMR; % B/A) of the C_{max} were 114 (90% CI: 94-138), 112 (90% CI:100-126) and 84 (90% CI: 64-110). GMR of the AUC were 121 (90% CI:106-138), 113 (90% CI: 105-122) and 95 (90% CI:84-107), for d4T, 3TC and nevirapine, respectively.

In Pedimune Junior, GMR (% C/A) of C_{max} were 91 (90% CI:67-124), 91 (90% CI: 70-118) and 98 (90% CI:86-111).GMR of AUC (90% CI) were103 (90% CI: 96-109), 99 (90% CI: 91-108) and 91 (90% CI: 73-115), for d4T, 3TC and nevirapine, respectively. GMR were within 80 to 125%.

In this PK study the authors found the profile of d4T, 3TC and nevirapine in Pedimune Baby and Junior to be comparable to the individual branded products. They wrote; "Based on the results of this pilot study, it is acceptable to start testing the pharmacokinetics and dosing requirements of Pedimune Baby and Junior in HIV-infected children even though the formal bioequivalence study by Cipla Pharmaceuticals has not yet been completed."

C O M M E N T

Obviously, these FDCs are a very welcome development as current practice yields suboptimal levels of nevirapine in a substantial number of children, particularly the very young (see the following two studies).

A small number of children are currently being treated with Pedimune within the CHAPAS 1 phase 1/2 trial in Zambia (sponsored by the MRC in London). This study will include evaluation of PK of nevirapine, d4T and 3TC in two daily paediatric doses of Pedimune in African children with and without malnutrition and in different age groups. It will also look at possible PK interactions between nevirapine and concomitant medications such as rifampicin and fluconazole.

Children on this trial will be randomised to start with Pedimune full dose vs a dose escalation schedule. So far, approximately 25 children have been enrolled (target 200) and early data will be presented at Toronto.

Ref: L'homme R, Dijkema T, Warris A et al. Pharmacokinetics of two generic fixed dose combinations for HIV-infected children (Pedimune Baby & Pedimune Junior) are comparable to the branded products. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 23.

Caution against dividing adult FDCs (Triomune) for young children

Polly Clayden, HIV i-Base

While we await paediatric FDCs, several programmes are treating children with divided fixed dose combinations (FDC) Triomune (d4T+3TC+nevirapine) tablets. Although this strategy is important and included in some national guidelines (including Malawi's), this is not a long-term solution as previous studies have found cut up tablets for young children can result in under dosing of nevirapine.

There are limited PK data on nevirapine in children treated with divided tablets and in whom malnourishment is common.

In an oral presentation Dr L'homme presented findings from a study to determine the extent of the subtherapeutic concentrations (<3.0 mg/L) of the nevirapine component and to investigate predictors of nevirapine concentrations in children treated using this strategy.

This study included 127 HIV positive children aged 3 months - 16 years (median 8.4 years) treated at the Queen Elizabeth Central Hospital, Blantyre, Malawi and the University Teaching Hospital, Lusaka, Zambia who had received divided Triomune at a range of doses (see table one) for at least a month.

Steady-state plasma nevirapine concentrations were determined in the children. Centre-stratified regression with backwards elimination ($p < 0.1$) was used to identify predictors from height-for-age, BMI-for-age, age, sex, post-dose sampling time and dose/m²/day.

The 71 Malawian children were similar ages (median 8.4 years), but more malnourished (BMI-for-age -0.89, height-for-age -3.15) and had longer post-dose sampling times (8.9 hours) than the 56 Zambian children (8.5 years, -0.50, -1.84, 3.5 hours respectively).

Table 1: Triomune tablets and daily nevirapine dose

Number of Triomune tablets	Total daily dose (mg)	Number of children n=127
¼ once daily	50	6
¼ twice daily	100	9
¼ once daily, ½ once daily	150	18
½ twice daily	200	52
½ once daily, ¾ once daily	250	12
¾ twice daily	300	2
¾ once daily, whole once daily	350	5
whole twice daily	400	23

Overall, the median nevirapine concentration was 6.0mg/l (IQR 3.8-8.2mg/L) percentage of children receiving sub-therapeutic doses of nevirapine (<3.00mg/L) in this analysis was 18% (see table 2).

Table 2. Percentage of patients with subtherapeutic nevirapine (<3.0mg/L)

Overall	18 %
>300mg/m ² /day	3 %
240-300	20 %
<240	25 %

The median nevirapine levels were 4.8mg/L [IQR: 2.8, 6.5; range: 0.15,15.4] and 7.0 mg/L [IQR: 5.4,10.5; range 0.15,17.1] in Malawian and Zambian children respectively. Only the children receiving the nearly adult dose (350-400mg nevirapine/day) received the target dose of 300 mg/m²/day (median 337 mg/m² [IQR 303-366; range 274-454], with only 2% of these children with <3 mg/L (considered subtherapeutic).

Those prescribed 50-200 mg/day (quarter/half tablets) were more frequently underdosed (median 236 mg/m² [IQR 217,267; range 120- 354], with 21% <3mg/L); as were those prescribed >200-<350mg (median 263 mg/m² [IQR 260,271; range 245-292], with 21% children <3mg/L.

The investigators found lower height-for-age (indicating stunting) (+0.37 mg/L per unit higher [95% CI -0.013, +0.75], p=0.06), lower prescribed dose/m² (+0.67 mg/L per 50mg/m² higher [+0.014, +1.32], p=0.05) and younger age (+0.15 mg/L per year older [-0.022, +0.31], p=0.09) were independently associated with lower nevirapine levels.

They reported no significant independent effect of lower BMI-for-age (indicating wasting) (-0.33mg/L per unit higher [-0.76, +0.09], p=0.12), although this was a stronger predictor for the Malawian children (-0.51 [-1.01, -0.02], p=0.04).

The investigators concluded that dividing Triomune could put children at risk for nevirapine underdosing. They wrote: "To avoid nevirapine underdosing in young children, divided FDC Triomune should be used with caution; the use of quarter tablets is not recommended. Nevirapine levels may be reduced in stunted but increased in wasted children. Further studies investigating these relationships are required."

Ref: L'homme R, Ellis R,J, Ewings F et al. Nevirapine concentrations in HIV-infected children treated with divided fixed dose combination tablets in Malawi and Zambia. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 2.

University of Liverpool audit of paediatric TDM

Polly Clayden, HIV i-Base

In an oral presentation, Sara Gibbons, from the University of Liverpool, Pharmacology and Therapeutics, presented data from the group's therapeutic drug monitoring (TDM) service [1].

Data from the Collaborative HIV Paediatric Study (CHIPS) Cohort - that includes 757 children in the UK and Ireland - show that 73% of HIV-positive children have received antiretroviral therapy. A previous CHIPS analysis has found that 40.5% children in this cohort had been under-dosed during their drug history [2].

Pharmacokinetic data of antiretroviral drugs in this population are limited. Additionally appropriate paediatric antiretroviral formulations are not always available, leading to frequent unlicensed and off-label use. In Europe, of the 11 PI or NNRTI formulations available to treat adults, 8 are licensed for paediatric use, but with age restrictions ranging from 2 months to 16 years.

The investigators performed a retrospective audit on TDM requests (1999-2005) from the UK and Ireland where the patient was <18 years at the time of request. Data were classified by age, with patients grouped according to British National Formulary guidelines for dosing in children (i.e. neonates=up to 1 month; infants=up to 1 year; younger children=1-5 years; older children=6-12 years; adolescents=over 12 years). The variability in drug concentrations and the relationship between concentrations and age were evaluated.

The investigators noted that 20.6% of requests had missing data, in particular, time post dose, frequency of dose and amount of dose. They reported difficulty in accessing dose/kg or dose m² as 16.8% of patient's weights were not recorded.

During the period of analysis the Liverpool group received 911 requests for TDM. They found that the three most frequently requested drugs were lopinavir/r (35.0%), nevirapine (27.1%) and efavirenz (19.9%). Unlicensed drugs for paediatric use accounted for 16.8% of requests. Stratified by age: 4.0% neonates, 8.0% infants, 26.3% young children, 33.9% older children and 27.8% adolescents, made up the requests.

Plasma concentrations (at any time post dose) falling below adult targets are shown in Table 1.

Table 1: Plasma concentrations falling below target

	Neonates	Infants	Young children	Older children	Adolescents
Lopinavir/r	-	16.7% (4/24)	19.4% (18/93)	19.0% (19/100)	25.5% (25/98)
Nevirapine	46.9% (15/32)	44.4%(20/45)	22.2% (22/99)	20.9% (9/43)	21.4% (6/28)
Efavirenz	-	-	25.9% (7/27)	19.5% (22/113)	26.8% (11/41)

The investigators found that plasma concentrations below target were frequently also below the limits of quantification (LOQ), in patients receiving lopinavir/r. For lopinavir/r, the absolute percentages below the LOQ were 8.3% infants, 15.1% young children, 17.0% older children 6-12 years and 19.4% adolescents. Percentages for nevirapine were 4.4% infants, 6.1% young children, 9.3% older children and 10.7% adolescents. They noted that the lack of information regarding previous doses limits the use of these data for rigorous population PK analysis.

They concluded that although these data are limited by small sample sizes and potential selection bias, they found greater variability in paediatric drug concentrations than adults. Infants may be particularly at risk for under-dosing especially with nevirapine and adult target values may not be appropriate for paediatric populations. They added that drug formulations might be an additional barrier to achieving adequate concentrations.

C O M M E N T

The BMJ paper on underdosing concludes:

“Three key points emerge. Firstly, rigorous pharmacokinetic and pharmacodynamic data for children are needed before drug licensure. Secondly, effective formal systems for early appraisal, dissemination, and implementation of important modifications to treatment recommendations are needed universally. Thirdly, improved methods of pharmacovigilance are needed to monitor drug utilisation, efficacy and toxicity after drug licensing.

The European Union and the United States have recently committed to promoting research specific to children’s medicines while protecting children as participants in clinical trials.

The UK Department of Health has launched the Medicines for Children Research Network (www.liv.ac.uk/mcrn), which aims to develop closer links between the drugs industry, regulators, families, and paediatricians, links that will be needed to meet the challenges of developing and manufacturing appropriate paediatric drugs (www.hivforum.org). Our study shows that, even for paediatric HIV—a new disease with rapid drug development and good dialogue between all these parties—antiretroviral dosing seems to have similar problems to the ones that antibiotics have always had. The Medicines for Children Research Network initiative to tackle these issues is timely.” [2]

References

- Gibbons S, Back D, Khoo S. An audit of TDM in paediatric subjects from the UK and Ireland. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abs 8.
- Menson EN, Walker S, Sharland M et al. Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study. *BMJ* 2006 332: 1183-1187.

Age-dependent pharmacokinetics of 3TC in children

Polly Clayden, HIV i-Base

The antiretroviral 3TC is licensed for treatment of HIV positive children from 3 months to 16 years. The recommended paediatric dose is 4mg/kg BD compared to the adult dose of 150mg BD (equivalent to 2mg/kg BD). The prescribing information from the originator company states: “Total exposure to lamivudine, as reflected by mean AUC values, was compatible between paediatric patients receiving an 8mg/kg/day dose and adults receiving a 4mg/kg/dose.”

In an oral presentation David Burger from Radboud University Medical Centre Nijmegen, presented findings from a study to investigate an age effect on 3TC PK and whether systematic clearance is increased in younger children.

Data were selected from children who participated in various PK studies undertaken by the group. Children were receiving 3TC 4mg/kg BD for at least 2 weeks before a full 8-12h PK curve was recorded. Data from HIV positive adults from the study of Bruno et al. (*Clin Pharmacokinet* 2001; 40: 695-700) were used as adult controls for comparison.

The study included a total of 40 children: 16 boys and 24 girls with a median age of 7.3 years (range: 1.7 to 18 years). The investigators found AUC, C_{max}, CL/kg and V_d/kg were significantly related to age with younger children having lower

exposure to 3TC. Half-life and C_{min} were not influenced significantly by age. They noted: "The age of 6 years appeared to be a cut-off for a change in pharmacokinetic parameters of lamivudine in this dataset", with younger children ($n=17$) having an AUC 42% lower and a C_{max} 51% lower (both $p=0.001$) than older children ($n=23$).

Additionally, CL/kg and Vd/kg were 74% and 109% higher in children 6 years and below vs. in children aged 7 years and older. They found body surface area (BSA) was less strongly related with age, suggesting that a BSA adjusted dose would have resulted in less variability exposure across the different age groups.

The mean C_{max} and AUC in children aged 7 years and older were similar to historical adult controls: C_{max} 1.93 vs. 2.08 mg/L, AUC 7.05 vs. 8.54 mg/L.h, respectively. There was no sex difference in exposure. There was no difference in children aged 7-12 and >12 years; AUC 7.1 vs. 6.9mg/L.h respectively.

They reported that although a dose of 4mg/kg BD achieves adequate exposure in children aged >7 years (a child of 10 years weighing 35kg will receive an adult dose of 150mg BD) this is not the case for children 6 years and younger.

Dr Burger suggested various explanations: Lower bioavailability? Increased renal clearance? Larger volume of distribution? Oral solution bioequivalent with tablets? He explained that there was no evidence of suboptimal response in younger vs. older children in previous studies and that plasma concentrations are a surrogate marker; intracellular triphosphate is pharmacologically active. Additionally, age dependent variability of 3TC AUC may fall within the range of exposure needed for optimal efficacy, so perhaps targeting adult AUC is unnecessary.

He raised the question: "How have paediatric doses been determined? Adult AUC target? Clinical study with PK/PD analysis? He added: "Most young children live in developing countries and are treated with generics, often containing lamivudine, there is an urgent need for operational research."

Ref: Burger D, Verweel G, Verwey-Van Wissen C et al. Age-dependent pharmacokinetics of lamivudine in HIV-infected children. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 20.

Use of small sample drug level monitoring for paediatric PI concentrations

Polly Clayden, HIV i-Base

A poster from J Lam and coworkers from the University of Southern California (USC), Pharmacology, Los Angeles, USA reported their methodology for total drug analysis from plasma with protein precipitation. This methodology simultaneously analyses multiple protease inhibitors in a single run, with a smaller injection volume, making it easier to use TDM, particularly in paediatrics, than previously published assays.

The investigators added a volume of 100 μ L of 500 ng/mL of SQV as the internal standard to 100 mcg/mL of each plasma standard. The entire sample was protein precipitated by adding 500 μ L of acetonitrile and centrifuged at 13,000 rpm for 5 minutes. The supernatant was evaporated to dryness, reconstituted with 150 μ g/mL of mobile phase (58%: [v/v] acetonitrile + 42% 20 mM NH_4 Acetate, pH4.5), and then centrifuged for 5 minutes at 13,000 rpm. An aliquot of 135 μ g/mL of the supernatant was transferred into HPLC injection vials.

A volume of 10 μ L per sample was injected and the concentration was determined using a Sciex API 3+ mass spectrometer coupled with an Agilent 1100 HPLC and well plate autosampler. The analytes were separated using a Hypurity C18 column (50 x 4.6 mm, 5 μ m), where the flow-rate was 0.4 mL/min to elute the PIs.

The investigators found the CVs for both intra and inter-day precision were <10% for each compound. Accuracy was measured at >85%. Retention times were 1.44, 2.57, 4.12, 4.28, and 4.35 minutes for ritonavir, saquinavir, nelfinavir, lopinavir, and atazanavir, respectively. The total sample run time was 7.2 minutes.

The mass transitions were 705.3 to 335.3, 568.2 to 330.2, 721.2 to 296.2, 629.4 to 447.6 and 671.3 to 570.3 for atazanavir, nelfinavir, ritonavir, lopinavir, and saquinavir, respectively.

This methodology was validated over the concentration ranges of 0.025-2.0 μ g/mL, for all of the protease inhibitors.

The investigators explained that this validated LC/MS assay method uses a small sample volume with a low CV. Use of a small sample volume is advantageous, especially when TDM used for paediatric patients. They noted: "The ability to minimise the amount of blood extracted, handle small patient samples, and rapidly analyse them will enable TDM and pharmacokinetic studies to be used in the paediatric setting."

Ref: Lam J, M. Neely JM, Bi L, Louie S et al. LC/MS analysis of protease inhibitors. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 17.

Intracellular and plasma measurements of AZT and 3TC and their metabolites in neonates

Polly Clayden, HIV i-Base

Neonates receive antiretroviral prophylaxis often involving AZT either alone or in association with 3TC. Since access to intracellular NRTI triphosphate (TP) measurement is limited, pharmacological intracellular data are still lacking.

A poster from L. Durand-Gasselín and coworkers presented findings from a study to measure AZT and 3TC plasma levels, as well as intracellular phosphorylated metabolites concentrations, in HIV exposed babies born to HIV positive mothers.

52 HIV exposed neonates (age range: 0-45 days) received AZT (8mg/kg/24h), either alone (n = 32) or with 3TC (4mg/kg/24h) (n = 20). Plasma and PBMCs were isolated from blood and intracellular NRTI metabolites (AZT-TP, d4T-TP, 3TC-TP) and plasma NRTI (AZT, d4T, 3TC) concentrations were determined using validated LC-MS/MS assays.

The investigators found plasma AZT and intracellular AZT-TP levels in the neonates decreased significantly with age ($p < 0.0001$). The median AZT-TP concentration reached 202.2 fmol/ 10^6 cells (CV%=44) between days 1 and 8, but only 62.9fmol/ 10^6 cells (CV%=65) between days 32 and 40. They suggest that this phenomenon could be explained by the maturation of intestinal, hepatic and renal functions occurring during the first weeks of life.

Therefore, they observed high AZT and AZT-TP levels during the first week as compared to adult historical data. Intracellular levels of d4T-TP closely correlate with those of AZT-TP with an average d4T-TP to AZT-TP ratio of 0.28. Plasma 3TC and intracellular 3TC-TP levels did not differ significantly by age. The median 3TC-TP concentration was 19 pmol/ 10^6 cells, which is consistent with adult data.

They noted that babies receiving AZT monotherapy, whose mother's treatment included 3TC, had residual plasma 3TC and intracellular 3TC-TP up to one week after birth. The investigators wrote: "We observed high concentration of AZT and related intracellular metabolites (AZT-TP and d4T-TP) during the first week of life. Following the first fortnight, intracellular NRTI-TP measurements showed no major difference with adults in term of 3TC-TP levels and metabolic pathway from AZT to d4T and d4T-TP." They added: "These characteristics, in favor of efficacy, could have some drawbacks in terms of mitochondrial toxicity."

Ref: Durand-Gasselín L, Pruvost A, Dehéé A et al. Intracellular and plasma measurements of AZT and 3TC and their metabolites in newborn babies from HIV infected mothers. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 25.

Effect of pregnancy on PK of protease inhibitors

Polly Clayden, HIV i-Base

Previous studies investigating the PK of protease inhibitors show reduced exposure during pregnancy. M. Regazzi and coworkers from a multicentre cohort in Italy evaluated nelfinavir and lopinavir plasma levels in a group of HIV-positive pregnant women after receiving multiple doses.

A group of 29 women in the 3rd trimester of pregnancy were selected from an ongoing national surveillance study. All women achieved steady-state plasma concentrations while on a HAART regimen containing nelfinavir (1250 mg BD, n=20) or lopinavir/r (400/100 mg, BD, n=9).

Nelfinavir samples were obtained pre-dose (C_{trough}) and 0.5, 1, 2, 3, 4, 5, 6, 8, 12 hours post-dose. For lopinavir, C_{trough} and 3 hour plasma samples were obtained. The results were compared to results from a control group of HIV positive non-pregnant women (nelfinavir, n=21; lopinavir: n=12).

Additionally, the investigators evaluated placental transfer in a subgroup of 6/20 mother/infant pairs receiving nelfinavir and 6/9 receiving lopinavir/r by comparing drug concentrations in samples collected at delivery.

They found median nelfinavir PK values were: AUC (0-12h) 25.76 mcg.h/mL (range:12.61-42.74) in pregnant women vs. 32.49 mcg.h/mL (range:19.16-63.81) in controls ($p < 0.05$). CL/F was significantly higher in pregnant women than in controls, 48.5 L/h (range: 29.3- 99.1) vs 38.5 L/h (range:19.6-65.2), but the difference did not remain after CL/F was adjusted for patient weight. Additionally, median C_{trough} was significantly ($p < 0.01$) lower in pregnant vs controls, 0.8 mcg/mL (range: 0-2.6) vs 1.5 mcg/mL (range: 0.5-4.9). In the 6 women evaluated at delivery, the median plasma concentration was 0.15 mcg/mL (range: 0-1.82) and 3 women (50%) had undetectable levels.

Median lopinavir C_{trough} levels were similar in pregnant women and controls: 4.3 mcg/mL (range: 3.0-8.3) and 5.2 mcg/mL (range: 0.3-16.0). Only 1/9 pregnant women had C_{trough} level below the recommended lopinavir target of 4.0mcg/mL. The median C_{3h} was significantly lower ($p < 0.01$) in pregnant women: 4.2 mcg/mL (range: 2.2-9.7) vs 9.8 mcg/mL (7.0-20.5). At delivery the median lopinavir concentration was 0.22 mcg/mL (range: 0-6.8), with 5/6 women having levels below 4.0mcg/mL. No measurable nelfinavir or lopinavir or nelfinavir and concentrations were found in any of the cord blood samples.

The investigators concluded that HIV positive pregnant women receiving nelfinavir without any concomitant PIs frequently show subtherapeutic levels of nelfinavir in late pregnancy. They found that lopinavir showed better PK, with similar C_{trough} levels in the two groups.

They wrote; "The difference between the two drugs in achieving therapeutic levels may be explained by the inclusion of ritonavir in lopinavir regimen. Nelfinavir and lopinavir did not cross the placenta to an appreciable extent and thus should not be expected to provide any direct protection for the newborn."

C O M M E N T

Concordant with previous findings some presented at CROI and covered in April HTB [2, 3, 4, 5]:

<http://www.i-base.org.uk/htb/v7/htb7-4/Pharmacokinetics.html>

References:

1. Regazzi R, Villani P, Florida M et al. Effect of pregnancy on protease Inhibitors (PIs) pharmacokinetics in HIV-1 infected women. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 27.
2. Khuong-Josses M-A, Boussaïri A et al. Nelfinavir plasma concentrations in 40 pregnant women. 13th CROI. Abstract 707.
3. Stek A, Mirochnick M, Capparelli E et al. Reduced lopinavir exposure during pregnancy: preliminary pharmacokinetic results from PACTG 1026. XV Intl AIDS Conference, Bangkok. Abstract LbOrB08.
4. Lyons F, Lechelt M, Magaya V et al. Adequate trough lopinavir levels with standard dosing in pregnancy. 13th CROI 2006, Denver. Abstract 709.
5. Mirochnick M, Stek A, Capparelli E et al. Adequate lopinavir exposure achieved with a higher dose during the third trimester of pregnancy. 13th CROI, Denver. Abstract 710.

Using enzyme inducers to reduce the half-life of nevirapine

Polly Clayden and Ben Cheng, HIV i-Base

Several studies have reported the development of resistance to nevirapine even after taking a single dose of the drug, which is commonly used in the resource-limited setting for the prevention of mother to child transmission. This is likely due to the long half-life of nevirapine that results in the drug being found in blood for many days after taking the one dose.

A poster from Rafaella L'homme and coworkers from the Radboud University Nijmegen Medical Centre presented findings from a study exploring the novel strategy of using enzyme inducers to reduce nevirapine half-life and thereby reduce the risk of developing resistance.

This small study evaluated the use of several different strategies including using carbamazepine, phenobarbital, phenytoin, St. John's Wort tea, retinyl palmitate and beta-carotene, and cholecalciferol.

This was a phase-I single-centre, open-label, two period, nine-group, PK study. A single 200 mg dose of nevirapine was administered to 36 HIV negative non-pregnant women in both period 1 and 2, blood samples were taken twice weekly for 21 days. In period 2 additional interventions (single dose carbamazepine, phenobarbital or phenytoin; phenytoin for 3 or 7 days; St Johns Wort, vitamin A or cholecalciferol for 14 days) were administered to all participants except for the control group. The primary end point was the ratio of nevirapine half-life in period 2 to nevirapine half-life in period 1.

Three of the interventions resulted in the half-life of nevirapine being significantly reduced. These included a single 400mg dose of carbamazepine ($p=0.002$), once a day 184mg phenytoin for three days ($p=0.001$) and once a day 184mg phenytoin for seven days ($p=0.002$). The half-life of nevirapine was reduced by 35.3%, 38.2% and 35.9% respectively. This resulted in a 4.5 – 8.8 day reduction in time to when nevirapine could not be detected in blood. The other five interventions had no effect on the nevirapine half-life.

These interventions now need to be studied in the real world setting to determine if this will lead to a decreased risk of developing resistance to nevirapine among pregnant women taking single dose nevirapine to prevent HIV transmission to their newborns.

Ref: L'homme R, Dijkema T, A. van der Ven A et al. Enzyme inducers reduce nevirapine half-life. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 5.

Relationship between nevirapine concentrations and virological failure in a clinical setting

Polly Clayden, HIV i-Base

Previous studies have reported high frequency of sub-optimal nevirapine Ctrough levels but no guidelines have suggested a way to manage these patients. Should a clinician confirm the inadequate concentration on another sample because of high intra-patient variability or increase nevirapine dose?

N Machefert from the Centre Hospitalier Universitaire, Toxicologie et Pharmacocinétique, Poitiers, France and coworkers performed a retrospective assessment of the risk of virological failure in a clinical setting for patients having one or more sub-optimal nevirapine Ctrough (<3 ug/mL). Additionally, the study was to determine the extent of the intra-patient variability among this group.

The authors evaluated 38 patients receiving standard nevirapine dose as part of their antiretroviral regimen. Nevirapine Ctrough concentrations were determined from 245 samples collected at each clinic visit through out the course of their treatment. Viral load and adherence, recorded at each clinic visit, were also evaluated. Virological failure was defined as >1000 copies/mL. The number of patients with one or more Ctrough <3 ug/mL were compared to the virological failure group.

Patients received nevirapine for a mean of 700 days; 8/38 patients had virological failure. There were an average of 6 Ctrough measurements available per patient. The investigators found 24/ 38 (63%) patients had at least one inadequate Ctrough during the course of their treatment. 7/8 (88%) patients had more than one inadequate Ctrough in the viral failure group vs 9/30 patients in the group without virological failure, p=0.01. Additionally 6/8 patients in the virological group were considered as non-adherent (confirmed by undetectable plasma concentration measurement during the course of their treatment).

They reported that the intra-individual variability was significant with a mean value of 35% [range: 5-200%] in all patients but only 20% [range: 5-45%] excluding non-adherent patients. The investigators wrote: "This study confirm the high frequency of inadequate Ctrough in clinical setting and suggest that only patients exhibiting more than one inadequate NVP Ctrough are at risk of virological failure. In routine practice, before nevirapine dosage adjustment, inadequate Ctrough should be confirmed and adherence should be assessed."

Ref: Machefert N, Dupuis A, Le Moal G et al. Relationship between nevirapine concentration and virological failure assessed in a clinical setting. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 70.

Summary of drug interaction studies

Simon Collins, HIV i-Base

Several studies presented data on new drugs interactions. Some of these studies had been presented at earlier meetings, and the summary table of interactions from EACS, ICAAC and CROI, published in the April issue of HTB [1] may be a useful additional guide in association with those reported in the Table 1 below.

Table 1 – PK and drug interaction studies at 7th Intl PK Workshop, Lisbon

ARV	Interaction	Results	Recommendation	Reference
Lopinavir/r 533mg/133mg bid	Nevirapine 200mg bid at steady state	LPV/r Ctrough maintained above minimum target in 14/15 PI/NNRTI-naïve patients, but widely interpatient variability	Increasing LPV/r dose to 533/133 is appropriate with NVP. TDM is recommended. Data needed on new Meltrex formulation of Kaletra.	Else L et al. Abstract 67. [2]
TPV/r	Methadone (single dose 5mg at TPV/r steady state)	Methadone AUC, Cmax and C6H all decreased by ~50% ↓ (similar to other RTV- boosted PIs)	Dose of methadone may need to be increased	Sabo JP et al. Abstract 42. [3]
Etravirine (TMC-125)	Sildenafil (Viagra) 50mg dose at TMC-125 steady state	Sildenafil AUC, & Cmax decreased by 43% & 55% ↓ and active metabolite reduced by 59% & 75% ↓ TMC-125 →	Dose administration of sildenafil should be tailored to individual response	Schöller M et al. Abstract 45. [4]

TMC-278 (investigational NNRTI)	Rifampicin	TMC-278 AUC, Cmax and Cmin decreased by 80%, 69% & 89% ↓	TMC-278 and rifampicin should NOT be used together	Van Heeswijk R et al. Abstract 74. [5]
TMC-278 (investigational NNRTI)	Ketoconazole	TMC-278 AUC, Cmax and Cmin increased by 49%, 30% & 76% ↑	Dose adjustment dependent on further studies.	Van Heeswijk R et al. Abstract 74. [5]
Breacanavir/ ritonavir (300/100mg BD)	Atazanavir 300mg once-daily	All increased: Breacanavir by 38%, ritonavir by 56% and atazanavir by 44%	Consider dose reduction of atazanavir. (Confirm with TDM)	Ford S et al. Abstract 76. [6]
LPV/r	ezetimibe	No significant interaction	Can be coadministered.	Moltó J et al. Abstract 50. [7]

References

Unless stated otherwise, all references are to the Programme and Abstracts of the 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Available online at:

<http://www.hivpresentation.com>

1. Pharmacology and drug interaction studies in adults: summary table from CROI, ICAAC and EACS conferences. HIV Treatment Bulletin April 2006.
<http://www.i-base.info/htb/v7/htb7-4/Pharmacology.html>
2. Else L et al. The pharmacokinetics (PK) of lopinavir/ritonavir (LPV/r) 533/133 mg bid plus nevirapine (NVP) (200 mg bid) in adult HIV-1 infected individuals. Abstract 67.
3. Sabo J et al. Stereoselective pharmacokinetics (PK) of methadone after coadministration with steady-state tipranavir/ritonavir 500/200 mg bid (TPV/r) in healthy volunteers. Abstract 42.
4. Schöller, M et al. Effect of TMC125 on sildenafil pharmacokinetics Abstract 45.
5. van Heeswijk R et al. The effects of CYP3A4 modulation on the pharmacokinetics of TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI). Abstract 74.
6. Ford S, Murray S, Anderson M et al. Breacanavir/ritonavir and atazanavir/ritonavir increased following repeat co-administration. Abstract 76.
7. Moltó J et al. The effect of ezetimibe (EZT) on the steady-state pharmacokinetics of lopinavir (LPV). Abstract 50.

Effects of ketoconazole and rifampin on TMC278

Ben Cheng, HIV i-Base

TMC278 is a new non-nucleoside reverse transcriptase inhibitor in early stage clinical development. It had been previously reported that many of the commonly used HIV treatments and drugs used to treat and prevent opportunistic infections might interact with TMC278.

Two separate studies, involving 16 HIV-negative individuals in each study, evaluated how ketoconazole and rifampin might affect TMC278 drug levels. Rifampin significantly reduced TMC278 levels by an average of 80% over a 24 hour period and perhaps more importantly, TMC278 levels were reduced by 89% at its lowest level (commonly referred to as Cmin), usually found right before taking the next dose. TMC278 had no effects on rifampin drug levels. This marked reduction in TMC278 levels has led to the recommendation that the two drugs should not be used together.

The second study found that ketoconazole increased TMC278 levels by an average of 49% over a 24 hour period and TMC278 reduced ketoconazole levels by 24%. It is likely that there will have to be a change in the dose of TMC278 if the drug is used in combination with ketoconazole.

Ref: van Heeswijk R et al. The effects of CYP3A4 modulation on the pharmacokinetics of TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI). 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 74.

Breacanavir interaction study with ritonavir and atazanavir

Ben Cheng, HIV i-Base

Breacanavir is a new protease inhibitor that is currently in clinical studies and it is being studied in combination with low dose ritonavir. A drug interaction study involving 48 HIV-negative individuals participated in this study to evaluate the effects of

atazanavir and ritonavir on brecaonavir drug levels.

The results from the study showed that the addition of atazanavir (300mg once a day) to brecaonavir/ritonavir (300mg/100mg every 12 hours) led to higher brecaonavir, ritonavir and atazanavir drug levels. AUC levels of all drugs increased: brecaonavir by an average of 38%, ritonavir by 56% and atazanavir levels by 44%. Results from this study suggest that atazanavir further increases brecaonavir levels on top of the increase already seen with low dose ritonavir and a reduction in the dose of atazanavir should be considered.

Ref: Ford S, Murray S, Anderson M et al. Brecaonavir/ritonavir and atazanavir/ritonavir increased following repeat co-administration. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 76.

Fixed-dose formulation of efavirenz/tenofovir/FTC bioequivalent to separate dosing

Simon Collins, HIV i-Base

A study by Mattias and colleagues from Gilead Sciences reported pharmacokinetic bioequivalence between the co-formulated fixed dose combination of efavirenz, tenofovir and FTC and plasma levels achieved when each drug was taken as single drug formulations.

48 HIV-negative volunteers were enrolled in a randomised cross-over study, using either test or reference formulations for one week, followed by a one week washout before switching formulations for a further week. Intensive PK was performed after each treatment.

Bioequivalence was assessed by 90% CI for the geometric least square means for Cmax AUC-t and AUC-infinity for each drug.

C O M M E N T

This is the first collaboration between two research-based pharmaceutical companies (Gilead and BMS) to produce a three-drug fixed-dose formulation. Although the project was announced by both companies in December 2004, several earlier attempts failed to produce bioequivalent results. This highlights the practical complexity of pharmacology, in an area than many people would expect to be routine and straight-forward.

Matthias A, Plummer A, Kearney B et al. Bioequivalence of the co-formulation of efavirenz/emtricitabine/tenofovir DF. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 82.

Saquinavir/r (1000/100mg) levels reduced when taken fasted and should be taken with food

Simon Collins, HIV i-Base

Marta Boffito and colleagues from the Chelsea and Westminster Hospital, compared absorption of saquinavir 500mg (dosed at 1000mg SQV with 100mg RTV, twice daily) when taken with a high calorie fat-containing meal (~1070kcal; 46-66g of fat), to when taken under fasted conditions. [1] An interim analysis of 10/22 patients who completed this cross-over study, where three consecutive doses were taken in either fed/fasted or fasted/fed state, separated by one week.

Administration of SQV/r under fasted conditions resulted in an approximate 70% decrease in SQV PK parameters, and are detailed in Table 1. There was no significant change in ritonavir PK. The researchers concluded that saquinavir/r should be taken with food in order to ensure maximum therapeutic exposure.

Table 1: Saquinavir levels (fed and fasted)

	<i>Fed</i>	<i>Fasted</i>
<i>AUC ng.h/mL</i>	38,927	11,476
<i>Cmax ng/mL</i>	6,399	1,587
<i>Ctrough ng/mL</i>	1,294	373

Ref: Boffito M et al. Effect of a fat-containing meal on the pharmacokinetic (PK) profile of saquinavir 500mg tablet/ritonavir (SQV/r) 1000/100 mg BID in HIV-infected individuals. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 66.

Lack of food effect with Meltrex formulation of lopinavir/r

Simon Collins, HIV i-Base

Chiu and colleagues from Abbott laboratories presented two posters comparing food effect and drug level variability of the new Meltrex formulation of lopinavir/r (Kaletra) compared to the original soft gel capsule formulation. [1]

In a crossover study, in 46 HIV-negative adult volunteers received single doses of lopinavir/ritonavir 400/100 mg as tablet (test, T) or SGC (reference, R) under moderate-fat meal conditions, separated by washout periods of ≥ 5 days. Drug sequences were randomly assigned to TTR and RTT in three crossover periods. A linear effects model was used to estimate lopinavir and ritonavir PK area under the plasma concentration time curve (AUC), C_{max} and concentration at 12 hours post-dose (C₁₂). The total variance, detailed in Table 1, was calculated as the sum of the within- and between-subject variances.

Table 1: Inter- and intra-patient variability between SGC and Meltrex formulations of lopinavir/r

Between-patient variability

	SGC	Meltrex tablet
Lopinavir:		
C _{max}	0.302	0.199
AUC	0.409	0.199
C _{12H}	0.436	0.177
Ritonavir:		
C _{max}	0.536	0.350
AUC	0.467	0.202
C ₁₂	0.613	0.214

Within-patient variability

	SGC	Meltrex tablet
Lopinavir:		
C _{max}	0.012	0.014
AUC	0.024	0.018
C ₁₂	0.025	0.021
Ritonavir:		
C _{max}	0.043	0.032
AUC	0.040	0.018
C ₁₂	0.070	0.029

The researchers concluded that the Meltrex formulation of lopinavir/r provides more consistent PK performance within, and between, subjects compared to the soft gel capsule.

A second poster at the Workshop presented data on the lack of a food effect with the new Meltrex formulation of lopinavir/r. [2] Lopinavir/ritonavir soft gelatin capsule (SGC) and oral solution formulations must be administered under fed conditions in order to maximize bioavailability of lopinavir. Compared to fasting, the bioavailability under moderate-fat and high-fat meal conditions increased by 56% and 96%, respectively, for the SGC formulation.

In this study, 107 healthy subjects in 2 randomised, open-label studies received single doses of lopinavir/ritonavir 400/100 mg SGC and tablet formulations in a crossover fashion under three different controlled meal conditions: fasting, moderate- and high-fat meals. Results were compared to the SGC under the moderate-fat meal condition and bioequivalence AUC criteria were met because the 90% CIs were contained entirely within the 0.8-1.25 range.

The authors concluded that the tablet formulation under different meal conditions resulted in lopinavir average concentrations and maximum exposures similar to the approved SGC reference regimen, and that the Meltrex tablet formulation may be taken without regard to food.

C O M M E N T

These studies were performed in HIV negative volunteers. As yet, there is no data from the Meltrex formulation in HIV-positive patients.

References

1. Chiu YL et al. Assessment of pharmacokinetic variability for lopinavir/ritonavir (LPV/r) tablet and soft-gel capsule (SGC) formulations. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 78-A.
2. Chiu YL et al. Lack of food effect on the bioavailability of lopinavir/ritonavir tablet formulation. 7th Intl Workshop on Clinical PK of HIV Therapy, 20-22 April 2006, Lisbon. Abs 78-B

Food interaction reduces ddl intracellular absorption and supports requirement to take fasted

Simon Collins, HIV i-Base

Girard and colleagues from St Antoine Hospital, Paris, presented data on intracellular (IC) levels of ddA-TP, the active metabolite of ddl, under fed and fasted conditions. Plasma concentrations of ddl are reduced by 17-28% when taken with food, and ddl is therefore recommended to be taken on an empty stomach and two hours before food. This randomised cross-over study in 24 patients with viral load <200 copies/mL on ddl/EC-containing regimens before food (fasted) and with a light meal.

ddA-TP levels were measured in 12 subjects (18 observations) and ddl levels were measured in 24 subjects (36 observations). Irrespective of food status, the IC ddA-TP PK profile was flat, in contrast to the peak and valley observed in the plasma ddl PK profile. Summary statistics for ddl and ddA-TP PK parameters show a 23% reduction in IC ddA-TP AUC, and a 34% reduction in plasma ddl exposure when ddl was dosed with food. All patients maintained viral suppression during the study.

The study concluded that plasma ddl and IC ddA-TP levels were reduced when ddl was dosed with a light meal. The clinical relevance of this food effect remains unclear.

C O M M E N T

Given that ddl is generally used in patients with some NRTI-resistance, and is often a component of regimens in multiple drug experienced patients, achieving optimal concentration in these patients will be important.

The flat IC exposure curve, together with long half-life of ddl suggests that observing fasted administration is probably more critical than exact time of dosing. Given the difficulties associated with fasted dosing, this may be useful for patient to consider, in situations when they may have eaten: delaying dosing for two hours is likely to be better than dosing at the exact time with a meal.

Ref: Girard PM, Benech H, Gengron A et al. Food effect on the intracellular (IC) pharmacokinetics of Dideoxyadenosine Triphosphate (ddA-TP), the active metabolite of didanosine (ddl), in treated HIV-1 infected patients. 7th International Workshop on Clinical Pharmacology of HIV Therapy, 20-22 April 2006, Lisbon. Abstract 79.

Conflicting results on how T-20 affects tipranavir

Mark Mascolini, for HIVpharmacology.com

Two small cohort studies reached opposite conclusions on whether the fusion inhibitor enfuvirtide raises levels of the protease inhibitor tipranavir, and 7th HIV Pharmacology Workshop attendees could not sort out the discrepancy in an open discussion.

Daniel Gonzalez de Requena (University of Turin) measured tipranavir levels in 55 people beginning 500/200 mg of tipranavir/ritonavir twice daily with or without enfuvirtide. Defining troughs as levels measured 11 to 13 hours after dosing, he found a significantly higher mean trough in people taking enfuvirtide (41,069 ng/mL \pm 20,174 ng/mL) than in those not taking the fusion inhibitor (27,261 ng/mL \pm 17,516 ng/mL) ($P = 0.011$). Ritonavir troughs were also significantly higher with than without enfuvirtide.

Tipranavir elimination half-life averaged 9.69 hours in the enfuvirtide group and 5.36 hours in the no-enfuvirtide group. Volume of distribution of tipranavir also proved higher with enfuvirtide than without it (9.85 versus 6.5 L). Tipranavir area under the concentration-time curve (AUC) and peak concentration did not differ significantly between groups. Because of these findings, Gonzalez speculated that higher tipranavir volume of distribution and longer half-life with enfuvirtide could explain the higher tipranavir concentrations. He did not report any between-group differences in antiviral efficacy or tipranavir/ritonavir tolerability.

Adrian Curran (University Hospital Vall d'Hebron, Barcelona) recorded nonsignificantly lower tipranavir troughs in 11 people taking the boosted protease inhibitor with enfuvirtide than in 4 not injecting enfuvirtide. Analyzing 44 tipranavir trough samples, he recorded a median reading of 35.30 mg/mL (interquartile range 28.00 to 43.30 mg/mL) with enfuvirtide and 39.45 (27.00 to 44.50) mg/mL without enfuvirtide ($P = 0.7$). Ritonavir troughs were moderately lower with enfuvirtide than without it (0.13 versus 0.20 mg/mL, $P = 0.08$). Men had significantly lower tipranavir troughs than women (34.42 versus 43.69 mg/mL, $P = 0.005$), but weight did not correlate with tipranavir trough. Gonzalez saw no weight difference in his enfuvirtide and no-enfuvirtide groups, and both groups were predominantly male. As in the Turin study, Curran recorded no differences in tipranavir peaks or AUC with versus without enfuvirtide.

Moderating a discussion of the two studies, Michael Kurowski (Therapia, Berlin) noted that the interaction Gonzalez reported comes as a surprise since tipranavir and enfuvirtide have entirely different chemical structures and metabolism mechanisms. He stressed the small numbers in both analyses and agreed that a formal pharmacokinetic study—not additional case reports—are needed to resolve the conflict.

Source: HIVpharmacology.com

References:

1. Daniel Gonzalez de Requena, A. Calagno, Stefano Bonora, et al. Unexpected drug-drug interaction between tipranavir/ritonavir and enfuvirtide. 7th International Workshop on Clinical Pharmacology of HIV Therapy. 20-22 April 2006. Lisbon. Abstract 52.
2. Adrian Curran, R. Lopez, L. Pou, et al. Pharmacokinetic evaluation of potential interaction between tipranavir and enfuvirtide. 7th International Workshop on Clinical Pharmacology of HIV Therapy. 20-22 April 2006. Lisbon. Abstract 53.

SPECIAL REPORT

Autologous stem cells transplant (ASCT) in HIV-infected individuals with a relapsed non-Hodgkin's lymphoma (NHL) or Hodgkin's disease (HD)

Svilen Konov, HIV i-Base

Abbreviations used in the article: ASCT-autologous stem cells transplant, CR-complete response, HD-Hodgkin's disease, NHL-Non Hodgkin's lymphoma, PBSC-peripheral blood stem cell transplantation, PR-partial response

The diagnosis and treatment of lymphomas in HIV-positive patients still poses significant challenges in clinical practice. Even though HAART has improved survival, lymphomas are still a major cause of morbidity and mortality.

For example, as a part of a broad study on survival rates among patients with particular cancer conditions in New York, Biggar et al. reported higher risk of mortality in HIV-positive patients with non-CNS related NHL between 1996 and 2000 compared to HIV-negative patients (95% CI: 1.6-2.2 and HR=1.9). These researchers concluded that with many cancers there remains an increased risk of dying within 24 months in people with AIDS compared with persons without AIDS who had the same cancers and "these survival gaps can focus attention on opportunities to improve cancer care in people with AIDS." [1]

This article reports on the option for patients with non-refractory relapsed lymphoma of using autologous stem cell transplant (ASCT) which allows 2-3-fold higher dosing of chemotherapy, by providing a stronger defense against toxicity associated with these drugs.

Background

Currently, in the UK, the standard of care for patients with lymphomas includes biopsy for diagnosis. Tissue samples are examined using flow cytometry to describe the clusters of differentiation and genetic examination for abnormal chromosome translocation. Modern genetic testing allows a sample to be tested against an array of 18 000 genes on a single glass chip.

The main difference between the Hodgkin's disease (representing about 15% of all lymphomas) and non-Hodgkin's lymphomas (about 85%) is the affected lymph cells. While HD affects the B-lymphocytes and is characterised by the presence of Reed-Sternberg cells, NHL can involve T-cells (including natural killer cells). Both diseases occur most commonly in lymph nodes above the collarbone, but HD is also more likely to appear in the mediastinum (especially in younger patients), while the NHL is more likely to appear in the mesenteric nodes as well. In addition, HD is more likely to present systemic "B" symptoms at the time of diagnosis.

The modern classification of lymphomas recognises that their clinical grouping (i.e. low grade, indolent, aggressive, etc.) is unsatisfactory and puts a particular stress on a combined definition of morphology, immunology, genetic features and clinical manifestation.

Treatment of lymphoma in HIV-positive patients

As different lymphomas have markedly different clinical behaviour, some recommendations emphasise that treatment decisions should be based on the specific lymphoid neoplasm, following the WHO classification shown in Table 1.

Table 1: WHO classification of lymphoid neoplasms

Source: <http://www.lymphomainfo.net/nhl/classify.html#location> Accessed on 21.05.2006

<p>B-Cell Neoplasms</p> <p>I. Precursor B-cell neoplasm: Precursor B-lymphoblastic leukemia/lymphoma</p> <p>II. Mature (peripheral) B-cell neoplasms</p> <p>B-cell chronic lymphocytic leukemia/ small lymphocytic lymphoma</p> <p>B-cell prolymphocytic leukemia</p> <p>Lymphoplasmacytic lymphoma</p> <p>Splenic marginal zone B-cell lymphoma (+/- villous lymphocytes)</p> <p>Nodal marginal zone lymphoma (+/- monocytoid B-cells)</p> <p>Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type</p> <p>Hairy cell leukemia</p> <p>Plasma cell myeloma/plasmacytoma</p> <p>Follicular lymphoma, follicle center</p> <p>Mantle cell lymphoma</p> <p>Diffuse large cell B-cell lymphoma:</p> <ul style="list-style-type: none"> - Mediastinal large B-cell lymphoma - Intravascular large B-cell lymphoma - Primary effusion lymphoma <p>Burkitt's lymphoma/Burkitt's cell leukemia</p> <p>B-cell proliferations of uncertain malignant potential</p> <p>Lymphomatoid granulomatosis</p> <p>Post-transplant lymphoproliferative disorder</p>	<p>T-Cell and Natural Killer Cell Neoplasms</p> <p>I. Precursor T cell neoplasm: Precursor T-lymphoblastic lymphoma/leukemia</p> <p>Blastic NK lymphoma</p> <p>II. Mature (peripheral) T cell and NK-cell neoplasm:</p> <p>T cell prolymphocytic leukemia</p> <p>T-cell granular lymphocytic leukemia</p> <p>Aggressive NK Cell leukemia</p> <p>Adult T cell lymphoma/leukemia (HTLV1+)</p> <p>Extranodal NK/T-cell lymphoma, nasal type</p> <p>Enteropathy-type T-cell lymphoma</p> <p>Hepatosplenic gamma-delta T-cell lymphoma</p> <p>Subcutaneous panniculitis-like T-cell lymphoma</p> <p>Mycosis fungoides/Szary's syndrome</p> <p>Primary Cutaneous Anaplastic large cell lymphoma T/null cell</p> <p>Peripheral T cell lymphoma, unspecified</p> <p>Angioimmunoblastic T cell lymphoma</p> <p>Primary Systemic Anaplastic large cell lymphoma, T/null cell</p> <p>T-cell proliferation of uncertain malignant potential</p> <p>Lymphomatoid papulosis</p> <p>Hodgkin's Lymphoma (Hodgkin's Disease) (B Cell Origin)</p> <p>Nodular lymphocyte predominance Hodgkin's lymphoma</p> <p>Classical Hodgkin's lymphoma</p> <ul style="list-style-type: none"> - Nodular sclerosis Hodgkin's lymphoma - Lymphocyte-rich classical Hodgkin's lymphoma - Mixed cellularity Hodgkin's lymphoma - Lymphocyte depletion Hodgkin's lymphoma
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Treatment approaches include:

- Radiotherapy (commonly 4-6 weeks, ex: in adult Hodgkin's, doses of radiation usually vary between 3,000 and 3,600 cGy to clinically uninvolved sites, and 3,500 to 4,400 cGy to regions of initial nodal involvement);
- Chemotherapy (most commonly CHOP-cyclophosphamide, adriamycin, vincristine, and prednisone, administered in cycles of 4 weeks, where the total treatment lasts for at least 6 cycles);
- Immunotherapy (monoclonal antibodies-rituximab, ibritumomab tiuxetan, tositumomab, 131I Lym-1;
- T-cell immunotherapy with polyclonal activation of T-cells with antibodies); and,
- A combination of the above mentioned treatments.

Bone marrow transplants and peripheral blood stem cells transplants are two newer treatments, that have been used either in combination with, or after, established treatment. Both treatments are steadily moving from the clinical trial area to mainstream therapy, including for HD and aggressive (often relapsed from chemotherapy) NHL.

The treatment of lymphomas, both relapsed and primary refractory, in patients with AIDS or HIV-infection poses a number of difficulties. These include:

- Limitations in individualising HAART (many patients have developed resistance to ARVs)
- Managing interactions with other medications used post-lymphoma therapy (antifungals, antivirals, etc.)
- Discordant immunological responses, and
- General weakness of patients' immune systems.

There is also a perception of an insufficient evidence-base to offer autologous stem cells transplants (ASCT) to HIV-positive patients. Other reasons for ASCT exclusion are complex, but include availability of technology in the local oncology centre, availability of expertise of on performing the intervention (both apheresis and application of the collected material), cost, and sometimes, a conservative medical view (based on mainly pre-HAART era studies),

In practice, HAART has allowed broader and more aggressive therapeutic approaches, as patients have better haematological reserves and better tolerability to intensive chemotherapy. In addition, the development of ASCT technology has led to decreased mortality, to the extent that transplantation is now sometimes used for older HIV-negative patients, as well as patients with comorbidities. Furthermore, the increased experience with HAART and antibiotic co-administration, allows researchers and medical professionals to reconsider the opportunities that ASCT interventions provide.

Data endorsement for ASCT in HIV-seropositive patients with relapsed or primary refractory disease

Recent studies, summarised in Table 2 clearly indicate that patients with AIDS/HIV-infection and relapsed or primary refractory lymphomas benefit from ASCT and its utilisation should be approached.

Gabarre et al [8] in France used ASCT combined with radiation and chemotherapy regimens in HIV-infected patients with Hodgkin disease and non-Hodgkin lymphoma. The study included 14 subjects both primary refractory and multiply relapsed. At reporting time, 6 months after treatment, the survival rate (according to the number of subjects who reported) was 43% [8].

A multi-centre study from Italy also followed a cohort of 16 patients with both refractory and relapsed conditions. Patients received BEAM (carmustine, cytarabine, etoposide, and melphalan) prior to ASCT. One patient did not undergo stem cells collection and three were unsuccessful in producing quality cells that would allow ASCT. After all treatments, nine patients had data for evaluation. Intent-to-treat analysis showed median disease-free survival was 11 months, with 8 patients achieving CR or PR after ASCT. The projected 2-year survival of the cohort is 39% [5].

One of the most recent studies is from Spain that also used BEAM as an initial regimen which defined CR as also including patients who have been on more than one line of chemotherapy prior to the ASCT, as well as patients with Burkitt-type lymphoma who achieved a CR after a second, more powerful therapy. All subjects, apart from one, were already in CR upon initiation of ASCT. Survival was 73% (disease free). One patient suffered from herpes zoster and another one from pulmonary aspergillus at time of reporting [11].

The most convincing results using ASCT for HIV-positive individuals with non-Hodgkin lymphoma is from Krishnan A and colleagues from the City of Hope National Medical Center, Duarte, California, US [2]. The study has the longest follow-up with a median period of observation of 31.8 months. It included HIV-positive patients with non-Hodgkin lymphoma who failed to achieve CR after a standard dose of chemotherapy or had a chemosensitive relapse after an initial CR. The cohort included 20 patients with a median age of 44 (range 11-68) at ASCT. Median CD4 count when diagnosed with lymphoma was 174 cells/mm³ and viral load was 26,120 copies/mL. At study entry, 17 patients had an undetectable viral load and the other three ranged between 700 and 6500. 15 patients used PI-based HAART and the rest used NNRTI-based regimen. 17 received a chemotherapy-based regimen and 3 radiation-based. All patients were exposed to ASCT and were maintained on their HAART regimen. The disease free survival was impressive at 85%.

Studies with long-term follow-up (Krishnan A. et al) verify that ASCT can offer long-lasting remissions, and that it can be a potentially curative option for patients with a poor response (and therefore poor prognosis) from conventional therapy [2]. HIV disease did not progress as a result of the transplants. Even though CD4 cells were still reduced six months month after therapy, they returned to the pre-transplant point about a year after the intervention.

Caveats to be considered include the difficulties at apheresis, and in particular the stem cell mobilisation. Individual ARV treatment regimens often need to be modified, in a way that minimises the risk of resistance after ACST. In this respect, AZT cannot be used both pre- and post-apheresis. Appropriate prophylaxis (for instance, oral acyclovir for a year after the transplantation to avoid herpes zoster complications) may reduce the risk of other opportunistic infections, although trimethoprim sulfamethoxazole cannot be used before apheresis [3].

Conclusions

These studies clearly show that although more data on the long-term follow-up, or on the dynamics of immune reconstitution after ASCT, are badly needed, there is adequate proof that ASCT is a feasible and beneficial treatment option for HIV-seropositive patients with HIV-related relapsed chemosensitive lymphomas, and this strategy should be offered as a therapeutic option.

This is particularly true if patients have stable HIV-infection, marked by low viremia to optimise the stem cells mobilisation and minimise risk of OIs. ASCT should be considered earlier after demonstration of chemotherapy sensitivity for those patients with first relapse or with primary refractory disease. [3]

In the UK, hospitals with experience and which can provide expert advice on the ASCT in HIV-seropositive individuals with NHL or HD are Chelsea and Westminster Hospital, Barts Hospital and Hammersmith Hospital.

C O M M E N T

High dose chemotherapy and ASCT is only likely to be effective in patients with relapsed lymphoma, whose lymphoma remain sensitive (non-refractory) to drug treatment. It is more likely to be useful for Hodgkins disease, where most UK experience in HIV-positive patients has been reported (with low numbers of patients having successfully been treated at the Chelsea and Westminster, Barts and Royal London, and Royal Free Hospitals).

ASCT is less likely to be useful for NHL because of the approximate 40% mortality, half of which is attributed to resulting opportunistic infections, and half to the lymphoma itself not responding to chemotherapy; or from a relapse in CSF which is also unlikely to respond to treatment.

Table 2: Literature review of recent ASCT studies in HIV-positive patients

Study	No. of pts, disease types and disease status pre-transplant	CD34+ cells collected (x10 ⁶ /kg)	Med. (range) no. of apheresis sessions	Day of engraftment median no		CD4 count and viral load changes during high dose chemotherapy and autologous peripheral blood stem cell transplantation	Outcome
				Neutrophils:	Platelets:		
Campbell et al., 1999 [7]	1 NHL Pre-transplant: CR	8.2	1	9	10	CD4 count: Baseline: Not available At 13 months: 220 cells/mm ³ VL: Baseline: 5000 copies/mL At 13 months: 5000 copies/mL	CR alive at 15 months
Gabarre et al., 2000 [3]	4 HD 4 NHL Pre-transplant: 3 CR 2 PR 3 Resistant	Mean 7.17 (range 4.5-17.6)	1 (1-4)	12 (9-18)	12 (9-23)	CD4 count: Baseline: Median 122 cells/mm ³ VL: Undetectable in 7	5 CR 4 alive at completion of study
Molina et al., 2000 [9]	2 NHL Pre-transplant: 2 CR						2 CR (at 20 and 28 months)

Krishnan et al., 2001 [6]	2 HD 7 NHL Pre-transplant: 6 CR 2 PR 1 relapse	Med. 10.6	1 (1-3)	11 (9-12)	10 (7-15)	CD4 count Post PBSC: Median nadir 138 cells/mm ³ (range 25-411 cells/mm ³) at a median of 2 months Recovery: Measured in 6 patients Returned to pretransplant levels by median 14 months (2-28 months) VL Pre-treatment: Undetectable in all Post PBSC: 6 pts rise in VL post PBSC 3 VL remained undetectable At 12 months post PBSC Undetectable in 5 of 7 evaluable patients	7 CR median follow up 19 months (range 12-36 months)
Re et al., 2003 [5]	8 HD 8 NHL Pre-transplant: 15 relapsed or refractory 1 PR	Assessable in 15 12 adequate collection: Median 6.8 (4.1-8.3) Mobilisation failed in 3	2 (2-3)	10 (8-10)	13 (8-18)	CD4 count: Mean Baseline: 236 cells/mm ³ (Range 17-506) +1 month Post PBSC: 154 cells/mm ³ +3 month Post PBSC: 93 cells/mm ³ +6 months Post PBSC: 186 cells/mm ³ VL Baseline: 5 Median 4,000 copies/mL (Range 690- 36,896) & in 11 undetectable Post PBSC: Remained undetectable in 8 of 11	9 assessable 7 CR 2 PR 2 relapses at +5 and +12 months 6 alive and in CR after a median of 8 months (range 2-17 months)
Gabarre et al., 2004 [8]	6 HD 8 NHL						5 alive 4 CR after a median of 25.5 months (range 14-49) 1 PD + 36 months
Serrano et al., 2005 [4]	3 HD 11 NHL Pre-transplant: 10 CR 4 PR	Median 4.7 (1.8-21.2)	1 (1-3)	16 (9-33)	20 (11-36)	CD4 count No significant change during PBSCC (median 186 cells/mm ³ versus 172 cells/mm ³ ; p=0.349) ‘Transitorily decreased’ after PBSC +12 months no significant different before PBSC (200 cells/mm ³ vs 172 cells/mm ³ ; p=0.138) VL: Remained undetectable in 3 patients throughout stem cell collection and PBSC	8 CR Median follow up 30 months (7-36 months)
Krishnan et al., 2005 [†] [2]	20 2 HD 18 NHL Pre-transplant: 6 CR 5 PR 9 relapse	Median 10.6	4	11 (9-23)	No data	CD4 count Baseline: median 175 cells/mm ³ (25-1064). +6 months: nadir +12 months: Recovery to pretransplant levels median 187 cells/mm ³ +24 months: median 472 cells/mm ³ VL: Baseline: 17 undetectable & in 3 ranged from 700-6500cp/mL +12 months: 12 undetectable & 4 detectable	17 alive Median follow up 31.8 months (5.5-70)

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GUIDELINES

US Adult Treatment Guidelines Updated

The Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents was revised in May 2006.

Changes to these guidelines include new recommendations for resistance testing, treatment interruption, and HBV/HIV co-infection. Tables have been revised to include up-to-date information about drug interactions and about the lopinavir/ritonavir 200/50 mg tablet formulation (Meltrex).

<http://aidsinfo.nih.gov/guidelines/>

C O M M E N T

The recommendation for genotypic resistance testing cover newly diagnosed individuals (whether or not they are considering ARV treatment) and all treatment naïve patients before starting treatment. This was first included in BHIVA guideline in 2003.

The recommendation for starting treatment remains ' when CD4 count is 200-350 cells/mm³, and first-line therapy remains: efavirenz plus 3TC/FTC plus AZT/tenofovir; or lopinavir/r plus 3TC/FTC plus AZT.

One of the key differences between UK guidelines is the continued use of AZT as a preferred first-line choice of nucleoside, without any reference to recent research showing that AZT causes lipoatrophy. AZT remains unlisted as a cause of lipoatrophy in both the text and in the tables summarising side effects. Evidence supporting this risk was considered sufficiently strong for this caution to be introduced in the UK guidelines in July 2005.

Recommendations for management of patients coinfecting with hepatitis B, includes not using 3TC, FTC or tenofovir as the only HBV-active treatment in HAART regimens, due to the risk of HBV resistance to these agents.

While BHIVA guidelines only recommend use of boosted-PI regimens, the US guidelines only recommend boosting atazanavir when used with tenofovir or efavirenz, and include un-boosted fosamprenavir as an alternative option.

The US guidelines also include several references to drugs that are now discontinued, including saquinavir sgc (Fortovase), ddC (zalcitabine) and amprenavir (Agenerase), though these may have been retained for historical reasons.

Draft BHIVA immunisation guidelines online

Compared with HIV-seronegative individuals, HIV-seropositive persons may have an increased risk of infection or experience more severe disease following exposure to vaccine-preventable diseases. The positive impact of antiretroviral therapy on the natural history of HIV infection makes the formulation of HIV-specific immunisation guidelines important at this time.

These guidelines contain evidence-graded recommendations that can assist the judicious use of active and passive immunisation in HIV-infected adults as a cost-effective way of reducing the disease burden for individual patients while also providing a wider public health benefit.

The primary objective is to inform clinical practice, based on the best available evidence and expert consensus opinion at the time of development. Given the lack of controlled studies, the recommendations are often an expression of a consensus derived from descriptive studies, clinical experience and expert opinion. The current draft will be revised following a period of consultation. Feedback on any aspect of the guidelines is strongly encouraged.

To view the guidelines, please go to the BHIVA website:

<http://www.bhiva.org>

Please forward your comments to the BHIVA Secretariat at:

bhiva@bhiva.org

TREATMENT ACCESS

FDA tentative approval for generic abacavir

Simon Collins, HIV i-Base

On 18 May 2006, the Food and Drug Administration (FDA) granted tentative approval for a generic version of abacavir, manufactured by Aurobindo Pharma LTD. of Hyderabad, India.

This is the first FDA approval for a generic version of abacavir. Tentative approval makes this product available for consideration for purchase under the President's Emergency Plan for AIDS Relief (PEPFAR).

The agency's tentative approval means that Aurobindo's product meets all of FDA's manufacturing quality and clinical safety and efficacy standards, but existing patents and/or exclusivity prevent its marketing in the United States at this time.

The list of approved drugs tracked in HTB over the last year is shown in Table 1.

Table 1: FDA tentative approvals of generic ARVs

Date	Drug	Company
May 18, 2006	abacavir sulfate tablets, 300 mg	Aurobindo Pharma, India
March 27, 2006	zidovudine 100mg capsules	Aurobindo Pharma, India.
March 6, 2006	copackaged AZT/3TC + efavirenz	Aurobindo Pharma, India.
December 27, 2005	nevirapine oral suspension, 50 mg/5 mL	Aurobindo Pharma, India.
December 21, 2005	stavudine oral solution, 1 mg/mL	Aurobindo Pharma, India.
November 4, 2005	lamivudine oral solution, 10 mg/mL	Aurobindo Pharma, India.
September 7, 2005	zidovudine oral solution	Aurobindo Pharma, India.
August 25, 2005	zidovudine 300mg tablets	Aurobindo Pharma, India.
July 13, 2005	zidovudine 300mg tablets	Ranbaxy Laboratories, India
July 7, 2005	lamivudine + zidovudine FDC	Aurobindo Pharma, India.
July 1, 2005	stavudine capsules	Aurobindo Pharma, India.
June 24 2005	efavirenz	Aurobindo Pharma, India.
June 20, 2005	nevirapine tablets	Ranbaxy Laboratories, India
June 20, 2005	nevirapine tablets	Aurobindo Pharma, India.
June 15, 2005	lamivudine tablets, 150 and 300 mg	Aurobindo Pharma India.
May 27, 2005	lamivudine tablets, 150mg	Ranbaxy Laboratories, India
January 26 2005	copackaged AZT/3TC + nevirapine	Aspen Pharmacare, S Africa.
December 3, 2004	didanosine (ddI) ER capsules, 200, 250, 400mg	Barr Laboratories, USA
May 17, 2004	FDA issue guidance document that describes the new process to expedite approval of low cost, safe and effective co-packaged and fixed dose combination (FDC) HIV therapies so that high quality drugs can be made available in Africa and developing countries around the world under the President's Emergency Plan for AIDS Relief (PEPFAR).	

Source for Table 1: individual FDA list serve posts

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

C O M M E N T

This is the first generic formulation of abacavir to be approved by the FDA and is an essential addition to the list of generic drugs that can now be used by the PEPFAR programme.

Although the FDA approval process has approved at least 15 ARV formulations since the programme was first announced in May 2004, it is difficult to know how many PEPFAR programmes have switched to these equivalent but less expensive formulations.

Anecdotally, activists report that programmes in Kenya, Tanzania and Zambia still use Brand drugs, but there currently seems no centralised report of any switch to these new formulations.

Source: FDA list serve

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

ITPC publish updated report on access to treatment

In the week prior to the United Nations General Assembly Special Session on HIV/AIDS (UNGASS) the International Treatment Preparedness Coalition (ITPC) issued a report 'Missing the Target – Off Target for 2010: How to Avoid Breaking the Promise of Universal Access'.

The report is an update of 'Missing the Target' – the International report on scale-up of AIDS treatment in six countries around the world, released last November. The report received international media attention and its major recommendations were endorsed by the 'Lancet Infectious Diseases' in January 2006.

The report is written by ITPC researchers in Russia, India, Nigeria (three of the "next wave" countries with explosive epidemics), the Dominican Republic, Kenya and South Africa.

ITPC found that the world will fall far short of the internationally declared goal of "near universal access" to AIDS treatment unless specific barriers to treatment scale up are addressed urgently. Our update finds that despite some progress, serious barriers – including halfhearted national and international leadership, weak management at all levels, sluggish implementation of reforms, poor logistics and technical support, and serious funding shortfalls – have not been adequately addressed and continue to plague delivery of AIDS treatment in less developed countries.

While some progress has been made in every country, most of the barriers identified in the original report remain, including:

- In the Dominican Republic treatment delivery is expanding but people in some of the poorest areas with the highest rates of HIV are still not being reached. Government and donor agencies are still not collaborating efficiently, scarce resources have been squandered, and second line drugs cost 10 to 20 times more than first line generics.
- In India, hundreds of thousands of people in need still do not have access to antiretroviral therapy, even though the number of treatment centers has increased. National treatment guidelines need to be reformed and clear action to reach children and ensure greater equity in care is needed.
- In Kenya, AIDS treatment services have been undercut by growing food shortages in some areas. Stigma and critical shortages of healthcare workers continue to be major problems. Government delays in submitting audit reports held-up the release of Global Fund monies.
- In Nigeria, more treatment centers have opened across the country, but the suspension of two grants by the Global Fund -- because the country failed to meet targets on drug access and demonstrate transparency -- is potentially devastating to the government's pledge to make treatment available and free.
- In Russia, government funding has grown, but these new resources have yet to translate into significant increases in treatment delivery. There is an urgent need for services appropriate for injection drug users, as well better health care worker training, more efficient drug procurement, and comprehensive anti-stigma efforts.
- In South Africa, the number of people on treatment has increased, but scale-up efforts continue to lag due to inadequate national leadership, government efforts to inhibit civil society participation, pervasive AIDS denialism, and a virtually non-functional Global Fund Country Coordinating Mechanism. Children and men also need greater access to treatment.

The report and related documents are available online:

<http://www.aidstreatmentaccess.org>

Protesters evicted from UN headquarters, New York

In the final hours of negotiations of the UN High-Level meeting on HIV/AIDS in New York this week, more than 100 civil society organisations worldwide staged an unprecedented protest shouting "The Declaration must include: treatment, targets, women and girls, harm reduction vulnerable groups". As they were herded out from the hall by security guards they chanted "Silence is Death".

They were rejecting a draft political declaration that fell far short of expectations at a time when 8000 people a day die of AIDS globally.

Governments failed to make commitments in five areas critical to ending the global AIDS epidemic.

According to the civil society coalition monitoring the UN drafting process the following concrete pledges are missing from the draft Declaration:

- Targets for universal access to prevention, treatment, and care, such as ensuring access to treatment for 80% of all people living with HIV worldwide by 2010;
- Comprehensive prevention strategies for all vulnerable populations;
- Substitution therapy for intravenous drug users, and
- Women's reproductive and sexual health and rights.

The document further fails to identify highly vulnerable and marginalized groups, such as sex workers, injecting drug users, prisoners, migrants, and people in conflict situations.

"We came here because in the last five years many new issues have emerged that were not anticipated when the 2001 Declaration of Commitment was signed. This new draft declaration is simply not bold enough. It does not address the changing realities of the AIDS epidemic," said one of the protesters. "Today, for example, we can afford to treat people with antiretroviral therapy - which we couldn't do five years ago because drug prices were still so high. But in the room right now, governments have refused to set a target for treatment because they are afraid that this will be used to hold them accountable."

Since 2001 the AIDS epidemic has shifted. In Eastern Europe, for example, there is an explosion of new infections among intravenous drug users, who need immediate access to clean needles and substitution therapy to avoid infection. In sub-Saharan Africa, there has been a feminization of the epidemic. Women now make up the majority of those infected.

Yet commitments to providing substitution therapy and to promoting women's rights were rejected by conservative governments.

Many of the goals left out of today's draft declaration would have represented a significant advancement to the 2001 Declaration of Commitment. According to another protester, "We demand a political commitment from governments that moves our struggle against AIDS forward rather than back."

Source: Press release UNGASSHIV.org

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

This site include many official UN documents including the new draft declaration and reports together with news links to external media regarding the UNGASS 2006 Review, and text from speeches given by Civil Society speakers at UNGASS.

Community opposition filed against tenofovir patent application in India

On 9 May 2006 the Indian Network for People Living with HIV/AIDS (INP+) and the Delhi Network of Positive People filed an opposition at the Delhi Patent Office to a patent application for tenofovir disoproxil fumarate (TDF).

"For many of us living with HIV/AIDS, newer drugs like tenofovir offer new hope of continuing treatment. With patents interfering with our lives we have no choice but to oppose them", says Loon Gangte, from the Delhi Network of Positive People, speaking at a press conference held in Delhi.

The World Health Organisation (WHO) recognises the importance of tenofovir and recommends on their website the drug for use in first and second-line drug regimens in resource poor settings. Widely available in the US and Europe, tenofovir is commonly prescribed because there are fewer known side effects associated with the use of this drug in adults.

However, tenofovir is largely unavailable and often unaffordable in the developing world and treatment providers, such as Médecins Sans Frontières (MSF), are keen to source it from India. The first generic version of tenofovir has been marketed in India since 2005. If the patent application filed by Gilead Sciences is granted, generic production of the drug will be blocked until 2018.

Public interest lawyers providing legal support to INP+ argue that forming a salt (fumaric acid) out of an existing compound (tenofovir disoproxil), is a common practice within the pharmaceutical industry, and should not be considered a new invention.

“If this patent is granted, it will set a dangerous precedent for global access to newer essential drugs”, explains Anand Grover, Director of the Lawyers Collective HIV/AIDS Unit. “Tenofovir production, just like that of other newer essential drugs, would remain solely in the hands of a single pharmaceutical company and block the generic competition that is needed to bring prices down,” he added.

The medical humanitarian organization MSF today expresses its support for Indian civil society groups in their legal battle against a patent application for the key AIDS drug tenofovir. ‘In our HIV treatment programmes, high price and a lack of availability is severely restricting access to treatment. We clearly need more than one source for essential drugs,’ says Hans van de Weerd Head of Mission of MSF in India.

Cancer patients recently opposed a patent application for an anti-cancer drug on the grounds that the application claimed a new form of an old drug. The patent was subsequently rejected by the patent office. K.K. Abraham from INP+: “This patent application should also be rejected because with the patent we will not be able to afford treatment.”

Under the 2005 Indian Patents Act, anyone can submit comments in opposition of a patent before the patent office decides to grant or reject it.

Source: MSF Press Release (10 May 2006)

C O M M E N T

The single most important factor in making HIV a treatable infection throughout the world, irrespective of a country's wealth, was undeniably the ability for Indian generic manufacturers to competitively manufacture antiretroviral drugs at a fraction of cost charged in Western countries.

While some research-based pharmaceutical companies offer discounted prices for some drugs that are lower than generic versions (generally protease inhibitors), reducing costs to more affordable levels has historically only followed price reductions from generic competition.

Additionally, countries not eligible for the discounted price of \$208 per patient per year – including Brazil, India, Thailand and China are forced to pay the full price of \$ 5,718 per patient per year. Although classed as middle-income countries they often have either high incidence of HIV, generally amongst the poorest members of society, and a lack of health care systems. In practice this means tenofovir is rarely available in many countries for patients who need second-line therapy.

In a statement from Gilead, the company said that they would use the expected patent responsibly, and would not block access to their medication in India or in other resource-limited countries. They stated that they are ‘pursuing a broad policy of non-exclusive, voluntary licensing under this patent to generic manufacturers in India for the local Indian market as well as provision for manufacturers to export product to the 97 developing world countries included in Gilead’s access program’. The statement continued ‘the specifics of these plans have not been finalised, and we will provide more details as soon as possible. We believe that multiple manufacturers will ensure competitive prices and the broadest access possible in these least developed countries.’

Last year, the Indian Parliament approved the country’s new Patent Act, thereby allowing pharmaceutical products to be patented in India. This new law put some serious constraints on generic competition but also included some potentially important features such as “automatic licensing” and the possibility for anyone to object to a patent before it is granted.

Although the law was not passed until last year, from as early as 1995, companies could start filing patent applications for pharmaceuticals in India with the patent offices. The backlog of thousands of patent applications includes antiretroviral drugs (ARVs) such as tenofovir DF and Combivir (AZT/3TC). Although this is a voluntary process, it is expected that all research-based companies have filed patents for all existing ARVs.

Not all patent applications are valid. The Indian Patent Act, if rigorously interpreted, provides several grounds for rejecting a patent, for instance if the pharmaceutical substance claimed is only a new form of a known substance. For example, in January 2006, the Indian patent office rejected the application for Novartis’ anti-cancer drug imatinib mesylate (Gleevec), on the grounds that the application claims a ‘new form of a known substance’ (Novartis’ patent application was related to a particular crystal form of the salt of imatinib mesylate). The rejection was a major victory for the Cancer Patient Aid Association of India and some Indian generic companies, which had both submitted a pre-grant opposition to the patent office. The rejection of the Gleevec patent gives reason for optimism.

Gilead’s patent for tenofovir disoproxil fumarate (Viread) was filed with the Delhi Patent office in 1998. The Lawyers Collective, in collaboration with the Alternative Law Forum, is currently drawing up an extensive list of drugs based on medical needs and for which patent applications are pending in India.

On March 30th 2006, The Indian Network for People Living with HIV/AIDS (INP+), the Manipur Network of Positive People (MNP+), represented by the Lawyers' Collective HIV/AIDS Unit officially submitted their opposition to a patent application filed in the Kolkata patent office by GlaxoSmithKline (GSK) for Combivir, a fixed-dose combination of two essential AIDS drugs zidovudine/lamivudine. The opposition is based on technical and health grounds. Clearly concerned that the granting of such a patent will increase the burden on developing countries already struggling to treat patients, INP+ objected to the Combivir patent application on the ground that it does not claim a new invention but instead simply the combination of two existing drugs.

RESISTANCE

Web resources for HIV-1 genotypic-resistance test interpretation

An article in the 15 April issue of Clinical Infectious Diseases, by Tommy Lui from US Division of Infectious Diseases, and and Robert Shafer from Stanford University, usefully describes the scientific principles of HIV-1 genotypic-resistance test interpretation and the most commonly used Web-based resources for clinicians ordering genotypic drug-resistance tests.

Prospective controlled studies have shown that patients whose physicians have access to drug-resistance data, particularly genotypic-resistance data, respond better to therapy than control patients of physicians without such access.

However, interpreting the results of HIV-1 genotypic drug-resistance tests is one of the most difficult tasks facing clinicians caring for HIV-1-infected patients because of the complex interactions among the many mutations that contribute to drug resistance; the varying levels of reduced susceptibility caused by these mutations; and the inability of drug-resistance tests to detect minor, yet clinically relevant, drug-resistant variants in a patient's virus quasispecies.

Web sites providing HIV-1 resistance summaries:

International AIDS Society, USA

http://www.iasusa.org/resistance_mutations/mutations_figures.pdf

Expert summary of the most clinically relevant mutations.

HIV Sequence Database, Los Alamos National Laboratories

<http://www.hiv.lanl.gov/content/hiv-db/COMPENDIUM/2005/part1/clark.pdf>

Summary of nearly all HIV-1 mutations associated with in vitro or in vivo drug resistance.

http://resdb.lanl.gov/Resist_DB/default.htm

Searchable form of Los Alamos summary.

Stanford University HIV Drug Resistance Database

<http://hivdb.stanford.edu/cgi-bin/PIResiNote.cgi>

<http://hivdb.stanford.edu/cgi-bin/NRTIResiNote.cgi>

<http://hivdb.stanford.edu/cgi-bin/NNRTIResiNote.cgi>

Graphical summaries of PI, NRTI and NNRTI drug-resistance mutations, respectively.

http://hivdb.stanford.edu/pages/genotype-clinical.html#ARV_Summaries

Antiretroviral drug summaries by drug.

<http://hivdb.stanford.edu/cgi-bin/PositionPhenoSummary.cgi>

Drug-resistance mutation phenotypic data.

http://hivdb.stanford.edu/pages/genotype-clinical.html#Summaries_of_Clinical_Studies

Summary of published studies linking baseline genotype and virologic response to a new treatment regimen.

Ref: Liu TF, Shafer RW. Web resources for HIV-1 genotypic-resistance test interpretation. Clinical Infectious Diseases 2006;42:1608-1618.

TB COINFECTION

HIV linked to lower rifampin and ethambutol AUCs in TB cohort

Mark Mascolini, HIVpharmacology.com

HIV infection independently predicted lower rifampin and ethambutol exposure in a cohort of 142 people beginning first-line therapy for drug-sensitive pulmonary tuberculosis.

South African researchers measured 8-hour area under the concentration-time curve (AUC) for rifampin, isoniazid, pyrazinamide, and ethambutol after 2 months of daily in-hospital treatment. They used multiple linear regression to sort out variables associated with variation in AUCs.

HIV infection correlated with a 39% lower rifampin AUC and a 27% lower ethambutol AUC. Women had higher rifampin and isoniazid AUCs than men but lower ethambutol concentrations. Older patients had higher levels of isoniazid and ethambutol. Patients with a history of anti-TB therapy had lower ethambutol concentrations. And dose per kilogram of body weight correlated with AUCs of all four drugs.

The authors caution "further studies are required to assess the implications of variations in antituberculosis drug concentrations for efficacy and safety before decisions are made to change the dosing strategy in patients at risk."

Ref: Helen McIlleron, Peter Wash, André Burger, Jennifer Norman, Peter I. Folb, Pete Smith. Determinants of rifampin, isoniazid, pyrazinamide, and ethambutol pharmacokinetics in a cohort of tuberculosis patients. *Antimicrob Agents Chemther* 2006;50:1170-1177.

Source: HIVpharmacology.com (April 2006)

SEXUALLY TRANSMITTED INFECTIONS

LGV in the UK: almost 350 cases reported and still predominantly affecting HIV-positive gay men

Michael Carter, aidsmap.com

Over 300 cases of the sexually transmitted infection (STI) lymphogranuloma venereum (LGV) have been diagnosed in the United Kingdom, according to figures presented to a sexual health conference on May 10th. Nearly all the cases involved gay men, many of whom were HIV-positive. Co-infection with other sexually transmitted infections such as hepatitis C virus, was also common.

LGV is a form of chlamydia, and although endemic in many parts of the world, it was rarely seen in Europe and North America after the introduction of antibiotics. However, in 2004 a cluster of LGV infections was seen amongst gay men who had attended sex parties in the Netherlands. The infection was quickly disseminated across western Europe and cases have also been reported in the United States.

In October 2004, enhanced national surveillance of LGV was commenced in the United Kingdom and investigators from Imperial College, University of London, presented data on the epidemiology of the infection in the United Kingdom, based upon reports received until the end of March 2006.

The investigators reported that a total of 341 cases of LGV had been diagnosed in the United Kingdom with detailed information being available for 283 cases. All but three of these cases involved gay men. The LGV epidemic was focused in London, where almost three quarters of infections were located. A secondary focus of the infections was Brighton (14%), with the remaining cases distributed across the country.

Most patients (94%) presented with symptoms of inflammation of the rectum (proctitis), although 30% also had flu-like symptoms and in a small proportion of individuals (3%) the infection was silent.

Source: aidsmap.com

Links: LGV Special report in HTB (July 2005)

<http://www.i-base.info/htb/v6/htb6-5/Lymphogranuloma.html>

ON THE WEB

Conference abstracts and reports:

The presentations given at the following Workshops are now available on line:

<http://www.HIVpresentation.com>

4th European HIV Drug Resistance Workshop

29 - 31 March 2006, Monaco

7th International Workshop on Clinical Pharmacology of HIV Therapy

20 - 22 April 2006, Lisbon, Portugal

2nd International Workshop on Clinical Pharmacology of Hepatitis Therapy

25 April 2006, Vienna, Austria

The presentations can be viewed online (either in thumb-view or enlarged). In addition a pdf version of the presentation can be downloaded for personal use only.

Abstracts and Meeting reports will be published in reviews in 'Antiretroviral Therapy' and the website offers a free copy from a link to an online request form.

Online medical resources:

HIV InSite: Gateway to HIV Knowledge

New and revised chapters to this comprehensive online resource added in April and May.

<http://hivinsite.ucsf.edu>

HIV antibody assays

Niel Constantine, PhD

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

Cryptococcosis and HIV

Judith A. Aberg, MD, William G. Powderly, MD

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

Cytomegalovirus and HIV

W. Lawrence Drew, MD, PhD, Jacob P. Lalezari, MD

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

Radiographic assessment of HIV

Philip C Goodman, MD

<http://hivinsite.ucsf.edu/InSite?page=kb-04-01-16>

HIV transmission and prevention in prisons

Elizabeth Kantor, MD

<http://hivinsite.ucsf.edu/InSite?page=kb-07-04-13>

Serious bacterial infections in children with HIV

Shirley Jankelevich, MD

<http://hivinsite.ucsf.edu/InSite?page=kb-05-01-01-01>

PLoS Medicine (Public Library of Science)

Volume 3(2) February 2006

How Do Viral and Host Factors Modulate the Sexual Transmission of HIV? Can Transmission Be Blocked?

Kalpana Gupta et al.

<http://dx.doi.org/10.1371/journal.pmed.0030079>

Volume 3(3) March 2006

Associations among Race/Ethnicity, ApoC-III Genotypes, and Lipids in HIV-1-Infected Individuals on Antiretroviral Therapy

Andrea S. Foulkes et al.

<http://dx.doi.org/10.1371/journal.pmed.0030052>

How to Take HIV Antiretroviral Medications on Time without a Watch in Rural Uganda

Marissa Maier et al.

<http://dx.doi.org/10.1371/journal.pmed.0030161>

Volume 3(4) April 2006

Modelling the Impact of Antiretroviral Use in Resource-Poor Settings

Rebecca F. Baggaley et al.

<http://dx.doi.org/10.1371/journal.pmed.0030124>

*Vaccine research:***New HIV vaccine website**

<http://www.aidsvaccineclearinghouse.org>

The AIDS Vaccine Advocacy Coalition (AVAC) has launched AIDS Vaccine Clearinghouse, a new source of AIDS vaccine information on the Internet. The website provides a gateway to information and a link to people and organizations interested in AIDS vaccine advocacy, research and global delivery.

The Clearinghouse is divided into separate content sections that include General & Introductory Information; Vaccine Science, Research & Development; Clinical Trials Around the World, including a list of clinical trials and trial sites with contact details to get more information; and Communities and Cohorts, with special sections dedicated to issues related to adolescents, women, gay men, sex workers, injecting drug users (IDUs) and African-Americans.

AVAC is simultaneously launching a new Advocates' Network – an electronic resource for organizations and individuals interested or already involved in advocacy for the development of vaccines for HIV/AIDS. Linked to the Clearinghouse, the Advocates' Network will provide regular electronic announcements, updates and notices of events or activities related to AIDS vaccine and other prevention research. You can join the Network by sending an e-mail to:

advocates_network@avac.org.

FUTURE MEETINGS**HIV highlights meetings**

Europe: Brussels - 23 June, 2006

US: New York City - 28 June, 2006

Several international HIV workshops have restricted entry criteria or are oversubscribed, and cannot be attended by all clinicians. In order to translate the latest findings presented at these meetings to all those clinicians and researchers who have not been able to attend the conferences Virology Education has organised several HIV Highlights meetings:

The meetings focus on the highlights of the 7th International Workshop on Clinical Pharmacology of HIV therapy (20-22 April, Lisbon, Portugal) and the 15th International Drug Resistance Workshop (13-17 June, Sitges, Spain). Original slides will be presented by members of the Organizing Committees of these meetings.

Topics:

- New Antiretroviral Drugs
- Mechanisms of HIV Drug Resistance
- Pathogenesis, Epidemiology, Fitness and Resistance
- New Resistance, Technologies and Interpretation
- Clinical Implications
- Therapeutic Drug Monitoring
- HIV Clinical Pharmacology

Speakers include: Brendan Larder, HIVRDI Cambridge UK, Charles Boucher, University Medical Center Utrecht NL, Terry Blaschke, Stanford University Medical School US, Daniel Kuritzkes, Brigham and Women's Hospital Harvard US and David Burger, Radboud University Nijmegen NL

Admission is free. For more information and registration please visit:

www.virology-education.com

8th Annual Conference of National HIV Nurses Association (NHIVNA)

29-30 June 2006, Leeds

One of the highlights of the conference will be the presentation of the latest research, education and clinical practice initiatives in HIV nursing during the oral presentation sessions.

NHIVNA is also inviting applications for a number of scholarships and awards.

If you want to make enquiries about the conference for 2006 please contact Andy Rogers on 020 8369 5383 or via email andy@mediscript.ltd.uk.

Programme and details can also be downloaded from the NHIVNA website:

www.nhivna.org.uk

IAPAC European Sessions 2006

12-13 October 2006, Budapest

The International Association of Physicians in AIDS Care (IAPAC) and the European AIDS Clinical Society (EACS) will co-host the third annual IAPAC European Sessions in Budapest.

IAPAC European Sessions is a symposium that allows HIV-treating healthcare professionals to learn from each other while working toward solutions to on-going clinical questions.

This meeting empowers attendees to benefit from the collective knowledge and experience of their peers. After short presentations on critical treatment issues, the floor is opened to debate and discussion. This interactive symposium work is crucial given that years after the development of highly active antiretroviral therapy (HAART) there remain contentious and mystifying problems in the medical treatment of patients with HIV/AIDS.

This year's Sessions include:

- Implications of a decade of HAART
- Navigating ARV drug resistance
- Sociobehavioural aspects of HIV care
- Emerging issues in HIV care

To see the full program and faculty presenters, visit the iapac web site:

<http://www.iapac.org>

14 Retrovirus Conference (CROI)

February 25-28, 2007, Los Angeles

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

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

<http://www.retroconference.org>

PUBLICATIONS & SERVICES FROM i-BASE

i-Base website redesigned - March 2006

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

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

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

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

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

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

The site is also more accessible for those with impaired sight. For those who understand these matters, all pages conform to at least the W3C-WAI Level A and most to level AAA.

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

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

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

A new page has been added on how to adapt and translate treatment resources, and included examples from projects we have worked with outside the UK.

An average of 2000 pages a day are served from the site.

Treatment training for advocates

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

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

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

<http://www.nkplus.org>

UK CAB: reports and presentations

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

Reading material, reports and presentations from these meetings (the 16th meeting was on 24 February 2006) are posted to the i-Base website.

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

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

World CAB - reports on international drug pricing

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

The latest report is from a meeting held in January 2005 with four Indian generic manufacturers.

An earlier report is from a meeting in February 2004 with three major brand manufacturers.

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

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

Introduction to combination therapy

June 2005 edition

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

Printed and/or PDF versions of earlier versions of this booklet are available in Bulgarian, Chinese, English, French, Georgian, Italian, Latvian, Macedonian, Portuguese, Russian, Slovak, and Spanish. Please see the 'translations' page or the website for more details.

Guide to HIV, pregnancy & women's health

Spring 2005 edition

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

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

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

April 2005 edition

Also updated and revised in April 2005, this is a non-technical patient guide to changing treatment and what to do if treatment fails.

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

Guide to avoiding & managing side effects

February 2005 edition

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

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

Chinese, French, Italian and Spanish translations of the previous edition are still available.

Translations of i-Base guides

Original material published by i-Base can be translated and reprinted, and have so far been produced in 27 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 on all information.

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

Chinese

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

Bulgarian

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

French

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

Greek

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

Hindi

- Treatment training for advocates [736Kb]

Italian

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

Nepalese

- Treatment training for advocates [1.3 Mb]

Portuguese

- Introduction to combination therapy [696 Kb]

Russian

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

Serbian

- Introduction to combination therapy [227 Kb]

Spanish

- Avoiding & managing side effects [210 Kb]
 - Introduction to combination therapy [192 Kb]
- HIV, pregnancy and women's health

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>

Questions answered in May include:

- Do I need to worry if I am late with my meds?
- How can I choose a clinic in the UK?
- Is treatment the same for people starting with a low or high viral load?
- What are polyps? And am I right in thinking they can be pre-cancerous growths?

Find HTB on AEGiS

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

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

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

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

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

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

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

h-tb

HIV Treatment Bulletin

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

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

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subscriptions@i-base.org.uk

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Editor in Chief: Paul Blanchard

Editor: Simon Collins

Commissioning Editor: Polly Clayden

Medical Consultants:

Dr Sanjay Bhagani, Royal Free Hospital, London.

Dr Karen Beckerman, Bellevue Hospital, New York.

Dr Martin Fisher, Brighton & Sussex University Hospitals.

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HTB is a not-for-profit community publication that aims to provide a review of the most important medical advances related to clinical management of HIV and its related conditions as well as access to treatments. Comments to articles are compiled from consultant, author and editorial responses.

Some articles are reproduced from other respected sources and copyright for these articles remains with the original authors and sources, as indicated at the end of each article.

We thank those organisations for recognising the importance of providing widely distributed free access to information both to people living with HIV and to the healthcare professionals involved in their care. We also thank them for permission to distribute their excellent work and we encourage HTB readers to visit the source websites for further access to their coverage of HIV treatment.

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**HIV i-Base
Third Floor East
Thrale House
44-46 Southwark Street
London SE1 1UN
T: +44 (0) 20 7407 8488
F: +44 (0) 20 7407 8489**

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

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HIV i-Base

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

REFUNDS FROM THE TAX MAN

From April 2005 the Inland Revenue is operating a system whereby you can request that any refunds from them should be paid to a charity of your choice from the list on their website. If you feel like giving up that tax refund we are part of this scheme and you will find us on the Inland Revenue list with the code: **JAM40VG** (We rather like this code!) Any amount is extremely helpful.

Whichever of the above schemes you might chose to donate to i-Base we would like to thank you very much for your support.

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Third Floor East, Thrale House, 44-46 Southwark Street, London SE1 1UN
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Introduction to Combination Therapy (June 2006)

1 5 10 25 50 100 Other _____

Earlier versions are available in FRENCH, ITALIAN, SPANISH, PORTUGUESE, CHINESE, and GREEK as pdf files on the i-Base website

Changing Treatment - Guide to Second-line and Salvage Therapy (April 2005)

1 5 10 25 50 100 Other _____

Guide To Avoiding and Managing Side Effects (February 2005)

1 5 10 25 50 100 Other _____

Earlier versions are available in SPANISH (as a print version) and in FRENCH, SPANISH, ITALIAN, and CHINESE as pdf files on the i-Base website

Phoneline support material (pls specify required number of each)

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

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

1 Sheet 1 pad 5 pads 10 pads Other

Office use:

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