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EDITORIAL

April's pharmacology meeting in Cannes provides the scientific focus for this issue and we cover the research that will have the most immediate impact on clinical care.

Following the results of the 2NN study, presented at Retrovirus, there was particular interest at this meeting in studies looking at concentrations, toxicities or interactions of the NNRTIs. We also include reports on intracellular levels of NRTIs, gender differences and the clinical role of TDM in Europe and the US.

From the Retrovirus meeting we cover the abundant PK interaction studies presented there, including both drug-drug interactions and the effects of food and alcohol. This may seem of only marginal interest, but with ever more new drugs and complex therapy, should inform treatment decisions of every HIV treatment prescriber.

As we go to press a big news story gains momentum – The Treatment Action campaign (TAC) has launched a campaign of civil disobedience to protest against the South African Government's negligent response to the HIV epidemic and the urgent need for a comprehensive public sector treatment plan including antiretrovirals. Global support is mobilising and in London a picket was back outside South Africa house for a day of solidarity on 24th April organised by the International Community of Women (ICW), STOPAIDS and the UK HIV/AIDS Consortium.

A detailed explanation of the campaign is contained in the document "Dying for Treatment", which can be read at

http://www.tac.org.za/Documents/CivilDisobedience/briefingdocument.htm

CONFERENCE REPORTS

The 4th International Workshop on Clinical Pharmacology of HIV Therapy, Cannes, France, 27-29 March 2003

Stephen Taylor MRCP PhD, HIV i-Base

The fourth in this annual series of workshops returned to Europe, after having made its first appearance in the USA last year. This spring meeting marks one of the year's highlights for those interested in HIV Pharmacology and is usually a perfect forum to generate active research discussions. This year approximately 150 delegates composed of HIV clinicians, pharmacists, researchers, activists and industry travelled to the French Riviera, to share the latest data concerning HIV pharmacology.

Following the presentation of the 2NN study at the Retrovirus conference earlier this year participants were particularly eager to hear of any drug concentration response or toxicity relationships pertaining to the NNRTIs and whether therapeutic drug monitoring (TDM) of these agents will be of potential benefit. Several papers attempted to shed some light on the pharmacokinetic/pharmacodynamic (PK/PD) relationships of the NNRTIs.

These reports cannot hope to cover the wealth of papers presented at this workshop (the abstracts will shortly be posted on HIV-Pharmacology.com) but instead cover some of the papers with most potential clinical relevance presented at the meeting. These include:

- Nevirapine and efavirenz concentrations related to antiviral response
- Variability in NVP/EFV drug concentrations in women and men
- NFV concentrations in HIV/HCV coinfected patients
- Bioequivalence of new 625mg NFV tabs and 250 mg tabs
- Potentially important probenecid/protease inhibitor drug interactions
- Gender differences in NNRTI concentrations
- Intracellular triphosphate concentrations higher in women and related to virological response
- Over-expression of MDR-1 in the placenta
- Maternal-foetal transfer and amniotic fluid accumulation of ARVs
- New test to measure intracellular levels of nucleosides
- Clinical role of TDM in Europe and the US
- Launch of TDM guide

This year's workshop provided clinicians and pharmacists with much to digest and much new data that has potentially important clinical implications. The meeting continues to provide an important forum in which to present both basic science research as well as pharmacologically driven studies. It is likely only to grow in importance within the HIV calendar.

Full content of the meeting including poster and abstracts, together with a conference report will be available at:

http://www.HIVpharmacology.com

Can low NVP plasma concentrations explain the results seen in the EFV and NVP containing arms of the NARVAL study?

Giles Peytavin of the Bichat Claude Bernard Hospital in Paris presented data that evaluated this issue [1]. In the Narval trial - a study including drug experienced but NNRTI naïve individuals - the multivariate analysis looking at predictors of virological success at week 12, suggested that the use of EFV rather than NVP was significantly associated with a better virological outcome. In this presentation the investigators postulated that suboptimal NNRTI concentrations could partially account for this finding.

Of the 541 patients, 42% and 24% received either EFV 600mg QD or NVP 200mg BD respectively as part of their new regimen. Virological success was defined as VL < 200copies/mL at week 12. EFV concentrations were considered adequate if they were above 1,100 ng/mL for EFV or above 4,000 ng/mL for NVP. Plasma concentrations of NVP and EFV were measured at weeks two, six and 12.

Reporting the results of the study, 56% and 28% of patients treated with EFV or NVP respectively had a VL < 200 copies/mL at week 12. The median plasma EFV concentrations were 2,400 ng/mL (10-14,300, n=288). EFV plasma concentrations were considered adequate in 90% of patients using this agent. In contrast the median plasma NVP concentrations were 4,500 ng/mL (50-29,000; n= 166) and were considered adequate in only 54% ($p<0.0001$) of patients. The authors speculated that these findings could explain why EFV and not NVP was associated with virological success in the multivariate analysis. They then went on to suggest that the usefulness of TDM in these HAART experienced but NVP naïve patients may be to "dose increase" a proportion of patients who may benefit from higher drug concentrations, considering that over 50% of this cohort were deemed to have sub optimal NVP concentrations.

Up to one third of patients receiving standard doses of NNRTIs may be being underdosed

Investigation into the plasma concentration effect of nevirapine (NVP) and efavirenz (EFV) was the subject of another oral presentation given by Dr Garraffo and colleagues from Nice University in France [2]. These investigators performed a retrospective study to try to correlate plasma drug levels with antiviral efficacy. Four hundred and forty-seven trough NNRTI concentrations (328 EFV samples and 119 NVP) were obtained over a two-year period from either drug experienced or drug naïve individuals. Drug concentrations were adjusted according to the French ANRS target values. These are 1,100-5,000ng/ml for EFV and 3,000-8,000 ng/ml for NVP.

Attempts were made to correlate drug concentrations with viral load response; the development of K103N and Y181C mutations and drug related side effects. The most startling finding was that 30% of trough levels were under the target concentration while only 2.5% were above them.

For drug naïve patients on EFV it was found that those with an undetectable viral load or the greatest viral load decrease had significantly higher plasma EFV concentrations than those with a lesser response, 1,770 ng/ml +/- 1,120 vs 1,490+/-770 $p<0.05$. No such difference was found in the pre treated group.

Unsurprisingly, the presence of the NNRTI mutations was significantly higher in treatment-experienced patients than naïve patients (38% vs 3 %, $p<0.02$). However, what was of great Interest was that a greater proportion of individuals with the K103N or Y181C mutations had plasma NNRTI concentrations below the target range.

Although these studies are subject to all of the criticisms that can be levied at retrospective analyses it remains a dramatic fact that one third of patients on the current standard of care regimens were deemed to have suboptimal NNRTI concentrations as judged by French pharmacologists. Clearly what is required is a prospective concentration controlled NNRTI study.

Nelfinavir concentrations are significantly higher in HIV/ HCV co-infected patients with cirrhosis

One of the most potentially useful applications of therapeutic drug monitoring is to individualise dosing in certain patient populations. HIV infected patients with hepatitis or chronic hepatitis C represent one such growing group. Dr Mario Regazzi from Pavia, Italy presented some of the first pharmacokinetic data on nelfinavir (NFV, Viracept) concentrations and its metabolite M8 in HIV/HCV co-infected patients with and without cirrhosis [3].

This study investigated 42 HIV-positive/HCV-negative individuals and 24 HIV-positive/HCV-positive patients without cirrhosis and 14 HIV-positive/HCV-positive patients with cirrhosis confirmed by biopsy. All patients were at steady state for NFV treatment, which was part of their antiretroviral regimen. Dosages were either 1,250mg BD or 750mg BD. More than seven plasma samples per patient were obtained and analysed for NFV and M8 using validated assays. The pharmacokinetic parameters are given in the Table 1 below.

Table 1: Pharmacokinetc parameters

NFV	HIV+/HCV		HIV+/HCV+ without cirrhosis		HIV+/HCV+ with cirrhosis
	n	PK parameters	n	PK parameters	n	PK parameters
Cmax (mg/mL)	25	5.2–2.2	15	7.7–3.4	12	10.6–6.3
Tmax (h)	25	2.7–1.0	15	3.3–0.8	12	3.4–1.4
Ctrough (mg/mL)	25	2.3–1.2	15	3.5–2.7	12	7.2–3.2
AUC 0-24 (mg.h/mL)*	50	60.44–17.05	29	104.55–37.75	14	168.49–88.95
CL/F (L/h/kg)	50	0.66–0.24	29	0.43–0.17	14	0.30–0.12

As can be seen the HIV-positive/HCV-positive with and without cirrhosis had a significantly lower “oral clearance” of NFV compared to HIV-positive/HCV-negative individuals (65% and 35% lower $p<0.05$) this manifested as a 155% and 58% higher AUC in cirrhotic and non-cirrhotic patients respectively.

Interestingly even the HCV-negative individuals in this study had an AUC 0-24 hours (normalised for a dose of 2,500mg a day) greater than the patients taking NFV in the Dutch ATHENA Cohort [4] (47.6mg.h/mL in the ATHENA cohort vs 60.4 mg.h/mL in the HIV positive/HCV negative Italian cohort).
This presentation generated much debate at the meeting as how this data should be interpreted; some individuals suggested that NFV doses should be reduced to prevent long-term toxicities. A contrasting view was put forward by Charles Flexner of John Hopkins University, USA, who postulated that these patients with hepatic impairment might do virologically very well using NFV, as patient failures with NFV are often driven by non-suppression rather than toxicity. Also he claimed that work by his group presented at last year’s meeting suggested that NFV toxicity with regard to diarrhoea was not dose dependent but an idiosyncratic response. Other members of the audience urged caution at maintaining patients’ NFV concentrations at potentially supra-therapeutic concentrations for prolonged periods of time.

Less diarrhoea and bioequivalence with the new nelfinavir 625mg tablet

Sticking to the NFV and diarrhoea theme, several presentations addressed the pharmacokinetics and bioequivalence of the new formulation NFV 625 mg tablet. These tablets contain the same amount of NFV but the excipient carrier compounds have been entirely changed in the new formulation, a move that may improve tolerability. In summary, when the 625mg was dosed as two tablets BD it showed almost identical PK parameters to five of the traditional 250mg tablets BD [5, 6, 7].

For those with a scatological sense of humour, the presentation by Margaret Johnson from the Royal Free Hospital in London was listened to with great interest. Patients were issued with “stool diaries” and completed these on a daily basis using the “Bristol stool and urgency algorithms”. On a more serious note, in this switch study, from old to new, the number of diarrhoea events of grade three or four severities reduced significantly upon changing to the new formulation.

It is likely that this new formulation tablet will be welcomed by all those currently taking the old formulation NFV tablets, as it will reduce pill burden and should improve tolerability. Whether it will increase the number of new patients starting NFV as a single protease inhibitor remains to be seen. After this meeting some pharmacologists may suggest that a higher dose of NFV than is currently marketed maybe more virologically effective while not increasing side effects.

Submission of the new formulation to the European Medicines Evaluation Agency is set for May this year.

The potential for probenecid to have a serious interaction with HIV-1 protease inhibitors

Marten Huisman from the Netherlands Cancer Institute [8] presented a basic science paper concerning the stimulation of the multidrug resistance protein (MRP2) by probenecid. However, this work may have important clinical implications in a ways he had not envisaged.

MRP2 is a glycoprotein found in the gut wall of humans and animals. Previous work by Huisman and colleagues has demonstrated the protease inhibitors ritonavir (RTV, Norvir), saquinavir (SQV, Fortovase) and indinavir (IDV, Crixivan) are substrates for MRP2 and that other drugs including probenecid can stimulate this protein. In the paper presented probenecid was being used to see if the reduced oral bioavailability of SQV fed to PGP deficient mice may be attributable to stimulation of MRCP2. Briefly, he found that co administration of probenecid and SQV to PGP deficient mice reduced the AUC of radiolabled SQV by 12 and 14 fold respectively.

However, during the course of his talk it became apparent to certain clinicians and pharmacists in the audience that the potential of probenecid to prevent RTV uptake may have profound consequences for protease inhibitor receiving patients treated for syphilis. The hypothesis runs something like this: if an HIV-1-positive person receiving Kaletra (lopinavir (LPV) and ritonavir (RTV) in combination) acquires syphilis, he/she is then likely to be treated with a one to two week course of probenecid as an adjunct to his/her penicillin. If probenecid does interfere with RTV absorption (as yet unproven in humans in vivo) then essentially LPV concentrations may fall to near zero without the boosting effect of RTV. The consequences are obvious. A probenecid and protease inhibitor interaction study is urgently needed!

C O M M E N T

Probenecid is unlikely to be the only pharmaceutical with action on MRP2, for instance, it is known that fibrates induce MDR-2 gene expression in the mouse. Perhaps even food substances may influence these proteins or genes in a similar way that garlic has been found to affect PGP expression.

Some of these factors may be contributing to the observed interindividual variations in ARVs found with TDM. It should also be noted that MDR-2/3 is involved in phospholipid transport in the liver and may also have some part to play in the disturbances of trigylceride and cholesterol metabolism seen after ARV initiation.

A summary article on the role and manipulation of MDR in the setting of cancer chemotherapy is available with free full text at:

http://jncicancerspectrum.oupjournals.org/cgi/content/full/jnci;95/4/255

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PK studies reveal significant sex/gender differences

Steve Taylor and Polly Clayden, HIV i-Base

Gender differences in nevirapine and efavirenz PK. Fact or fiction?

A presentation from Charles la Porte from the University of Nijmegen investigated possible differences between the sexes in the PK of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) nevirapine (NVP) and efavirenz (EFV) [1]. This Dutch group have previously reported gender-related differences in the PK of the PIs indinavir and lopinavir [2,3] and have

additionally observed high plasma levels of NVP and EFV in female patients through their TDM service. To date there is no literature describing gender-related differences of NNRTIs.

In this study the investigators collected retrospective data obtained from 100 women and 268 men receiving NVP and 38 women and 156 men receiving EFV. Samples were included for patients using 200mg NVP BID and 600mg EFV QD and information on gender, age, weight, indication for TDM, co-medications, plasma level and time between last dose and sampling was recorded. Toxic levels were described as >6.0 mg/L for NVP and >4.0 mg/L for EFV.

Differences in plasma levels were compared using a Mann Whitney test and Pearson Chi-Square and risk factors for the incidence of toxic drug levels were analysed by logistic regression.

NVP concentrations were significantly higher in women than men with a median NVP plasma concentration of 6.7 mg/L (IQR 4.9-7.9) in women vs 5.5mg/L (4.4-7.0) p=0.006. Unsurprisingly weight was also significantly lower in women than men 64kg (57.5-78.00) vs 77.2 (70.5-85.00) p<0.001. Women were also generally younger 35 (29-41) vs 44 (37-51) years. None of the other factors analysed were significantly different. Using their definitions 57% of the females compared with 40.7% of the males were classified as having “toxic levels”.

Almost identical findings were presented for EFV concentrations with median plasma concentrations in women being 3.0 mg/L (2.2-4.7) which were significantly higher than those in men 2.3 mg/L (1.5-3.4) p=0.03.

After ruling out patient weight using logistic regression analysis, the investigators cited gender alone to be the predicting factor for a toxic plasma level (p=0.02 for NVP and p=0.03 for EFV). They found no differences between genders, when considering the indication for TDM, co-medication and time between intake and sampling.

In summary, the investigators found both NVP and EFV levels to be higher in women than men in this cohort, which they speculate may in turn lead to greater incidence of drug toxicity. Dr La Porte noted that: “physicians should be alert to an increased risk for toxicity in females.”

Intracellular concentrations of 3TC-TP and AZT-TP are higher in women and may explain toxicity and antiviral response

Continuing the theme of gender and drug levels Peter Anderson from the University of Colorado presented an excellent paper on sex differences in intracellular triphosphate (TP) concentrations and intracellular dose response.

Currently nucleoside analogue reverse transcriptase inhibitors (NRTIs) are used as the backbone to virtually all antiretroviral regimens. Limited observational data has suggested that women may experience both stronger virological responses and greater toxicities related to NRTI use compared to men, but to date there has been no suggested explanation for these effects.

Unlike NNRTIs and PIs, NRTIs require intracellular phosphorylation to achieve their active state. Several papers presented at this meeting strengthened the observation that there is a very poor correlation between plasma levels of NRTIs and their intracellular active forms. However few studies have attempted to characterise the active forms of these drugs, predominantly due to the technical complications involved. The study summarised here is shortly to be published in AIDS. The premise of the study was that potent antiviral effects and excess toxicities sometimes observed in women starting HAART maybe related to the intracellular concentrations of the nucleoside triphosphates.

The patients enrolled were part of a concentration-controlled study of IDV, AZT and 3TC [Fletcher AIDS]. Stored PBMCs and plasma were analysed for intracellular triphosphates and plasma concentrations respectively. ZDV and 3TC tri-phosphate concentrations were obtained from 33 subjects providing 310 samples. Analysis revealed that the half-life of AZT triphosphate and 3TC triphosphate were 7 and 22 hours respectively (which is in keeping with previous studies). Triphosphate levels were quantified using enzyme-linked immunoassay for ZDV and LC/MS/MS to measure 3TC. 2.3-fold higher triphosphate concentrations of ZDV were found in women (n=4, 42 samples) compared to men (n=29, 268 samples) p=0.002 and 1.6 fold higher concentrations of 3TC p=0.003.

Obviously a potential limitation of this study is the small sample size (particularly the number of women represented), and this finding requires confirmation in larger studies. Nevertheless it may provide a plausible explanation for the increase in toxicity sometimes reported in women using NRTIs.

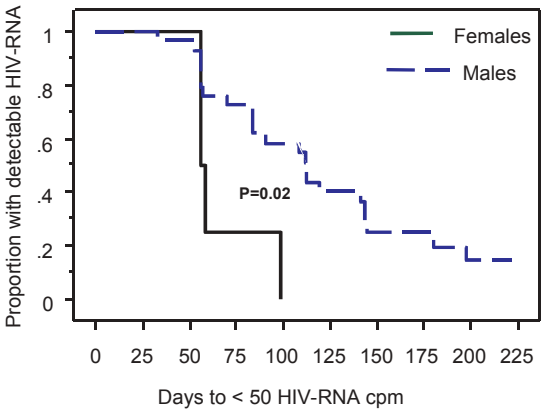
Intracellular triphosphate concentrations are related to antiviral response

The same study also revealed another important effect of these concentrations - in answer to the question “were these higher triphosphates exerting any extra ARV potency?” it was found that time to reach <50 copies/mL was half the number of median days in women compared to men (p=0.02). Importantly the increased AZT-TP and 3TC TP was the only significant difference

between the men and women shown in the table below:

	Males N=29	Females N=4	P (male vs female) Mann-Whitney
Age (years)	36 (30 to 42)	33 (27 to 38)	0.47
Weight (kg)	76 (56 to 112)	68 (52 to 84)	0.35
Baseline HIV-RNA (log copies/ml)	4.6 (4.2 to 5.0)	4.6 (4.1 to 5.0)	0.87
ZDV Css (ng/mL)	190 (164 to 216)	210 (185 to 230)	0.41
ZDV-TP (fmol/106 cells)	**46 (30 to 67)**	**106 (73 to 155)**	**0.003**
ZDV Sample Times (hr post dose)	2.8 (2.0 to 5.4)	3.4 (2.0 to 5.8)	0.68
3TC Css (ng/mL)	473 (407 to 543)	589 (491 to 689)	0.12
3TC-TP (fmol/106 cells)	**8096 (6481 to 9801)**	**12619 (10128 to 15852)**	**0.002**
3TC Sample Times (hr post dose)	4.3 (2 to 7.8)	3.0 (2.0 to 5.2)	0.55
IDV Cmin (ng/mL) 130 (90 to 160)	120 (90 to 155)	0.85	

Females had a faster time to < 50 cpm



(Table and slide courtesy of P Anderson unpublished data)

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C O M M E N T

It is strange in the nevirapine/efavirenz study that there was no difference in co-medications as one might, for example, expect some oral contraceptive use among women.

In the NNRTI study many in the audience felt the gender difference might simply be explained by body weight (an important finding in its own right) but in the logistic regression model presented, gender was the single predicting factor for potentially toxic NVP levels whereas age and body weight were not. Despite the limitations the potential effect of gender on NNRTI concentrations and toxicity may turn out to be important.

Several areas within this research require clarification in future trials, not least the therapeutic ranges used within these studies. In fact, one of the major rate limiting steps in establishing effective TDM services is setting biologically relevant cut offs for both efficacy and/ or toxicity. Currently these are based on a small amount of published data and expert opinion. [refs Acosta , ARHR, BACK AIDS]. For example the so-called "toxic threshold in this study" for NVP is 2,000ng lower than the French ANRS guidelines.

The effect of long term high drug concentrations in virologically suppressed individuals is currently unknown. However, like the protease inhibitors, higher drug concentrations are probably required in drug-experienced populations than in drug naïve patients. Therefore

maintaining the balance between virological efficacy and minimizing toxicity may be difficult in more experienced patients.

In the intracellular study, triphosphate concentrations were deemed an independent predictor of response even when the baseline viral load was controlled for, although It is possible that being female or having high intracellular triphosphate concentrations may be associated with another as yet unmeasured mechanism associated with beneficial response.

This is the first report of a relationship between intracellular drug concentrations and antiviral effect. This obviously opens the door to potential therapeutic interventions.

Pregnancy-related PK studies

Polly Clayden, HIV i-Base

Two small French studies at this meeting looked at maternal-foetal aspects of pharmacokinetics and genomics. Again the findings were intriguing but the clinical implications are unclear.

Over-expression of MDR-1 in the placenta

An oral presentation from Dr Maryse Camus was based on the hypothesis that P-glycoprotein (P-gp) may play an important role in limiting the materno-foetal transfer of antiretroviral drugs.[1] P-gp is a transporter of a large number of agents including PIs, which are now more frequently given to HIV-positive women during pregnancy. P-gp is expressed in the placenta and localised on the foetal side of trophoblastic cells.

Dr Camus explained that in France (similar to much of Western Europe) 36% of women were diagnosed during pregnancy and 50% of these women were between 30 and 39 years of age. HIV in pregnancy presents the unique challenge of treating maternal disease and preventing mother to child transmission.

This investigation evaluated P-gp expression in placentas from HIV-positive and negative women (n=24 and n=18 respectively). The HIV-positive women gave their informed consent for the use of their placentas in this study.

The investigators found a mean of seven-fold statistically significant increase in MDR1 expression in the placentas from HIV-positive women. This over-expression was similar with ZDV monotherapy or with more complex therapy.

	HIV-negative	HIV-positive	
Median	1.7 – 2.6	11.2 –17.4	*p < 0.001*
Min	0.05	0.5	
Max	7.6	72.7	

They suggest that this upregulation of MDR-1 in placentas from HIV positive women might contribute to "…diminish the foetal exposure to antiretroviral treatments or to other P-gp substrates and modulate their materno-foetal transport across the placental barrier".

Maternal-foetal transfer and amniotic fluid accumulation of ARVs

A study from Dr Chuppuy and colleagues (only in abstract form at this workshop) investigated placental transfer and amniotic fluid concentrations of antiretroviral drugs given to HIV positive pregnant women [2].

Maternal plasma, cord blood plasma and amniotic fluid samples were obtained from mother-infant pairs at time of delivery (n=103).

The investigators evaluated the most frequently used combinations in this cohort – AZT/3TC/NFV (n=20), AZT/3TC/NVP (n=13), AZT/3TC (n=8), ddI/d4T/NFV (n=7). They found a significant relationship between maternal and cord blood plasma concentrations for AZT/3TC, ddI, d4T, NFV and NVP.

Cord/maternal plasma concentration ratio was reported to be high for AZT (R=1.22), d4T (R=1.32), 3TC(R=0.93) and NVP (R=0.88). They were low for ddI (R=38) and NFV (R=0.24). They also found concentrations of 3TC in amniotic fluid to be higher than in maternal and cord blood plasma with median of 0.45, 0.41 and 1.68mg/L respectively.

These findings regarding the NRTIs are consistent with previous reports. NFV crosses the placenta with a cord/maternal plasma ratio of NFV. The investigators conclude "our findings could have important implications for the choice of the drugs during pregnancy."

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C O M M E N T

The biological function of P-gp is to exclude drugs and toxins from drug sensitive anatomical sites, such as the brain and testes and foetus. Hence overexpression of P-gp in the placenta is understandable reaction to the presence of drugs.

In most therapy situations maximal drug penetration into all anatomical body sites would be desirable. However, pregnancy may be an exception. It could be argued that as long as the mother's systemic viral load is fully suppressed, then excluding drug from the baby may not be a bad thing, certainly with respect to reducing foetal toxicity. Obviously, the drugs won't have the same PEP effect within the baby but as most transmissions occur at or around birth it is questionable how important this is.

New test to measure intracellular levels of nucleosides

Simon Collins, HIV i-Base

Grassi and colleagues from the Pharmacology and Immunology Unit of CEA (French Atomic Energy Commission) presented several examples of results from their research into developing an assay to measure intracellular levels of nucleoside triphosphates in PBMCs using liquid chromatography coupled with mass spectrometry (LC/MS/MS). Unlike protease and NNRT inhibitors, plasma levels of nucleoside analogues do not generally or usefully correlate with intracellular levels and measuring intracellular levels are not particularly easy even in a research setting.

Simpler assays to monitor these levels are much needed. In addition to individual monitoring, they would enable a more thorough understanding of the importance of both drug and food interactions, drug dosing and the safety of changes to once-daily dosing and the comparison of new formulations.

From a patient perspective, the ability to measure intracellular levels more easily would have clarified the confusion over the various formulations of ddI and changing recommendations for the interaction with food, and more recently the three-way interactions between ddI, food and tenofovir.

Validation for the direct LC/MS/MS is within international guidelines of 15% in routine conditions. The assay also allows simultaneous quantification of several nucleotides. They are explained in detail in published articles in *Anal Chem* 74(16):4220-4227 (2002) and *Rapid Commun Mass Spectrom* 16:555-565 (2002).

Using the assay to examine intracellular behaviour of d4T and ddI, they report half-lives of d4T-TP at around seven hours and >24 hours for ddA-TP (the intracellular metabolite of ddI) and report a weak correlation between intracellular levels of each in treatment naïve patients using d4T and ddI together.

This team also outlined again their research that generated significant attention at the Glasgow Conference last November and recently published in March 7th issue of AIDS. When measuring levels of AZT-TP when developing this test, they unexpectedly discovered significant levels of d4T triphosphate in 10 d4T-naïve patients who were taking AZT-containing combinations. This may provide insight into the complicated cross-resistance between the two drugs. How and why d4T-TP should be detected at all is still unexplained, and it is unclear whether it is formed as part of the process of AZT phosphorylation or as a breakdown product of AZT-TP.

It is hoped that further development of the assay will lead to new and exciting pharmacological research and add to our knowledge of how to most effectively use many of the oldest and most essential HIV drugs that continue to provide the backbone for current treatment.

Ref: Grassi J, Becher F, Pruvost A et al. New light on the intracellular pharmacology of NRTIs in HIV-infected patients. 4th Intl Workshop on Clinical Pharmacology of HIV Therapy, Cannes 27th-29 March 2003. Abs 52 P7.1.

C O M M E N T

Regarding the biological plausibility of *in vivo* AZT to d4T conversion may certainly be possible, as AZT and d4T are structurally very closely related and it would only require a single reduction reaction to chemically convert AZT to d4T.

If this reduction reaction could occur enzymatically in vivo this might explain the findings. What was surprising is the amount of d4T triphospate detected in some of the patients. This may also account for some of the cross toxicities seen with these agents.

Case studies for therapeutic drug monitoring (TDM)

Simon Collins, HIV i-Base

The clinical utility of therapeutic drug monitoring (TDM) was discussed at the meeting in a special roundtable session with HIV clinicians and pharmacologists using several real patient cases. As well as highlighting the complexity of most cases, the forum also provided a timely opportunity to discuss clinical scenarios where TDM may be most useful in supporting patient management.

Discussion of clinical management highlighted the importance that summary case notes often provided insufficient detail, but nevertheless, even when pressed to play 'devil's advocate' the strength with which some panel members refused to use the information provided by TDM was somewhat surprising.

Case 1

The first case was whether TDM would be useful for a 28-year-old woman, on first-line therapy for 14 months with d4T/3TC/NVP, who weighed 52kg and who has just developed raised liver enzymes.

In order to provide an answer the level of enzyme elevation needed clarification because it is unusual for levels to only increase after such a long otherwise stable period. Where TDM is not available, and levels were seriously elevated, switching nevirapine to a protease inhibitor was thought reasonable by most panel and audience members – but in practice this is likely to have a significant impact on quality of life for the patient in terms of pill count and side effects.

Detailing the case further, TDM was performed, and nevirapine levels were found to be elevated: did panel members think this would change the utility of TDM?

For David Burger, this provided very useful information. Previous studies, including presentations at this workshop, have highlighted the fact that women, particularly patients with low weight, are at increased risk of toxicity with nevirapine and are likely to experience higher drug levels. TDM is routinely used for all patients using PI or NNRTI-based combinations in the Netherlands, so if this patient were treated in Nijmegen and found to have very high drug levels, Dr Burger would feel confident in carefully adjusting the dose and checking the new level.

Jonathan Shapiro said that even if drug levels were five times higher than the recommended trough of 3.4mg/L, he would not feel confident in adjusting the nevirapine dose – citing nevirapine's low genetic barrier to resistance. He would prefer to change to a protease combination rather than use TDM to achieve and manage treatment at lower drug levels.

Case 2

A second case was that of an African-American woman, who weighed 130kg, and who was treatment naïve when starting d4T/3TC/lopinavir/r five months ago with a baseline viral load of 80,000 copies/mL. Her viral load after four months was 3,000 copies/ml and is now 3,200 copies/mL.

Here there was general consensus over patient management, and concern that viral load was not checked after the first month. Most clinicians would have hoped to pick up a failing treatment much earlier. Adherence was a possible explanation, as was pre-existing resistance that could have prevented the patient from benefiting from three fully active drugs.

Abbott researchers confirmed that drug clearance could be affected by weight but that this would only be expected with extremely light or heavy individuals, but also that a weight-related response was not seen in registrational studies of lopinavir/r.

Although weight impacts volume distribution, this is based on lean body mass. Peaks may be lower and troughs higher but this may not *a priori* be due to weight.

When either high or low weight is an issue for drug absorption, this presents a very good case for TDM, said Courtney Fletcher who would perform the intervention much earlier at two weeks into therapy - after drug levels have achieved steady-state but when any changes can also have an immediate effect. Genotype and TDM would be used together to prevent failure and protect the first combination.

Case 3

The final example was that of a 54-year-old male smoker with a family history of heart disease who is on a third-line regimen containing lopinavir/r and who has cholesterol levels above NCE threshold.

Switching to a non-PI based regimen is unlikely to be possible due to previous resistance but there was a general consensus on the importance of multiple approaches: diet; exercise; stopping smoking, perhaps with Zyban: statin treatment – after checking for interactions for both Zyban and statins and lopinavir/r; consideration of switching to atazanavir – with an eye on previous resistance – and the approach here might be different depending on whether the patient was currently virally suppressed.

This is a real-life situation that is increasingly common. In this case TDM showed he had high trough levels of lopinavir/r, and

with the support of TDM together with dietary changes and exercise, he was able to reduce the lopinavir/r dose to 2x400mg capsules BID, and still maintain trough levels >4.0mg/L.

Researchers from Abbott suggested confirming the phenotype prior to changing a dose for treatment experienced patients in case the higher level was needed, and they also suggested that there was unlikely to be a clinically relevant interaction with Zyban – a previous case study had shown no increased risk of compulsion when used with lopinavir/r – although closer monitoring would be prudent.

In summary, these discussions were as interesting from the approaches to patient management as well as the specific interpretation of information from TDM, in modifying dosing while maintaining efficacy – resulting in improved and safe choices for patients. Some clinicians still remain unconvinced – but these real-life examples suggested to many others that there were practical benefits that become available with the additional information that TDM provides.

Ref: Roundtable discussion: clinical implications of TDM. 4th Intl Workshop on Clinical Pharmacology of HIV Therapy, Cannes 27th-29 March 2003.

C O M M E N T

What was perhaps most enlightening about this round table discussion was the division of opinion between American physicians and the Europeans on the potential usefulness of TDM. However, in this debate the UK sided with the French, Dutch and Germans in feeling that it provided yet another important piece of data in conjunction with genotyping, adherence support etc to assist clinical decision making. Clearly more prospective studies on the clinical utility of TDM are required.

Launch of guide to the use of drug level monitoring

To clarify situations when TDM may add benefit that were highlighted in the roundtable session, the organisers of the meeting launched a new resource tool entitled “Optimising TDM in HIV Clinical Care”. This guide to utilising TDM was developed by the Editorial Board of the HIVPharmacology.com website, a specialist information site committed to reporting advances in HIV pharmacology and supporting clinicians in the application of pharmacological concepts.

The guide is a pocket-sized reference document aimed at clinicians interested in integrating TDM into their patient care. It highlights specific indications for TDM including special patient groups and a helpful step-by-step guide to performing TDM. The guide provides recommendations for using TDM to manage co-infections or drug-drug interactions that might complicate therapy. In special groups such as paediatric patients or pregnant women, TDM may be particularly helpful in identifying the treatment programmes best suited to individual patient’s needs.

Dr David Burger, from the University Hospital Nijmegen, the Netherlands, a leading advocate for pharmacologic monitoring of antiretroviral drugs and responsible for pioneering research in this area, advises physicians: “The level of inter-patient variability that we observe for some drugs can be striking and interactions between medications mean that the potential for patients to receive suboptimal levels cannot be overlooked. We can no longer assume that one dose fits all.”

Optimising TDM in HIV Clinical Care is available in PDF format:

http://www.hivpharmacology.com

or free-of-charge in printed form from Virology Education.

http://www.virology-education.com

Further Conference Reports from 10th Conference on Retroviruses and Opportunistic Infections (CROI)

Pharmacokinetics papers at CROI

Graham McKerrow and Simon Collins, HIV i-Base

The following is a summary of research into the pharmacokinetics of HIV treatment presented at the 10th Conference on Retroviruses and Opportunistic Infections (CROI) at Boston, 10-14 February 2003.

Abstracts, including all abstracts referred to in references to the following reports, as well as many of the full posters, and

webcasts from the symposium sessions and special lectures together with accompanying slides, are available at:

http://www.retroconference.org/2003/

Lower dose ddI with tenofovir results in similar drug exposure to a higher ddI dose alone

Researchers at Gilead Sciences conclude from a study in 28 patients that the administration of ddI EC (didanosine, Videx) 250mg with TDF (tenofovir DF, Viread) staggered or simultaneously with or without a meal results in similar ddI exposures to a 400mg dose of ddI EC alone.

Previous studies have identified increased ddI exposure when the two drugs are co-administered. ddI dose reduction may reduce ddI-associated adverse events. The objective of the study was to evaluate ddI PK following a dose reduction when ddI is administered in the fasted state and TDF is administered with a meal per current dosage and administration instructions. The study also evaluated the PK of ddI following a simplified dosing regimen of simultaneous co-administration in both fasted and fed state.

The researchers found that when administered in a staggered fashion a 250mg dose of ddI EC plus TDF resulted in an equivalent AUC to 400mg dosed alone. ddI AUCs were slightly higher (+14%) and lower (-11%) when simultaneously co-administered with TDF in the fasted and fed states, respectively. Observed ddI Cmax values were only slightly lower following 250mg plus TDF versus a 400mg dose alone. Within the interaction with TDF, ddI exposure was minimally affected by either staggering of doses or the effect of food.

Ref: B. P. Kearney, E. Isaacson, J. Sayre, et al. Didanosine and tenofovir DF drug-drug Interaction: assessment of didanosine dose reduction. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 533

Atazanavir and ritonavir plasma levels reduced by up to 25% when tenofovir is added to salvage regimen

Plasma levels of both atazanavir (ATV) and ritonavir (RTV, Norvir) seemed to be reduced in patients on salvage therapy after the introduction of tenofovir DF (TDF, Viread), according to researchers in Paris who conducted a prospective, open label, multi-centre trial of treatment-experienced patients. TDF and an RTV-enhanced ATV regimen were combined as salvage therapy; the PK part of this study is described in the poster.

The study looked at patients with HIV RNA >10,000 copies/ml after failure of regimen lines containing at least two PIs and one NNRTI. For the first two weeks patients were randomised to unchanged PI and NRTIs (group 1) or to a combination of ATV (300mg once a day), RTV (100mg once a day), and unchanged NRTIs (group 2). From weeks 2–26, all patients received ATV/RTV, TDF 300mg (once a day) and recycled NRTIs. Fifty-three patients were randomised in the study. Samples for ATV and RTV PK were drawn at week two and week six in 11 patients from group 2. Ten male patients (mean 45 years) completed the PK study.

Geometric mean at week two and six and their ratio (standard 90%CI), median and range of Tmax) are shown in Table 2 below.

Table 2: Geometric mean at week two and six and their ratio

	ATV			RTV		
	wk 2	wk 6	wk 6/wk 2	wk 2wk	6wk	6/wk 2
Cmax (ng/ml)	4,422	3190	0.72 (0.50–1.05)	886	642	0.72 (0.43–1.21)
Tmax (h)	3 (2–5)	5 (1–5)	-	3 (2–8)	3 (0-5)	-
AUC24 (ng.h/ml)	46,073	34,459	0.75 (0.58–0.97)	7,011	5217	0.75 (0.44–1.24)
Cmin (ng/ml)	636	491	0.77 (0.54–1.10)	43	39	0.91 (0.73–1.13)
C24 (ng/ml)	696	513	0.74 (0.53–1.02)	50	44	0.88 (0.69–1.13)

The researchers conclude: “At week two, ATV PK parameters when combined with RTV are in agreement with data obtained in healthy volunteers. After TDF introduction, both ATV and RTV parameters seemed to be reduced. These preliminary findings suggest that decrease in ATV concentrations at week six could result from lowered RTV concentrations, even though the differences on most parameters did not reach statistical significance. The impact of TDF on ATV PK when given alone is unknown. Mechanism of this interaction, likely to occur at the absorption level, needs further investigation.”

Ref: A. M. Taburet, C. Piketty, L. Gérard et al. Pharmacokinetic parameters of atazanavir/ritonavir when combined to tenofovir in HIV infected patients with multiple treatment failures: a sub-study of Puzzle2-ANRS 107 Trial. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 537.

Lopinavir/r and phenytoin levels both significantly reduced when coadministered

The co-administration of LPV/r (lopinavir/ritonavir, Kaletra) and the anticonvulsant phenytoin (PHT, Dilantin) used in the treatment of epilepsy, results in a two-way drug interaction whereby both LPV/r and PHT concentrations are decreased, researchers in North Carolina, Kansas and at Abbott Laboratories in Illinois conclude from their open-label, randomised, two-period crossover, steady-state PK study. Regimens may need to be adjusted as a result.

The study had two arms. Arm A (n = 12) received: Day (D) 1–10: LPV/r 400/100mg BID; D 11–22: LPV/r 400/100mg BID + PHT 300mg QD and Arm B (n = 12) received: D1–11: PHT 300mg QD; D 12–23: PHT 300mg QD + LPV/r 400/100mg BID.

Trough and AUC levels for lopinavir and phenytoin and trough levels of ritonavir all significantly decreased between day 11 and day 22 by approximately 25-50%.

The researchers conclude: "PHT appears to increase LPV clearance, which is not offset by ritonavir present in the formulation. LPV/r appears to induce metabolism of PHT. This two-way drug interaction is likely to be clinically significant, particularly for those with reduced viral susceptibility to LPV. Dosage or medication regimen adjustments may be necessary for optimal management."

Ref: M. L. Lim, S. S. Min, J. J. Eron et al. A Two-way Drug Interaction Between Lopinavir/Ritonavir and Phenytoin. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 535

Food intake essential when using NFV

An exploratory PK study of the effect of food intake on single dose NFV (nelfinavir, Viracept) concludes that: "food intake has a marked effect on nelfinavir PK with the highest levels achieved after the greatest food intake." The need for food intake with NFV has been established, but the effect of varying food intake on optimising pharmacokinetics has not been well studied.

Researchers from Agouron Pharmaceuticals and Pfizer conducted a phase 1, randomised, open label crossover study to evaluate the impact of total kilocalories and fat content on single dose PK parameters of the NFV 250mg tablet formulation in 24 normally healthy volunteers. The four food intakes studied were: fasting; 125kcal with 20% fat; 500 kcal with 20% fat and 100kcal with 50% fat.

Nelfinavir AUC and Cmax approximately doubled with the lightest meal and increased 3-5 fold with meals containing 500-1000 kcal and 20%–50% fat.

The researchers also noted that: "M8 concentrations rose with increasing food intake, but the percentage of M8 relative to nelfinavir remained the same, approximately 15%-20%. The contribution of different quantities of fat intake on PK and the effect of food on steady state PK in HIV patients require further study."

Ref: C. Petersen, E. Pun, R. Strada et al. Pharmacokinetics of nelfinavir (Viracept 250 mg tablet): effect of food intake on single-dose PK parameters. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 544

C O M M E N T

Without detailed information on diet and food interactions it is impossible for patients to know whether they are actually being adherent, and this information should clearly be part of the initial data required for approval. When low nelfinavir plasma levels were found in the ATHENA study, the first recommendation was to confirm that dietary advice was being followed, and this alone led to achieving normal levels in about 50% of cases.

It is always essential for 'food' to be defined when required to obtain reliable and stable drug absorption.

Tenofovir does not influence the PK of d4T XR

TDF (tenofovir, Viread) did not influence the PK of d4T XR (stavudine, Zerit extended release) Bristol-Myers Squibb researchers conclude from a study. D4T XR does not require dose modification when co-administered with TDF, they say.

A single centre, open label study looked at the effect of the once-daily formula of d4T and TDF co-administration on the PK

of d4T XR and TDF in 18 healthy subjects. On day 1: subjects received a single 100mg oral dose of d4T XR with a light meal (373 kcal). Days 2–8: subjects received once-daily 300mg oral dose of TDF with a light meal (373 kcal). Day 9: subjects received a single 100mg oral dose of d4T XR with 300mg of TDF and a light meal (373 kcal). Serial blood and urine samples were collected at selected times over a 24-hour period on days 1, 8, and 9 for PK assessments

The researchers report that plasma d4T concentration-versus time profile for the d4T XR+TDF treatment was super-imposable on the profile for the d4T XR alone treatment. The geometric mean (%CV) for Cmax and AUC, and median Tmax values were 274 (31%) ng/mL, 2,682 (29%) ng.h/mL, and 5 h, respectively, for the d4T XR alone treatment; the corresponding values for the d4T XR+TDF treatment were 275 (26%) ng/mL, 2,765 (28%), and 4 h, respectively.

Ref: S. Kaul, K. Bassi, B. Damle et al. Lack of interaction between stavudine extended-release formulation and tenofovir disoproxil fumarate. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 534

Use of PIs in transplant patients increases cyclosporine AUC, requiring dose reduction

The use of protease inhibitors in HIV-positive transplant patients "markedly" increases the AUC of the immunosuppressant agent cyclosporine (CsA, Neoral; Sandimmune), and requires progressive dose reduction, conclude researchers at the University of California at San Francisco who studied CsA-ARV interactions.

The researchers also concluded: "PI values may be low at baseline, and addition of CsA post-transplant may further lower PI levels, although this effect seems to diminish over time. Little interaction between CsA and NNRTIs were observed."

PK studies were obtained in 17 HIV-positive liver and kidney transplant subjects pretransplant, and during weeks 1–2, 4–8, 12, 28, and 52 and year 2 post-transplant. All subjects were on protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) or both; CsA was added post-transplant.

Pretransplant PI AUCs tended to be approximately 20% below the literature mean AUC for each PI measured (indinavir, nelfinavir, saquinavir), and decreased further during the first 12 weeks post-transplantation, before returning to pretransplant values. The exception was lopinavir/ritonavir (LPV/RTV) AUCs, which were five to six times higher than the literature mean for LPV AUC, and up to three times higher than that for RTV pretransplant through week 12. NNRTI (efavirenz, nevirapine) AUCs were generally near the literature mean AUC both pre- and post-transplant. CsA AUCs were generally lower for patients on any ARV compared to CsA AUCs in HIV-negative transplant patients, especially in the first few weeks after transplantation. Over time, for patients on PIs, the CsA dose had to be decreased by more than 75% to maintain CsA AUCs within range, while CsA dose and AUCs remained essentially unchanged for patients on NNRTIs. Despite the decreasing dose of CsA for those on PIs, the amount of CsA delivered, when adjusted for dose and body weight, was at least twice that for NNRTIs, due to progressive increases in intestinal CsA bioavailability.

Ref: L.A. Frassetto, M. Baloum, M.E. Roland et al. Two-year evaluation of the interactions between antiretroviral medication and cyclosporine in HIV+ liver and kidney transplant recipients. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 540

The PK of adding IDV to LPV/RTV regimens

Adding IDV (indinavir, Crixivan) 400mg BD to LPV/RTV (lopinavir/ritonavir, Kaletra) containing regimens did not significantly alter median LPV PK parameters in a British-Canadian study. However, wide inter-patient variability existed. IDV concentrations in blood plasma (BP) (Cmin), cerebro-spinal fluid (CSF), and seminal plasma (SP) were above target concentrations in 5/8, 4/4, and 3/4 samples, respectively.

Combination therapy including three protease inhibitors may be an option for drug-experienced patients. However, drug interactions can lead to toxicities or sub-therapeutic drug concentrations. Researchers at Birmingham, Liverpool and Toronto hypothesised that adding IDV 400mg BD to LPV/RTV would result in therapeutic concentrations of both drugs in the BP and therapeutic levels of IDV in CSF and semen.

Ten HIV-1-positive men on LPV/RTV (and at least one NRTI, and 3 with NVP) participated in a PK study. Sampling was performed prior to and two weeks after adding IDV to stable regimens. Blood was drawn at 0h and then 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 10, and 12 hours post-observed drug intake. CSF and semen were obtained 12 hours post-drug intake. BP, CSF, and seminal plasma (SP) drug concentrations were determined by validated HPLC-MS/MS.

No significant differences in LPV/r parameters were found when co-dosed with 400mg IDV (LPV Cmax, Cmin, AUC 0-12h increased by 9%, 46% and 20% respectively, all not statistically significant). Marked inter-patient variability was reported in LPV concentrations in plasma. All CSF samples of LPV were below the limit of detection without IDV but these rose to significant levels following IDV use.

IDV concentrations were above protein corrected minimum levels in all patients in semen and 7/8 patients in plasma. IDV levels in all CSF samples were in excess of non-protein corrected IC95 levels.

Virologically, the addition of IDV suppressed plasma viral load to <50 copies/mL in 2/8 men with detectable levels on LPV/r and 2/4 men with low level viraemia in semen became undectectable <400 copies/mL.

Ref: Isaac A, Taylor S, Rubin G et al. Lopinavir/ritonavir combined with twice-daily indinavir: pharmacokinetics in blood, CSF, and semen (The Protect Study). 10th Conference on Retroviruses and OIs, Boston 2003. Poster 531

C O M M E N T

This very interesting study suggests an intensification strategy that should involve minimal toxicity and low cost. The clinical implications of drug penetration to sanctuary sites is still poorly understood, but remains a concern for long-term treatment success and should be the focus for further study.

The study produces important information given the increased use of multiple PI therapy, especially in treatment experienced patients, but also for treatment naïve patients looking to reduce reliance on nucleosides.

NFV decreases the bioavailability of both lopinavir and ritonavir, while lopinavir/r increases dose-normalised bioavailability of nelfinavir and M8

NFV (nelfinavir, Viracept) decreases the bioavailability of both LPV and RTV (lopinavir, ritonavir, Kaletra), while LPV/r (Kaletra) increases dose-normalised bioavailability of NFV and M8, according to research carried out by Abbott Laboratories.

The Abbott researchers conclude that: “The dose of LPV/r may need to be increased when co-administered with nelfinavir, particularly in HIV patients with extensive protease inhibitor experience or reduced viral susceptibility to LPV. Concentrations of nelfinavir are similar when dosed at 1000mg BID with LPV/r compared to NFV 1250mg BID alone.”

Ref: C. Klein, R. Bertz, E. Ashbrenner, T. Chira et al. Assessment of the multiple-dose pharmacokinetic interaction of lopinavir/ritonavir with nelfinavir. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 536

No significant interaction between enfuvirtide and saquinavir/r, ritonavir or rifampicin

Co-administration of ENF (enfuvirtide, T20) with SQV/r (ritonavir boosted saquinavir), RTV (ritonavir alone), or the anti-tuberculous agent rifampicin did not lead to clinically relevant interactions and was well tolerated, according to three international PK studies.

ENF is the most clinically advanced in a new class of drugs, the HIV-1 fusion inhibitors. It is administered subcutaneously at a dose of 90mg BID. As a synthetic peptide, it is not expected to be subject to drug-drug interactions experienced by many of the conventional antiretrovirals (ARVs). The researchers conclude: “Consistent with the expectations of a peptide drug, low potential for drug-drug interaction is confirmed for ENF by these investigations.”

Ref: M. Boyd, K. Ruxrungtham, X. Zhang et al. Enfuvirtide: investigations on the drug interaction potential in HIV-infected patients. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 541

Pharmacokinetics and pharmacodynamics of low-dose mycophenolate mofetil in early stage HIV

Mycophenolate mofetil, (CellCept) the immunosuppressant used in patients receiving kidney transplants, has been proposed to increase the potency of some antiretroviral agents. An international study compared the pharmacokinetics and pharmacodynamics of two doses: 250mg BID and 500mg BID.

The researchers conclude: “Sera from the majority of patients receiving low doses of mycophenolate mofetil (250mg or 500mg BID) inhibit lymphocyte proliferation during most of the interdose intervals despite low MPA plasma levels. For some patients higher doses could be necessary, the capacity of sera to inhibit CEM proliferation can help to identify those patients. Cmax is the only parameter higher in 500mg BID vs 250mg BID, while the AUC, Cmin or inhibition of lymphocyte proliferation were similar in both groups.”

Ref: J. Martorell, M. Brunet, F. García et al. Pharmacokinetics and pharmacodynamics of low-dose mycophenolate mofetil in early stage HIV-infected patients successfully treated with HAART. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 538.

Mycophenolate mofetil lowers plasma nevirapine concentrations but has no effect on intracellular triphosphate concentrations of 3TC and abacavir

Recent studies suggest a potential role for mycophenolate mofetil (MMF) in the treatment of HIV-1. MMF interferes with cellular guanosine nucleotide biosynthesis, thereby limiting lymphocyte proliferation. This might limit the availability of target cells for HIV-1 infection. In vitro MMF has a direct anti HIV-1 effect and increases the efficacy of abacavir (ABC). An international study of 14 patients looked at the effect of MMF on the pharmacokinetic parameters of a number of antiretroviral drugs, and on the intracellular deoxycytidine triphosphate (Dctp) and deoxyguanose triphosphate (Dgtp) pools and triphosphate concentrations of lamivudine (3TCTP) and ABC (CBVTP).

In this small cohort of patients, MMF reduced the plasma concentration of nevirapine but had no effect on plasma indinavir and abacavir concentrations. In contrast to the researchers' hypothesis, there was no consistent effect of MMF on the intracellular concentrations of dCTP, dGTP, or 3TCTP. They conclude that additional PK and efficacy data are required to determine the impact of MMF when added to existing antiretroviral therapy.

Ref: S. Sankatsing, P. Hoggard, D. Back et al. Mycophenolate mofetil lowers plasma nevirapine concentrations but has no effect on intracellular triphosphate concentrations. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 539

Co-administration of atazanavir and efavirenz; the effects of atazanavir on oral contraceptives

Atazanavir (ATV) is a potent, safe, and effective once-daily azapeptide protease inhibitor currently in Phase III development. Two individual pharmacokinetic (PK) drug interaction studies were reported. The first study was conducted to assess whether efavirenz (EFV), a metabolic enzyme inducer, had an effect on ATV exposure. The second study was conducted to assess whether ATV had an effect on either ethinyl estradiol (EE) (a substrate of UDP-glucuronosyl transferase 1A1) or norethindrone (NE), a combination oral contraceptive (OC).

The researchers report that once-daily co-administration of 300mg ATV, 100mg RTV and 600mg EFV preserved ATV exposure vs 400mg ATV alone and allows co-administration of ATV and EFV.

They also conclude: "Co-administration of OC and 400 mg ATV will not impact OC effectiveness. No dose adjustment of OC is recommended. In both studies, no serious laboratory or clinical adverse events were observed."

Ref: D. Tackett, M. Child, S. Agarwala et al. Atazanavir: A summary of two pharmacokinetic drug interaction studies in healthy subjects. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 543.

The effect of alcohol on protease inhibitor exposure in chronic heavy drinkers

The effect of ethanol (alcohol) on the PK of drugs has not been fully investigated. Twenty-five per cent of HIV-infected subjects are heavy drinkers and susceptible to drug-drug interactions between ethanol and antiretroviral therapy. Ethanol may induce cytochrome p450 (CYP) metabolism when used chronically. However, when taken acutely, ethanol will inhibit drug metabolism due to competition with CYP isozymes. It has been hypothesised that chronic ethanol use will result in diminished HIV protease inhibitor (PI) exposure while acute ethanol use will result in increased PI exposure.

Researchers in San Francisco and Seattle prospectively enrolled HIV-infected subjects managed with nelfinavir (NFV) (n = 27) or indinavir (IDV) (n = 8), to evaluate the acute and chronic effects of ethanol on protease inhibitor pharmacokinetics.

The researchers conclude that results to date suggest minimal effect of ethanol on PI exposure. The slight increase in NFV AUC with ethanol use implies ethanol co-administration can occur without risk of suboptimum PI exposure. Furthermore, there appears to be no difference in the effect of ethanol on PI PK when used chronically versus acutely.

Ref: F. Aweeka, P. Lizak, L. Karan et al. The effect of ethanol on protease inhibitor exposure in chronic heavy ethanol users. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 545

Administering rifampin with IDV/RTV 800/100mg risks subtherapeutic concentrations of IDV

There is clinically significant interaction between IDV (indinavir, Crixivan) and rifampin, used in the treatment of MAC and TB infections, report Danish researchers. In their study of the pharmacokinetic interaction between rifampin and the twice-daily combination of indinavir and low-dose ritonavir in HIV-infected patients, they saw a dramatic decrease in IDV C12h. They conclude that it is not possible to administer rifampin together with the IDV/RTV 800/100mg regimen without risking subtherapeutic concentrations of IDV.

Ref: U. Justesen, A. Andersen, N. Klitgaard et al. Pharmacokinetic interaction between rifampin and the twice-daily combination of indinavir and low-dose ritonavir in HIV-infected patients. 10th Conference on Retroviruses and OIs, Boston 2003. Poster 542.

Pediatric studies from CROI

Polly Clayden, HIV i-Base

There were a number of reports pertaining to paediatric HIV at the tenth Conference on Retroviruses and Opportunistic Infections, particularly focusing on neonates and vertical transmission and metabolic abnormalities in children receiving antiretrovirals.

Simplification of neonatal prophylaxis

Since the widespread adoption of the 076 protocol in the industrialised world, the maternal monotherapy component of this strategy has largely been replaced by combination therapy to treat maternal disease in pregnancy. However, neonates born to HIV-positive mothers still typically receive zidovudine (ZDV, Retrovir) four times a day, in accordance with the original protocol, for the first six weeks of life to reduce mother to child transmission.

A poster from O'Meara and colleagues from Dublin reported substitution of a four week, twice daily regimen for the original six week four times a day strategy.[1] The rationale for this was based upon the success of four-week post exposure prophylaxis strategies for adults.

The investigators speculate that regimen simplification could help adherence and limit toxicity, particularly ZDV-associated anaemia, and they report findings from an audit of 229 infants born to mothers with HIV, performed between November 1994 and June 2002.

Of the group studied, 67% of the 202 HIV-positive mothers were African and 94% received ARV during pregnancy (67% triple therapy, 23% dual therapy, and 9% ZDV). 90% of the women had intrapartum intravenous ZDV; 14 infants received only the post partum component.

Mode of delivery included: 61% vaginal deliveries, 25% elective C-section, and 14% emergency C-section. Of 229 infants, 41% received triple therapy (four weeks ZDV/3TC/NVP, 2mg/kg, one or two doses), 25% received 3TC/ZDV, and 31% ZDV. Prescribed duration of post partum prophylaxis was four weeks for 223 infants. Out of the group of infants receiving ZDV monotherapy - 99 (43%) received 4mg/kg BID and 130 (57%) 2mg/kg four times a day. Some 97% of infants completed the prescribed regimen and 225 were uninfected. Only one infant was not followed up after delivery.

Overall, 33/228 (14%) had Grade 3 or 4 anaemia (15% BD vs 14% four times a day zidovudine); 88/228 (38%) had Grade 3 or 4 neutropenia (30% BD vs 40% four times a day zidovudine). All resolved to £ grade 2 after 12 weeks. A slight trend toward less neutropenia in BD zidovudine recipients was also observed.

Despite the limitations of a retrospective audit spanning eight years and using various ZDV regimens, the investigators reported that this study suggests that efficacy will not be affected by shortening the six-week neonatal component. The overall transmission rate was 1.3- 1.7% and the three known infected infants were reported to have been infected in utero so that the reduced duration of therapy would not have affected outcome.

Concern that a switch to BD zidovudine dosing might be accompanied by greater haematologic toxicity was not proved and the only predictor of neonatal anaemia was in utero exposure. The incidence of anaemia and/or neutropenia was not increased in infants receiving dual or triple therapy in this study.

Anecdotally it seems that several groups already use simplified strategies for neonate prophylaxis (and regimens that do not contain ZDV in cases where the mother has resistance to this agent) but to date there have been no published data to support this.

IL-2 production in HIV exposed uninfected infants of mothers given NVP prophylaxis

Single dose nevirapine (NVP, Viramune) given to HIV-positive mothers in labour followed by a single dose to the neonate is used widely as a strategy to reduce mother to child transmission in resource poor settings. However, the mechanisms of this strategy are unclear.

A poster from Kuhn and colleagues reported from a study investigating immunologic responses among infants born to HIV-infected mothers [2]. In this study cord blood was collected from 25 deliveries in which nevirapine was given at the onset of labour and compared to cord blood from 115 deliveries in which no antiretrovirals were given. In addition cord blood from 20 HIV-negative mothers was used as a control.

IL-2 production was measured using the Quantiglo immunoassay (R&D, Oxon, UK) and HIV-stimulated IL-2 production was detected among 18/115 (16%) deliveries if no antiretroviral drugs were given prior to birth, but among 0/25 deliveries if nevirapine was given ($p = 0.03$). No HIV-stimulated responses were detected among the control group.

The investigators reported similar results if the evaluation was restricted to those deliveries in which the infant was confirmed to be uninfected. Maternal plasma viral load and CD4 counts at delivery were similar among those with or without HIV-stimulated IL-2 responses (mean 4.23 log10 copies/ml vs ml vs 4.11 log10 copies/ml; mean 479 vs 541 cells/ml respectively).

They concluded that single-dose nevirapine given shortly before birth may have immunologic consequences detectable in

cord blood and that further characterisation of these consequences may help identify how single dose nevirapine is effective in reducing perinatal HIV transmission. The investigators noted: "Studies of newborn immune responses to HIV need to take into consideration use of antiretroviral drugs prior to birth."

Mother to child transmission of mixed maternal HIV variants

A poster from Cosgrove and colleagues compared maternal and infant isolates from HIV-positive mothers and their infected infants in order to track mixed variants detected in maternal samples, following mother to child transmission [3].

HIV isolates from 18 mothers enrolled in the WITS study, at or near delivery, were compared with paired sequences either for their infected infants at birth (n=5) or at first available positive culture (n=13) and with follow-up infant isolates within the first year (n=18). Nucleotide sequences for protease codon 1 through RT codon 324 were determined using Bioinformatics software created to analyse positions with mixed sequence in maternal and/or infant isolates.

Fifty-four (54) total isolates from 18 mother/baby pairs were sequenced. The investigators observed 327 mixed positions, including 208 maternal mixed sites, three infant birth mixtures, and 50 mixed positions at first available infant culture. Maternal mixtures per isolate (median 13.5, mean 14.3) were much more prevalent than mixtures in earliest infant isolates (median 0, mean 3.1) ($p < 0.001$, chi squared). Of 208 maternal mixed positions, only 17 were transmitted to the infant, all of these in three mother/baby pairs with high numbers of maternal mixed positions (19, 20, and 26). Of the remaining 191 maternal mixtures, infants showed wild type alone significantly more frequently (143/191, 75%), than mutant alone (48/191, 25%) ($p < 0.05$). Most maternal mixtures were at third codon positions.

From maternal mixtures, wild-type alone was most likely to be transmitted to the infants (68%), especially at resistance positions (6/6, 100%). Very few maternal mixtures were transmitted to the infant (8%).

The investigators concluded that mother to child transmission represents a "…population bottleneck for the virus" and only a small fraction of maternal genotypes are transmitted vertically. They added: "From maternal mixtures the wild type component is more likely to be transmitted to the infant, including at resistance positions."

Influence of maternal viral load on infant disease progression

A meta analysis from Tatsioni and colleagues evaluated whether HIV RNA levels of mothers at or close to the time of delivery affects the rate of disease progression among vertically infected children, and whether it correlates with early levels of HIV RNA in the infant and has an influence on infant disease progression [4].

The investigators performed their analysis using data from eight studies from centres in Europe and the US with 574 HIV-infected infants with available maternal viral load measurements at or close to the time of delivery and clinical follow-up. The primary outcomes were disease progression to category C or death (n = 178). The secondary outcome was death (n = 86).

Maternal viral load significantly increased the risk of disease progression ($p = 0.02$). The association with disease progression risk was strong in the first six months of life ($p = 0.001$), but not subsequently. Across all studies, maternal viral load at or close to delivery correlated with early infant viral load ($r = 0.26$, $p < 0.001$).

It is hoped that according to current standard of care in the industrialised world, treating maternal disease appropriately for a woman's own health and in turn preventing mother to child transmission would be reason enough to aim for an undetectable maternal viral load particularly at or close to delivery. This analysis also reveals (in keeping with previous data) maternal viral load to be a strong independent predictor of infant disease progression especially in the first six months of life. The correlation was similar whether or not mother and infant pairs received antiretroviral therapy.

Gender differences in mother to child transmission

An investigation into gender and susceptibility to infection and disease progression in children, reports a significant increase in transmission to girls and in particular African girls, compared to boys [5].

This poster from Newell and colleagues on behalf of the *European Collaborative Study* (ECS) found, in this non-breastfeeding population, a higher prevalence of mother to child transmission among girls (adjusted odds ratio 1.44 p=0.018). ECS is a prospective cohort study, in which infected and uninfected children born to HIV-infected mothers are followed from birth in nine European countries.

This study, initiated in 1987, recorded an overall vertical transmission rate of 10.9%, which has declined significantly in recent years to a current average of less than 1%. The study also evaluated various virological and immunological parameters in both infected and uninfected children.

Distinct gender differences observed in mother to child transmission suggesting an "…underlying important genetic component in immune response to HIV-1" which the investigators speculate could have implications for therapy decisions.

In contrast an oral presentation from Read and colleagues on behalf of the *Breastfeeding and International Transmission Group,* reported that girls were 40% less likely to become infected with HIV through breastfeeding transmission (late postnatal transmission) [6].

In this meta-analysis combining data from nine randomised, placebo controlled trials of breastfeeding populations in South, East and West Africa (PETRA, ANRS, HIVNET 012 etc), the investigators set out to estimate the contribution of late postnatal transmission of HIV through breastfeeding to the overall risk of mother-to-child transmission, to characterise the timing and to identify determinants of breastfeeding transmission. Data for children born before January 2000 were analysed.

The investigators defined early transmission as being infants having a positive DNA PCR before four weeks and late transmission as infants having a negative DNA PCR before they were four weeks old, but a positive test after four weeks. Unknown timing of transmission was defined as one positive DNA PCR after four weeks.

There were 5,871 deliveries evaluated, including 4,085 children with appropriate data. Of these, 993 (24%) were definitively infected, with 314(32%) early, 225 (23%) late infection and 454 (46%) unknown timing of transmission. The probability of transmission was 7%, 12% and 15.6% at six, 12 and 15 months respectively. Late transmission occurred throughout the period of breastfeeding, and the estimated risk of late transmission throughout the breastfeeding period was fairly constant.

In addition the investigators reported lower CD4 count (women with CD4 < 200 cells had an eight-fold increased risk of transmission to their infants) and that girls were 40% less likely to become infected with HIV through breastfeeding despite identical duration of breastfeeding between the sexes.

Gender theorists in the audience were quick to speculate that behavioral mechanisms could be responsible for this significant difference: are male children likely to be fed for longer or fed more frequently, or are genetic factors responsible? But this study did not evaluate breastfeeding practices, and many questions remain concerning nurture vs nature. The investigators suggest that, “the association of gender with late transmission of HIV should prompt further research into the potential underlying mechanism(s), both biological and cultural.”

It was very clear though (particularly given the impressive sample size) that breastfeeding risk varies according to maternal CD4 count, with lower CD4 count associated with higher risk, reflecting more advanced maternal HIV disease and, possibly, higher viral loads in maternal plasma and breast milk. And that late transmission makes a considerable contribution to mother to child transmission rates overall (24% - 42%) among breastfeeding populations.

ALVAC vaccine in neonates

An oral presentation and a poster from McFarland and colleagues presented findings from the PACTG 326 phase I/II study of the safety and immunogenicity of ALVAC vCP205 vaccine given to neonates [7,8]. In the absence of antiretroviral therapy for the mother to prevent vertical transmission, an effective vaccine for the neonate could be a potential strategy for reducing mother to child transmission through breastfeeding.

ALVAC-HIV vCP205 (Aventis Pasteur) is recombinant canarypox, expressing gag, env and protease genes of HIV that is safe and immunogenic in adults.

Twenty-eight infants were randomised to receive high dose, low dose or placebo vaccine. Doses were given to 28 infants at week 0 (£ 72 hours of birth), and at weeks four, eight, and 12. All infants were monitored for local/systemic toxicity, laboratory abnormalities, lymphoproliferative (LPA), and cytotoxic T-cell (CTL) responses. Infants in both high and low vaccine arms showed positive LPA responses to gp160 and p24. These responses were observed as early as two weeks (and as late as two years after immunisation). CTL responses were also observed to gag, env or env/gag as early as two weeks and up to a year following immunisation. The investigators also reported some CTL response from the infants in the placebo arm.

Some mucosal response was demonstrated in 33% of infants in the high dose arm at 12 weeks and 22% at 24 weeks. The investigators reported that overall the vaccine produced cell mediated responses in approximately one third of neonates immunised. They also reported a transient mucosal response in infants in the placebo arm that they speculated could be explained by HIV exposure in uninfected infants.

Although the sample size is extremely small and the degree of immunogenicity modest, the investigators concluded that these data suggest that vCP205 is safe and immunogenic in infants. HIV-specific cell-mediated responses could be induced early in life, warranting further study of HIV vaccines in neonates.

Structured treatment interruption

Studies of structured treatment interruptions (STI) in adults have reported induction of HIV-specific responses mediated by CD4 and CD8 cells that may enhance control of viremia. To date there have been no reports of the effect of STI in children.

A poster from McFarland and colleagues on behalf of the PACTG 1015 group (with a second poster describing additional details on virologic effects) reports interim data from an ongoing study looking at a novel approach to antiretroviral therapy in children [9,10].

In this study eligible patients are aged four to 21 years old, with a CD4 percentage of >20%, an undetectable viral load <400 copies/mL for a year prior to study entry, and are receiving HAART including a PI but excluding abacavir or an NNRTI.

Children undergo sequences of HAART and treatment interruptions – beginning with three days interruption and subsequently

lengthening by two days alternated with a minimum of three weeks of HAART (or time to achieve <50 copies/mL). The maximum interruption allowed in the protocol was seven weeks off therapy.

The investigators report results from 10 children. They found that viral load largely rebounded fairly quickly (within five to nine days of interrupted therapy) and in addition they reported, increases in the frequency of HIV specific CD4+ and CD8+ interferon gamma secreting T cells and modest increases in the percentage of activated CD8 cells (CD38+/HLA-DR+).

They conclude that "these data suggest that STI during established HIV infection in children increases the frequency and antigenic breadth of HIV-specific CD4+ and CD8+ cell responses" and they also report that "in the early stages of a progressively increasing STI regimen in paediatric populations, viremia has resumed sooner than has been reported in adults, and there have been no difficulties in achieving subsequent virologic suppression."

STI strategies for children are currently being mooted among paediatric groups including the European PENTA network and clearly there are interesting scientific questions to be answered in children. This strategy would almost certainly be too complicated to perform other than within a research setting though – families already undergo considerable challenges achieving adherence in children with HIV, although for some simpler strategies may be welcome. At present many groups treating children with HIV would consider interrupting their therapy far too much of a risk.

Metabolic complications

A number of posters investigated metabolic complications in children, often with conflicting findings.

Ramos and colleagues assessed the prevalence in their cohort of such abnormalities [11]. The investigators reported findings from a group of 49 white children (25 girls, median age of 127 months [53-219]). Of this group the median CD4 count was 842 and 59% had HIV-RNA below 300 copies/ml. Median duration of HAART was 54 months (16-68) and all but three children were receiving a PI-containing regimen.

They describe a high prevalence of metabolic complication, with hypercholesterolemia and hypertriglyceridemia present in 69% and 23% of children respectively. Hyperinsulinemia was detected in 24% whereas an increase in C-peptide occurred in 10%. Hyperlactatemia was observed in three children (all asymptomatic). Lipodystrophy was diagnosed in 12 children (11 female) and osteopenia in 21 (38%). They found no association with lipodystrophy and osteopenia, hyperlipidemia, or hyperinsulinemia.

In a larger study by Vigano and colleagues on behalf of the Italian Register on HIV in Children and the European Collaborative Study, the investigators performed a similar analysis of 374 children from 23 clinics across Europe [12].

One hundred and ninety-six of the children evaluated were female, and their median age was five years. Seventy-four per cent of the children were receiving triple therapy. They reported that 28% of children had one clinically determined sign of fat redistribution, of whom 23% had signs of peripheral lipoatrophy alone (fat wasting of the face, arms, legs or buttocks), 37% signs of central obesity alone (fat accumulation in the abdomen or dorsocervical spine, or breast enlargement), and 41% combined lipodystrophy. The most common sites of fat redistribution were the abdomen, face, legs, and arms (21%, 12%, 12% and 11% of the group respectively). Dyslipidemia was present in children, of whom 42% (42/101) also showed fat redistribution.

The investigators found female gender, CDC clinical stage C and current use of triple therapy to be significantly and independently associated with any fat redistribution (and also for lipoatrophy and central obesity). They also reported that older children (> 12 years) were more likely to develop central obesity. They did not find length of time on ARV to be associated with fat redistribution or metabolic abnormalities.

Duration of PI therapy was evaluated, in addition to age and adherence as factors in elevated total cholesterol (TC) in addition to the relationship of TC with hypertension and obesity in children.

Farley and colleagues on behalf of the PACTG 219C team evaluated 1,927 children between four and 19 years. [13] PACTG 219C is a prospective cohort study to examine long-term outcomes in HIV-infected children and in HIV- children born to HIV-infected women.

12.8% of children had abnormal cholesterol levels, defined as a level higher than 95th percentile of the gender, race and age specific targets (TC > 95). The gender distribution was balanced and the median age was 10 years. They found that TC > 95 was significantly associated with white race (prevalence shown in brackets) - (19%), younger age < 6 yrs (19%), current PI use (17%), > 3 yrs of PI use (16%), parent/patient report of no missed doses in the past three days (15%), HIV-1 RNA < 400 copies/ml (22%), and CD4% > 25 (14%).

However, TC > 95 was not associated with hypertension or obesity. Receipt of an NNRTI non-PI regimen was protective ($p = 0.033$).

The investigators reported the following independent variables to be highly statistically significant (all $p < 0.004$): present PI use, two or more PIs currently used, report of no missed doses past three days, younger age, and white/Hispanic ethnicity. Current PI usage was associated with 3.6 times the risk of TC > 95. Each additional PI currently being taken resulted in 72%

increase in risk. Duration of treatment with the specific PIs lopinavir/ritonavir or nelfinavir was associated with increased risk (p = 0.011 and 0.028, respectively).

They concluded that hypercholesterolemia was associated with PI use (particularly dual/triple PI), excellent adherence, younger age, and white/Hispanic ethnicity, but not hypertension or obesity

Another poster from Vigano and colleagues – whose group in Milan has generated some of the most interesting research into metabolic disorders in children – assessed the effect of impaired growth hormone (GH) secretion on excess accumulation of visceral fat as characterised in adults [14].

In this study, 25 pubertal HAART-treated children were assessed for growth hormone (GH) secretion. Additionally fasting serum insulin-like growth factor-1 (IGF-1), IGF binding protein 3 (IGFBP3), insulin, cholesterol (total, HDL, LDL), triglycerides, and nitric oxide levels were also determined. Total and regional body composition and intra abdominal adipose tissue content (IAT) were also assessed.

Of the children evaluated, 10 had visceral fat accumulation and 15 did not. The two groups were similar in the following parameters: age (14.8 vs 13.8 yrs), BMI (19.3 vs 20.2), female/male ratio (7/8 vs 7/3), and months of HAART exposure (55.5 vs 54.5).

Children with excess accumulation of visceral fat showed lower GH area under the curve (AUC, 16.4 vs 31.6 mcg/hr/l; $p < 0.05$), IGF-1 (384 vs 515 ng/ml, $p < 0.05$), IGFBP3 (4.3 vs 4.7 mcg/ml, $p < 0.05$), nitric oxide (11.5 vs 27.9 mmol/l, $p < 0.05$) and higher insulinemia (17.8 vs 9.8 mcIU/ml, $p < 0.05$) than children without. Lipid profiles were similar in both groups.

Children with excess visceral fat, as compared to children without, showed increased fat mass (11.0 vs 6.8 kg, $p < 0.005$), trunk fat (6.6 vs 3.7 kg, $p < 0.0001$) and fat/lean ratio (0.31 vs 0.17, $p < 0.001$.

The investigators conclude: **"**Impaired GH secretion is detectable in pubertal HAART-treated children with increased visceral adiposity and hyperinsulinemia." And they recommend that "the monitoring of GH secretion could be included in the evaluation of HIV-associated lipodystrophy in children," and speculate that their data may indicate a possible role for rGH therapy.

Schwarzwald and colleagues reported findings from a prospective cross-sectional study evaluating the prevalence and relationship to protease inhibitor-containing HAART of osteopenia and osteoporosis in HIV-infected children [15].

Twenty-seven children were evaluated in this study of which 66% were receiving a PI, the mean duration of therapy was 42 months, 13 were girls and the mean age was 11 years old. The investigators reported that of this group, 52% had osteopenia and 23% osteoporosis. Boys were more likely to have osteopenia or osteoporosis than girls ($p=0.02$) and longer duration of PI therapy correlated with greater risk ($p<0.001$). Neither age, ethnicity nor CDC classification correlated with greater risk of osteopenia or osteoporosis.

From this small sample size a high prevalence of osteopenia and osteoporosis (74% overall) was reported. This is of great concern as most bone formulation takes place before the age of 30 and failure to form adequate bone mass during this critical period of childhood and young adulthood development may have serious consequences in later life.

Finally, McComsey and colleagues report findings from a study of a nine month course of calcium and vitamin D supplements received by 23 children receiving ARV, 48% of whom were classified as osteoporotic [16].

The investigators reported that during the study period no significant decrease in bone mineral density occurred. In addition, no improvement in bone loss was observed in the children who received the course of calcium/vitamin D supplements.

It appears as with reports from adult cohorts that the prevalence of metabolic complications is high in children and the long term consequences of these effects are of great concern. Additionally as with adults there is still a lack of clear case definitions for these complicated disorders.

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ANTIRETROVIRALS

T-20 access programme to continue in UK for a further two months

The programme providing access to T-20 prior to market approval was originally scheduled to run from November 2002 to March 2003.

However, Roche has announced that it will be extending this for a further two months "to tide us over to launch of T-20, which is expected [in Europe] in late May/June 2003". Criteria and logistics remain the same for this extended time period and includes a commitment to provide free drug during this period and until one month after launch. Any patient resident in the UK is eligible for consideration.

Anyone interested in more information on this programme or wishing to register a patient should call Julia Nicholson on 01707 6234.

Durability and success capability of HAART: 4.5 years follow-up

From NATAP.org

Researchers from the Royal Free Hospital, London, looking into viral breakthrough after suppression with highly active antiretroviral therapy (HAART) studied the experience of 233 individuals with viral loads of less than 50 copies/ml followed for up to four years

Fiona Lamp and colleagues write: "...if initial viral suppression is achieved, and adherence to therapy can be maintained, the chance of treatment failure is extremely low." In this study there was a total of 12 viral failures after three years on HAART. Patients were followed for 4.5 years and there were no viral failures after three years.

The occurrence of viral breakthrough on treatment was examined in 233 previously antiretroviral-naive HIV-infected patients who started HAART and who achieved initial viral suppression to less than 50 copies/ml. The rate of viral breakthrough despite the continuation of therapy was 3.6 per 100 person-years (12 cases occurred during 332.8 person-years of follow-up). Viral suppression on HAART is proving extremely durable in those who can tolerate these regimens over long periods.

It is known that current HAART regimens initially reduce the viral load to less than 50 copies/ml in the majority of drug-naive individuals within 24-32 weeks. Whether current regimens have the potential to sustain this level of viral suppression indefinitely is uncertain. Drug toxicity and the complexity and inconvenience of treatment schedules present major obstacles to the continuous, long-term use of HAART. A key question, however, is whether HAART regimens would have sufficient sustained intrinsic efficacy, even if it were possible to maintain good adherence indefinitely. A recent report from the Frankfurt clinic cohort found that viral rebound (occurring after viral suppression to less than 50 copies/ml with HAART) was associated with complete treatment interruption in the vast majority of cases, leaving few cases that could be attributed to genuine treatment failure. Researchers investigated the occurrence of viral breakthrough despite the continuation of therapy among patients from the Royal Free Hospital HIV clinic, who had achieved initial viral suppression with HAART.

The rate of viral breakthrough on treatment was assessed in all 233 patients who fulfilled the following three criteria: (1) they were naive to antiretroviral drugs when they started a three-drug HAART regimen (either three nucleoside inhibitors including abacavir, or two nucleoside inhibitors plus one non-nucleoside reverse transcriptase inhibitor, or two nucleoside inhibitors plus a protease inhibitor (PI), including ritonavir-boosted PI), (2) they reached a viral load of less than 400 copies/ml within 32 weeks of starting HAART; and (3) they also reached a viral load of less than 50 copies/ml without having previously interrupted treatment or experienced viral breakthrough. Both (2) and (3) were necessary as the lower limit of quantification of viral load

(using the Roche reverse transcriptase-polymerase chain reaction-based approach; Roche Molecular Systems, Welwyn Garden City, UK) was 400 copies/ml from 1996 to 1998, and has been 50 copies/ml only from 1998 onwards.

Viral breakthrough on treatment was defined as either the first of two consecutive values greater than 400 copies/ml, or a value greater than 50 copies/ml that was followed by the initiation of at least two new drugs. If all antiretroviral drugs were stopped after viral suppression to less than 50 copies/ml, the follow-up time was right-censored at that point and simultaneous or subsequent viral rebounds were not counted. Therefore, the follow-up time for each individual was defined as the time from a viral load of less than 50 copies/ml to the first of: viral breakthrough, stopping all drugs, or the final viral load measurement.

Twenty-one per cent of subjects were female; the main HIV exposures were homosexual (60%) and heterosexual (34%) sex. HAART was started at a median age of 35 years and on a median date of December 1998 (range September 1996-November 2000). Baseline median (interquartile range; IQR) viral loads and CD4 cell counts were 5.3 (4.8-5.7) log copies/ml and 194 (76-302) cells/mm3, respectively. Nucleoside combinations in the initial regimen were zidovudine/lamivudine 125 (54%), stavudine/lamivudine 74 (32%) and other 34 (14%). Other drugs were nevirapine 57 (24%), efavirenz 44 (19%), nelfinavir 49 (21%), indinavir 32 (14%), ritonavir 21 (9%), ritonavir-boosted protease inhibitor 27 (12%), and abacavir three (1%).

The median (IQR) weeks from the start of HAART to the first measured values of 400 copies/ml and 50 copies/ml were 10.1 (7.4, 15.9) and 26.1 (17.9, 42.4), respectively. Overall, there were 1,277 viral load measures made over a total of 332.8 person-years of follow-up after the first viral load of less than 50 copies/ml, an average of one measure per 13.5 weeks per patient. The maximum follow-up times were 4.5 years from the start of HAART and four years from the first viral load of less than 50 copies/ml. Overall, only 12 individuals (5.2%) experienced viral breakthrough on therapy (11 according to the first failure criterion and one according to the second criterion). Therefore, the rate of viral breakthrough on treatment was 3.6 per 100 person-years, equivalent to one individual with viral breakthrough per 27.8 person-years of follow-up.

Researchers examined the records of the 12 patients who had experienced viral breakthrough, and found that eight had subsequently had a resistance test. Results were available for six of these; major resistance mutations were present in five of the six. Information on adherence was available for six of the 12 patients; adherence difficulties were noted in three. These three did not include any of the five patients in whom major resistance was detected.

The low rate of viral breakthrough on treatment observed in this study confirms the results of a similar analysis based on the Frankfurt clinic cohort. This suggests that if initial viral suppression is achieved, and adherence to therapy can be maintained, the chance of treatment failure is extremely low. Other studies have indicated that non-adherence may be the most important reason for the initial lack of response to HAART and subsequent viral rebound. In this study, the intention was to count only viral breakthrough on treatment. However, it seems that lack of adherence may have been associated with at least some of the cases of viral breakthrough.

Drug resistance appeared to be a major explanatory factor, but whether this in itself was caused by adherence difficulties in some patients is unclear. If some of the cases of viral breakthrough were related to adherence, the true intrinsic treatment failure rate would be even lower. In the Frankfurt study, the rate of viral breakthrough decreased as the time since starting HAART increased. In the present analysis there was no significant change over time in the rate of breakthrough, although no cases occurred after three years. If the rate of 0.036 per person-year that these researchers observed were to continue indefinitely, the median time before an individual experienced viral breakthrough would be approximately 20 years.

Whether sustained adherence to treatment over such long periods will be achievable with the drugs that are currently available is extremely doubtful. The development of drug regimens that overcome some of the current problems of toxicity and inconvenience would therefore be a major advance in enabling the successful long-term treatment of HIV. In conclusion, viral suppression on HAART is proving extremely durable in those who can tolerate these regimens over long periods.

Source:
http://www.natap.org/2003/april/040303_4.htm

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C O M M E N T

This highlights the critical importance of the first weeks and months of therapy for all critical aspects of ARV treatment – for treatment choice, monitoring, adherence, resistance, side effect management and (probably) therapeutic drug levels. Investment of resources to achieve this initial viral suppression will be repaid with long-term treatment success. Many patients still do not understand the critical nature of these first weeks of therapy.

It also emphasises that continual attention to adherence is necessary to guard against adherence fatigue which may set in after years of pill swallowing as well as the obvious need for the development of non-toxic regimens.

Older HIV-positive patients in the era of HAART: changing of a scenario

Most of the epidemiological features of older HIV-infected patients were determined before the introduction of HAART in 1996. Since then, highly active antiretroviral therapy (HAART) has been reported to have a less beneficial effect on the immunological outcome in older patients, with an apparent reduction in the intensity and the rapidity of the immunological response in most older patients. However, older age did not appear to significantly affect the long-term virological outcome of HAART-treated patients.

The authors used a prospective case-control study to determine the impact of HAART on the virological and immunological response in a cohort of older HIV-positive patients when confounding variables - adherence to therapy, side effects and non-HIV-related co-morbidities - were evaluated.

Patients age 50 or older and patients aged 20-35 who were given HAART regularly, with a follow-up of at least six months, were included as cases and controls respectively, ratio 1:2. Controls were matched by sex, year of HIV diagnosis and the presence of AIDS-defining conditions. Patients were considered regularly HAART-treated if they had been taking HAART for at least three months.

The researchers considered three outcomes: immunological success; virological success; and viro-immunological success defined as a CD4 T-lymphocyte count greater than 200 cells/mm3 and an HIV viral load less than 50 copies/ml, both conditions together, respectively, at the end of the follow-up. Investigators used a modified version of the Charlson co-morbidity index to assess the significance of non-HIV-related conditions.

The study compared 58 cases with 116 controls. The median age for cases was 57.5, 30.9 for controls. Seventy-six percent of participants in both groups were men; 48 percent were in stage C of HIV infection. The mean of CD4 T cells was significantly lower in cases, the study reports, whereas the mean of the HIV viral log load was similar in the two groups.

Cases had more co-morbid conditions than controls (44.8% versus 15.5%); one-third had cardiovascular diseases. Cases also had a higher mean Charlson index than controls. Researchers observed no statistically significant differences between the two groups in the type, number and duration of HAART regimens. Both groups had a high adherence to HAART. Frequent adverse reactions included dyslipidemia, digestive intolerance and lipodystrophy.

The investigators found immunological success in 69% of the cases and 79% of the controls. They observed a statistically significant reduction in the HIV viral load in both cases and controls comparing baseline with the end of the follow- up values.

Virological success occurred in 79% of cases and 72% of controls. Sixty-four percent of cases and 62% of controls showed viro-immunological success. Comparing mean baseline with the end of follow-up values, the authors found a statistically significant increase in CD4 T-cell numbers. The authors' multivariate analysis showed that after adjustment for sex and Charlson index, no statistically significant difference existed between cases and controls for immunological, virological and viro-immunological success. They obtained similar results when they added HIV- and HAART- related variables to the model.

"In conclusion," they noted, "an early diagnosis of HIV infection in older patients is mandatory because the use of HAART allows them to achieve the same viro-immunological response as younger individuals."

Source: CDC HIV/STD/TB Prevention News Update

Ref: Tumbarello R et al. Older HIV-positive patients in the era of highly active antiretroviral therapy: changing of a scenario. AIDS (01.03.03) Vol. 17; No. 1: P. 128-131.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12478081&dopt=Abstract

Immune reconstitution in older HIV-positive individuals

David Margolis MD, NATAP.org

Kalayjian and colleagues from the ACTG presented clinically important findings from ACTG protocol 5015 at the Retrovirus Conference. [1] Older age has been known to be a predictor of accelerated HIV-disease progression, regardless of whether or not a patient is treated with HAART. However this could be due to various epidemiological factors in older individuals with HIV infection.

ACTG 5015 directly compared the virological and immunological responses to a single, standardised antiretroviral regimen in two age-defined cohorts treated at multiple clinics across the US. Antiretroviral therapy-naive subjects either older than 45 years or younger than 30 years with HIV-RNA >2000 copies/ml and CD4 <600 cells/mL were treated with lopinavir/ritonavir, d4T and FTC. Forty-five older (median age 50; range 45-79 yrs) and 45 younger (median 26; 18-30 yrs) subjects with similar demographic characteristics were enrolled.

At baseline viral loads were similar, while the older group had lower CD4 counts (155 vs 287; $p = 0.029$), naive CD4 numbers (37 vs 105; $p < 0.001$), and naive CD8 numbers (125 vs 185; $p = 0.030$). After 48 weeks of therapy, HIV-RNA was suppressed

to <50 copies/ml with equal frequency in the two groups (73% of older subjects vs. 67% of younger). Although there were a few more episodes of grade three or four toxicity, the onset of lipodystrophy or diabetes, or death in the older group, there were too few observations to reach statistical significance.

Changes in absolute CD4 counts, CD4%, CD8 counts and CD8% were not different in the two groups. However, the older group gained fewer naive CD4 cells (47 vs. 85; p = 0.028) and the rise in naive CD8% was lower (9 vs. 13; p = 0.019). The increase in naive CD8 cells was also lower, but did not achieve statistical significance. Data on thymic size also suggested that thymic mass increased to a lesser extent in older subjects.

These findings may weigh in the mind of the clinician when a decision to withhold or begin therapy in an older HIV-infected patient is being made. More toxicities and deaths were observed in the older cohort, although a larger or longer study would be needed to make this a significant finding. Although many of these events are likely drug-induced, the choice of withholding therapy in late stage disease is also unattractive. Therefore in HIV-infected individuals >45 years old, both increased disease progression, poorer immune reconstitution, and possibly poorer tolerance for therapy in late disease could encourage the earlier initiation of HAART.

Reference

1. Kalayjian et al. Older age is associated with reduced naïve T-cell responses to antiretroviral therapy: 48-week results of ACTG protocol 5015 (abstr. 346) at the Retrovirus Conference (Feb 10-14, 2003)
http://www.retroconference.org/2003/Abstract/Abstract.aspx?AbstractID=449

Source: NATAP.org
http://www.natap.org/2003/Retro/day54.htm

TREATMENT ACCESS

The City turns up the heat on drug companies to make treatment available in poorest countries

Graham McKerrow, HIV i-Base

Leading British financial institutions have warned drug companies that blocking affordable access to treatments in poor countries could undermine public confidence in them and do long-term damage to their share value.

The warning comes from major investors, including Jupiter, Schroders and Legal and General Investment Management, which together account for £600 billion of investments. The investors fear that the determination of the pharmaceutical giants to block the Doha trade agreement, which would allow developing countries to side-step patents on new drugs and make their own generic medicines, could provoke public anger.

International Development Secretary Clare Short has also warned that European and American resistance to the Doha trade liberalisation was trapping the developing world in poverty. The Doha meeting of the World Trade Organisation said that access to medicines for treating HIV, TB and malaria would be agreed by the end of last year. Ms Short said in a speech to the Royal Institute for International Affairs in March that stalemate at the next WTO ministerial conference in September would be a "tragic missed opportunity". As well as agreement on medicines, she is urging deals to tackle unfair trade and boost growth in the developing world.

Also in March, ISIS Asset Management and the Universities Superannuation Scheme (USS) used an investor statement to encourage pharmaceutical companies to work with governments to make medicines more accessible throughout the world. They published 'good practice' guidelines that encouraged dual pricing so that drugs would be cheaper in poor countries, and called for "sensitivity to local circumstances" when considering enforcing patents or licensing local manufacturers to produce generic drugs.

ISIS and USS urged companies not only to work with governments but also to pressure the governments of wealthy nations to give money to the Global Fund for AIDS, TB and Malaria.

Olivia Lankester, senior analyst at ISIS, told the Guardian newspaper: "Our main concern is that continuing high-level criticism of the sector will, over time, damage its ability to operate." She said she thought controversy could undermine the companies' arguments for strong patent protection that enables them to recoup drug development costs. ISIS's view was that the companies should act out of self-interest.

Lancet commentary concludes that prevention and treatment in South Africa are affordable and desirable

Graham McKerrow, HIV i-Base

A commentary in The Lancet says that in relative terms, South Africans are among the world's big spenders on health care, and that universal HIV prevention and treatment in the country is both affordable and desirable. [1]

Josef Decosas of the international, child-focused development organisation Plan International, writes that in 2000 South Africa spent 8.8% of its gross national product (GNP) on health, which placed it in 17th position among the nations of the world, just ahead of Belgium. Most of South Africa's health care costs are paid for with private money; government spending on health amounts to only 3.7% of GNP.

Decosas considers a report by Nathan Geffen and colleagues at the University of Cape Town, which calculates the bill for a comprehensive healthcare response to HIV similar to that in Brazil. [2] By 2015, the most expensive year of their calculation, universal public provision of prevention and treatment would cost 20.3 billion rand (£1.6 billion) – about 1.74% of GNP. This would include the treatment of opportunistic infections and the provision of antiretroviral therapy. It would represent at 50% increase in public spending relative to GNP, from 3.7% to 5.4%.

ARVs would account for 99% of the additional cost, while universal provision of voluntary counselling, HIV testing, control of STDs and prevention of mother to child transmission are "surprisingly inexpensive" and could be achieved "without a perceptible increase in healthcare spending".

Decosas says the report takes great care in calculating costs including allowing for training and improvements to infrastructure. The report also outlines certain costs that would be incurred by not responding to the epidemic with universal provision of treatment and care, but the authors did not include these "savings" in their overall estimate of costs.

Nevertheless, Geffen and colleagues write in their conclusion that the Government would save seven billion rand on hospitalisation and orphan costs that it is already committed to meet. They also estimate that the use of generic drugs could save a further four billion rand. They write that costs peak in 2015 and then drop and level off after that.

"A 50% increase in the budget for public health care in relation to the GNP over 12 years seems feasible," writes Decosas, "but the other hurdle is to convince politicians that this increased spending will do any good… The Government now has another piece of information to support the expansion of the public health response to AIDS. Let us hope it uses it."

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1. Decosas J. HIV prevention and treatment in South Africa: affordable and desirable. The Lancet, 361: 1146-7
2. Geffen N, Natrass N, Raubenheimer C. The cost of HIV prevention and treatment interventions in South Africa. CSSR working paper no 28, Centre for Social Science Research, University of Cape Town, Cape Town, South Africa, 2003.
http://web.uct.ac.za/depts/cssr/papers/wp28.pdf

Links:

http://www.plan-international.org/

http://www.thelancet.com

http://www.tac.org.za

South Africa treatment protests go global

Graham McKerrow, HIV i-Base

International protest is being mobilised to protest globally against the South African government's refusal to provide universal HIV/Aids treatment to its citizens. Some activists spoke with mock nostalgia about returning to picket South African embassies.

The Treatment Action Campaign (TAC) has launched a campaign of civil disobedience in South Africa to back their demand for a comprehensive treatment plan, said its spokesman Nonkosi Khumalo. They are calling for international demonstrations of support. Khumalo said ANC leaders were showing some arrogance in their attitude towards its campaign.

TAC is taking Health Minister Manto Tshabalala-Msimang and Trade and Industry Minister Alec Erwin, to court, accusing them of culpable homicide for failing to use state resources to fight the epidemic.

Khumalo said protests including sit-ins at government buildings were planned. One hundred and sixty people were arrested at a protest in Cape Town, but the Gauteng and KwaZulu-Natal branches of TAC report no arrests because police had refused to arrest people.

"In the next phase of our protests, we are looking at importing generic drugs ourselves and giving them to doctors at public hospitals," said Khumalo.

Gilead to sell tenofovir at cost to 68 countries

Graham McKerrow, HIV i-Base

Gilead Sciences announced in April what it called the Gilead Access Programme, which will provide tenofovir DF (TDF, Viread) at no profit to all African countries and 15 others classified as "least developed" by the United Nations. TDF will be available to private and public programmes in the 68 countries for $39 for a 30-day supply, or $1.30 a day. The company said the price covered the cost of manufacture and the administration of the scheme. The company will supply programmes directly and not use third parties. The pills will be a different colour to those it sells in rich countries to combat the diversion of reduced-price drugs for resale at higher prices in richer countries.

The Gilead scheme will include assistance to projects seeking reduced-price TDF, and research and advice on providing treatment in poor settings. The company is also preparing a reduced-price scheme for middle-income countries in Eastern Europe, Asia and Latin America.

Complete programme information and requests forms are available at

http://www.gileadaccess.org

Those without internet access can call the Gilead Access Programme in the United States on +1-800-445-3235 or +1-650-574-3000 or in Uganda at +256-41-340-806.

New advocacy coalition demands emergency funding from rich governments for Global Fund

A coalition of public health advocacy organisations has announced the launch of "Fund the Fund," a campaign to pressure governments of wealthy countries to contribute resources to the Global Fund to Fight AIDS, TB, and Malaria.

The advocates say that none of the world's wealthiest governments has contributed an amount on par with the size of their economies. Instead, the US, Japan, France, Germany, Britain, Canada, Italy, and other countries have all given far less than their fair share.

Forty representatives from non-governmental organisations and activist groups from Europe, US, Japan and Canada held a two-day summit in Paris in March. The meeting heard that the Global Fund was facing a budget shortfall of $1.6 billion to meet the anticipated need in the third round of grants in October. Launched in January 2002, the Global Fund has disbursed $1.5 billion in grants to 160 programmes in 85 countries.

"People with AIDS and their advocates - at the frontline of the AIDS crisis - and Fund the Fund, will not allow the rich governments of the world to walk away from the Global Fund and betray the hopes of the 42 million people now living with HIV/AIDS," said Khalil Elouardighi of ACT UP-Paris. "Heads of state must not turn their backs on millions of people in need only two years after authorising the Fund's creation at the G8 summit in Genoa in July 2001."

The meeting in Paris was organised by AIDES, France's largest AIDS service organisation; Health GAP (Global Access Project) a US based activist group; and ACT UP Paris.

Source: Fund the Fund press statement

Link:
http://www.fundthefund.org/

C O M M E N T

Two years ago treating poor people living with HIV in poor countries was a daunting prospect. The cost and the logistics seemed insurmountable. A few kind people collected unwanted drugs in rich countries, and sent them where they were needed; but it was hopelessly inadequate. Meanwhile, 39 companies, many with turnovers bigger than the GDP of entire nations, hired lawyers to stand up in a South African court and defend the rules that allowed the companies to keep their drugs from people who needed them. The companies said they wouldn't lose control of their patents and they couldn't enforce different prices in different parts of the world.

However, change was in the air for the pharmaceutical industry. Companies like Cipla and Ranbaxy in India produced generic antiretrovirals. Brazil showed that a medium-income country could provide generic drugs to its HIV-positive citizens. In July 2001 the Kenyan Parliament approved legislation that permitted the importation and manufacture of generic drugs in defiance of the global pharmaceutical industry. This time last year members of the South African Treatment Action Campaign and Medecins Sans Frontieres were infringing GlaxoSmithKline and Boehringer-Ingelheim patents to import generic drugs from Brazil. Last summer a major American healthcare provider barred GSK sales representatives from its clinics in protest at the prices GSK charged in developing countries. This mounting global anger at the prices and patent laws that were denying millions of people with HIV access to treatments sparked an extraordinary exchange of experiences and assistance at the International AIDS Conference in Barcelona last year. South African activists

unveiled plans to force compulsory licences to permit the local production of generic antiretrovirals, Thailand offered the low-cost transfer to other poor countries of the technology for the production of generics, and 14 Caribbean countries signed an agreement for the purchase of cut-price antiretrovirals from six pharmaceutical companies. Importantly, many researchers reported to delegates on studies showing how to provide effective treatment in so-called resource-poor settings. The momentum of change had become unstoppable. The establishment of the Global Fund to Fight AIDS, TB and Malaria also held out the promise of $10 billion a year to fund treatment in poor countries.

After the conference, GSK announced that it would cut the prices of some of its ARVs and anti-malarial drugs by up to 38% for 63 countries. Last month we reported that the Pharmacia Corporation announced a pilot programme for expanding access to medicines in developing countries and that Boehringer, BMS, GSK, Roche and Merck had agreed to cut their ARV prices by an average of 55% - for six Central American countries. Now we report that Gilead is slashing the price of tenofovir for 68 countries.

The international campaign against the patent laws that let millions die from treatable illnesses has led to an anarchy in the pharmaceutical industry with governments passing laws to side-step international patents, and smaller companies manufacturing generic drugs.

The 6th International Congress on Drug Therapy in HIV Infection, held in Glasgow last November, heard evidence that a fixed dose combination pill of generic lamivudine, stavudine and nevirapine (Triomune) met bioequivalence criteria when compared with the branded drugs. There is speculation that Triomune could aid adherence by combining in one pill three drugs that in rich countries are made by separate companies.

Now the big players in the pharmaceutical industry are unpopular and they have rivals producing cheaper - and perhaps better - generics and so they risk missing out on business that will be paid for with the Global Fund's billions. They are also losing control over their patents. These developments have shaken the multi-billion dollar, multi-national companies to the point where institutional investors fear for their share values. And nothing speaks louder to a multi-national company than share price, and no one speaks to them with more force than do institutional investors. This campaign is far from won; there are still millions of people untreated. But now we know that if a pharmaceutical company feels it is in its self-interest it can slash drug prices in poor countries.

Pressure is beginning to bring results. Now, the World Trade Organisation must act to liberalise the patent rules, and the governments of rich countries must fork out for the Global Fund.

METABOLIC COMPLICATIONS

Statins and fibrates both relatively effective for PI-induced hyperlipidemia

Brian Boyle MD, for HIVandHepatitis.com

Hyperlipidemia occurs in some patients treated with highly active antiretroviral therapy (HAART), especially when a protease inhibitor (PI), is included in the regimen. These hyperlipidemias have proved to be quite difficult to treat, at least if the goal is the return of the patient to the cholesterol and triglyceride levels recommended in the (US) National Cholesterol Education Program guidelines.

In a study published in AIDS, investigators from Italy evaluated the use of two groups of agents used in the treatment of HAART-induced hyperlipidemias, the statins and fibrates. The study was an open-label, randomized, prospective study with 106 evaluable patients who had been on PI-based HAART for at least 12 months, had a viral load <50 copies/mL, and had hypertriglyceridemia of at least six months duration that was unresponsive to dietary changes. The patients were treated with bezafibrate, gemfibrozil, fenofibrate, pravastatin, or fluvastatin for at least 12 months.

The investigators found that after 12 months of follow-up, the fibrate-treated patients had reductions in triglycerides and cholesterol of 40.7% and 21.9%, respectively ($P < 0.001$), while the patients treated with statins had reductions of 34.8% and 25.2%, respectively ($P < 0.001$). Comparing the efficacy of the fibrates and statins, no significant differences were found regarding the reductions in hyperlipidemia. All regimens were relatively well tolerated and there were no unexpected adverse events.

The authors conclude, "All administered statins and fibrates revealed a similar, significant efficacy in the treatment of diet-resistant hyperlipidemia, and showed a favourable tolerability profile." These data support the conclusion that although some patients may not return to levels of lipids recommended by the National Cholesterol Education Program guidelines, significant improvements in both triglycerides and cholesterol can be achieved by the use of either fibrates or statins in patients with HAART-induced hyperlipidemia.

Ref: Calza L et al. Statins and fibrates for the treatment of hyperlipidemia in HIV-infected patients receiving HAART. AIDS 2003;17(6):851-859.
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C O M M E N T

It has been shown previously that lipid lowering agents lower lipids in hyperlipidemia associated with antiretroviral therapy. The crucial question, however, is how much is enough to achieve a clinical benefit. Given the modest success of statins and fibrates in primary and secondary prevention of myocardial infarction or stroke (no effect on overall mortality reported in up to seven trial years, decrease in MI <30%) the number to be treated to save a life may even be higher in the antiretroviral setting. Significant changes in laboratory markers may not translate into survival benefits.

Pioglitazone subjectively improves body shape abnormalities

Brian Boyle MD, for HIVandHepatits.com

Lipodystrophy is a multifactorial syndrome that occurs in HIV-infected patients. It is clear that many factors play a role in the development of this condition, including disease and host-related factors and the use of highly active antiretroviral therapy (HAART).

Unfortunately, treatment options remain limited and some studies have been discouraging regarding potential treatments to correct or mitigate this dread condition.

Some preliminary data have indicated that anti-diabetic drugs, including the glitazones, may have some impact on the fat distribution in non-HIV lipodystrophy. The glitazones have been theorised to be able to prevent the toxic effect of protease inhibitors on adipogenesis in vitro by enhancing perixosome proliferator-activated receptor activity.

In a study published in AIDS, investigators at the HIV clinic of University Hospital Geneva assessed the safety and preliminary efficacy of treatment with pioglitazone for six months in 11 patients with lipodystrophy who were receiving highly active antiretroviral therapy (HAART).

The enrolled patients' ages ranged from 30 to 51 years, all had undetectable viral loads, and the mean CD4 cell count and duration of HAART was 683 cells/mm3 and 3.8 years, respectively. In the study, pioglitazone was given at a dose of 30mg per day for three months and then 45mg a day for an additional three months.

A dual-energy X-ray (DEXA) absorbtiometry scan was performed at baseline and at month six to assess body composition. In addition, standard analyses were performed to quantify the fat content in various body regions of interest and lipids and insulin levels were measured.

The investigators found that body fat mass (total and leg) increased significantly, but there were no changes regarding the lipid profile. In the study, all but one patient had an increase in total fat mass as measured by DEXA scan after six months of pioglitazone treatment, with a median increase from 15.4% to 18.5% (P = 0.05). In addition, patient satisfaction was evaluated by questionnaire and a comparison of photographs showed that six out of 11 patients detected small improvements in a lipoatrophic area, one patient experienced a significant improvement in his physical appearance, two patients showed a continued progression of their lipodystrophy, and two patients did not notice any changes. No serious side effects were observed.

The authors conclude: "We found that pioglitazone treatment for a period of at least six months in non-diabetic HIV-positive patients on HAART was well tolerated and was associated with an increase in total body fat as well as a subjective improvement in body shape in seven out of 11 patients."

The authors urge that further, larger studies be conducted to evaluate this potential treatment for lipodystrophy.

Ref: Calmy A et al. Glitazones in lipodystrophy syndrome induced by highly active antiretroviral therapy. AIDS 2003,17:770–772.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12646807&dopt=Abstract

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C O M M E N T

This was an small, uncontrolled study and only produced a very modest effect (median 3% total fat increase after six months treatment). These results are difficult to interpret and are in contrast to findings from a better designed study with rosiglitazone. Data from non-HIV lipodystrophy were generated with troglitazone another member of this family which was taken off the market due to hepatotoxity.

It is interesting that no changes were found in lipid profile, as pioglitazone has favourable effects on lipids in type 2 diabetes, in contrast to rosiglitazone.

RESISTANCE

Study reveals new reverse transcriptase mutations

Brian Boyle MD, HIVandHepatitis.com

Many clinicians recognise that resistance testing remains a work in progress. Significant progress is being made, however, in understanding resistance and the complex interactions that different viral mutations have on drug sensitivity as well as replication capacity.

In a recent report from the Stanford group studying these issues, new reverse transcriptase (RT) mutations and three complex series of patterns of nucleoside analogue (NA) resistance were reported.

The study, published in AIDS, was designed to characterise RT mutations by their association with the extent of past NA therapy and to identify mutational clusters in RT sequences from persons receiving multiple NAs. To accomplish this objective, the investigators analysed a total of 1,210 RT sequences from persons whose history of antiretroviral therapy was known, 641 of which were performed at Stanford University Hospital and 569 were from previously published data.

The investigators found that mutations at 26 positions were significantly associated with NA usage. These included 17 known resistance mutations (positions 41, 44, 62, 65, 67, 69, 70, 74, 75, 77, 116, 118, 151, 184, 210, 215, 219) and nine previously unreported mutations (positions 20, 39, 43, 203, 208, 218, 221, 223, 228). The nine new mutations correlated linearly with number of NAs used and 777 out of 817 (95%) instances occurred with resistance mutations known to be associated with the NAs.

Importantly, the investigators found that mutations at positions 203, 208, 218, 221, 223, and 228 were conserved in untreated persons and those at positions 20, 39, and 43 were polymorphisms. Finally, the investigators expanded on the knowledge regarding the NA resistance mutation clustering, with most NA-associated mutations clustered into one of three groups: (A) 62, 65, 75, 77, 115, 116, 151; (B) 41, 43, 44, 118, 208, 210, 215, 223; of (C) 67, 69, 70, 218, 219, 228.

The authors conclude, “Mutations at nine previously unreported positions are associated with [NA] therapy. These mutations are probably accessory because they occur almost exclusively with known drug resistance mutations. Most [NA] mutations group into one of three clusters, although several (e.g., M184V) occur in multiple mutational contexts.”

Ref: Gonzales M et al. Extended spectrum of HIV-1 reverse transcriptase mutations in patients receiving multiple nucleoside analog inhibitors. AIDS 2003;17(6):791-799.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12660525&dopt=Abstract

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Stanford Resistance Database
http://hivdb.stanford.edu/

IMMUNOLOGY

Tissue T-cell analysis represents renewed challenge to ‘tap and drain’ orthodoxy

Richard Jefferys, TAGline

One of the central tenets of HIV pathogenesis is that the virus causes a slow but progressive decline in CD4 T-cell counts. This decline is clearly evident in peripheral blood samples, but it is far more difficult to assess changes in the total CD4 T-cell population. It is estimated that only 2% of all CD4 T-cells are in the blood at any given time, making this a rather narrow window onto the body as a whole. Estimates of total body CD4 T-cell counts at different stages of HIV infection have been attempted - sometimes based on samples from lymph nodes in addition to peripheral blood - but there are many other inaccessible tissues where CD4 T-cells can reside.

In order to try and evaluate virus-induced changes in total body CD4 T-cell counts more accurately, a group of German researchers employed an animal model of HIV infection. Thirty-two rhesus macaque monkeys infected with SIV (HIV’s simian counterpart) were included in the study, and 11 uninfected monkeys served as a control group. Twelve infected macaques

had to be euthanised during the study due to signs of AIDS, while the remaining 20 were sacrificed at various time points from 12-78 weeks after infection with SIV. Samples were taken from a total of 14 different body tissues, including six lymph nodes, the spleen, thymus, liver, lung, bone marrow, brain and intestine. The researchers calculated that, taken together, these tissues contain about 50% of the total number of T-cells found in a macaque. This represents the most comprehensive analysis of T-cell numbers in SIV infection conducted to date.

The most surprising result of the study was that, during the asymptomatic phase of SIV infection, the absolute numbers of both CD4 and CD8 T-cells were significantly increased compared to uninfected control animals. When T-cells in all the sampled tissues were added up, the total T-cell count was increased threefold in asymptomatic SIV-infected macaques compared to the uninfected controls. In the animals developing symptoms of AIDS, T-cell numbers in the blood were significantly decreased compared to the controls, but total body T-cell counts were similar.

Further analysis revealed that while T-cell numbers were further increased in most non-lymphoid organs compared to asymptomatic infection, counts declined in the lymph nodes, spleen and bone marrow. The most dramatic T-cell loss in macaques with AIDS was documented in the thymus, with 8/11 animals showing a decline in thymocytes (thymic T-cells) of an order of magnitude or greater. In contrast, the number of thymocytes was slightly increased in asymptomatic infection compared to controls, although this difference did not reach statistical significance.

Focusing on CD4 T-cells, the researchers calculated the sum for all samples and found that numbers increased from an average of 3.5 billion in uninfected macaques to 6.6 billion in asymptomatic SIV infection. In animals with AIDS the average total was 4.7 billion, but the increase compared to controls was not statistically significant and the authors note that "for ethical reasons, animals were sacrificed with the first signs of immunodeficiency. For this reason and especially in the light of a complete loss of thymocytes in these animals, it seems plausible that total CD4 counts would have dropped further."

CD8 T-cells followed a similar pattern, although the increase in asymptomatic infection was even more dramatic, with counts rising from an average of 3.5 to 11.5 billion cells. Total CD8 T-cell counts in animals with AIDS were statistically indistinguishable from uninfected controls.

The research team acknowledges that these results were "completely unexpected" given the documented loss of CD4 T-cells from the blood in asymptomatic HIV infection. They believe the explanation lies in the combination of increased proliferation and redistribution of CD4 and CD8 T-cells that occurs in both SIV and HIV infections.

(To investigate the role of proliferation in this study, the expression of Ki67 (a cellular protein mainly expressed by proliferating cells) was assessed in T-cells from the various body compartments. An overall increase in turnover of 4-fold for CD4 T-cells and 12-fold for CD8 T-cells was seen in asymptomatic animals. In macaques with AIDS, CD8 T-cell proliferation remained elevated but CD4 T-cell proliferation returned to levels seen in uninfected controls.)

The implications of these data for models of HIV pathogenesis are also considered by the authors. They note that the famous "tap & drain" theory (proposed by David Ho) is not supported by their results, since it suggests that T-cell proliferation occurs in order to replenish cells that have been directly killed by HIV and thus would not explain an overall increase in total body T-cell counts or the increased proliferation of CD8 T-cells seen in this study.

Instead, the researchers believe that their data is more consistent with a model of chronic immune activation (most recently outlined by William Paul and Zvi Grossman in Nature Medicine), where the replication of HIV (and associated presence of HIV antigens in the lymph nodes) continually drives the proliferation of both CD4 and CD8 T-cells. Additionally, they point out that, "As immune activation induces trapping of T-cells in lymphoid organs and differentially influences the distribution of CD4 and CD8 T-cells, this model could also explain the altered distribution of lymphocytes found in the SIV-infected macaques."

Source: TAGline, March 2003
http://www.thebody.com/tag/mar03/tissue_analysis.html

Ref: Sopper S, Nierwetberg D, Halbach A et al. Impact of simian immunodeficiency virus (SIV) infection on lymphocyte numbers and T-cell turnover in different organs of rhesus monkeys. Blood 2003 Feb 15;101(4):1213-9

NUTRITION

Integrating nutrition therapy into medical management of HIV: a supplement of Clinical Infectious Diseases

Graham McKerrow, HIV i-Base

The 1 April issue of the journal Clinical Infectious Diseases (Volume 36, Supplement 2) reports on the current management of nutrition in HIV infection. Drawing on the work of more than 50 authorities in the field, the supplement looks at:

- General nutrition management in HIV-positive patients
- An assessment of nutritional status, body composition, and HIV-associated morphologic changes
- Weight loss and wasting
- Lipid abnormalities
- Body habitus changes related to lipodystrophy
- Insulin and carbohydrate dysregulation
- Lactic acidemia
- Emerging bone problems, and
- Food and water safety

In an introduction to the supplement John G Bartlett of Johns Hopkins University, writes that the science and strategies for management of HIV infection move with a velocity that is unparalleled by any other important disease in the history of medicine. Nutritional issues have moved at the same or an even quicker pace. Most of the issues addressed in the supplement are complications that arise from the medical developments and are among the most challenging concerns we face.

Bartlett concludes his introduction: "Relevance is placed in perspective by the observation that modern management of HIV infection now requires substantial expertise in dealing with nutritional issues and access to this expertise, despite the fact that there have been virtually no guidelines that specifically target the nutritional care of the HIV-infected population. This report on the nutrition management and concerns of HIV infection is consequently welcomed as timely, authoritative, and greatly needed."

Judith Nerad and colleagues at the, John H. Stroger Hospital, Chicago, write that nutritional management is integral to the care of all patients infected with HIV. HIV infection results in complicated nutritional issues for patients, and there is growing evidence that nutritional interventions influence health outcomes in HIV-infected patients. The authors define levels of nutritional care, and discuss when patients should be referred to dietitians with nutritional and HIV expertise.

Tamsin A Knox of Tufts University School of Medicine, Boston, and colleagues argue that nutritional status should be assessed at regular intervals as part of the management of HIV infection. The simplest approach to assessment is serial weight measurement. A comprehensive nutritional assessment includes:

1. anthropometric measurements of body composition;

2. biochemical measurements of serum protein, micronutrients, and metabolic parameters;

3. clinical assessment of altered nutritional requirements and social or psychological issues that may preclude adequate intake; and

4. measurement of dietary intake.

Techniques for measuring body composition of fat and lean body mass include anthropometry and bioelectric impedance analysis. Other techniques, including dual X-ray absorptiometry (DXA), hydrodensitometry, total body potassium measurement, and cross-sectional computed tomography or magnetic resonance imaging are available in research centres. Anthropometry, including waist-hip ratios, regional DXA, and cross-sectional imaging, is best for detecting morphologic changes associated with fat redistribution syndrome. Nutritional assessment and intervention in children with HIV can help to prevent stunted growth and development.

Steven Grinspoon and Kathleen Mulligan, for the Department of Health and Human Services Working Group on the Prevention and Treatment of Wasting and Weight Loss, outline the problems and dangers of weight loss and muscle wasting. Wasting, particularly loss of metabolically active lean tissue, has been associated with increased mortality, accelerated disease progression, loss of muscle protein mass, and impairment of strength and functional status. Factors that may contribute to wasting include inadequate intake, malabsorptive disorders, metabolic alterations, hypogonadism, and excessive cytokine production. Evidence now demonstrates that nutritional counselling and support, appetite stimulants, progressive resistance training, and anabolic hormones can reverse weight loss and increase lean body mass. Despite a growing body of evidence on the importance of nutritional intervention to prevent wasting in adults, maintain growth velocity in children, and promote restoration of weight and lean body mass in stable, low-weight patients, no therapeutic guidelines currently exist for the management of weight loss and wasting in HIV-infected patients. The authors recommend principles and guidelines for assessment and management of weight loss and wasting in patients with HIV/AIDS.

The supplement is available at:

http://www.journals.uchicago.edu/CID/journal/contents/v36nS2.html

HEPATITIS COINFECTION

BHIVA HIV/hepatitis B and HIV/hepatitis C co-infection guidelines posted to web for consultation

Guidelines for HIV and Hepatitis B and C coinfection are now posted to the BHIVA website in a first draft as part of a public consultation. Comments are now welcomed.

The authors introduce the process on the website:

"In an area that is rapidly changing such as this, it should come as no surprise that there was quite vigorous discussion between members of the guidelines committee as to what to advise. This was especially the case with regard to the treatment recommendations:

- Should dual therapy with both lamivudine and tenofovir be recommended for all patients with HIV and hepatitis B as part of their antiretroviral regimen, or should we await the outcome of clinical trials?
- Is pegylated interferon to be recommended for treatment of Hepatitis C in HIV-positive patients in all circumstances or should we await the outcome of the NICE recommendations?
- Is there enough evidence to recommend pegylated interferon rather than standard interferon in patients with genotype 2 and 3, given that the price differential may influence funding from the commissioners?

Your comments will be greatly appreciated. Please give feedback on these two guidelines by e-mailing Gary.Brook@nwlh.nhs.uk or there will be a chance to discuss them at the BHIVA conference on the 26th of April 2003."

Gary Brook and Janice Main on behalf of the BHIVA HIV/Hepatitis Guideline Committees.

http://www.bhiva.org/guidelines.htm

Draft versions of the above guidelines may be downloaded as pdf files.

HIV and Hepatitis B: http://www.bhiva.org/HBV.pdf

HIV and Hepatitis C: http://www.bhiva.org/HCV.pdf

C O M M E N T

Comment from both clinicians and patient groups are vital to this process, particularly as the final recommendations may impact on final access to treatment across the UK. Despite being on-line for over six weeks, very few comments have been so far submitted, and active involvemnet in this process is encouraged.

Index of biochemical markers could reduce need for biopsy by half in HIV/HCV co-infected patients

Simon Collins, HIV i-Base

Liver biopsy is widely accepted as the gold standard for assessing hepatitis C (HCV) related fibrosis, but the procedure is invasive and can lead to complications, including haemorrhage and death. A paper published in a recent issue of AIDS suggests that an index of non-invasive tests may reduce the need for biopsy in over half the current cases.

Yves Benhamou and colleagues from Hopital Pitié-Salpetriere, Paris, looked at the predictive value of fibrosis from an index of non-invasive biochemical markers and whether this correlated with biopsy results in patients with HIV/HCV co-infection.

The cross-sectional, cohort study assessed 130 HIV/HCV-co-infected patients with a liver biopsy and serum samples for markers of liver fibrosis. The index incorporated age, sex, [alpha]2-macroglobulin, apolipoprotein A1, haptoglobin, bilirubin, and [gamma]-glutamyl-transpeptidase (GGT), derived using multivariate logistic regression, was compared with liver histology. HIV-specific indices including the CD4 cell count and HIV-RNA load were also constructed. The diagnostic values of the indices were compared using receiver operating characteristic (ROC) curves. Main outcome was measured by septal fibrosis (F2-F4) by the METAVIR classification.

By multivariate analysis, the most informative markers were [alpha]2-macroglobulin, apolipoprotein A1, GGT, and sex. The area under the ROC curve of the five-marker index was 0.856 – 0.035 which is not significantly different from the HIV-specific indices. On a scale from zero to 1.00, the five-marker index had a positive predictive value of 86% for scores greater than 0.60, and a negative predictive value of 93% for scores of 0.20 or less.

The authors report that the accuracy of this index mean that these thresholds could reduce the need for liver biopsy by 55% while maintaining an accuracy of 89%. They also suggest that as "staging by biopsy is limited by semiquantitive scaling and sampling error, particularly in early stages and in cirrhotic patients with regenerative nodules", that the estimates of the biochemical index could "actually provide a more accurate view of fibrogenic events occurring in the entire liver".

Ref: Yves Benhamou and Thierry Poynard et al. AIDS 2003; 17(5):721-725.

C O M M E N T

This study (and previous studies in mono-infected patients by the same group) is a landmark in the quest for non-invasive markers of liver damage in patients with chronic hepatitis C. Using an index based on sex, age, and five commonly available biochemical markers, the authors were able to predict a fibrosis score of F2 (a level at which treatment with interferon and ribavirin is generally recommended), with a fairly high accuracy. This index has been named 'Fibrotest'. The authors conclude that using this index a liver biopsy could be avoided in 55% of the patients.

In an editorial that follows in the same issue of *AIDS*, Soriano et al argue whether liver biopsies, or assessment of the stage of fibrosis, are necessary at all in patients with HIV/HCV co-infection when treatment decisions are being made. They point out that the vast majority of patients with HIV/HCV co-infection will have appreciable fibrosis and therefore should be offered treatment. Furthermore, with the advent of combination therapy with pegylated interferon-alpha and ribavirin, where excellent results have been demonstrated in mono-infected patients, the major considerations in the decision making process should be CD4 counts and possible drug-interactions.

To put all this into perspective, let us consider the facts. In Western Europe and the USA, genotype 1 HCV accounts for almost two-thirds of all infections. HIV co-infection does accelerate the progression of HCV related fibrosis. With the advent of HAART, HCV related liver disease is now a leading cause of morbidity in co-infected patients. Treatment with interferon and ribavirin is curative. Liver biopsies (the gold standard for assessing liver damage) are uncomfortable and associated with risks in a minority of patients. Pegylated interferons in combination with ribavirin have improved the HCV clearance rates to over 75% in patients with genotypes 2/3 mono-infections and up to 45% in genotype 1 infection. Furthermore, responses, in terms of HCV viral load at week 12 of treatment, accurately predict long-term clearance rates. Having said all that, the early results of pegylated interferon-alpha and ribavirin in co-infected patients are largely disappointing, especially for patients with genotype 1 infections. Although final results from some of the larger randomised-controlled trials are still awaited, it is unlikely that we will see final HCV-clearance rates anywhere near the responses seen in mono-infected patients. Furthermore, there are significant drug-interactions with ddI and ribavirin. It is, however, still likely that the 12-week HCV viral load response will predict the final response.

So how does all this influence clinical practice? At the Royal Free Hospital in London, all patients with chronic genotype 2/3 HCV/HIV co-infection are offered therapy with pegylated interferon-alpha and ribavirin, bearing in mind drug-interactions and contra-indications to interferon-alpha and ribavirin. Therapy is stopped after 12 weeks if there has not been at least a two-log reduction in HCV viral load. Patients with genotype 1 HCV co-infections are less likely to respond to current therapy and therefore are offered a liver biopsy for accurate assessment of fibrosis. Those with moderate to advanced fibrosis are encouraged to try at least 12 weeks of therapy.

Once the biochemical markers in the Fibrotest index are routinely available, this will reduce the number of repeated liver biopsies (patients not on treatment and not having cirrhosis need repeated assessments every three to five years), although we would encourage at least one biopsy to ensure co-relation with the Fibrotest index, and encourage a biopsy for patients that fall in the 'grey' zone of scores between 0.2 and 0.6.

HCV protects against abnormal blood lipids in HAART-treated HIV patients

HIV-positive patients treated with HAART who are also coinfected with hepatitis C virus (HCV) are less likely to have abnormally high levels of cholesterol or triglycerides according to a small Spanish study published as a research letter in the April 2003 edition of *AIDS*.

Investigators looked for the prevalence of hyperlipidemia and its risk factors among 197 HIV-positive men attending an outpatient clinic in Vizcaya, Spain. Patients had an average age of 36.8 years, most had injecting drug use as their risk factor for HIV and all were clinically stable.

Blood samples were obtained after an overnight fast. Hyperlipidemia was defined as total cholesterol or triglyceride levels greater than 200mg/dl.

In total, 29.9% of patients were found to have hyperlipidemia. Patients who had been receiving HAART for longer (average 26.7 months versus 24.4 months) were found to have a higher risk of abnormal lipid levels. Changes in body fat distribution were found more often in patients with high blood lipids (38.8%) compared to those with normal lipids (27.7%).

When investigators looked at the anti-HIV drugs that their patients had been treated with, they found that 'patients treated with efavirenz had higher rates of hyperlipidemia than patients treated with nevirapine (49% versus 20.7%, respectively), and than those treated with PI (31.5%)'.

However, the most interesting finding of the study was 'the appreciably lower rate of hyperlipidemia' seen in HIV/HCV coinfected patients. The difference could not be attributed to viral load, as the proportion of HIV/HCV and HIV monoinfected patients with undetectable viral load was almost identical (66% versus 67%). Rather, the investigators attributed the difference to 'HCV-induced hepatic dysfunction'.

The protective effect of HCV infection on lipids was only seen when a patient was treated with HAART, leading the investigators to theorise that 'the interactions of HAART on lipidic metabolism seem to be neutralised by the HCV infection'. However, higher rates of body fat redistribution were found in patients coinfected with HIV/HCV (27% versus 11.8%).

C O M M E N T

It is difficult to know what to make of this study, and the article title is probably premature until confirmed by further research.

HCV/HIV-coinfection is a marker for iv-drug use which is associated with malnutrition (social reasons, lack of appetite due to opoids/ constipation). This may result in lower lipids, which has been shown previously. In contrast, high triglycerides have been observed in a minority of HCV-monoinfected patients which are thought to be the result of high endogenous interferon levels. In addition, lipodystrophy is usually associated at least with higher triglycerides.

HCV levels in semen

Jules Levin, NATAP.org

It is generally considered today that rates of sexual HCV transmission are low, about 5%. However, there is much controversy about how and when HCV is transmitted sexually. Although HCV has been found in semen, there does not appear to be evidence yet that the exchange of semen transmits HCV. But I think further research is needed to examine if there are circumstances or conditions in which HCV can be transmitted by semen and how HCV can be transmitted sexually.

The CDC says risk for sexual transmission increases if a person has multiple sex partners and is active sexually. Remember HCV is transmitted by blood-to-blood contact. Studies show that risk for sexual transmission may be increased when the following circumstances are present during sexual contact: STDs, open sores, anal sex, and sex during menstruation; several studies show increased risk for sexual transmission among men who have sex when risky sexual behaviors which may draw blood are used such as fisting. Recent studies suggest that a high HCV viral load may promote sexual transmission.

Since higher HCV viral load in HIV-infected individuals has been observed at times it raises the question whether HCV sexual transmission is a greater risk for HIV-infected individuals. I don't think this has been adequately studied. Studies do show that among pregnant women HIV increases the risk for HCV transmission several times.

HCV is usually transmitted via the blood, but HCV RNA has been detected recently in seminal fluid. This study was done to study HCV seminal shedding and factors that could influence the presence of HCV in the seminal fluid of men coinfected with HCV and HIV-1. HCV and HIV-1 genomes were assayed in multiple paired blood and semen samples obtained from 35 men enrolled in an assisted medical procreation protocol.

HCV RNA was found intermittently in semen samples from nine patients (25.7%). Samples from nine men with HCV RNA in their semen and 26 men without were compared to further analyse these parameters. No correlation was found between HCV RNA in the seminal fluid and age, HCV virus load, the duration of HIV-1 infection, HIV treatment, the CD4+ cell count, HIV-1 virus load or HIV-1 detection in the semen.

The intermittent detection of HCV RNA in semen samples support the systematic search for HCV RNA in semen and the use of processed spermatozoa in assisted medical procreation of infertile HCV serodiscordant couples.

Ref: Pasquier C, Bujan L, Daudin M et al. Intermittent detection of hepatitis C virus (HCV) in semen from men with human immunodeficiency virus type 1 (HIV-1) and HCV. J Med Virol 2003 Mar;69(3):344-9.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12526044&dopt=Abstract

C O M M E N T

In practice condom will protect against HCV and HIV, in contrast to HBV. Sound advice is to use themto protect you against the low risk of sexual HCV transmission and get vaccinated against hepatitis B and hepatitis A.

ON THE WEB

A guide to the best new reports and resources posted on the internet.

Conferences abstracts and reports:

38th Annual Meeting of the European Association for the Study of the Liver (EASL)

Originally scheduled for March 29 - April 1, 2003 in Istanbul, Turkey, the 38th Annual Meeting of the European Association for the Study of the Liver (EASL), was cancelled by the organizers due to the war in Iraq. The meeting has been rescheduled to take place in Geneva from 3-6 July – see 'Meeting Announcements' below. Abstract summaries of oral and poster presentations related to treatment for chronic hepatitis C and hepatitis B, including coinfection with HIV, are available at HIVandHepatitis.com

http://www.hivandhepatitis.com/2003icr/38easl/main.html

First European HIV Drug Resistance Workshop

6 - 8 March 2003 Luxembourg

Programme and abstracts are now available online together with meeting report by Yasmin Halima.

Site requires first-time free online registration.

http://www.hivpharmacology.com

Further Coverage of 10th Retrovirus Conference

Medscape articles require first-time free online registration.

Complications of HIV Disease and Therapy

http://www.medscape.com/viewprogram/2261

Metabolic Complications and Cardiovascular Sequelae of HIV Infection and Treatment

Graeme J. Moyle, MD, MBBS

Opportunistic Infections: They Still Exist, Even in North America and Western Europe

Henry Masur, MD

HIV Infection in Children

http://www.medscape.com/viewprogram/2262

HIV Transmission in Infants; Disease Progression in Children; Treatment Effects and Side Effects in Children and Adolescents

Karin Nielsen, MD, MPH

Pathogenesis of HIV Disease

http://www.medscape.com/viewprogram/2263

Viral Factors in the Pathogenesis of HIV Infection- Jeffrey Laurence, MD

Host Factors in the Pathogenesis and Therapy of HIV Infection - Robert W. Shafer, MD

Viral and Host Factors in HIV Neuropathogenesis - Justin C. McArthur, MD

Medscape articles:

Medscape requires first-time free online registration.

HIV Research in 2003: Moving Forward, One Step at a Time

Mark A. Wainberg, PhD

http://www.medscape.com/viewarticle/451704

Q&A About Enfuvirtide (Fuzeon, T-20): Interview With Jonathan M. Schapiro, MD

http://www.medscape.com/viewarticle/451622

From: Journal AIDS

Severe Hepatotoxicity During Combination Antiretroviral Treatment: Incidence, Liver Histology, and Outcome

http://www.medscape.com/viewarticle/450964

From: AIDS Reader

RNA Silencing: A New Therapeutic Strategy Against HIV

Jeffrey Laurence, MD

http://www.medscape.com/viewarticle/450272

Musculoskeletal Manifestations of HIV Infection

Ann-Marie Plate, MD, Brian A. Boyle, MD

http://www.medscape.com/viewarticle/450275

From: AIDS Clinical Care

Rapid Fingerstick Testing: A New Era in HIV Diagnostics

Bernard M. Branson, MD et al

http://www.medscape.com/viewarticle/451739

Newsletters and journals:

IAPAC Monthly February 2003

http://www.iapac.org/iapacmonthly.asp?catid=14

- Report from the President - Hope for turning of the tide
- Needed: Committed and daring voices
- HIV care in 2003: A viewpoint
- Will AIDS finally teach us the meaning of sustainable human development (for all)?

AIDS Treatment News – April 4, 2003

Including an interview with Cal Cohen MD Part Two

http://www.aids.org/immunet/atn.nsf/page/i-latest

STEP Perspective - Winter 2002/2003

http://www.thebody.com/step/winter03/contents.html

Including:

Methadone and HIV Medications: Drug Interactions by Barb Falkner, B.Sc. (Pharm.) and Bradley Kosel, Pharm.D.

from Seattle Treatment Education Project - Winter 2002/2003

http://www.thebody.com/step/winter03/methadone.html

Depression and HIV in the Era of HAART By Andrew Elliott, M.D., M.P.H.

http://www.thebody.com/step/winter03/depression.html

The PRN Notebook –March 2003

The March 2003 issue of The PRN Notebook is available online in both HTML and PDF formats.

http://www.prn.org/

2003 Review of experimental antiretrovirals

Scott M. Hammer, MD and Harold C. Neu

Metabolic and morphologic complications in HIV disease: Whats new?

Kathleen Mulligan, PhD and Donald P. Kotler, MD

Youth and HIV: the epidemic continues

Donna Futterman, MD

Identifying HIV treatment and research priorities in resource-poor settings

Miriam Rabkin, MD, MPH

Hopkins HIV Report – March 2003

http://www.hopkins-aids.edu/publications/report/report_toc_03.html

- Treatment Interruption
- Treatment of Tuberculosis in the HIV-Infected Patient
- Immune-Based Therapy in HIV
- When to Start HAART, and What to Start
- Taking HAART to Heart: Antiretroviral Toxicities
- Drug Resistance and Treatment of Experienced Patients
- HIV and Hepatitis

GHMC Treatment Issues – March 2003

http://www.gmhc.org/living/treatment/ti1703/ti1703.html

Contents include:

- Long Path to Approval -A look back at the road to T-20
- Fuzeon Data Review - A capsule review of T-20 efficacy data together with TAG position paper
- $15 Million for Infrastructure but No AIDS Drugs for Jamaica - Richard Stern
- International Treatment Preparedness Summit Opens
- It's Time to Face the Zerit Problem- Nelson Vergel asks for caution on d4T

TAGline - April 2003

http://www.thebody.com/tag/tagix.html

- Full Count: Roche Tempts Fate With High Profile T-20 Launch
- Tipping Point: MSF, Oxfam Redefine the Possible, and Y2K Activist Trek to Durban Marks a Watershed
- TAG at Ten: The Year 2001

Other articles:

Nutritional Care Manual for HIV-positive people

A manual with a global perspective on nutritional care and support for people living with HIV/AIDS from the World Health Organization and Food and Agriculture Organization of the United Nations.

http://www.fao.org/DOCREP/005/Y4168E/Y4168E00.HTM

MEETING ANNOUNCEMENTS

Dates for upcoming meetings are included below. Please check with their websites for full details.

UK Resistance and PK Workshops

5 - 6 June, 3-4 July and 27-28 November 2003

Three interactive educational workshops on resistance testing and pharmacological assessment in HIV have been organised, principally aimed at consultants, and specialist registrars.

Training, including detailed case studies, will be provided by Professor Clive Loveday and Dr Stephen Taylor.

Places are limited to 25 per course and regitration fee of £50 includes overnight accomodation in London, plus all meals.

Please contact Mediscript on 020 8446 8898 for further details.

EASL rescheduled

The 38th Annual Meeting of the European Association for the Study of the Liver (EASL), previously postponed (from 29 March to 1 April 2003 in Istanbul, Turkey) due to the outbreak of war in Iraq, has been rescheduled and will now be held in Geneva, Switzerland, from 3 to 6 July, 2003. See website for details.

http://www.easl.ch/easl2003/

5th Workshop on Lipodystrophy and Adverse Drug Reactions and Lipodystrophy in HIV

8–11 July 2003, Paris, France.

Registration is now available on-line, including press, scholarship and community awards.

http://www.intmedpress.com/lipodystrophy

2nd IAS Conference on Pathogenesis and Treatment of HIV/AIDS

Registration is now available on-line, including press, scholarship and community awards.

13-16 July 2003. Paris, France.

http://www.ias2003.org/

PUBLICATIONS AND SERVICES FROM i-BASE

New i-Base '.info' web address

Our web address has changed slightly and is now:

http://www.i-Base.info

More than 500 people a day visit the site, where you can read all i-Base publications, fill in our readership survey, find details of the UK Community Advisory Boards (UK-CABs), learn about the organisation, our phone service and meetings, and access our archives and an incomparable range of links.

The site can also be used to order publications and regular subscriptions to be delivered by post or email (as pdf files).

Translations of 'Introduction to Combination Therapy'

This essential non-technical patient guide to combination therapy has recently been translated into Portuguese, Latvian and Slovak, by HIV-positive support organisations in those countries. The Portuguese version is available to download as a pdf file and reprint from the i-Base website:

http://www.i-base.info/pdf/guides/nonuk/COMBO_PORTUGUESE_jan03.pdf

For Latvian and Slovak copies please contact the I-Base office.

Printed versions of this booklet are also available in English, French, Italian, Spanish, Chinese and Macedonian. The guide 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 drug resistance and how to avoid it. To order copies, see below

Changing Treatment: a guide to second-line and salvage therapy

Updated January 2003. These treatment guides are reviewed every six months to ensure the latest information is available. Many factors contribute to whether a combination works and in salvage therapy it is important to look at all of these together.

The section on treatment strategies has been rewritten and updated and includes a new section on viral fitness and alternating treatment regimens. The information on expanded access and experimental treatments has also been updated.

Since the previous edition several new treatments have become available to use in salvage therapy and these are also included in the guide:

* T-20 has reported clear benefits for people resistant to current drugs - marketing approval is expected in mid 2003 and prior to this will be available in a limited expanded access programme from early 2003.

* Atazanavir appears to increase cholesterol and triglycerides less than other PIs and is available in an expanded access programme for people with raised lipids on current PIs.

* Tipranavir, a PI with activity against currently resistant HIV, will be available during 2003 in an limited emergency access programme.

For additional free copies, including bulk orders see below

UK-Community Advisory Board reports and presentations

The UK-Community Advisory Board (UK-CAB) was set up by HIV i-Base last year as a network for community treatment workers across the UK and has so far held three meetings. Each meeting includes two training lectures and a meeting with a pharmaceutical company.

The programme, reading material and powerpoint slides from the presentations to the fourth meeting held on January 31st are now posted to the i-Base website. This meeting focused on gender issues and HIV, and also on hepatitis and coinfection.

http://www.i-base.info/ukcab/jan03/index.html

Transcriptions and slides of training sessions from previous meetings also on the site include:

Genetics, resistance and HIV – by Professor Clive Loveday

Approaches to Salvage Therapy – by Dr Mike Youle

Pregnancy, HIV and Women's Health - by Dr Karen Beckerman

Fertility treatment and sperm-washing techniques – by Dr Leila Frodsham

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

Guide to Avoiding and Managing Side Effects

A comprehensive 36-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.

It is written by people who are HIV-positive, who have been on most of the treatments, who have had many of the side effects and who have learnt to negotiate their own healthcare.

French, Spanish and Chinese translations of this booklet are also available. To order copies, see below.

Positive Treatment News (PTN)

The latest issue of Positive Treatment News, our magazine for positive people, looks at adherence (missed any pills recently, need any advice?), the latest information about side effects and treatments, and the benefits and risks of joining a drug trial or study.

There is also a detailed look at weight loss and what can be done about it, the official treatment guidelines, salvage therapy and treatment information provision for the African community. To order copies, see below.

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 on our website (http://www.i-base.info) and in a printed version. The printed version is available at most HIV clinics in the UK and is available free by post: see below for details.

Treatment information request service

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 also mail or email copies of the latest research studies relevant to the caller.

For 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 Wednesday from 12 noon to 4pm.

All calls are in confidence and are free within the UK.

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http://www.i-base.info

Copies of publications can also be ordered by post or fax using the form on the back page of this journal. These methods of ordering are suitable for all our publications: HIV Treatment Bulletin (HTB), Positive Treatment News (PTN) and all our treatment guides and reports.

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Guide To Avoiding and Managing Side Effects *(August 2002)*
IN ENGLISH

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Introduction to Combination Therapy *(August 2002)*
IN ENGLISH

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Changing Treatment - Guide to Second-line and Salvage Therapy *(April 2002)*

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Positive Treatment News (PTN) *from Spring 2003*

1 ☐ 5 ☐ 10 ☐ 25 ☐ 50 ☐ 100 ☐ Other_____ _____ _____

Paediatric HIV Care - March 2001 - Report from i-Base Paediatric Meeting

1 ☐ 5 ☐ 10 ☐ Other_____ _____ _____

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

1 ☐ 5 ☐ 10 ☐ Other_____ _____ _____

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