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EDITORIAL

This issue has reports from the recent 2nd European HIV Drug Resistance Workshop and 5th International Workshop on Clinical Pharmacology of HIV Therapy conferences plus two final Retrovirus reports. One of the most import presentations from the PK meeting was the analysis of tipranavir interactions with other protease inhibitors (see page 3).

In this issues Treatment Access, Graham McKerrow provides a round up of recent developments in pricing agreements and access issues in resource poor countries.

We are hardly the first to point this out, but we could never have imagined five years ago, that effective fixed dose combinations would become available at less than 3% ot the original cost of HAART and that agreement for global funding would be approved approved for many programmes.

However, even when funding has been approved, or new lower price deals announced, the reality is that very few HIV-positive people have so far actually received antiretrovirals.

Whether even 300,000 people will be on-treatment by 2005 is still in doubt, and we're almost halfway through 2004.

CONFERENCE REPORT

5th International Workshop on Clinical Pharmacology of HIV Therapy

1-3 April 2004, Rome, Italy

This international meeting continues to provide a lively and important platform for a wide range of research.

Although not yet posted as HTB went to press, the programme and abstract book from this meeting are due to be posted to:

http://www.virology-education.com

Unless otherwise stated all references are to the Programme and Abstracts for the 5th International Workshop on Clinical Pharmacology of HIV Therapy, Rome, March 2004.

Large reductions in plasma PK levels of saquinavir, amprenavir and lopinavir/r levels when given with tipranavir/ritonavir

Simon Collins, HIV i-Base

One of the most important studies presented at the workshop was the first analysis of interaction between tipranavir and other protease inhibitors, from the BI 1182.51 trial. The results have important implications for people currently using tipranavir in regimens that also contain saquinavir, amprenavir or lopinavir/r.

Tipranavir is used at a dose of 500mg boosted by 200mg ritonavir, both twice daily. This study was designed to look at the pharmacokinetic interaction with a second protease inhibitor (saquinavir, amprenavir or lopinavir/r). Ritonavir is a potent CYP3A4 inhibitor and tipranavir is a CYP3A4 inducer.

Patients were enrolled who were too heavily resistant for the registrational RESIST phase-3 tipranavir trials. Enrolment criteria included triple-class experience and three or more universal protease-associated mutations from codons 33, 82, 84 and 90 (UPAMs). Tipranavir/r was added after two weeks to steady-state optimised background (OB) including each boosted-PI and compared to a tipranavir/r-only + OB regimen.

Results from 296 patients were included in this analysis: 296 in the safety data set, 290 in the PK trough data set and 86 patients (out of 134 patients in the intensive PK substudy) had evaluable data at two visits to be included in the intensive PK data set reported here.

The addition of tipranavir/r at week two sent the levels of each of the original PIs through the floor to barely detectable in many patients and to less that the previous median levels in > 80% of patients.

No dosing recommendation can even be made for these second protease inhibitors when used with tipranavir. Concentrations fell well below target for the majority of patients although a small number of people did achieve therapeutic levels. This can only be supported by individual drug level monitoring.

Table 1. Median trough concentrations of concomitant protease inhibitors (mg/mL) before and after tipranavir:

All figures approximate

	TPV/r	APV/r	SQV/r	LPV/r
n	66	76	75	79
Week 0		1.9	0.4	5.5
Week 2		1.9	0.5	5.5
Tipranavir added at week 2:				
Week 3		0.8	<0.1	3.0
Week 4		0.8	<0.1	3.0
% reduction		50%	>80%	45%
VL reduction				
Week 2	-1.2	-0.2	-0.3	-0.4
Week 4	-1.2	-1.2	-1.2	-1.2
Week 8	-0.5	-0.8	-0.7	-0.7

Tipranavir concentrations appeared similar in patients using saquinavir and there appeared to be a trend for slightly higher levels in the amprenavir and lopinavir/r groups.

Side effects were similar in each arm with 55-60% of patients in each arm reporting at least one side effect. Of these, diarrhoea and nausea were the most common. Incidence of laboratory abnormalities was similar in all arms, with raised triglycerides being the most commonly reported lab event.

Virological efficacy in the study was clearly driven by tipranavir with patients in all groups achieving median change of >1log reductions by week 4, once tipranavir was included in the combination. In this highly experienced group, this unfortunately only provided a short-term effect and by week 8 median viral load was rebounding to approximately -0.5 log below. Whether this trend continues further will be shown in the next analysis from 24-week data from this study due to be presented in Bangkok in July.

Ref: Curry K, Samuels C, Leith J et al - Pharmacokinetics and safety of tipranavir/ritonavir (TPV/r) alone or in combination with saquinavir (SQV), amprenavir (APV), or lopinavir (LPV): interim analysis of BI 1182.51. Abstract 5.1.

Good generic drugs and good adherence in Rwanda

Polly Clayden, HIV i-Base

A report from the ESTHER treatment programme - a collaboration between Rwanda and Luxembourg - described good quality generic drugs and good adherence in 70 Rwandan patients at the Centre Hopital de Kigali.

The study performed an analysis of antiretroviral generic drugs (tablets, capsules and syrups) available in Rwanda. Zidovir, Nevimune and Lamivir are manufactured by Cipla, and Avolam, Coviro and Triviro by Ranbaxy.

Drug contents as a percentage of the manufacturer's claim are described in the following table:

	Drugs analysed	Label claim (mg/mL)	Mean amount (mg/mL)	Drug content/ Label claim (%)
SYRUPS				
CIPLA				
ZIDOVIR	zidovudine	10	9.4	94.0
NEVIMUNE	nevirapine	10	8.1	81.0
LAMIVIR	lamivudine	10	10.5	105.0
TABLETS/CAPSULES				
RANBAXY				
AVOLAM	lamivudine	150	158.9	105.9
TRIOVIR	lamivudine	150	151.9	101.3
LNS30	stavudine	30	28.0	93.3
	nevirapine	200	183.2	91.6
COVIRO	lamivudine	150	157.2	104.8
LS30	stavudine	30	29.5	98.3

COVIRO	lamivudine	150	158.2	105.5
LS 40	stavudine	40	39.8	99.5
CIPLA				
NEVIMUNE	nevirapine	200	176.0	88.0
ZIDOVIR 100	zidovudine	100	107.6	107.6
ZIDOVIR 300	zidovudine	300	330.0	110.0

The investigators concluded: "Average drug content/label claim = 99.0%, results are in accordance with the manufacturers' claims. Good quality generic drugs are available in Rwanda."

The study also assessed adherence in two groups of patients by measuring their NNRTI levels at four hours post dose: efavirenz by HPLC/UV-DAD (n=27) and nevirapine by GC/MS-SIM (n=43).

The investigators reported 87% of patients overall to be in the therapeutic range or above and therefore considered them to be adherent.

C O M M E N T

Although it is encouraging to see this study, it is important to note that this analysis describes pharmaceutical equivalence not bioequivalence - ie the study reports drug content *in vitro*. So we do not have the complete story and it would not be possible to extrapolate PK from these data.

Using TDM to assess adherence is probably not its best use but again it is encouraging to note that 87% of patients in this group were in the therapeutic range.

Ref: Schneider S, Schuman M, Omes et al. Antiretroviral therapy among advanced stage, indigent patients in the funded ESTHER programme in Kigali, Rwanda. Abstract 1. Poster 1.1.

Steady state PK of nelfinavir and M8 in pregnancy

Polly Clayden HIV, i-Base

A study from Rolf van Heeswijk and colleagues from the Ottawa Health Research Institute in Canada evaluated the pharmacokinetics and its active metabolite M8 during pregnancy and post partum.

A group of 11 women receiving 1,250 mg BID of nelfinavir and two nucleosides were assessed in this longitudinal study. Twelve hour nelfinavir and M8 levels were analysed by LC/MS/MS at a median of 33 weeks during the third trimester and a second analysis was performed post partum at a median of eight weeks following the first sampling.

The investigators reported the post partum geometric mean nelfinavir AUC 0-12h, Cmax and C12h to be 31.0 h mg/L, 4.84 mg/L and 1.21 mg/L respectively (comparable with population values). The geometric mean ratio (GMR) third trimester/post partum (90% CI) for nelfinavir AUC 0-12h, Cmax and C12h was 0.76 (0.54–1.06), 0.81 (0.57–1.15) and 0.43 (0.25–0.76) respectively.

For the M8 AUC 0-12h, Cmax and C12h GMR (90% CI) was 0.32 (0.18-0.55), 0.31 (0.19-0.51), and 0.30 (0.14-0.64) respectively. The median ration of the AUC 0-12h of M8 and NFV during the third trimester and post partum was 11% and 27% respectively and the GMR and 90% CI was 0.42 (0.33–0.53).

The investigators noted a trend towards reduced exposure to nelfinavir during pregnancy (AUC reduced by 24%) that they suggest is due to induction of CYP3A4 and/or CYP2D6. They also reported significant reductions in concentrations of the active metabolite M8 (reduced by 70%) during pregnancy, which may be due to induction of CYP3A4 and/or inhibition of CYP2C19 and the clinical implications of which are unclear.

All women in this study maintained an undetectable plasma viral load and a stable CD4 cell count during pregnancy and post partum.

C O M M E N T

These and other data (Kosel et al, AIDS 2003;17:1195-9) indicate that total plasma concentrations of nelfinavir are reduced during the later stages of pregnancy. This may be due to physiological changes in the volume of distribution and in clearance. Kosel et al also noted individual variability, which suggests that a universal increase in nelfinavir dose is unlikely to be possible. The effect seen of pregnancy on M8 concentrations is even greater which seems to support dose adjustment in pregnancy, however, the virological outcome of

undetectable plasma viral load in all eleven mothers, is consistent with clinical experience.

The move away from using nevirapine, particularly for those mothers with high viral loads and CD4 counts greater than 250 cells/mm^3 requiring short course antiretroviral therapy, is likely to result in greater use of protease inhibitors. There is an urgent need for data on how best to prescribe these in pregnancy, an area which to date has been neglected. Meanwhile, there is a strong case for TDM in pregnancy with cautious dose adjustment.

Ref: Van Heeswijk R, Khaliq Y, Gallicano K et al. The steady state pharmacokinetics of nelfinavir and M8 during pregnancy and postpartum. Abstract 9. Poster 3.2.

Higher nelfinavir concentrations improve response in children

Polly Clayden HIV i-Base

David Burger from the University Medical Centre in Nijmegen, Holland, presented data from a pharmacokinetic substudy of the PENTA 5 trial, in which naïve children received nelfinavir plus two nucleosides.

All participating children received NFV 25-30 mg/kg TID or 45-55 mg/kg BID with food. Trough samples were taken between week 20 and 80. NFV troughs <0.8 mg/L were considered subtherapeutic. Viral load <50 copies/mL was measured at week 24 and 48.

Forty-four children were enrolled in this substudy of which data from 32 were evaluable (22 boys, 10 girls). The investigators reported an average trough of 2.1mg/L (n=18; CV: 66%) for children receiving NFV BID and 1.7 mg/L (n=14; CV 90%) for those receiving the drug TID.

Seven (22%) children had a subtherapeutic NFV trough (0.10-0.53 mg/L) and the researchers reported no difference between the children with subtherapeutic and therapeutic concentrations with regard to: gender, baseline HIV-1 RNA, daily NFV dose and dose frequency. Viral load less than 50 copies/mL was reported in 43% and 295 at weeks 24 and 48 respectively.

However of the 25 children with a NFV trough concentration above 0.8mg/mL, 72% and 80% had HIV RNA <50 copies/mL at weeks 24 (p=0.20) and 48 (p=0.02) respectively.

The investigators concluded TDM of NFV appears to have the same relevance in children as in adults and a target of 0.8mg/L improves treatment outcome in children.

Ref: Burger D, Bergshoeff A, de Groot R et al. Maintaining the nelfinavir trough concentration above 0.8 mg/L significantly improves virological response in HIV-1-infected children. Abstract 10. Poster 3.3.

PK of once daily lopinavir/r in children

Polly Clayden, HIV i-Base

A report from Glenda Verweel et al from University Medical Centre in Rotterdam evaluated the pharmacokinetics of children on a QD dosing schedule of lopinavir/ritonavir.

A group of 14 children on stable antiretroviral therapy with HIV-1 RNA below 50 copies for at least six months were switched to receive LPV/r 460/115 mg/m^2 QD with zidovudine and lamivudine BID as part of the RONDO trial. The LPV/r dose was given with food.

Samples were taken at 0, 2, 4, 6, 8, 12, 18 and 24 hours post dose. The target range for Cmin was 1.0mg/L. The children received a median dose of 400mg LPV (range 282-533mg). The median dose per m^2 was 461 mg (448-883 mg). The investigators reported steady state AUC (0-24h), Cmax, Tmax and Cmin (24h) to be similar to LPV/r dosed at 800/200 mg QD in adults.

Of the children, only 3/14 had Cmin (24h) levels considered to be too low, leading to dose increase. At three months follow up, 12/13 children for whom data were available had HIV-1 RNA <50 copies/mL and one child had 52 copies/mL.

C O M M E N T

Like pregnant women, these last two studies show that if ever there is a population for which TDM is strongly indicated it is children.

Ref: Verweel G, van der Lee M, de Groot R et al. Pharmacokinetics of once daily lopinavir/ritonavir in HIV-infected children. Abstract 7.1

CONFERENCE REPORT

2nd European HIV Drug Resistance Workshop

11-13 March 2004, Rome, Italy

Mike Youle, for NATAP

Unless otherwise stated, all references are to the Programme and abstracts for the 2nd European HIV Drug Resistance Workshop: from basic science to clinical implications.

Understanding developments in HIV drug resistance for new drugs and targets — atazanavir, fusion (T-20) and receptor inhibitors

The annual European gathering of resistance aficionados took place recently on a hill above the Vatican and conformed to the best of Italian characteristics: good food, exquisite style and a complete disregard for time-keeping. I chaired a session that started 90 minutes late but since the presentations and discussion were so engrossing no one but the most anally retentive cared a jot.

The attachment of HIV to the cell is a potentially very attractive proposition since the likelihood of toxicity from these compounds is low and an interesting subject of discussion at this conference. The meeting opened with an excellent overview of "Research on Anti-HIV Resistance in Europe" by Anne-Mieke Vandamme who has just finished editing the new European Guidelines for Resistance testing which will be available soon. She spoke of the central problem that HIV therapy effectively treats the condition but a consequence is a rise in resistance since even the best agents leave a window of replication and inadequate treatment or poor adherence lead to a selection of resistant strains which can then be transmitted, more of which later. So what are the answers? Certainly one is to develop new agents and she showed various lists of the new drugs in development, which appear to be licensed at the rate of 1-2 per year. But from her perspective as a virologist the newer therapies have inherent problems since most are aimed at existing targets and thus have potentially reduced efficacy through cross resistance.

In the next five years it is possible that we will have seven new NRTI's, five NNRTI's, five PI's, nine entry inhibitors and perhaps three-four other agents but in Anne-Mieke Vandamme's view drugs are not coming fast enough to keep up with the rising tide of resistance especially in highly treated populations where 3 class resistance is already approaching 40-50%.

She showed the major groups who are working on HIV drug resistance but bemoaned the fact that much of the peer-reviewed money has been for establishing networks but not for actually conducting research projects. Apart from the ANRS in France, other European countries appear to feel that the pharmaceutical industry should provide the major part of funding for such research, which of course brings its own difficulties.

An excellent aspect of Anne-Mieke Vandamme's talk was a case study in which clearly a mixture of an inexperienced or ill informed physician had prescribed a poor regimen that had been wrongly taken by the patient, leading to pan-resistance when the treatment had been started well after the 1996 HAART threshold. This resulted in a salvage treatment scenario for no good reason, emphasising that most therapy failure, and ipso facto problematic HIV care, is based on bad medical decisions. Leaving antiretroviral treatment to experts in centres of excellence would probably reduce this. She finished her presentation with a few suggestions of areas of importance such as the development of fusion inhibitor (T20) and other entry inhibitor assays, further study of the epidemiology of drug resistance and establishing the role of resistance testing of proviral DNA.

The first subject discussed in the main body of the meeting was the Epidemiology of Primary Drug Resistance and Viral subtypes. Sally Blower from USFC gave an overview of modelling work she has done of drug resistance transmission in Africa, the potential for which has been a traditional argument against the widespread use of antiretrovirals in resource poor settings. She estimates that of the 34-46 million infected in the subcontinent, 6 million need immediate treatment, which the UNAIDS 3 x 5 programmes is attempting to achieve. The models that were published by her last year in Science estimate that by 2006 40% of treated individuals will have drug resistance to some degree. She then moved focus to consider the potential for HIV therapy to eradicate the epidemic by preventing transmission, a kind of secondary chemoprophylaxis. Her conclusions were that unlike the developed countries where a high proportion of those infected are on antiretrovirals, it is unlikely that the treatment levels seen in Africa will have any chance of slowing the epidemic.

Jan Albert of the Swedish Institute for Infectious Disease Control broached the difficult problem of transmission of drug resistance [1]. An expert panel is to be convened to try to address some of the difficulties in defining the field, since nothing currently exists to help the virologist identify whether or not drug resistance transmission has occurred, for there are no guidelines of interpretations systems available. He raised the difficulty of treating the presence of singleton mutations (single codon changes such as K101E or M36I) as evidence of transmission since few treated patients carry single mutations, and

he posed the question “Who are the source patients for these infections?” He cited two studies where half of the purported drug transmissions were singleton mutations and suggested that either these were natural variants or a result of the reversion of more complex resistance patterns if indeed they were transmissions.

Further epidemiologic data were presented by David van der Vijver on behalf of the CATCH study team, which tracked the occurrence of resistance in 2208 subjects across 19 European countries [2]. While the prevalence of resistance was higher in B subtypes (13%) versus those harbouring non-sub-type B viruses (5%) this sub-analysis which merely looked at those from the main cohort who had been infected for less than a year revealed an increase in the proportion of individuals with non-B viruses which rose from 17% in the 1996-9 period to 28% between 2000 and 2002 (P<0.001).

The breakdown showed that 95% of MSM had B, whereas only 72% of IDU patients and 58% of heterosexuals carried this sub-type. The effect of immigration, especially more recently, and the rates of non-B virus were discussed as well as the variable pen trance of treatment into various transmission groups, which may explain these findings.

Deenan Pillay from University College London gave a poster review of this section and clearly laid out some of the problems associated with the current ways of looking at the subtype issue. In 12 abstracts, looking at subtypes, he found six methodologies varying from comparison to a standard strain through, amino-acid weighting within sequences of the virus to formal phylogenetic testing. In addition, the proportion of non-B using these different tests varied widely from 45% in Greece down to 8% in Germany.

Next was a section on new agents and their pathways to resistance. Rich Colonno from Bristol Myers Squibb (BMS) gave an elegant presentation on the available data for the recently licensed protease inhibitor atazanavir [3]. He first listed the primary and secondary mutations known to be associated with reduced sensitivity of the virus to atazanavir. These included the usual suspects (primary G48, V82, I84 and L90, along with so far unique I50L). Resistance was defined as the presence of the I50L or a greater than 2-fold phenotypic change from baseline to >2.3-fold. In the naïve studies all individuals seem to preferentially follow the I50L pathway to resistance which seems to induce hypersensitivity of around 10% to other protease inhibitors, which of course may argue for the use of atazanavir up front to allow some form of sequencing, although previous history has not been kind to this strategy and the argument for Kaletra has always been that no primary resistance occurs, so why not use it first line.

He next showed the results of the experienced studies and clearly the virus takes another pathway more frequently here with only 36% (13) individuals in the 043 protease inhibitor experienced study developing I50L, while the rest presented with standard PI mutant virus, which of course showed cross resistance to other PIs. The same story has emerged for the ritonavir boosted second line PI studies such as 045 where 21% (5) had I50L compared to 79% (19) with other mutation patterns. Interestingly, none of the subjects who received atazanavir combined with saquinavir and who showed a sub-optimal response compared to the ritonavir boosted arms followed the I50L pathway and all revealed other more commonly seen PI mutation patterns. Finally, hyper susceptibility to other PI’s was only found in the setting of I50L. In the questions that followed the talk, Françoise Brun-Vèzinet remained unconvinced that enough data were yet available on boosted atazanavir to be clear on the route the virus would take to resistance under atazanavir, and Yasmin Halima asked the very pertinent question as to the effect of drug levels on this pathway. It has been received wisdom from BMS that therapeutic drug monitoring is not necessary with atazanavir but I feel that many of us who use this tool within clinical practice for other PI’s would not necessarily agree with this, and in fact a study linking drug levels with outcomes was presented by Soriano and his group at CROI two months ago suggesting that there is a link.

Continuing the theme of assessing new compounds, there was a fascinating talk by Rafael Nájera on natural resistance mutations to fusion inhibitors (T-20) and polymorphisms in the gp41 sequence of both B and non-B subtypes from patients in Spain [4]. The group studied the de novo resistance to several fusion inhibitors (T-20, 5-helix, C-34 and RPR 103611) in 170 individuals of whom 19 were primary infections and 131 were on HAART. RNA was extracted from plasma samples and sequencing undertaken of gp41 by nested PCR, then resistance mutations were assessed within the heptad repeat 1 and 2 regions which are blocked by fusion inhibitors. Polymorphisms were found in 42.3% of subjects (28.5% in B subtypes; 72.2% in non-B sub-types) and mutations which have been associated with resistance to T-20 in 11.2% (3.5% on HAART/T20; 7.6% on T-20 functional monotherapy). The N42S polymorphism had the characteristic of increasing susceptibility to T20 in B sub-types.

This study raises some concerns that T-20 naïve individuals may have a variable response due to innate conformational changes in gp41 due to these mutations and that resistance testing may be helpful in predicting response to the drug. Further work in this area was shown by a group from the retrovirology group in Centre de Recherche Public-Santé in Luxembourg [5]. They created a recombinant virus into which was inserted a mutation I37V which has been associated with resistance to T-20 both in the test-tube and after giving the drug as monotherapy. The findings were that the virus was less fit but did not exhibit a reduced susceptibility to T-20 and thus of itself did not result in T-20 resistance.

A final piece of the story was provided by Poveda and co-workers from Madrid, who examined the consequences of T-20 therapy in multi-drug resistant patients who received T-20 as part of a salvage regimen. Of eight patients, all of whom experienced a decrease in viral load >0.5log after starting their new regimen, one remained suppressed <50copies/mL while

the other seven rebounded rapidly after commencing treatment. Six of these exhibited a N43D mutation and showed between 15 and 143-fold resistance to T-20, two subjects also had a G36V or D leading to high level resistance. These patients were also noted to have a wide range of baseline susceptibilities to T-20 (IC50 range from 20-400) and this may be important in the future assessment of suitability of subjects for T-20 or other fusion inhibitor drugs. This is definitely a field in which we are working with little data at the moment and as this increases a clearer picture will emerge of how to evaluate and interpret resistance to this new class of drugs.

Further discussion of entry inhibitor resistance was provided by Francois Clavel, who first talked about receptor blockers and the potential pathways to resistance, specifically what happens to X4 virus when R5 is inhibited and how much X4 is required to outgrow R5 suppression. A difficulty remains that the current assays are at best semi-quantitative with a rather uncertain level of sensitivity, which precludes accurate prediction of what actually happens. Some data exist that suggest that in the presence of a receptor blocker you can overcome the effect by adding more virus and that artificially producing V3 loop mutations allows resistant viruses to use low density receptors preferentially. Some of the receptor blockers (SCHC for instance) may not bind but rather alter the binding characteristics of the virus.

With regard to the fusion inhibitors, of which really enfuvirtide (T-20) is the only one for which we have long-term clinical data, he described the very variable levels of resistance to fusion inhibitors between isolates and the reported effect of mutations on HR2, notably S138A (and from another study 113, 126 and 135) having an effect on HRI where T20 binds. These codons are actually opposite the area of gp41 (codons 36-43) which are at the site of action of T20 so in structural terms this makes sense. He also presented a table of report variation in natural susceptibility of HIV strains to a raft of entry inhibitors. These range from 1-23 fold for PRO-542 to 1-10,000 fold for the BMS-806 compound that has now been superseded by a new construct. Finally, isolates show at least a 2-log variation in susceptibility to T-20 although this did not appear to be clinically significant from the TORO studies.

He then tried to explain these phenomena in terms of the mode of action of the current agents and concluded that the receptor or target density, as well as the speed of the action in the window of opportunity during the events leading to fusion, predict the effect of the drugs. He concluded “HIV entry is not just another target since all envelopes are escape mutants” and the high variability of this region will cause difficulties. In addition, he commented that the current assays we have specifically for R5 and X4 are in their infancy. We obviously have a lot to learn in this new area of HIV control.

Source: NATAP.org

References

1. Albert J, Guidelines for identification of transmission of drug resistant HIV. Abstract 1:P1.1
2. Van der Vijver DAMC, Wensing AMJ, Op de Coul E et al. Increasing prevalence of HIV-1 non-B subtypes across Europe from 1996-1999 to 2000-2002; results from the CATCH study. Abstract 3:P1.3
3. Colonno R, McLaren C and Kelleher T. Pathways to atazanavir resistance in treatment-experienced patients on atazanavir containing regimens. Abstract 28:P3.1
4. Carmona R, Munoz M, Perez-Alvarez L et al. Natural resistance mutations to fusion inhibitors and polymorphisms in gp41 sequence of recombinant forms, non-B and B subtypes from HIV-1 infected patients in Spain. Abstract 29:P3.2
5. Roman F, Ammerlaan W, Plesseria JM et al. The gp41 mutation I37V does not lead to enfuvirtide (T-20) resistance. Abstract 30:P3.3

CONFERENCE REPORT

Further reports from Retrovirus

11th Conference on Retroviruses and Opportunistic Infections (CROI)

8-11 February 2004, San Francisco

See also HTB 5,3. Unless stated otherwise, all references are to the Programme and Abstracts of the 11th CROI.

HIV-associated dementia and cognitive dysfunction

Paul Blanchard, HIV i-Base

The introduction of increasingly effective antiretroviral drugs has resulted in increased survival of patients with HIV-infection. Prior to the availability of such drugs the development of HIV-associated dementia (HAD) was a much feared and serious consequence of advancing HIV disease. The precise impact of HAART on HAD and the associated cognitive dysfunctions remains, however, to be fully determined.

In the pre-HAART era the mean CD4 count at the time of diagnosis of HAD was 50–100 cells/mm^3. Post 1996 and the introduction of more effective ARVs this has risen to around 160 cells/mm^3. The reason for this elevation is unclear but both the nadir CD4 cell count and disease duration are likely confounding variables in the current HAART era.

Changes in the natural history of HAD have also been noted. In the pre-HAART era the mean time from diagnosis to death was six months, this has now been lengthened to 44 months. A consequence of such prolonged survival is that the prevalence of HAD is actually increasing. There is also a suggestion that the actual cognitive deficit in HAD may be changing with the increasing use of HAART – involving more cortical type abnormalities and less basal ganglia. The fact also remains that HIV encephalopathy continues to be present in 25% of patients at autopsy, a rate that has not changed since the widespread use of HAART.

Data presented at the 11th CROI provided some additional clues as to how HAD is now manifesting in those patients receiving more effective antiretrovirals.

Neurocognitive impairment in HAART treated patients and survival

Before the introduction of HAART, HAD was recognised as an independent risk factor for death. Tozzi and collegues from the National Institute for Infectious Diseases, Rome, Italy presented prospective data on mortality among patients referred for neuropsychological examination since 1996. [1]

On testing, of 432 enrolled subjects, 238 (55.1%) were found to be neurocognitively impaired and 194 (44.9%) unimpaired. All subjects were treated with HAART regimens which were changed accordingly with the availability of new drugs and by individual patient response. Median follow up period was 32.4 months and overall 47 deaths were recorded – 38 among impaired and 9 among unimpaired patients.

At enrolment neurocognitively impaired and unimpaired patients did not differ in terms of gender, plasma viral load, or positive HBV surface antigen. However, impaired subjects were older, less educated, had a lower CD4 cell count, more advanced HIV disease, higher prevalence of intravenous drug use, higher prevalence of HCV and showed a higher rate of virological failure during subsequent HAART regimes.

Differences in survival according to neurocognitive status were assessed by means of the Kaplan-Meier method and by the Cox proportional hazard model. After 84 months of follow-up the estimated survival proportions were 68.5% in the impaired group and 84.9% in the unimpaired group ($p<0.01$). After adjusting for confounding variable the multivariate analysis revealed that neurocognitively impaired patients still showed an increased risk of death as compared to unimpaired patients (HR=2.4; 95% CI: 1.1 – 5.1).

After stratification for virological response to HAART, the estimated risk of death for impaired patients was still significantly higher among the subgroup with virological failure (HR=2.9), but no longer significant among the subjects with durable virological suppression (HR=1.0).

The authors conclude that “Among HIV-positive patients receiving HAART, patients with HIV-associated neurocognitive impairment had an independent and statistically significant higher risk of death then subjects without neurological impairment. …this highlights the clinical relevance of HIV-related CNS involvement even in the HAART era.”

The association between neurocognitive impairment and virological failure revealed in this study requires further investigation. Might impairment be a predisposing factor for poor adherence?

HIV dementia, aging and HAART

Age is a suggested risk factor for the development of HAD. With increasing survival rates aging is a real possibility for many with access to effective antiretrovirals. Would increasing age also, therefore, lead to increased risk of HAD, even if viral replication is suppressed?

Lorenzini and colleagues, again from Italy, attempted to answer this question using a nested longitudinal study on a national cohort of HIV-infected patients with neurological diseases. [2]

From 2000 to 2003, 195 patients with HIV encephalopathy were notified (these consisted of 53% HAD, 47% MCMD - Minor cognitive motor disorder). The overall prevalence was 21% with an increasing annual rate. Median age was 42 years and a previous ARV exposure was present in 45%, 28% were receiving HAART at diagnosis.

Stratifying patients according to age and exposure to antiretrovirals, among naïve patients the prevalence of HIV encephalopathy was higher in older subjects: 13.7% (20-39 years), 28.3% (40-49 years), and 37.5% (‡50 years). The same proportions for HIV dementia were 7.2%, 15.3%, and 27.3%. Among ARV-experienced patients no significant increase of HIV encephalopathy or HAD for older age was observed. An increased prevalence of HIV dementia among older naïve patients compared to older experienced patients was detected ($p = 0.05$).

The investigators concluded “…HAART appears to change the relationship between aging and developing HIV dementia, conferring a neuroprotective effect to older patients and affecting the increased prevalence rate of HIV dementia with increasing age.”

Can HAART improve cognitive function and do drugs need to reach the CNS?

It has been hypothesised by a number of researchers that neuropsychological impairment might progress despite virological and immunological response to ARV's. Poor CNS penetration of active agents and ongoing viral replication in a CNS "sanctuary" site may be one possible reason for continuing cognitive decline. Data on the natural history of HAD and cognitive function from longitudinal studies of those treated with effective ARV's is scant.

ACTG 362 started life as a study of prophylaxis intervention for MAC. After the impact of HAART made MAC prophylaxis extremely unusual the study was converted into an observational cohort of advanced AIDS patients (CD4 < 50 before entry). [3] A series of annual cognitive evaluations using three simple tests assessed speed of information processing, mental flexibility and working memory. At study entry most participants were immune reconstituted (mean CD4=230) and HIV suppressed (65% < 500 with only 14% >20,000 RNA copies/mL).

Prevalence of neuropsychological impairment (NPI) was estimated at 40% in advanced AIDS patients after prolonged immunological reconstitution on HAART. In addition, better performance was associated with continued or recently improved suppression of plasma HIV RNA levels, and was unrelated to CD4 count. In a univariate model of change, NPZ3 score (Z-scores of Digit Symbol Substitution and Trailmaking A and B) improvement was associated positively with plasma HIV RNA suppression (<500) at time of testing or suppression of HIV (>500 to <500) over the prior 16 weeks. Interestingly lowest lifetime CD4 count (nadir) did not correlate with changes in NPZ3 score.

It was concluded from these data that "…plasma HIV suppression appears to be critical to improvement of cognitive function" and that "…most advanced AIDS patients responding to HAART for prolonged periods do not experience detectable cognitive decline."

Two separate studies presented in poster form addressed the question of whether there is any additional benefit for cognitive function from drug regimens containing ARV's thought to have better CNS penetration. Caution must be observed in interpretation as one study was cross sectional [4] and the other had small numbers of subjects who were not antiretroviral naïve [5]. The cross sectional study revealed that 50.3% of subjects had abnormal neuropsychological performance.

The number of CSF penetrating drugs within each regimen was not correlated with neuropsychological performance. Indeed, the only HIV-related factor independently associated with neuropsychological disorder was plasma HIV-1 replication. The separate, prospective study compared neurological functioning between patients failing HAART placed on regimens containing at least one CNS penetrating agent to those with non-penetrating regimens.

Overall there was a significant improvement in neurological functioning at follow-up. However, no significant differences were found between 10 subjects with CNS penetrating regimens compared to 19 subjects on non-penetrating regimens. Both studies, therefore, found that effective virological suppression (measured by plasma HIV RNA) appeared to be more important than whether or not the regimen contained a CNS penetrating antiretroviral.

AIDS dementia complex, Alzheimer's disease and ongoing brain injury despite HAART

In perhaps the most disturbing presentation on CNS effects of HIV, Michael Weiner presented the results of his groups work on structural brain changes at the late breaker session [6]. This controlled, longitudinal study used structural MRI, MR spectroscopy, neuropsychological testing and EEG evoked response with measurement taking place with a two year interval. Both HIV-infected and HIV-uninfected subjects were studied with these groups being divided into heavy or light drinkers to control for the known effects of alcohol intake. A total of 128 participants took part.

The structural MRI results showed that over two years the HIV-infected subjects (all of whom were receiving ART) had greater rates of ongoing white matter loss than the controls (p=0.0013). The annual loss of white matter between HIV-infected and HIV-uninfected patients who were light drinkers was 1.2% and -0.6%, respectively (p=0.003). White matter atrophy was also found to be greater in those HIV-infected patients with higher viral loads when compared to HIV-uninfected patients. Subjects with viraemia had significantly greater annual loss of white matter compared to those with good suppression of HIV replication (1.3% vs. 0.6%, respectively; p=0.06). However, no significant differences were found between patients with suppressed infection and HIV-uninfected controls. No differences were found between the groups with regard to cognition or EEG-evoked response.

The study authors concluded that the rates of ongoing white matter atrophy, although significantly different from controls, were small and not accompanied by progressive cognitive impairment. They did caution, however, that the results suggest that even HAART treated individuals do have ongoing brain damage. Additionally, these effects over a number of years would be expected to produce cognitive impairment similar to that observed in Alzheimer's disease.

The development of Alzheimer's disease itself is also becoming an increasing concern for researchers and clinicians caring for those with HIV-infection. Increased age, high lipids, axonal injury and the effects of tat and quinolinic acid on the brain all point to a theoretically increased risk of Alzheimer's disease in HIV-infection [7].

Further data on the relationship between Alzheimer's disease and HAD was presented by Bruce Brew at this meeting [8].

As a marker for the increased risk of Alzheimer's cerebrospinal fluid (CSF) was examined for the presence of reduced amyloid beta 1-42 or increased amyloid beta tau (both of which are related to excess amyloid beta production). All subjects were HIV-infected patients with AIDS Dementia Complex. In total 25 patients CSF was analysed and the results revealed that amyloid beta 1-42 levels were significantly lowered and in the same range as those found in Alzheimer's Disease.

The researchers conclude that "…AIDS Dementia Complex may be complicated by an illness that at least at the biochemical level is similar to Alzheimer's Disease. Moreover, it raises the possibility that HIV patients in general may be at increased risk of Alzheimer's."

References

Unless stated otherwise, all abstract references are to the Program and Abstracts of the 11th Conference on Retroviruses and Opportunistic Infections (11th CROI). February 8-11, 2004. San Francisco, CA.

1. Tozzi, V et al. Neurocognitive impairment and survival in HIV-positive patients treated with HAART: results from an urban observational cohort. Abstract 507.
2. Lorenzini, P et al. HAART Modified risk of HIV dementia associated to increasing age. Abstract 489.
3. McCutchan, A et al. Improved cognitive function in immune reconstituted advanced AIDS patients is associated with maintenance of HIV suppression. Abstract 498.
4. Antinori, A et al. Antiretroviral drugs penetrating CSF do not influence neurocognitive performance in HIV-1-infected patients responding to HAART. Abstract 508.
5. Robertson, K et al. Neurological functioning and CNS penetrating antiretroviral regimens. Abstract 501.
6. Weiner, MW et al. Progressive white matter loss suggests ongoing brain injury in ART-treated HIV+ patients. Abstract 33 LB.
7. Brew BJ. Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. *Aids* 2004,18 Suppl 1:S75-78.
8. Brew, B et al. Relationship between Alzheimer's disease and AIDS dementia complex. Abstract 472.

Diabetes and HIV and HCV; aging/HIV and diabetes

Judith A Aberg and Jules Levin, NATAP

This article reports on studies presented at the 11th Retrovirus Conference held in February 2004 and highlights the concern that persons with HIV can be at greater risk for developing diabetes. This report also highlights research findings that diabetes may be more prevalent in older HIV-positive individuals and may lead to cognitive impairment, thus identifying a new risk factor associated with aging and HIV.

Reports include:

- What is insulin resistance and diabetes and why is it important?
- HIV-positive men were three times more likely to have diabetes than HIV-negative men in MACS
- HIV-positive women: risk for developing diabetes is associated with over 50 years of age, smoking cigarettes, being Hispanic, body mass index (weight)
- Atazanavir did not impair sugar metabolism and raise triglycerides in healthy volunteers
- Comparative effects of nelfinavir and efavirenz on lipids and glucose in ACTG 384 Study
- Lipids and sugar metabolism improve after switch from protease inhibitor to nevirapine, efavirenz or abacavir regimens in NEFA Study
- Aging and HIV: diabetes found to be associated with cognitive impairment in older HIV-positive individuals; perhaps, a new risk factor for older HIV-positive individuals

What are insulin resistance and diabetes and why is it important?

There were several interesting abstracts presented at Retrovirus suggesting that insulin resistance and diabetes are associated with HIV and/or its therapies, particularly some of the protease inhibitors. First, I think it would be beneficial to briefly discuss what insulin resistance is and why one should be concerned about developing it. When one consumes carbohydrate, the body breaks it down into sugars, also called glucose. The body also produces insulin, which carries the sugar out of the bloodstream and into the tissue and cells.

The body does this so that it tries to maintain our blood sugar in what we label as a normal range of blood sugar. Some people require higher amounts of insulin to maintain glucose in a normal range and this is called insulin resistance. Insulin resistance by itself is associated with vascular disease and over time may progress to diabetes where the body can no longer keep the blood sugar in the normal range.

Mild diabetes can sometimes be managed by diet and exercise but frequently patients need to take pills or even shots of insulin to control the blood sugar. Uncontrolled diabetes may lead to kidney disease, blindness, neuropathies, vascular disease and

even death. But even insulin resistance without diabetes can have major unhealthy effects including elevated blood pressure, abnormal lipids and coronary heart disease, which also can lead to significant illness and death.

HIV-positive men were three times more likely to have diabetes than HIV-negative men in MACS

Brown and colleagues presented Prevalence and Incidence of Pre-diabetes and Diabetes (DM) in the Multicenter AIDS Cohort Study [1]. They examined the prevalence of hyperglycaemia (elevated blood glucose) in 1,107 men enrolled in the Multicenter AIDS Cohort Study (MACS), using data from April 1999 to September 2002.

Hyperglycaemia (pre-diabetes and DM) was defined as a fasting plasma glucose (FPG) >110 mg/dL, use of anti-diabetic medication, or self-reported diagnosis of DM. DM was defined as a FPG >126 mg/dL, use of anti-diabetic medication, or self-reported diagnosis of DM. Of the 1,107 men, 563 were HIV-negative and 544 were HIV-positive (423 on HAART).

Of HIV-positive men on HAART, 14% had prevalent DM at baseline compared with 5% in the HIV-negative group (odds ratio = 4.4; 95% confidence interval [CI]: 2.6, 7.4, after adjustment for age and body mass index [BMI]). For the 618 men with a FPG <105 mg/dL, no history of DM or use of anti-diabetic medication at baseline, 79 (13%) incurred incident hyperglycaemia in 1,054 person-years yielding an overall rate of 7.5 cases per 100 person-years (95% CI: 6.0, 9.4), and 38 incurred incident DM in 1,088 person-years, yielding an overall rate of 3.5 cases per 100 person-years (95% CI: 1.7, 3.7).

After adjustment for age and BMI, the hazard of pre-diabetes or DM among the HIV-positive HAART group was 1.8 times (95% CI: 1.1, 3.0) that of the HIV-negative group, and the hazard of DM among the HIV-positive HAART group was 3.1 times (95% CI: 1.3, 7.1) that of the HIV-negative group. Exposure to a HAART regimen including a PI (hazard ratio [HR] = 1.9; 95% CI: 1.1, 3.3), d4T (HR = 2.1; 95% CI: 1.1, 3.9) or efavirenz (HR = 3.9; 95% CI: 1.6, 9.5) were each significantly associated with a higher rate of incident pre-diabetes or DM compared to the HIV-negative group.

The study concluded that HIV-positive men with HAART exposure had an increased prevalence and incidence of pre-diabetes and DM. Exposure to a HAART regimen — including PIs, d4T, or efavirenz — was associated with an apparent increased risk of hyperglycaemia.

HIV-positive women and glucose metabolism: associated with diabetes - over 50 years of age, smoking cigarettes, being Hispanic, body mass index (weight)

Howard and colleagues presented Impaired Glucose Metabolism and Antiretroviral Use Among HIV-infected Women [2]. As with the study discussed above, many have focused on men and there is limited knowledge of the effects of HIV and its therapies on women.

They performed a 75-g oral glucose tolerance test in 125 HIV-infected and 90 at-risk HIV-uninfected women without a history of diabetes, and assessed the association of antiretroviral use and non-medication related factors with impaired glucose tolerance, diabetes mellitus, and insulin resistance (HOMA).

The median age was 45 years (range 35 to 70); 51% were black, 38% Hispanic, 10% white; 38% had a family history of diabetes mellitus and 13% reported giving birth to a baby >9 lbs; median body mass index was 28.8 kg/m2 and mean waist-to-hip ratio was 0.89; 90% had ever smoked cigarettes (median 15.0 pack-years); 68% were current smokers; 41% had a history of injection drug use with no difference by HIV status. Among HIV-infected women, 25% were HAART-naïve, 23% were on HAART but protease inhibitor (PI)-naïve, and 52% were on HAART with PI. Median duration of PI use was 43 months. Median CD4 count was 481 cells/mm^3.

The prevalence of diabetes (fasting glucose ‡126 mg/dL or 2-hour glucose ‡200 mg/dL) among all women was 6% (n = 14) and of impaired glucose tolerance (IGT, 2-hour glucose ‡140 and <200) was 11% (n = 23), with no difference by HIV status, HAART, or PI use.

Mean log insulin resistance (HOMA) (U/mL·mM) was lower among HAART-naïve HIV-infected women (0.40) compared with those on PI-HAART (0.45), non-PI HAART (0.48), or HIV-uninfected women (0.47), but this difference was not significant.

In a logistic regression model, factors independently associated with an abnormal oral glucose tolerance test (impaired glucose tolerance or diabetes mellitus) included age ‡50years (ORadj 4.5, 95%CI 1.5, 13.4) and smoking (ORadj 1.7 per 10 pack-years, 95%CI 1.2, 2.4), after controlling for HIV, HAART use, PI use, race, family history of diabetes, and waist-to-hip ratio.

In a linear regression model, factors independently associated with log insulin resistance (HOMA) among HIV-infected women included body mass index ($p < 0.0005$), Hispanic race ($p = 0.047$), and non-PI HAART ($p = 0.04$), after controlling for PI use and CD4 count.

They concluded that impaired glucose tolerance and diabetes mellitus were detected by oral glucose tolerance tests in a substantial minority of women, and were associated with traditional diabetes risk factors rather than HIV infection, PI or HAART use.

However, among HIV-infected women, non-PI HAART use was independently associated with greater insulin resistance. One

has to be careful in interpreting this study especially given the high background of traditional risk factors and one may need a much larger sample size to reduce the impact of these confounding factors. For example, the majority of the subjects were from ethnic backgrounds that clearly have a higher rate of diabetes plus 38% had a family history of diabetes. All in all, this is a first step and further studies among women and minorities are warranted.

Nevertheless, both these studies do demonstrate that significant numbers of persons have either diabetes or insulin resistance. There were a few studies exploring the effects of various ART. This can be quite complicated and some studies examined the effects of ART among HIV sero-negative subjects while others examined the effects among those subjects infected with HIV.

Reyataz: did not impair sugar metabolism and raise triglycerides in healthy volunteers

Investigators from Bristol-Myers Squibb presented The Effect of Atazanavir vs Lopinavir/ritonavir on Insulin-stimulated Glucose Disposal Rate in Healthy Subjects [3]. A proposed mechanism for why protease inhibitors may be associated with the development of diabetes is via blockade of the glucose transporters that take the glucose from the bloodstream into the tissues.

Atazanavir (ATV), unlike indinavir, lopinavir, and ritonavir, appears not to block glucose transport through the glucose transporter-4 insulin-sensitive transporter in vitro.

This study compared the effects of ATV and lopinavir/ritonavir (Kaletra, LPV/r) to placebo on insulin-stimulated glucose disposal rates. This was a randomised, double-blind, cross-over study of the effect of five days of treatment with ATV, LPV/r, or placebo on insulin-stimulated glucose disposal in healthy HIV-negative volunteers. Each subject was studied on two of three possible treatments using the hyperinsulinaemic euglycaemic clamp technique (180 minutes) with ‡14 days of wash-out.

Difference among groups in insulin-stimulated glucose disposal per unit of insulin and glycogen storage rate (proportion of total glucose disposal taken up by the tissue but not oxidised) was analysed by ANOVA. They studied 30 healthy HIV seronegative adult men with median age of 35 years (range 19 to 49), mean weight of 76.4 kg (SD = 9.9), mean body mass index of 24.0 kg/m^2 (SD = 2.4).

During steady-state euglycaemia (60 to 180 minutes), insulin levels were raised comparably (65.4, 63.0, 63.9 mU/mL) and glucose was clamped at ~75 mg/dL under all conditions.

LPV/r decreased the mean insulin-stimulated glucose disposal per unit of insulin (M/I) by 24% compared to placebo and by 23% compared to ATV. LPV/r decreased glycogen storage rate (GSR) by 35% compared to placebo and by 38% compared to ATV.

Treatment	M/I mg/kg*min/mU/mL Adjusted Mean – SE		GSR mg/kg*min	
LPV/r	7.54 – 0.84		2.61 – 0.37	
ATV	9.80 – 0.84		4.21 – 0.37	
Placebo (Pcb)	9.87 – 0.84		4.01 – 0.37	
	Difference (95% CI)	p-value	Difference (95% CI)	p-value
LPV/r vs. ATV	-2.26 (-3.95, -0.58)	p=0.011	-1.60 (-2.49, -0.71)	p=0.001
LPV/r vs. Pcb	-2.33 (-4.02, -0.64)	p=0.009	-1.41 (-2.30, -0.52)	p=0.003
ATV vs. Pcb	0.07 (-1.76, 1.62)	p=0.935	0.20 (-0.69, 1.09)	p=0.655

In conclusion, ATV did not reduce insulin sensitivity and had no effect on insulin-stimulated glucose disposal or GSR. In contrast, LPV/r induced insulin resistance and reduced the glucose disposal per unit of insulin and glycogen storage rate. These data are consistent with in vitro studies showing that ATV does not interfere with glucose transporter-4 activity and does not induce fasting hyperinsulinaemia, substantiating the findings of large clinical trials. In addition, fasting triglycerides were not affected by ATV, but increased a mean of 43% on LPV/r. This is welcomed and supporting evidence that ATV is not associated with the metabolic complications as many of the other antiretroviral drugs are.

Comparative effects of nelfinavir and efavirenz on lipids and glucose in ACTG 384 study

The ACTG 5005s team presented partial results of a metabolic substudy of a large, randomised study (ACTG 384) which compared the nucleoside (NRTI) backbones of either AZT/3TC or d4T/ddI with evafirenz (EFV), nelfinavir (NFV) or combined EFV/NFV regimens [4].

The primary objective of A5005s was to determine whether NFV- and EFV-based therapies differ with respect to changes in fasting lipids and insulin resistance. Secondary objectives included comparisons among NRTI regimens.

Antiretroviral-naïve subjects (n=334) received NFV (99), EFV (110), or both (125) plus zidovudine (ZDV) + lamivudine (3TC) (154) or didanosine (ddI) + stavudine (d4T) (180) in a substudy of a 3x2 randomised factorial trial. Fasting samples were collected at entry, 8, 16, 32, 48, and 64 weeks. Primary analyses (Wilcoxon tests) are intent-to-treat; changes from entry are reported as median [IQR] at week 32. The EFV+NFV group was excluded from NFV vs EFV comparisons, but included in NRTI analyses.

- Lipid values (mg/dL) increased in all groups. The proportion with total-cholesterol >200 increased from 13% to 45% at week 32 (cholesterol went up);
- Those with HDL (good)-cholesterol <40 fell from 75% to 48% (each p <0.001), so there was a negative effect on good cholesterol.
- HDL-C (positive effect on good cholesterol) increases correlated with higher HIV RNA and lower CD4 at entry (each p <0.001).
- Similar increases occurred with both NFV and EFV in total-cholesterol (NFV 28 [9, 56], EFV 25 [9, 52], non-HDL-Cholesterol (22 [7, 52] versus 19 [0, 42]), and triglycerides (TG) (13 [-13, 56] versus 32 [-19, 76]).
- Only 6% with EFV and 5% with NFV had TG >400 at week 32.
- HDL-C increases tended to be greater with EFV (7 [2, 12]) than NFV (5 [0, 10], p = 0.11), with a more favourable change in total:HDL-C ratio with EFV (-0.4 versus 0.4, p = 0.03).
- There was some evidence of greater increases in total-cholesterol with ddI+d4T (45 [12, 71]) versus ZDV+3TC (29 [10, 55], p = 0.07) and non-HDL-C (35 [10, 60] versus 26 [0, 52], p = 0.12). HDL-C (8 [2, 14] versus 7 [0, 12]) and TG (30 [-13, 84] versus 25 [-14, 60]) increases were similar.
- Insulin resistance (by HOMA-insulin resistance) increased over time for the whole group. From a baseline of 1.39 [0.90, 2.05], median change at week 8 was 0.20 [-0.37, 0.72] (p = 0.03); no changes were significant within any group.
- At week 32, the overall median increase was 0.38 [-0.22,0.97] (p = 0.002), but differences in the change in HOMA-insulin resistance between groups were minimal: NFV 0.41 [-0.37, 1.43], EFV 0.39 [-0.17, 0.82] (p = 0.9); ddI+d4T 0.32 [-0.29, 0.85], ZDV+3TC 0.40 [-0.19, 1.30] (p = 0.4).

Summary

Overall, the PI NFV and the NNRTI EFV appear to have comparable effects on fasting lipids, with a better total:HDL-C ratio with EFV.

- Lipids tended to be slightly more favorable with ZDV+3TC than ddI+d4T.
- HDL-cholesterol changes correlated with entry HIV disease status.
- Insulin resistance worsened in the group as a whole, but did not differ between regimens.
- The lack of an early increase in insulin resistance with NFV suggests that acute insulin resistance is not a PI drug class effect.

This supports earlier studies that suggested that NFV does not significantly inhibit the gluc-4 transporter system as mentioned above. Nevertheless, insulin resistance did worsen over time in a subset of subjects and further study is warranted to explore these findings.

Lipids and sugar metabolism improve after switch from protease inhibitor to nevirapine, efavirenz or abacavir regimens in NEFA Study

In addition, Dr Fisac presented further data on the metabolic complications evaluated in the NEFA study [5].

NEFA was an open-label randomised study comparing three different protease inhibitor-sparing regimens (ABC-abacavir, EFV-efavirenz, and NVP-nevirapine) in HIV-positive individuals who had been previously exposed to protease inhibitor-containing regimens. A sub-study in 92 patients was conducted to evaluate the switching effect on metabolic and body composition parameters. The metabolic outcomes in 69 patients who maintained the initially allocated treatment for 24 months (ABC: n = 22; EFV: n = 21; NVP: n = 26) were presented.

Fasting serum total cholesterol, low-density lipoprotein cholesterol (LDLc), high-density lipoprotein cholesterol (HDLc), triglycerides, glucose, and insulin were determined. Insulin resistance by the homeostasis model assessment and total cholesterol:HDLc ratio were also calculated.

In an overall analysis, insulin, insulin resistance, total cholesterol, LDLc, HDLc, and total cholesterol:HDLc ratio improved

(baseline vs 24-month data). EFV and NVP arms showed similar metabolic benefits after two years of therapy.

The sample size is too small to compare individual PI-containing regimens at baseline. However, these results remain encouraging that metabolic complications that may be associated with certain PIs may improve after switching to a NNRTI.

Aging and HIV: diabetes found to be associated with cognitive impairment in older HIV-positive individuals; perhaps, a new risk factor for older HIV-positive individuals

Finally, we would like to mention a study that did not receive that much attention but one that brings up the issue of aging and how age plays into the role of HIV and its associated complications. A group of investigators from Hawaii has been following an aging population with HIV, "The Hawaii Aging with HIV Cohort" [6]. It is estimated that over 10% of newly diagnosed HIV infections occur in the population over the age of 50. Age plays a major role in the development of CHD, diabetes, hypertension and many diseases.

The impact on aging and its association with development of dementia in HIV is unknown. The investigators took a step further and asked whether the metabolic complications associated with HIV have even more of an impact on the aging HIV-infected population.

Participants were from one of two groups (under 40 or 50+ years old) within the HIV-positive arm of the Hawaii Aging with HIV Cohort. Evaluations included comprehensive neuropsychological testing. Three measures of cognitive functioning were constructed from combinations of scores on neuropsychological test results standardised within our sample: an overall measure of cognitive functioning, NPZ8; a measure of memory, NPZ3-memory; and a measure of psychomotor functioning, NPZ3-psychomotor.

Trained personnel obtained medical histories including established diagnoses for diabetes (DM) using a structured interview. Data from 169 participants (73 younger and 96 older) were available for these analyses.

- Frequency of DM was 8.9% (15.6% among older and 0% among younger).
- DM was negatively associated with overall cognitive functioning ($F = 19.15$, $p<0.01$), accounting for 11% of the variance in NPZ8 scores. DM was also negatively associated with psychomotor functioning ($F = 14.16$,pp < 0.01) accounting for 8% of the variance in NPZ3-psychomotor scores.
- There was no association between DM and NPZ3-memory scores.
- Controlling for age, ARV, current hypertension, current hypercholesterolaemia, pack-years of smoking, ethnicity, and duration of HIV infection, did not substantially alter these results.

These data suggest that diabetes is associated with decreased overall cognitive performance and specifically psychomotor performance in patients with HIV.

Our findings are driven exclusively by diabetes in older patients and thus, if confirmed, may represent a newly identified risk factor for older HIV-positive patients. This risk is independent of other vascular risk factors. The underlying mechanism is not clear. While speculative, this could be associated with metabolic dysfunction and abnormalities in glucose regulation. Further studies are certainly needed that explore the effects of HIV and its therapies on aging HIV-positive individuals, as many have other traditional risk factors for metabolic and cardiac diseases and we will need to know how best to manage them.

In summary, a quote from a colleague, Dr Donald Kotler: "Insulin resistance kills. Why would anyone think having HIV would be protective?" Dr Kotler's point is well taken. Although we do not know what the risk of progressing from insulin resistance to diabetes is among those infected with HIV, we do know insulin resistance without HIV is bad. Just as we cannot be passive and let individuals sit with high lipids and ignore markers for cardiac disease, we should be managing our HIV-infected patients with insulin resistance or diabetes as we would the general population. The question remains whether conventional therapies for diabetes will work similarly in the HIV infected population and further studies are warranted exploring the pathogenesis and management of insulin resistance in this population.

References

1. Brown TT, Cole SR, Li X et al. Prevalence and incidence of pre-diabetes and diabetes in the Multicenter AIDS Cohort Study. Abstract 73.
2. Howard A, Floris-Moore M, Arnsten J et al. Impaired glucose metabolism and antiretroviral use among HIV-infected women. Abstract 701.
3. Noor M, Grasela D, Parker R et al. The effect of atazanavir vs lopinavir/ritonavir on insulin-stimulated glucose disposal rate in healthy subjects. Abstract 702.
4. Dube M, Zackin R, Parker R et al. Prospective study of glucose and lipid metabolism in antiretroviral-naive subjects randomised to receive nelfinavir, efavirenz, or both combined with zidovudine+lamivudine (ZDV+3TC) or didanosine+stavudine: A5005s, a substudy of ACTG 384. Abstract 74.
5. Fisac C, Fumero E, Crespo M et al. Metabolic changes in patients switching from a protease inhibitor-containing regimen to abacavir, efavirenz, or nevirapine: 24-month results of a randomised study. Abstract 78.
6. Valcour V, Shikuma C, Shiramizu B et al. Diabetes and cognitive functioning among HIV seropositive patients. The Hawaii Aging with HIV Cohort. Abstract 502.

TREATMENT ACCESS

Outcomes after two years of providing antiretrovirals in Khayelitsha, South Africa

Polly Clayden, HIV i-Base

Two year patient outcome from Medicins Sans Frontiers' (MSF) best-known antiretroviral programme in Khayelitsha, South Africa was reported in the April edition of AIDS.

This analysis included all adults started on antiretroviral therapy from May 2001 to December 2002 (n=287). The median follow up time was 14.9 months for those surviving, and 13.9 overall.

In this cohort, 70% were women and patients had advanced disease - the median CD4 at base line was 43 cells/mm^3 (IQR 13-94 cells/mm^3) and 52% of patients had an AIDS diagnosis.

The majority of patients received NNRTI containing regimens: 60% began treatment with zidovudine, lamivudine and efavirenz and 38% with zidovudine, lamivudine and nevirapine.

The investigators reported HIV RNA viral load <400 copies/mL in 88.1, 89.2, 75.00 and 69.7% of patients at 3, 6, 12, 18 and 24 months respectively.

Survival at 24 months was estimated at 86.35% (95%CI, 81.7-89.8%). Stratified by CD4 count at initiation of treatment, estimates of survival were: 81.8% (95%CI, 74.7-87.0%) and 91.4% (95%CI, 84.9-95.1%) for those starting with CD4 <50 and >50 cells/mm^3 respectively. Of this group 155 (55%) patients initiated treatment with a baseline CD4 count of <50 cells/mm^3.

At 24 months on treatment the median increase in CD4 count was 288 cells/mm^3 (95%CI, 181-470).

Regimen changes due to adverse events attributed to a single agent were highest in those receiving nevirapine with 8.8% (product limit estimate) of patients changing to efavirenz within 24 months. Only 4.7% switched from zidovudine to stavudine, none from lamivudine and two patients were unable to tolerate efavirenz side effects. Overall by 24 months 8.4% (95%CI, 5.6-12.5%) had any regimen change due to intolerance.

Some regimen changes also occurred due to changes in circumstances: 10 patients switched nevirapine to efavirenz due to development of tuberculosis (nevirapine is contraindicated for co-administration with rifampicin) and three patients from efavirenz to nevirapine due to pregnancy or planning pregnancy. The investigators reported a cumulative probability of regimen change due to adverse events or contraindications of 15.1% (95%CI, 10.7-21.1%) of all patients receiving first line therapy within 24 months. Additionally 12 patients changed their regimen due to treatment failure by the end of July 2003.

The authors write: The results of this programme are comparable with data from observational settings in both developed and developing countries…These findings provide encouragement to those seeking to provide similar services in poor communities where HIV mortality and morbidity are high."

Full text online: *(after one-time free Medscape registraion)*

http://www.medscape.com/viewarticle/473042

Ref: Coetzee D, Hildebrand K, Boulle A et al Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. AIDS: Volume 18(6) 9 April 2004 pp 887-895

A round-up of news on access to treatments

Graham McKerrow, HIV i-Base

Bill Clinton brokers deal on lower prices

The Global Fund to Fight AIDS, Tuberculosis and Malaria, the World Bank, UNICEF and the Clinton Foundation have announced agreements that will make it possible for developing countries to purchase high-quality AIDS medicines and diagnostics at the lowest available prices.

The agreements pave the way for countries supported by the Global Fund, the World Bank and UNICEF to gain access to drug and diagnostic prices negotiated by the Clinton Foundation.

The prices have been negotiated by the Clinton Foundation with five manufacturers of ARVs and five manufacturers of HIV/AIDS diagnostic tests. These prices were announced originally in October 2003 and January 2004, and to date they have been available to the 16 countries in the Caribbean and Africa where the Clinton Foundation's HIV/AIDS Initiative is active.

Former US president Bill Clinton said: "I am grateful for this collective effort, which will soon help many hundreds of thousands of people, and eventually millions of people, live longer, healthier lives. With these agreements, we are one step closer to

making sure future generations can live without the scourge of AIDS. We are hopeful that developing countries and those who support them in the fight against AIDS will take full advantage of this agreement and act quickly to do all they can to help in this fight."

For the full version of this article go to:
http://www.theglobalfund.org/en/media_center/press/pr_040406.asp

Link:
http://www.worldbank.org/aids

UN welcomes 'Clinton deal'

Steven Lewis, the UN secretary-general's special envoy for HIV/AIDS in Africa issued a statement saying:

"I wish to join today with the legions of activists and advocates in Africa and worldwide who salute the quite remarkable collaboration on the provision of anti-retroviral drugs, jointly announced by The Clinton Foundation, The World Bank, UNICEF and the Global Fund. This initiative, along with WHO's "3 by 5" (putting three million people into treatment by the end of 2005) could well spell the turnaround of the HIV/AIDS pandemic in Africa. We've been desperately looking for a breakthrough. This could well be it."

"Simply put, the Clinton Foundation will negotiate the drug prices, UNICEF will employ its procurement capacity, and the Global Fund and World Bank will provide the funding. There will be protocols and administrative requirements of course, but nothing should now stand in the way of rolling out treatment to hundreds of thousands - soon to be millions - in the immediate future."

Agence France-Presse's report on the Clinton deal is at:
http://www.aegis.org/news/afp/2004/AF040416.html

Pharmacos 'aim to discredit WHO procedures and control $10b US spending'

Bill Haddad, Chairman/CEO of Biogenerics, representing Cipla Ltd, the Indian generics manufacturer, reports that a meeting in Gabarone, Botswana at the end of March between multinational pharmaceuticals, organised by the US government, was intended to sew up control of the spending of $10 billion by the Bush administration on HIV treatment and prevention in poor countries.

The multinational pharmaceuticals are campaigning against the use of fixed dose combinations (FDCs) produced by manufacturers of generic drugs which offer several drugs in one pill – where the equivalent brand-name drugs are made by different multinationals and are only available as separate pills.

Haddad says that for each life saved using Bush AIDS Initiative financing, three others will die. He reports:

"The Botswana meeting was politics posing as science organised on behalf of the multinational pharmaceutical companies by the United States government. The goals were/are to discredit the WHO pre-approval process for triple anti-retrovirals and to add US Food and Drug Administration approval as a pre-requisite for receiving the $10 billion allocated over five years for AIDS assistance under the Bush AIDS initiative announced by the President in his State of the Union message in 2003.

"The emergency Botswana Conference was conceived in Washington after a similar WHO meeting in December, 2003 failed to achieve the Pharma objectives. This time the US government was taking no chances: they cherry-picked the audience, found a remote location, controlled the agenda allowing no changes and took total control of the decision-making process."

Haddad's full statement can be read at:
http://lists.essential.org/pipermail/ip-health/2004-April/006218.html

Another view of this meeting can be found on the site of the US Department of Health and Human Services at:
http://www.globalhealth.gov/fdc.shtml

A report on the same meeting by the European AIDS Treatment Group is at:
http://www.eatg.org/modules.php?op=modload&name=News&file=article&sid=207&mode=thread&order=0&thold=0

381 NGOs call on US to accept the standards of the WHO's prequalification programme

In a letter delivered to Ambassador Randall Tobias, the global AIDS coordinator at the US State Department, 381 NGOs from 70 countries called on him to accept the standards of the WHO's prequalification programme and to support the procurement of generic medicines by recipients of funding from the President's Emergency Plan for AIDS Relief.

The full text of their letter is at:
http://www.eatg.org/modules.php?op=modload&name=News&file=article&sid=206&mode=thread&order=0&thold=0

Pressure mounts on Bush to allow US dollars to buy generic drugs

The Bush administration is coming under pressure to use the $10 billion it has allocated for spending on HIV treatment to be used to buy generic versions of drugs rather than the more expensive brand name drugs made by the big pharmaceutical companies. Such a decision would allow millions more people to be treated but would upset the administration's allies in the drug industry.

The Wall Street Journal's report on this can be seen at:
http://www.aegis.org/news/wsj/2004/WJ040306.html

MSF attacks Bush for rejecting generics

The medical charity Médecins Sans Frontières has accused George Bush of trying to "shut out the use of quality, effective generic AIDS medicines" but the administration says it is only trying to maintain quality, safety and effectiveness.

A Voice of America report on this is available at:
http://www.aegis.org/news/voa/2004/VA040313.html

An audio version is available at:
http://www.aegis.org/news/voa/2004/VA040313.mp3

MSF says US should accept FDCs

Ellen 't Hoen, of Médecins Sans Frontières (MSF), issued a statement at the Conference on Fixed Dose Combination (FDC) Drug Products: Scientific and Technical Issues Related to Safety, Quality, and Effectiveness.

She called upon the US to allow recipients of its funding to procure quality FDCs in addition to any other medicines that are needed, wherever they come from. She said the US should also support the WHO prequalification project.

She said failing to do so would lead to the setting up of parallel systems. "We cannot stress enough how disruptive it would be to set up parallel systems. Different treatment regimens in the same country - in some cases even in the same health care facility - would be disastrous. It would also be disastrous with regard to the development of urgently needed new FDCs, in particular paediatric formulations, which is unlikely to happen if FDCs are not endorsed by one of the key donors."

The full statement is at:
http://www.cptech.org/ip/health/aids/fdc/msf03302004.html

Many conference documents for the Gabarone meeting, letters to officials and statements about the meeting can be found at:
http://www.cptech.org/ip/health/aids/fdc/

US plan to fight AIDS is foundering

President Bush's proposal – made 15 months ago – to spend $15 billion fighting HIV around the world is foundering because of the prolonged battles over whether to use more expensive patented drugs or cheaper generic versions. Progress in distributing the drugs has been "excruciatingly slow" according to the New York Times. As a result, only 300,000 of the six million people who need treatment are receiving it.

The full NYT report is available for a fee at:
http://query.nytimes.com/gst/abstract.html?res=F00A14F83A540C7B8EDDAA0894DC404482

3x5 is failing, says Joepe Lange

Dr Joepe Lange of the University of Amsterdam, one of the world's leading figures in fighting HIV, has declared on a visit to the United States that the 3x5 initiative – the aim to treat 3 million people in poor countries by the end of 2005 – will fail to reach its target and he says the approaching International AIDS Conference in Bangkok in July will be a time of accountability.

Dr Lange told Positives4Positives newsletter, based in Wyoming: "All of the promises that the big multilaterals have been making about how many people would be on therapy by now, honest, that the 3x 5 Framework is not going to be met. And I think we have to be quite critical about that. It is an opportunity to not let them off the hook, and come up with an explanation of why we have this blah-blah, and why we're not going to reach that target"

He also said that one of the main characteristics of the IAC would be the focus on political leadership and to that end a number of world leaders have said they will attend including former President Clinton, Kofi Annan, Mr Wolfensohn, president of the World Bank, former President Nelson Mandela, and President Machel, whose wife is one of the patrons of the conference.

The newsletter can be read online at:
http://www.pos4pos.org/newsletter.htm

BMS overturns AIDS patent in Thailand

Bristol-Myers Squibb has given up its patent to manufacture generic ddI in Thailand in an historic decision that could cause drug prices to plummet.

The US company has agreed to return the patent that allows other manufacturers to produce ddI (didanosine, Videx) in a tablet.

The Department of Intellectual Properties in Thailand had granted this patent in 1988.

The decision is a great victory for AIDS activists in Thailand who fought a two-year battle to overturn the patent.

Merck grants efavirenz licence to South Africa

US pharmaceutical company Merck & Co is to license a South African company to produce a generic version of Efavirenz, which Merck sells as Sustiva. Thembalami Pharmaceuticals, part owned by Ranbaxy Laboratories of India, will provide efavirenz to several countries in southern Africa. Merck described the agreement as “a royalty-free deal”.

ANTIRETROVIRALS

US treatment guidelines updated – March 2004

The US Department of Health and Human Services updated its adult antiretroviral treatment guidelines on 23 March 2004.

The following changes have been made to recommended regimens for ARV-naïve patients:

- Fosamprenavir and ritonavir-boosted fosamprenavir are added as options for PI-based regimens and amprenavir and unboosted indinavir have been removed
- Abacavir plus lamivudine has been added as an alternative 2-NRTI backbone.

New safety information regarding the risks of nevirapine-associated symptomatic hepatic events has been added to the text of the guidelines (sections on “NNRTI-Based Regimens” and “Hepatotoxicity”) and the respective tables (Tables 12a, 12b, and 19).

Characteristics and drug interaction information for fosamprenavir have been added to the respective tables (Tables 17, 20, 21, 22a, 22b, 23, and 30).

A new table of antiretroviral dosing recommendations for patients with renal or hepatic dysfunction has been created (Table 13).

Link:
http://aidsinfo.nih.gov/guidelines/adult/AA_032304.html

Atazanavir launched in UK

Simon Collins, HIV i-Base

On 10 March, atazanavir, the once-daily protease inhibitor from Bristol-Myers Squibb, was approved as a ritonavir-boosted treatment in Europe for patients who have already used one previous treatment. Approval was not granted for treatment naïve patients, although in practice many doctors will be interested in this option. Atazanavir was approved in the US in June 2003 for both first-line and salvage therapy.

When boosted, atazanavir should be used in a 300mg once-daily dose boosted with 100mg ritonavir. Trials with unboosted atazanavir use 400mg once-daily. Patients with >5-fold ULN increases in bilirubin during expanded access to atazanavir in the UK were often managed by switching to the 400mg unboosted dose, although this is not possible if tenofovir is included in the combination because of a significant negative drug interaction.

The US product label was recently amended to include new information about two drug interactions. Firstly, the two-way interaction with tenofovir requires that atazanavir has to be boosted by ritonavir when used in a tenofovir-containing regimen (see above), and that the patient will also require monitoring for tenofovir-associated side effects (as tenofovir levels are increased).

Secondly, information regarding PDE5 inhibitors (sildenafil [Viagra], tadalafil [Cialis] and vardenafil [Levitra]) was added to the warnings and precaution sections. The information included is consistent with the recently approved saquinavir (Invirase and Fortovase) label.

EMEA documents including SPC:

http://www.emea.eu.int/humandocs/Humans/EPAR/reyataz/reyataz.htm

Revised US atazanavir label (pdf file):
http://www.fda.gov/cder/pdf.htm

Tenofovir/FTC co-formulation application made to EMEA

Application for marketing approval for a new dual-nucleoside formulation of tenofovir and the recently approved FTC (emtricitabine) was made to the US and European regulatory authorities by Gilead on 15 March 2004. Simultaneous submissions to each agency are likely to result in a decision on approval in six to nine months in both Europe and the US. Each drug is already approved as once-daily treatment.

Source: Gilead PR
http://www.gilead.com

Abacavir/3TC co-formulation available in expanded access

The once-daily coformulation of abacavir/3TC from GlaxoSmithKline is also progressing through the regulatory pipeline. Although expanded-access programmes are driven by medical urgency for a new compound prior to marketing approval, a programme is now available in the UK for patients who are in such a situation.

Doctors interested in accessing abacavir/3TC in this formulation should contact Jan Williams (named-patient administrator) on 020 8990 2317 or GSK Medical Information on 0800 085 8747.

Source: GSK expanded access programme

DRUG INTERACTIONS

Eating grapefruit triggers statin-related rhabdomyolysis

Graham McKerrow, HIV i-Base

Grapefruit consumption appears to have triggered a recent case of statin-associated rhabdomyolysis, doctors in Berlin report in Neurology.

The case involved simvastatin but Dr Jens Dreier and colleagues at the Charite Hospital say that other statins could also be affected by eating grapefruit.

Rhabdomyolysis is a rare but serious adverse event associated with statin therapy and three years ago the manufacturers Bayer AG recalled its cerivastatin (Baycol) after a series of cases that included more than 100 deaths.

The authors report that a 40-year-old woman was admitted to the hospital with lower extremity weakness. She exercised regularly at the gym and had been healthy until noticing slight muscle weakness and myalgia 10 days before being admitted. She had been taking simvastatin (Zocor) for two years to treat familial hypercholesterolaemia.

After discontinuing the drug and vigorous fluid replacement, the patient's condition improved and she was discharged after six days.

She had eaten one grapefruit a day for the two weeks prior to admission and the authors note that the fruit contains a chemical that inactivates the CYP3A4 enzyme that metabolises simvastatin and other statin drugs; they write that patients taking statins should be advised not to eat grapefruit.

Ref: Dreier JP and Endres M. Statin-associated rhabdomyolysis triggered by grapefruit consumption. Neurology. 2004 Feb 24;62(4):670.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14981197

LIPODYSTROPHY

FDA panel recommends approval of New-Fill

Simon Collins, HIV i-Base

On 25 March, the US Food and Drug Administration (FDA) convened a panel to review study results for accelerated approval of New-Fill (Sculptra). The studies that were reviewed included the early Vega Study from Paris and the study from the Chelsea and Westminster Hospital in London. New-Fill is now owned by Aventis/Dermik. The meeting also included public testimony from patients on how lipoatrophy made it difficult to lead a normal life and that treatment had changed their personal and professional lives.

New-Fill is already used in the UK to repair HIV-related facial lipoatrophy, but until National Health Service programmes are established, access has been largely limited to patients who can pay privately for this treatment. Approval in the US is likely to encourage NHS acceptance of this treatment.

The FDA panel voted 9-0 to recommend that FDA grant conditional approval for correction of facial shape and contour deficiencies resulting from facial fat loss associated with HAART for HIV. This does not mean that New-Fill has been approved but it is very unusual for a panel recommendation not to be followed. As conditions of approval, the panel recommended FDA require a two to five year post market study. Further research should attempt to establish differences, if any, of New-Fill therapy on women, minorities and patients with normal immune systems. The panel also urged FDA to go beyond strong labeling warnings to prevent New-Fill from being used off label for non-HIV patients.

Significant weight was given to the personal testimonies at the meeting.

Data slide presentation:
http://www.fda.gov/ohrms/dockets/ac/04/slides/4031s1.htm

Further report:
http://www.natap.org/2004/HIV/032904_02.htm

Lipodystrophy regresses in three patients switched to atazanavir

Graham McKerrow, HIV i-Base

Switching to atazanavir (ATV, Reyataz) 400 mg once a day from other PI-containing antiretroviral regimens resulted in decreases in total cholesterol and fasting triglyceride levels and in a regression of body fat accumulations in three patients in Germany, according to case reports outlined in a research letter published in 9 April issue of AIDS.

Georg Haerter and colleagues in Ulm and Stuttgart report that CD4 cell counts and viral responses were preserved with the ATV-containing regimens and they write: “We propose that in patients with lipodystrophy syndrome, switching to atazanavir from established PIs could lead to a reversal of the metabolic alterations and most notably to a rapid regression of pre-existing body fat accumulations.”

The three patients were included in the early access programme for ATV because they had elevated cholesterol and triglyceride levels. After switching, a reduction in fasting cholesterol, LDL-cholesterol and triglyceride levels was documented. In all patients the total bilirubin value increased under therapy with ATV but without clinical significance.

All three patients had a reduction in fat deposits, denoted in two patients by a reduction in their collar sizes and newly-recognised dents over the dorsocervical spine, and in the other patient by a reduction in waist size (American size 31 to 29). Body weight remained stable in all three patients.

The authors write that the clinical changes to the buffalo hump, with a reduction and a central dent over the spine and the reduced waist size were ‘obvious’, and that the constant body weights suggest that these changes were not due to modified diet or physical activities.

In all three patients, ATV was given unboosted, ie without a concomitant dose of 100 mg ritonavir.

The patients were:

i) Male, 37 years, started dual therapy in 1996, started a saquinavir-containing regimen in 2000, had a buffalo hump since July 2001, switched to ATV-containing regimen in April 2003.

ii) Female, 45 years, treated with PI-containing regimens since 1996, eight changes to regimen since, suffered the loss of subcutaneous adipose tissue from the extremities and abdominal fat accumulation with a low-grade buffalo hump, started ATV-containing regimen in February 2003.

iii) Male, 59, started PI-containing regimen September 1999, developed buffalo hump in 2001, switched to ATV April 2003.

Ref: Haerter G, Manfras BJ, Mueller M et al. Regression of lipodystrophy in HIV-infected patients under therapy with the new protease inhibitor atazanavir. AIDS 18(6) 9 April 2004, 952-955.
http://www.aidsonline.com

HIV AND PREGNANCY

Post partum complications in HIV-positive women

Polly Clayden, HIV i-Base

Mode of delivery for HIV positive women remains controversial. In the UK, the majority of deliveries to HIV positive women are by elective caesarean section that, performed before rupture of membranes, reduces the risk of mother to child transmission in women receiving no antiretrovirals or zidovudine monotherapy.

For women receiving HAART with a very low (<1000 copies) or an undetectable viral load at delivery, however, an elective caesarean section appears to offer no additional reduction in transmission. Furthermore, in the general population maternal morbidity following a caesarean section is 5-25 times higher than following a vaginal delivery.

A paper from the European HIV in Obstetrics Group - part of the European Collaborative Study - published in the April edition of AIDS, investigated the occurrence of clinical events in the immediate post partum period following both modes of delivery across 13 European centres. Two separate matched case-control studies (vaginal and elective caesarean deliveries) were conducted among HIV-positive and HIV-negative women delivering between 1992 and 2002.

The investigators reported overall complication rates of 29.2% (119/408) for HIV positive women, 19.4% (79/408) for HIV negative women, 42.7% (135 of 316) for elective caesarean sections and 12.6% (63 of 500) for vaginal deliveries. There were no major complications in either HIV positive or negative women delivering vaginally. However puerperal fever was the only minor complication for which HIV positive women were at higher risk compared to HIV negative women [odds ratio (OR), 4.5; 95% confidence interval (CI), 1.55-13.07, p=0.001)], especially after medio-lateral episiotomy.

In the elective caesarean section group (delivered at 37 to 39 weeks gestation), there were six major complications (five among HIV-positive women, one HIV-negative) (OR, 5.1; 95% CI, 0.58-45) and HIV-positive women had an increased risk of minor complications (OR, 1.51; 95% CI, 1.22-2.41, p=0.001) compared with HIV-negative women, mainly post partum anaemia not requiring blood transfusion.

The authors report a five-fold higher overall prevalence of post partum complications in the elective caesarean section group compared to the vaginal delivery group in both HIV positive and HIV negative women. They explain however that most complications were minor, anaemia and fever, and that serious complications occurred only in women delivering by elective caesarean section. They also reported an increased risk of minor complications following elective caesarean section and a smaller increased risk in complications following vaginal delivery in HIV-positive compared to HIV-negative women.

The authors stressed the importance of HIV positive women's participation in decisions regarding mode of delivery and that they be informed of potential risks and benefits of each mode of delivery.

COMMENT

The need for data comparing complications following pre-labour Caesarean section in women undergoing this surgery to reduce the risk of mother to child transmission has long been recognised. This study is therefore welcome and the observation that major complications are more common among HIV-positive women noted. Furthermore, vaginal deliveries result in fewer complications than elective caesarean section in both HIV-positive and HIV-negative women.

However, in the clinic, women elect for either a planned caesarean section or a vaginal delivery, but both groups may deliver by emergency caesarean section with the later more likely to occur in the vaginal delivery group (an 8-10% chance of undergoing emergency caesarean section due to labour complications is reported in this study). The true comparison should therefore be to compare outcomes following the choice of delivery mode using an intent-to-treat rather than an actual treatment analysis.

It is also notable that although minor, vaginal delivery for HIV-positive women is not totally complication free, showing a higher risk for puerperal fever in HIV-positive compared to HIV-negative women requiring a medio-lateral episiotomy. The authors write that their results suggest the need to adopt precautions to reduce the risk of infection specifically for HIV-positive women in this situation and that they may benefit from antibiotic prophylaxis.

Additionally the authors emphasise the importance of a woman's participation in decisions regarding mode of delivery (including the

possibility of an emergency caesarean section in labour after electing to have a vaginal delivery). The BHIVA conference in April 2004 included a presentation of the results of the BHIVA pregnancy audit (which we will report in detail in our next issue). This audit reports a 67% use of elective caesarean section amongst HIV-positive women in the UK including those receiving HAART. Anecdotally, it may be important to add, that although there is much discussion of maternal choice for HIV-positive pregnant women, as a community group with a treatment phoneline, we still receive calls from distressed women being unwillingly led to choose a planned caesarean section in situations where – although still a moot and hotly debated point – this surgical intervention seems to be unwarranted.

Ref: European HIV in Obstetrics Group. Higher rates of post-partum complications in HIV-infected than in uninfected women irrespective of mode of delivery. AIDS: Volume 18(6) 9 April 2004 pp 933-938

PAEDIATRICS

Children's HIV National Network (CHINN) Review

Following on from the 2004 report: Developing Paediatric HIV Clinical Services in London (available at www.bhiva.org/chiva) - which outlines aims to provide high quality specialist paediatric services local to children with HIV - the Department of Health in association with the Royal College of Paediatrics and Child Health and CHIVA are conducting a review of clinical services throughout the UK.

All HIV treating paediatricians will have received a questionnaire asking their views on current and future service provision and to identify an individual within their organisation to assist with the review.

Please send your views on the development of national networks for paediatric HIV by 14 May 2004 to:

Sheila Donaghy, Project manager
5th Floor, Lanesborough Wing
St Georges Hospital, Blackshaw Road
London SW17 0QT
Email: sheila.donagh@stgeorges.nhs.uk

FDA approves new paediatric dose of nelfinavir

Based on five clinical paediatric studies, the US Food and Drug Administration (FDA) has approved new dosing recommendations in patients two years of age and older who are receiving nelfinavir. In patients less than two years of age, nelfinavir was found to be safe at the doses studied, but a reliably effective dose could not be established.

The recommended oral dose of nelfinavir oral powder or 250 mg tablets is 45 to 55 mg per kilogram of weight (mg/kg) twice-daily or 25 to 35 mg/kg three-times-daily. All doses should be taken with a meal. Doses higher than the maximum adult dose of 2,500 mg per day have not been studied in children.

The following points are highlighted in the paediatric use section of the label:

- In paediatric patients two years of age and older receiving nelfinavir as part of triple combination antiretroviral therapy in randomised studies, the proportion of patients achieving an HIV RNA level less than 400 copies/mL through 48 weeks ranged from 26% to 42%.
- Response rates in children less than two years of age appeared to be poorer than those in patients two years of age and older in some studies.
- Highly variable drug exposure remains a significant problem in the use of nelfinavir in paediatric patients. Unpredictable drug exposure may be exacerbated in paediatric patients because of increased clearance compared to adults and difficulties with compliance and adequate food intake with dosing.

Source: Food and Drug Administration

OPPORTUNISTIC INFECTIONS

Surgery and HAART are an effective combination for treating HPV-associated lesions

Graham McKerrow HIV, i-Base

Data from an Italian study indicate that highly active antiretroviral therapy (HAART), per se, does not prevent the occurrence

of high grade cervical and anal human papillomavirus (HPV) associated lesions but they do suggest that lesion excision in conjunction with an effective antiretroviral therapy achieves a good response in the majority of cases.

Annarosa Del Mistro and colleagues at Padua and Vincenza looked at the effect of ART on the natural history of HPV associated genital lesions in 201 HIV-positive women who were followed up for 16 years. HPV sequences in cervico-vaginal cells were repeatedly detected in 126 women; 29 had transient HPV infection. Genital lesions were found in 137 patients; prevalence was comparable in women on different regimens.

The authors report that regression of low grade lesions was more prevalent among patients receiving HAART than among those receiving other regimens. High grade lesions regressed in most cases regardless of ARV regimen. HPV infection persisted in nearly 80% of the women.

They also report that rates of anal lesions in a group of 98 men during the pre-HAART period were similar to those reported during the HAART era.

The authors write: “Our data indicate that patients with HIV infection benefit from surgical therapy when performed in conjunction with any antiretroviral therapy regimen.” They say their findings suggest that lesion excision in conjunction with an effective antiretroviral therapy achieves a good response in the majority of cases. And they add: “Moreover, early intervention also appears determinant in avoiding more extensive surgery such as abdominal hysterectomy, that involves an increased risk of complications in HIV-infected women.”

Ref: Del Mistro A, Bertorelle R, Franzetti M et al. Antiretroviral therapy and the clinical evolution of human papillomavirus-associated genital lesions in HIV-positive women. Clin Infect Dis. 2004 Mar 1;38(5):737-42. Epub 2004 Feb 18.
http://www.ncbi.nlm.nih.gov:80/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14986260

OTHER NEWS

Postexposure prophylaxis does not lead to an increase in high-risk behaviour

Graham McKerrow, HIV i-Base

Postexposure prophylaxis (PEP) consisting of antiretroviral medication and behavioural counselling following a potential sexual exposure to HIV does not lead to an increase in high-risk behaviour in most people, according to researchers in San Francisco.

Jeffrey N Martin and colleagues conclude that their findings of “this lack of behavioural disinhibition” coupled with prior safety and feasibility data suggest that the use of PEP should be routinely considered following high-risk sexual exposures.

The researchers conducted a non-randomised trial of 397 adults with high-risk sexual or drug-use exposure within the previous 72 hours. The intervention consisted of antiretroviral medication for four weeks and five counselling sessions. Participants were followed for 12 months to record repeat requests for PEP, modifications to high-risk behaviour and the acquisition of STDs and HIV.

The majority of participants (83%) did not request a repeat course of PEP. Seventy-three percent reported a decrease compared to baseline in the number of times they performed high-risk sexual activities, 13% reported no change and 14% reported an increase. Most, (85%) had no change in the incidence of STDs, 8.5% had a decrease and 6.8% an increase. Three gay men seroconverted for HIV, none of which was associated with the presenting exposure; this represented a rate of 1.2 per 100 person years and was similar to rates in San Francisco for all gay men.

In their discussion the authors write: “Direct proof of the efficacy of non-occupational PEP in preventing HIV transmission is still needed. Although we saw no instances of chemoprophylactic failure, we would not have necessarily expected to observe any HIV seroconversions associated with the presenting exposures even without the provision of PEP, given our sample size, the low per-exposure infectivity of HIV and the likelihood that some participants had contact with uninfected sources. Therefore, our data should not be taken as evidence for the efficacy of PEP in preventing seroconversion. Unfortunately, definitive ascertainment of the efficacy of PEP following a sexual exposure through randomised placebo-controlled trials will be difficult because of the large sample size required. Until direct evidence regarding efficacy is available, decisions must nonetheless be made on how to manage individuals with high-risk sexual exposures. Given the indirect evidence of efficacy gleaned from the occupational setting and from animal studies, coupled with our findings on feasibility and safety, we believe that PEP, comprising both antiretroviral medication and risk-reduction counselling, should be routinely considered following high-risk sexual exposures.”

Ref: Martin JN, Roland, ME, Neilands T et al. Use of postexposure prophylaxis against HIV infection following sexual exposure does not lead to increases in high-risk behavior. AIDS :Volume 18(5) 26 March 2004 pp 787-792
ttp://www.aidsonline.com

Law would permit HIV-positive organ donation

Leading doctors and organ donation experts are supporting a proposed new law in Illinois that would allow HIV-positive people to donate organs to other positive people. Organs from people with HIV are currently discarded to prevent transmission of the virus. If the state legislature approves the bill, Illinois would be the first state to allow such transplants and campaigners believe it could lead to most other states in the USA following suit and the chance to prolong the lives of many people in need of donated organs.

An Associated Press report on this can be found at:
http://www.aegis.org/news/ap/2004/AP040323.html

A guide to applying to the Global Fund is released

A Guide to Applying to the Global Fund has just been published by the international campaign group Aidspan. It includes sections on Are you an Eligible Applicant?, Are you Ready to Apply?, Some Key Concepts to be Used in all Applications, and Some Warnings. The guide also reviews the most common strengths and weaknesses of proposals submitted to the Global Fund, and there is a step-by-step guide to filling out the proposal form.

The guide is at:
www.aidspan.org/guides

ON THE WEB

A selection of the most important reports and resources posted to the Internet over the last month is included below. Unless specified all material is available free online and without paid subscription.

Conference reports

9th European AIDS Conference

October 25-29, 2003 - Warsaw

IAPAC Monthly - Vol. 10, No. 1, January 2004

Mark Mascolini

How will 2003 be remembered, antiretrovirally speaking? Set aside, for the moment, the most obvious answer to that question: 2003 was the year when AIDS activism won its biggest prize-serious work toward making antiretrovirals as easy to get in Gaborone as in Hollywood, in Port-au-Prince as in Portland. Bill Clinton's AIDS foundation brokered a deal with four top generic drug makers to trim price tags even more for national antiretroviral rollouts in 12 Caribbean and four African countries. Attendees at Warsaw's 9th European AIDS Conference (9th EAC) heard of early antiretroviral success at a bucolic outpost in Botswana, whose government earned high marks for its commitment to nationwide treatment. Even foot-dragging South Africa took a big step in the right direction, promising a comprehensive treatment program of its own.

For the full-text of this article, click on the link below:

http://ww2.aegis.org/pubs/iapac/2004/ia040101.htm

Online medical training

HIV inSite Knowledge Base

Human rights and HIV/AIDS: related resources

Updated April 2004.

http://hivinsite.ucsf.edu/InSite?page=kbr-08-01-07

Epidemiology and HIV transmission in injection drug users: related resources

Updated April 2004.

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

Women and HIV

Meg D. Newman, MD, updated March 2004.

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03-01-12

Serious bacterial infections in children with HIV

Shirley Jankelevich, MD, updated March 2004.

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

How to tell patients they have (or do not have) HIV

Paul A. Volberding, MD, updated February 2004.

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03-01-03

Healthy babies, happy mothers: prevention of mother-to-child transmission of HIV training manual

A comprehensive manual that provides detailed instruction on how to implement PMTCT programs in a developing country setting. Includes project management tools, treatment algorithms and counseling guides. An excellent resource. Cameroon Baptist Convention Health Board PMTCT Program, February 2004. [pdf file is1.1MB]

http://womenchildrenhiv.org/pdf/p03-pi/pi-57-00.pdf

Newletters and journals

PRN Notebook – March 2004

http://www.prn.org/prn_nb_cntnt/current.htm

Mechanisms of HIV drug resistance: a primer

François Clavel, MD

Protease inhibitor therapy: boosted and double-boosted options to the fore

Schlomo Staszewski, MD

Management of HIV/HCV coinfection – an update

Ray Chung, MD

The changing face of HIV infection in children

Joseph S. Cervia, MD, FACP, FAAP

Buprenorphine and the treatment of opioid addiction

Sharon Stancliff, MD

Pre-press releases of two new PRN Reports are also available on line:

http://www.prn.org/prn_nb_cntnt/prepress.htm

Antiretrovirals for the world: needs and challenges

Alice Pau, PharmD

HIV and cardiovascular disease: responding to the risk

Marshall J. Glesby, MD, PhD

Journal of IAPAC – March 2004

Why people with HIV still DIE – and why they don't have to...

IAPAC Monthly - Vol. 10, No. 3, March 2004

Mark Mascolini

This article does not address [the thousands who die daily around the globe because they cannot get antiretrovirals], or people in the United States, for example, who die killing time on an AIDS Drug Assistance Program (ADAP) waiting list.

Instead, this *IAPAC Monthly* article considers the thousands who can and usually do get potent antiretrovirals but die anyway. Their numbers may be dwindling, but they are far from small. The US Centers for Disease Control and Prevention (CDC) estimates that 50,610 people with HIV died in the United States in 1995, the year before potent combinations turned the tide. By 1998 better treatment had more than halved that number, but 19,005 people with HIV still died in the United States.3 The tally continued to drop in the 21st century but stood at a still dismaying 16,371 in 2002.

For the full-text article, including links to references and tables, click on the link below.

http://www.aegis.org/pubs/iapac/2004/IA040301.html

Hopkins HIV Report - March 2004

The March 2004 Hopkins HIV Report has been added. Included are links to 11CROI and 2nd IAS HIV Pathogenesis and Treatment abstracts that are cited. Tables and graphics have also been restored in the abstracts. We were, unfortunately, unable to provide links to the ICAAC abstracts, since ICAAC/ASM restricts access to ASM membership only.

http://www.aegis.org/pubs/jhopkins/2004

JOB VACANCY

Treatment Information Officer

HIV i-Base has a vacancy for a part-time treatment information officer.

17.5 hours, 19-24k pro rata (negotiable based on experience)

The job description for this post includes providing treatment information and support to HIV-positive people via the i-Base phoneline and information request service. Currently the phoneline operates 12-4pm on Mondays, Tuesdays and Wednesdays. The post also includes writing articles for Positive Treatment News and involvement in other i-Base projects.

A good level of treatment knowledge is necessary for this position but training will also be provided. The post offers an excellent opportunity for people who already have a good understanding of the issues involved to both increase their knowledge and contribute to an important service.

The post requires a high level of motivation and the ability to work within a small committed organisation. Personal experience of HIV is important and applications are particularly encouraged from HIV-positive people.

For further details or an information pack please contact:

Simon Collins at i-Base on 020 7407 8488

or visit the i-Base website at

http://www.i-Base.info

Closing date for applications: 28 May 2004

PUBLICATIONS AND SERVICES FROM i-BASE

The i-Base website

Our web address is:

http://www.i-Base.info

All i-Base publications are available at our website, which is accessed by people all over the world; we have more than 5,000 successful page requests per week from about 80 countries on all continents.

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

Introduction to Combination Therapy

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

Printed and pdf versions of this booklet are available in Bulgarian, Chinese, English, French, Georgian, Italian, Latvian, Macedonian, Portuguese, Russian, Slovak, and Spanish. To order copies, see below and the page back.

Italian treatment guides

We have Italian versions of our three treatment guides: Introduction to Combination Therapy, Guide to Changing Treatment and Guide to Avoiding and Managing Side Effects. For details of what is in each guide, see under the separate headings on these pages. The guides are available in a single printed publication (to order, see below) or from our website.

Guide to HIV, pregnancy & women's Health

This patient guide helps women get the most out of HIV treatment and care before, during and after pregnancy. It should help whether you are on therapy or not and includes information for your own health and for the health of your baby.

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

Guide to changing treatment: second-line and salvage therapy

This is a non-technical patient guide to second-line and salvage therapy. This booklet helps patients in discussions with doctors, and covers what you can do if your viral load starts to rise, and the importance of considering or finding out why your current combination failed. To order copies, see below.

Guide to avoiding & managing side effects

This is 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.

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

Treatment information request service – 0808 800 6013

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

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

For 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.

UK-Community Advisory Board: reports and presentations

The UK-Community Advisory Board (UK-CAB) is a network for community treatment workers across the UK. Each meeting includes two training lectures and a meeting with a pharmaceutical company.

Reports and presentations for the eighth meeting, held on 27 February 2004, are posted to the i-Base website. The training session at this meeting included the second part of an introduction to statistics, given by Dr Caroline Sabin from the Royal Free Hospital. In the afternoon session, the CAB met BMS to discuss the new protease inhibitor, atazanavir.

http://www.i-base.info/ukcab/feb04/index.html

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

- **Genetics, resistance and HIV** - Professor Clive Loveday
- **Approaches to Salvage Therapy** - Dr Mike Youle
- **Pregnancy, HIV and Women's Health** - Dr Karen Beckerman
- **Fertility treatment and sperm-washing techniques** - Dr Leila Frodsham
- **Access to treatment for UK visitors, refugees and asylum seekers** - Linda McDonald
- **Resistance, Lipodystrophy and IAS Report** - Simon Collins
- **TB and HIV coinfection** - Dr Anton Pozniak

Treatment 'Passports'

These popular booklets are for HIV-positive people – whether newly diagnosed or positive for a long time - to keep a record of health and treatment history.

Like all i-Base publications, they are available free as single copies, or in bulk.

Copies can be ordered using the form on the back page or by visiting our website (details 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 in a printed version, in a pdf file that we can email to you, and on our website:

The printed version is available at most HIV clinics in the UK and is available free by post: see below for details.

Find HTB on AEGiS

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

http://www.aegis.com/pubs/i-base/2004

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

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

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

http//www.i-base.info/forms/index.html

Copies of publications can also be ordered by post or fax using the form on the back page. These methods of ordering are

suitable for all our publications: HIV Treatment Bulletin (HTB), Positive Treatment News (PTN), Treatment 'Passports' and all our treatment guides and reports.

All publications are available free of charge — including bulk orders for the UK or single copies for other countries.

h-tb

HIV Treatment Bulletin

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

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

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

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

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Guide To HIV, Pregnancy and Women's Health *(November 2003)*

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Introduction to Combination Therapy *(October 2003)*

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as pdf files on the i-Base website

Changing Treatment - Guide to Second-line and Salvage Therapy *(November 2003)*

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

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

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

Also available in SPANISH as a print version and in FRENCH, SPANISH, ITALIAN, CHINESE
as pdf files on the i-Base website

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

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

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