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EDITORIAL

This double issue of HTB includes i-Base coverage from three scientific meetings – all of which carried important studies relating to current clinical care - and all of which have now made the abstracts from these meeting available as pdf files that can be downloaded over the internet. Links to these files are included in the relevant reports and in the On the Web section.

Although this coverage dominated journal reviews and other news in this issue, access issues continue to make the biggest news.

At the International AIDS Society (IAS) meeting, results from the SIMBA study showed the potential to virtually eliminate post-natal transmission from breastfeeding by use of prophylaxis 3TC or nevirapine syrup being given to the baby. Other news, from both the resistance and IAS meetings, showed severe limitations of the use of single-dose nevirapine to prevent mother to child transmission.

Worryingly, the regulatory authorities in South Africa have decided to deregister nevirapine for MTCT – although this ruling has yet to be confirmed. On the face of it this move should be welcomed because single dose nevirapine is known to be less effective than other interventions and carries risk of resistance to mothers, however the regulatory authorities are taking a dangerous step by deregistering nevirapine for this indication without first introducing alternative – and better – programmes.

As we went to press, and only a few days after the South African Health Minister had asserted in a BBC radio interview that a diet of garlic and African potatoes was still more important to the health of HIV-positive people than HIV treatment - the South African government announced that it would make anti-retroviral drugs available for its citizens.

Cape Times said finally a 'yes' from the governments 'Dr No'.

As the Treatment Action Group writes in its press release: "There is cause for celebration and optimism."

http://www.tac.org.za

TREATMENT ALERT

EMEA public statement on early virologic non-response in patients with HIV infection treated with tenofovir in combination with lamivudine and abacavir

30 July 2003

http://www.emea.eu.int/pdfs/human/press/pus/2019403en.pdf

The European Medicines Evaluation Agency (EMEA) and its scientific committee (CPMP) have been made aware of reports of a high rate of early virologic non-response observed in a GlaxoSmithKline (GSK)-sponsored clinical study (ESS30009) of therapy-naïve adults receiving once-daily three-drug combination therapy with tenofovir (TDF, Viread), lamivudine (3TC, Epivir), and abacavir (ABC, Ziagen). The precise nature of any interaction leading to non-response in this study is not known.

For details of this study and of a pilot study by Farthing et al., see Annexe 1 below.

The CPMP, in its meeting held from 22 to 24 July 2003, has considered the results of the above mentioned studies and has requested the Marketing Authorisation Holders to further explore the nature of these interactions through in vivo/in vitro studies.

The final interim study (ESS30009) report, as well as the study reports of the other relevant ongoing studies, has also been requested. As soon as available, the results will be assessed by the competent authorities and the public will be updated accordingly.

As a precautionary measure, until the nature of these interactions is further explored, the EMEA wishes to point out the following information:

Information for physicians:

When considering a new treatment regimen for naïve or pre-treated patients:

Abacavir and lamivudine in combination with tenofovir should not be used as a triple antiretroviral therapy when considering a new treatment regimen for naïve or pre-treated patients and particularly as a once-daily regimen.

Patients well controlled on a tenofovir, lamivudine and abacavir regimen:

Any patient currently controlled on therapy with this combination should be frequently monitored with a sensitive viral load test

(limit of qualification <50 copies/ml), and considered for modification of therapy at the first sign of viral load increase.

Information for patients:

If you are currently receiving, or if you are about to receive, an antiretroviral treatment including abacavir (Ziagen) and lamivudine (Epivir) in combination with tenofovir (Viread), you should inform your doctor immediately.

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ANNEXE 1

Study ESS30009 is a randomised, open-label, multi-center study of the safety and efficacy of efavirenz (EFV 600mg daily, Sustiva, Bristol-Myers Squibb Co.) versus tenofovir (300mg daily) when administered in combination with an investigational abacavir/lamivudine (600mg/300mg daily) fixed-dose combination tablet as a once-daily regimen in antiretroviral-naïve HIV-1 infected adults. Shortly after initiation of this study, reports of poor efficacy in patients receiving TDF+3TC+ABC have been received. An interim analysis was conducted to assess virologic non-response, defined as either:

- failure to achieve a two log decrease from baseline by treatment week eight,
- or a one log increase above nadir on any subsequent treatment visit.

Results are shown in the following table:

	Number (%) of patients meeting the definition of Non-Response	
	TDF+3TC+ABC	EFV+3TC+ABC
HIV-1 RNA data for subjects on Rx for >/= 8 weeks	50/102 (49%)	5/92 (5%)
HIV-1 RNA data for subjects on Rx for >/= 12 weeks	30/63 (48%)	3/62 (5%)

The precise nature of any interaction leading to non-response in this study is not known.

Preliminary genotypes of viral isolates from 14 patients with non-response taking the TDF+3TC+ABC regimen have shown all 14 isolates had the M184V mutation in HIV reverse transcriptase. In addition, eight of the 14 (57%) isolates also had the K65R mutation.

On review of these results, the TDF+3TC+ABC arm has been terminated in this study.

In addition to study ESS30009, a pilot study by Farthing et al. (2nd annual meeting of the International AIDS Society, July, 2003, Paris, France) provided data in 20 patients receiving TDF+3TC+ABC once daily for initial therapy. As in ESS30009, a high rate of virologic non-response was documented.

CONFERENCE REPORT

XII International HIV Drug Resistance Workshop

Los Cabos, Mexico, 10-14 June 2003

Reports by Simon Collins, Polly Clayden, Graham McKerrow and Steve Taylor for HIV i-Base

Probably the most useful insights into the importance of future clinical developments come from the annual Resistance Workshop, restricted to around 150 researchers and this year only one HIV-positive community place. So while we'd like to bring you an in-depth report from the meeting, we will have instead to report from the abstracts.

These are now available online at:

http://www.mediscover.net/journals.cfm

The abstract book repays reading, and although some of these studies were subsequently presented at the IAS meeting in

Paris, among the technical presentations often focusing on the minutiae of resistance were many studies that included findings that impact directly on clinical care.

These included:

- Increases in transmission of drug resistant virus – which was detected in 11% of cases of primary infection in Europe (abstract 117) and in 17% of drug naïve individuals in the UK (abstract 124);
- Further discussion about coinfection and superinfection - data revealed that with coinfection, both viruses were likely to remain present over time, whereas in superinfection the new and fitter virus often outgrows the first (abstracts 62, 63);
- Much higher rates or nevirapine resistance than previously reported from single-dose nevirapine used to prevent mother-to-child transmission, were found by looking at earlier samples and minority viral populations - at least 75% of women showed evidence of resistance to nevirapine two weeks after a single-dose during pregnancy (abstracts 78, 79);
- Transmission of drug resistant virus does not readily revert to wild-type even in the absence of drug, and does not appear to carry substantial reduced replicative capacity (abstracts 80, 115);
- Currently available commercial resistance assays are insufficiently sensitive to detect low level resistance and minority populations (abstract 86, and 134, 143);
- Cross resistance between nevirapine and efavirenz can occur even in the absence of detection of key genotypic mutations detectable by population sequencing (abstracts 134, 143);
- Some drugs continue to contribute an antiviral effect, even in the presence of mutations (d4T – abstract 133, and 3TC – abstract 140);
- Replicative capacity results may be distorted by the presence of even low levels of wild-type virus in the assay (abstract 85);
- The choice of concomitant nucleosides and particularly thymidine analogue in tenofovir-including regimens may protect against MDR K65R mutation (abstracts 135, 136, 137) and possible CD8 mediated responses to tenofovir resistance from a macaques study (abstract 70). Other TDF related abstracts include 29, 30, 33, and 34;
- Indication that diversity in responses to controlling viraemia following treatment interruption (in the SSITT trial) can be explained by differences in virus, rather than host immune response (abstract 56);
- Analysis of residual viral replication below 50 copies – and the suggestion that resistance doesn't generally occur < 50 copies due to only localised immune responses and fails to generate HIV-specific memory cells which are required to generate new resistant variants within the memory pool (abstract 57);
- Frequent discordant resistance profiles between plasma and the genital tract, with nucleoside-associated mutations (to AZT and 3TC) maintained in the vaginal tract up to four years after discontinuing those treatments (abstract 68). A second study showed transmission of and maintenance of AZT resistant virus on the male genital tract (abstract 83);
- Immunological benefit of T-20 despite resistance and shift to NSI CCDR5 virus (abstract 72).

Short reports follow for each of these subjects. Unless stated otherwise, all abstracts in the references refer to the XII International HIV Drug Resistance Workshop, Los Cabos, Mexico, 10-14 June 2003 and are published as part of Antiviral Therapy Volume 8 Issue 3.

Transmission of drug resistance – at 11% in Europe and 17% in the UK

Confirmation of the increase in transmission of drug resistance was presented in several studies, and in pooled results in one large European study. The CATCH study (Combined Analysis of resistance Transmission over time of Chronically and acute HIV-infected patients in Europe) whose title doesn't exactly trip off the tongue provided evidence of an alarmingly high rate of transmission of drug resistance in Europe.

Wensing and colleagues presented results from an analysis of more than 1,400 baseline genotypic samples collected between 1996 and 2002 in 16 countries.

Reverse transcriptase (RT) and protease (PI) sequences were received from the following countries: Austria (60), Belgium (61), Denmark (132), Finland (8), Germany (62), Greece (40), Israel (104), Italy (296), Luxembourg (163), the Netherlands (25), Norway (23), Poland (35), Portugal (124), Serbia-Montenegro (10), Spain (23) and Switzerland (262). Mutations conferring resistance to nucleosides were seen in 6.9% of isolates, resistance to NNRTIs in 2.6% of cases and to PIs in 2.2%. Multi-drug resistant virus was observed in 1.7% of subjects.

Population characteristics were available for 975 samples, and primary drug mutations associated with protease inhibitors

and reverse transcriptase were detected in 11% and 9% respectively from these treatment naïve individuals. Primary mutations were detected in 11% (63/596) of seroconverters (infected <1 year) and 8% (30/379) of those with chronic infection. Thirty-one percent of the sequences were classified as non-B and in all countries except Israel, resistance was higher in subtype B sequences than non-B (12% versus 5%).

The UK appears to have higher levels than shown in this European study: the British picture was detailed in an abstract by Deenan Pillay on behalf of the UK HIV Drug Resistance Database – a collaboration between virology laboratories and major clinical centres to pool resistance data in the UK.

Firstly reporting on treatment experienced patients, just over 9,800 test results from around 7,000 patients were available from 1996 to March 2003, and the results were divided into three time periods: 1996-1998, 1999-2000 and 2001-2003. As resistance testing in widely used in early treatment failure, it is not unexpected that around 70% of samples in each period from treatment experienced patients showed at least one key RTI mutation. PI resistance in this group was detected in 26, 32 and 27% of the samples in each period and NNRTI resistance is still increasing in prevalence at 20, 40 and 48% of experienced patients over time – reflecting the prescribing practice for NNRTI first-line therapy in the UK.

Key resistance mutations in treatment naïve individuals (to compare to the CATCH study) were detected in 10, 16 and 17% of samples for the 1998-1999, 1999-2001 and 2001-2003 periods respectively.

C O M M E N T

These data support the decision in the BHIVA Treatment Guidelines to now recommend baseline resistance testing in the UK for all newly diagnosed individuals, even when immediate treatment is not being considered.

UK guidelines also now recommend resistance testing for chronically infected patients prior to initiation of therapy due to this increasing prevalence and the low cost.

With the high rate of transmitted drug resistance now in circulation this would seem entirely prudent. For those citing cost as an obstacle, deferral of commencement of treatment for just one month will cover the cost of assay.

References:

1. Wensing AMJ et al - Prevalence of transmitted drug resistance in Europe is largely influenced by the presence of non-B sequences: analysis of 1400 patients from 16 countries: the CATCH-Study. Abstract 117.
2. Pillay D, Green H et al – The UK HIV Drug Resistance Database: development and use for national surveillance. Abstract 124.

HIV coinfection, reinfection and superinfection

Several abstracts provided additional data on cases of HIV superinfection or coinfection. The term coinfection is usually preferred when there is evidence that the initial infection occurred with two or more different viral strains at the same time, or before an immune response to the first virus has developed. (the latter is sometimes called serial infection).

The term superinfection refers to instances when a second distinct virus infects an individual after they have developed an immune response to the first. The clinical concerns regarding superinfection are essentially twofold. Firstly the second virus may be more virulent and fitter than the initial strain. This may lead to a more rapid disease progression than might otherwise occur with the first virus only. Secondly, it is possible that the second strain may harbour drug resistant mutations, which may compromise the recipient's future or current treatment options.

On a very basic level the plausibility of coinfection or superinfection is evidenced by the very wide genetic variability of HIV and the frequency of recombinant viral forms in existence. (For viral recombination to occur at all infection of a single cell by two different viruses is required). However, detection of superinfection and coinfection is not straightforward and is an extremely labour intensive scientific process. In fact most cases have only been detected when individuals have been part of intensive primary infection studies. It is unlikely that superinfection will be the focus for large-scale studies and this has perhaps driven some of the scepticism of reporting and discussion.

Perrin and colleagues from the Swiss HIV Cohort Study followed five IVDUs who were either coinfected or superinfected with distinct viral types to study the persistence of different viral strains within a single individual over time. Three patients were coinfected with two different strains at the time of primary infection (sub-type B and Circulating Recombinant Form-11 (CRF-11)) and two patients initially infected with sub-type B and were later superinfected with CRF-11. All patients had been identified from their IVDU cohort, and cases of superinfection had been detected following unexpected clinical events.

The three coinfected patients were followed for 14, 20 and 24 months respectively and subtype specific PCR continued to detect both viruses over this period. Two of these individuals had viral loads >400,000 copies/ml.

The two cases of superinfection were both originally infected with subtype B and had previously controlled their HIV without

treatment, maintaining CD4 counts >500 cells/m^{m3} and viral loads <50 copies/ml for three and five years respectively. Superinfection with CRF-11 in these two cases was associated with high viraemia, rapid CD4 drop and acute retroviral syndrome. Interestingly CRF-11 was the only detectable virus shortly after the time of superinfection and during subsequent monitoring, although both viruses remained detectable in proviral DNA.

Palmer and colleagues provided further details on a patient infected with multidrug resistant virus that was detected during primary infection and reported at the 9th CROI (Daar et al, abstract 96). Within two months of infection, viral load dropped to <1000 copies/ml without treatment but four months after this rebounded to 10,000 copies and at this time point showed no evidence of resistant mutations.

Phylogenetic analysis showed two distinct subtype B viruses at different times after the initial infection. At month one this was entirely resistant virus (0.025% viral diversity) with all sequences containing 69SS insertion and K103N. Subsequent samples at months five, 13 and 17 showed contained a different viral strain and were wild-type with regard to drug resistance associated mutations. Single genome sequencing showed the wild type virus to be almost homogeneous (0.007% sequence diversity) indicating very recent infection (diversity increased to 0.062 and 0.18% at month 13 and 17 respectively).

Resistant virus indicated by the 103N mutation was reduced to levels of 0.1% and longitudinal follow up found no evidence of recombination between the wild type and drug resistant strains.

Readers interested in tracking these reports will be interested to know of a further two abstracts presented at the IAS meeting.

Burger and colleagues reported the case of a Kenyan woman who was infected prior to 1986 with subtype A virus. Complete RNA sequences from 1995 and 1997 were subtype A/C recombinants and heteroduplex tracking assays were unable to find evidence of subtype C in the 1986 samples.

Manigart and colleagues reported four cases of coinfection from a cohort of 147 commercial sex workers in Burkina Faso, two of which showed two distinct phylogenetic populations existing. Retrospective analysis of stored samples showed that each patient acquired a second virus at the same time that they experienced increases in plasma viraemia.

Although this study commented that superinfection is not an uncommon phenomenon, given the multiple opportunities for exposure, it is also surprising that it was detected as such a low level in the cohort as a whole.

Numerous posters on molecular epidemiology also documented geographical prevalence and development of both new and already recognised populations of recombinant virus within the diversity of HIV infections, including vertical transmission of dual infection.

C O M M E N T

These additional cases of superinfection add to the already published literature on this subject (Jost et al NEJM: September 2002; Altfeld et al. Nature. November 2002; Koelsch et al. AIDS May 2003).

They prove beyond doubt that superinfection with a second strain of HIV can occur with detrimental consequences to the individual affected. Several questions remain unanswered. Will superinfection with drug resistant HIV always lead to treatment failure in a person well controlled on drugs? Secondly, just how common is superinfection in day-to-day practice? A recent article published by Gonzalez et al in JID suggests this is a relatively rare event. However in the absence of the further clarification it is important to at least advise patients on the potential risks of superinfection.

References:

1. Palmer S et al - Population genetics in HIV-1 superinfection. Abstract 62.
2. Perrin L et al - Co- and super-infection: persistent replication of both HIV-1 strains? Abstract 63.
3. Burger H, Fang G, Kuikero C et al – Recombination following superinfection by HIV-1. 2nd IAS Conference, Paris. 13-16 July 2003. Abstract 71.
4. Manigart O, Courgnaud V, Sanou O et al – HIV-1 superinfections in a cohort of commercial sex workers in Burkina Faso as assessed by a novel autologous heteroduplex mobility procedure, ANRS 1245 study. 2nd IAS Conference, Paris. 13-16 July 2003. Abstract 72.

Single-dose nevirapine resistance in over 75% of mothers

Although there has always been an element of concern over this strategy - and certainly the recent IAS conference in Paris saw something of a “nevirapine backlash” with much discussion around alternative approaches (see IAS report later in this issue) – single dose nevirapine (NVP), given to the mother at onset of labour followed by a dose to the infant is a low cost and simple strategy to reduce mother to child transmission (MTCT) of HIV in resource poor settings.

However, in HIVNET 012 early findings demonstrated NVP resistance was detected in 21/111 (19%) of women at 6-8 weeks

and mutations were also detected in some women as early as seven days following the 200 mg maternal dose. Two posters reported further analysis of NVP resistance mutations and their rate of selection in women receiving NVP to reduce MTCT.

High frequency of mutations demonstrated in women with subtype C

To date, NNRTI-associated mutations have been shown in subtypes A and D and subtype B HIV-infected women. In a report from Kantor and colleagues the rate of selection of specific mutations and their persistence and fitness is described in a group of women with subtype C HIV. [1]

The investigators analysed reverse transcriptase sequences from 34 women from Chitungwiza, Zimbabwe, participating in the HPTN 023 – where women received single dose NVP at onset of labour. Samples were collected at weeks zero, two, eight and 20-32 post partum. Sequences were evaluated for subtype and recombination and assessed for NNRTI mutations at codons 98, 100, 101, 103, 106, 108, 179, 181, 188, 190, 225, 227, 230 and 238.

They reported that overall 25/33 (76%), of all samples were found to have NNRTI mutations at any time point, 21/28 (75%) of available samples at two weeks, 11/32 (34%) at eight weeks and 1/8 (13%) of available samples at 24 weeks. At two and eight weeks two or more mutations were found in 11/28 and 5/32 sequences, and a single mutation in 10/28 and 6/32 respectively.

Prevalence of common NVP associated mutations at two weeks included Y181C in 16/28 (57%), K103N in 4/28 (25%), V106A/M in 5/28 (19%) and Y188C in 4/28 (14%). The investigators report that reversion to wild type had occurred by week eight in 12/27 (44%) samples with week two mutations, where a week eight sample was available. K103N was detected in 9/32 (28%) and V106A and Y181C in 2/32(6%) each. Of seven women with mutations for whom late samples were available 6/7 with K103 had reverted to wild type.

The investigators concluded that samples taken within two weeks of receiving single dose NVP harboured a high frequency of NNRTI resistance mutations and that dual mutations may be mixtures of competing single mutants. There appeared to be rapid reversion to wild type occurring by eight and 24 weeks and although Y181C is predominant in early samples, K103N is the predominant mutation selected at eight weeks. They also noted: “Sequencing multiple clones from sequential time points will be useful for quantification and linkage of mutations. The change over time in the proportion of specific mutations may serve as an indication of *in viv*o fitness relative to wild type RT in subtype C HIV-1.”

Diverse mutations emerge rapidly: HIVNET 012

A further evaluation from Eshlemen and colleagues from the HIVNET 012 looked at NVP mutations detected by population sampling in early samples, collected at seven days. Some samples had more than one NVP mutation. In this study the investigators cloned and sequenced individual HIV-1 variants to examine their spectrum and generic linkage. [2]

The samples from five women had one to four nevirapine mutations. DNA amplified from those samples was cloned and inserted into plasmids that were subsequently isolated. At least ten plasmids were isolated and sequenced from each plasma sample.

Sequencing of cloned plasmids revealed diverse patterns of NVP mutations. The investigators reported some plasmids lacking NVP mutations (wild type) were isolated from each plasma sample. The other plasmids had detectable NVP mutations including K103N, V106A, V108I, V179D, Y181C, G190A, G190S, Y188c and Y188L.

Three of the five women had NVP mutations that were detected in plasmids but not by population sequencing and as many as seven different mutations were detected in plasmids from a single sample. The investigators noted that three women had plasmids with more than one NVP mutation, confirming that those mutations were genetically linked.

They concluded that cloning and characterisation of individual HIV-1 variants reveals rapid selection of diverse subpopulations, that some variants contained more than one NVP mutation, and many contained NVP mutations that were not detected by population sequencing. They added that detection of variants with NVP mutations only seven days after receiving single dose NVP suggests that these variants were present at low levels before receiving the NVP. The investigators also noted “Further studies of NVP resistance in women and children receiving single dose NVP may help optimise use of NVP for prevention of MTCT.”

C O M M E N T

Both studies confirm the well-recognised fact that single doses of nevirapine given to antiretroviral naïve women will result in selection of resistant variants. The scale of this is startling. Three-quarters of the samples obtained by Kantor et al two weeks after the dose was given had evidence of mutations. It also highlights how fast these mutations can disappear from the plasma, but although not present in later plasma samples they will be archived in pro viral DNA.

Neither study addresses the crucial question of the longer-term consequences of briefly selecting out resistant virus. It has been argued that such variants arise by natural mutation every day in untreated, infected individuals. However, this is not the same as flooding the long-

lived lymphoid cells and sanctuary sites, albeit briefly, by single dose intervention. Will this result in loss of efficacy in future pregnancies, or for those women able to access treatment for themselves? First line ART in many poorly resourced settings is with nevirapine-containing combinations, so this is not an academic question.

References**:**

1. Kantor R, Lee E, Johnston E et al. Rapid flux in non-nucleoside reverse transcriptase inhibitor resistance mutations among subtype C HIV-infected women after single dose nevirapine. Abstract 78.
2. Eshleman EH, Jones D, Guay et al. HIV-1 variants with diverse nevirapine resistance mutations emerge rapidly after single dose nevirapine: HIVNET 012. Abstract 79.

Transmission of drug resistant virus does not revert to wild-type and does not appear 'less fit'

Several studies looked at the natural history of transmitted drug resistance, finding results that are opposite to general assumptions.

The development and detection of drug resistance in patients infected with wild-type virus that develops when using antiretroviral treatment is well described. Reversion to majority wild-type population generally occurs shortly after discontinuation of the drug associated with that resistance, and the resistant strain remains archived in proviral DNA or existing as minority populations.

This does not appear to be the case for patients whose baseline infection is due to drug resistant virus.

Little and colleagues described the resistance profile over time (median 177 days, range 82-1,019) of 10 patients diagnosed with drug resistance during primary HIV infection (median 65 days from infection) who chose to defer treatment. Seven out of 10 had evidence of resistance to NNRTIs, 1/10 to PI and RTI, 1/10 to NNRTI and PI and 1/10 with resistance to all three classes.

Median baseline was 5.5 log (range 2.5-7.4) and replicative capacity (RC) was 87% that of wild-type (WT). Reversion of 103N to mixed N/K populations was a median 196 days (95% CI 153-238 days). No reversion of PI mutations was detected out to 64, 191 and 342 days in those three patients. Only one patient reverted to wild-type at 1,019 days. Reversion of resistance when it was detected was gradual and usually incomplete. Replicative capacity remained high in all patients indicating an additional concern in the management of future treatments for these patients.

Delaugerre and colleagues presented two cases of sexual transmission of multidrug resistant virus that persisted at two years without selective pressure of treatment and all mutations were found archived in cellular reservoirs. Viral load and CD4 counts for both these patients remained unchanged during the period of follow-up.

Coral and colleagues also reported little difference between viral load and CD4 responses in 46 seroconverters, 20% of whom were infected with drug resistance virus. Over median follow-up period of 3.5 years patients in each group lost an average of 46 cells/mm3 a year.

While this may provide some reassurance in the short-term, response and choice of available treatment when it is required, is likely to be significantly different.

C O M M E N T

These data suggest that in individuals newly infected with drug resistance virus, this resistant virus becomes that individual's "wild type". The only way they can lose these mutations is by the process of back mutation and this can take time, thus explaining the timeframe in these abstracts. This can give rise to "reversion mutants" such as the 215 D/S/N/C that can provide a clue to the transmission of drug resistant HIV - a so-called "fossil record" of resistance. People infected with resistant virus can subsequently go on to infect others with the same resistant virus. [4]

References:

1. Little SJ et al - Persistence of transmitted drug-resistant virus among subjects with primary HIV infection deferring antiretroviral therapy. Abstract 115.
2. Delaugerre C et al - Persistence of multidrug-resistant HIV-1 without any antiretroviral treatment two years after sexual transmission. Abstract 80.
3. Corral A et al - Impact of transmission of drug-resistant HIV viruses on viral load, CD4 counts and CD4 decline in recent seroconverters. Abstract 81.
4. Taylor S, Cane P, Hue S et al. Identification of a Transmission Chain of HIV Type 1 Containing Drug Resistance-Associated Mutations. AIDS Res Hum Retroviruses 2003; 19:353-61.

Standard genotype assays may miss 75% of mutations when present in less than 35% of plasma sample

Focusing on limitations of standard genotype analysis, Kearney and colleagues from NIH/NIAID also used single genome sequencing (SGS) to test the reliability for detecting minority populations.

They tested samples from 24 patients, either failing therapy or known to be infected with multi-drug resistant virus, by both standard and SGS and analysed with reference to the Stanford database.

All mutations present in composite genotype were detected by SGS. However, mutations present in <10% of single genomes, with one exception, were not detected by composite genotype. Mutations present in 10%-35% of single genomes were only detected in 25% of composite genotypes.

Several cases indicate the breadth of the missed mutations. Case one included 10 mutations conferring resistance to RTI, NNRTI and PI classes, but only present on 5-20% of the 20 genomes analysed. None of the PI mutations present in 15% of the genomes was detected by composite sequence including L10V, M46I, I84V and L90M.

A second sample missed five linked RT mutations present in 33% of genomes including K101E, Y181C, G190A and T215Y.

A third sample missed D67N in 30% of genomes and V118I present in 21%. All plasma samples contained at least one mutation that was identified by SGS but not by composite testing.

C O M M E N T

While these data appear alarming it is important to know that when a patient is on drugs and has truly developed resistance to these drugs with a documented rise in viral load the resistance mutations will generally be in excess of 50% of the total population and therefore will be picked up. However, once the selective pressure of the drug is removed their percentage in the viral population will fall quickly. Hence the rationale for obtaining the plasma sample for resistance testing while the patient is still taking the suspect drug.

Ref: Kearney M et al - Comparison of single-genome sequencing with standard genotype analysis for detection of HIV-1 drug-resistance mutations. Abstract 86.

Low-level resistance and minority populations: cross resistance between nevirapine and efavirenz occurs even in the absence of genotypic mutations found using population sequencing

Commercially available resistance assays are unable to detect minority virus that is present at less than 10-20% of an individual's viral population and this is recognised as one of their limitations. It may also explain why randomised trails for these tests are difficult to design to show the additional benefit that they undoubtedly offer.

Mellors and colleagues looked at the role of minor NNTRI mutations from the ACTG 398 study. This study randomised 212 NNRTI-naïve and 269 NNRTI-experienced patients to efavirenz, abacavir, adefovir and amprenavir plus either a second PI or placebo. Not surprisingly, failure to achieve viral suppression (<200 copies/ml) was associated with previous NNRTI experience and NNRTI mutations at baseline. However, genotyping did not detect NNRTI mutations in 50/216 baseline samples in the NNRTI experienced patients (23%), but this group performed no better than those that had shown NNRTI resistance, and much worse that the NNRTI-naïve group who similarly showed no mutations.

Minor resistant variants were sought using single genome PCR and sequencing in a subgroup of patients who were failing treatment without evidence of resistance, and variants encoding NNRTI resistance were identified by single genome sequencing in 6/10 NNRTI-experienced and in 1/8 NNRTI-naive patients. A second assay used to measure the frequency of efavirenz resistance (yeast-based chimeric Ty1/HIV-RT assay) detected efavirenz resistance in 8/10 (range of frequencies 10.9% - 0.8%) and 2/8 (0.6% and 0.3%).

The study concluded that prior NNRTI experience had selected for mutations but at a level that was too low to be detected by standard genotyping, and that this lead to failure of the efavirenz-based regimens.

Lecossier and colleagues from the Hopital Bichat-Claude Bernard in Paris looked more closely at the resistance samples from 16 patients failing a nevirapine-based combination that showed Y181C indicating nevirapine resistance but not K103N (which determines efavirenz cross-resistance).

Sequence selective real-time PCR was used and each sample was screened for either of the codon change for 103N, which were detected >1% viral population in 5/16 patients (range 1%-76%).

Both these studies should reinforce the caution against NNRTI recycling.

References:
1. Mellors J et al - Low frequency non-nucleoside reverse transcriptase inhibitor (NNRTI)-resistant variants contribute to failure of efavirenz-containing regimens in NNRTI-experienced patients with negative standard genotypes for NNRTI mutations. Abstract 134.
2. Hance AJ et al - Resistance genotypes in patients failing nevirapine: co-existence of majority viral populations expressing Y181C and minority populations expressing K103N. Abstract 143.

Persistent effect of d4T and 3TC, but not NNRTIs in the presence of associated genotypic mutations

At the 2003 Retrovirus Conference, a late breaker by Steven Deeks showed that some of his patients failing on PI+2 nukes regimens who discontinued the PI component showed little consequent effect on CD4, viral load or development of resistance over the subsequent year.[1] In contrast, those that discontinued their nukes experienced disease progression and higher viral rebound. These were preliminary and observational results but they generated a lot of interest.

Two abstracts at the resistance meeting looked at the effect of subtractive therapy with different drugs.

Residual activity of d4T but not NNRTIs

Use of increased numbers of drugs (5-9) in salvage regimens has often shown greater viral suppression than four-drug regimens, although this benefit comes from accurately targeted activity. Identifying agents without activity that could be reduced from these combinations would obviously help with reducing side effects.

Maldarelli and colleagues reported on five patients on multidrug salvage therapy with viral load >5000 copies/ml who interrupted either d4T for 14 days (n=3) or efavirenz for 21 days (n=2) following an initial 10-day sampling period. Results were presented from frequent viral load and composite genotype resistance tests during the interruption period. [2]

Viral load did not increase for the two patients who interrupted efavirenz – indicating no residual activity of this drug in plasma as would be expected from the K103N and Y188L genotypes present at baseline.

Interruption of d4T however leads to immediate increases in viral load, that were still increasing when d4T was restarted. Restarting d4T returned viral load to baseline. Despite multiple d4T-associated mutations at baseline (M41L, D67N, V118I, L210W, T215Y) d4T was still providing antiviral activity.

Similar results from withdrawing NNRTI treatment once genotypic mutations have been detected was presented in results from the French ANRS 107 Puzzle2 study, by Piketty and colleagues at the IAS conference. [3]

Including 3TC and maintaining M184V to reduce viral fitness

Limited evidence of reduced viral fitness generated by M184V mutation has been sufficient for many clinicians to continue to include 3TC in second-line and salvage regimens in order to maintain this mutation. Although the risk/benefit of this strategy in unclear it is certainly helped, and probably only possible, because of the low toxicity associated with 3TC.

Some support was given to this approach by Campbell and colleagues from the University of Colorado, although the approach and rationale to this study may not have been in their patients' best interest.[4]

Four patients taking AZT, 3TC and a PI with detectable viral load (range 4.26-5.53 log) discontinued 3TC and were followed for 20 weeks (n=3) and 24 weeks (n=1).

Within 12 weeks of withdrawal of 3TC, all patients' HIV RNA increased by >0.5 log copies/ml above baseline but there were differences in other details of the pattern of response between patients. Interruption of 3TC was associated with increased susceptibility to 3TC (>34-fold above baseline but also decreased susceptibility to AZT (9- and 10-fold). Viral replicative capacity increased from 1.2 – 2.7-fold. This occurred at the same time as return to 184M in one patient, prior to 184M in two patients and one patient continued to maintain 184V even in the absence of 3TC.

Although 184V returned again when 3TC was reinitiated, viral load did not return to baseline for two of these patients. Of concern is the additional protease mutations and reduced susceptibility that occurred in two patients while discontinuing 3TC.

C O M M E N T

Residual HIV activity despite partial resistance is the reason for higher rates of success with multi-drug rescue therapy using regimens with five to nine drugs. Accurately identifying drugs with activity in an individual patient remains a challenge.

One caution against interrupting drugs based on this approach is that resistance profiles in plasma and sanctuary compartment have frequently been shown to differ and lack of viral benefit in plasma viral load does not discount activity in CNS, genital tract or other compartments. Awareness of continued nucleoside activity despite resistance mutations is important in this setting.

References
1. Deeks S - When to switch antiretroviral therapy. 10th Conference on Retrovirus and opportunistic Infections. Abstract 188.
2. Maldarelli F et al - Short duration, single drug discontinuation to assess the activity of individual drugs in patients failing antiretroviral therapy. Abstract 133.
3. Piketty C et al – Virological and immunological impact of NNRTI withdrawal in patients with multiple treatment failures: a sub-study of Puzzle 2 – ANRS 107. 2nd IAS Conference, Paris. 13-16 July 2003. Abstract 544.
4. Campbell TB et al - Antiviral activity of lamivudine in persons infected with 140 HIV-1 that has M184V and multiple thymidine analogue mutations. Abstract 140.

Replicative capacity results complicated by minority wild-type virus

The unique co-transfection step inherent to single-cycle HIV resistance assays, can result in even relatively small amounts of wild-type virus (WT) within a viral population significantly affecting the apparent replication capacity (RC) and phenotype of mutant strains, conclude researchers from Abbott Laboratories in Illinois, USA.

The replication capacity and susceptibility of plasma isolates from patients who are off therapy or not adherent to treatment, in which wild-type virus may expand to significant levels, should be interpreted with caution, they say in an abstract presented to the Mexico resistance meeting.

In a typical single-cycle HIV phenotypic assay - the most common test for RC and phenotypic resistance - the 'pool' of DNA generated from patient plasma is transfected into target cells in order to capture and preserve the protease and reverse transcriptase sequence heterogeneity of the plasma virus. However, co-transfection of different viral variants into the same cell might provide the opportunity for genetic recombination or complementation, or both.

Hongmei Mo and colleagues found that four mutant constructs with different genotypes derived from dual protease inhibitor-experienced subjects receiving lopinavir/ritonavir (LPV/r) therapy displayed <5% RC when transfected alone. Co-transfection of as little as 9% of the WT clone increased the RC of the mutant clones to up to 14%. Co-transfection of a higher proportion of the WT clone further enhanced the RC of the mutants to 31–81%.

The LPV susceptibility of four mutant clones with sufficient RC for phenotypic evaluation when transfected alone ranged from 44- to 302-fold, compared to the WT clone. Incremental cotransfection of 9–50% of the WT clone decreased the LPV IC50 of the mutant clones by up to 96%, compared to WT.

Ref: Mo H, Lu L, Kempf D et al. The impact of minor populations of wild-type HIV on the replication capacity and phenotype of mutant variants in a single-cycle HIV resistance assay. Abstract 85.

Tenofovir, resistance and K65R and concomitant nucleosides

Further information about tenofovir resistance and approaches to using this new drug were provided in several abstracts. Much of this information, and the discussions it generates involve the development of the tenofovir-associated K65R mutation and this has an overlapping cross-resistance profile with abacavir and ddI.

Parikh and colleagues from the University of Pittsburgh looked at the frequency of K65R and its association with other nucleoside mutations in the Virco and Stanford databases. Susceptibility was determined using a single/multiple cycle assay. [1]

Among more than 60,000 samples in the Virco database containing nucleoside mutations, K65R increased in frequency from 0.8% in 1998 to 2.1% in 2002 and 3.8% in 2003. A mononuclear clone containing K65R showed reduced susceptibility of 2.5 to >10-fold to all D- and L-acyclic nucleoside but not to AZT. A strong negative correlation was found between presence of K65R and AZT-associated mutations. Addition of K65R to AZT-resistant clones (41L, 210W, 215Y and 67N, 70R, 215F, 219Q) increased AZT susceptibility 10-fold (reducing resistance from 30-fold to 3-fold).

In a second abstract, Winston and colleagues from the Chelsea and Westminster Hospital in London reported a similar increase in the incidence of K65R from 1.7% prior to October 2000 to 4% over the following two years to October 2002. Although abacavir, ddI and tenofovir were not associated alone with development of K65R, certain combinations were. Fourteen percent of isolates were from patients using tenofovir with ddI and 32% were using tenofovir, ddI and abacavir. Forty-one percent of resistance tests from people using tenofovir/abacavir/ddI showed K65R. Concurrent thymidine analogues reduced the risk of K65R by 76% (OR 0.24, 95% CI 0.1-0.5). [2]

Miller presented Gilead's resistance analysis from the 903 study that compared tenofovir to d4T, both against a backbone of 3TC and efavirenz. By week 96 approximately 12% of patients had failed virologically in each arm (n=36 tenofovir, n=38 d4T). [3]

K65R developed in almost one quarter of failures in the tenofovir arm (8/36), compared to around 5% of failures in the d4T arm (2/38). Development of K65R only showed low level changes in tenofovir susceptibility (mean 1.2-fold, range 0.9-2.2) increased susceptibility to AZT (0.5 fold) and low level changes for ddI and abacavir. The majority of patients in each arm showed resistance to efavirenz and/or 3TC and efavirenz resistance always preceded or accompanied K65R. A study by

Deval and colleagues suggested that M184V with K65R increased tenofovir sensitivity and reduced viral fitness at a molecular level by reducing binding of natural nucleotides, although aiming principally for maximal suppression with no development of resistance must still be preferable to strategies based on driving a virus with low replicative capacity. [4]

Data on the clinical responses following failure of tenofovir-based treatment has been previously presented on a handful of patients but included successful responses to subsequent therapy, including several patients with K65R who chose to continue tenofovir therapy.

Van Rompay and colleagues suggested that continued tenofovir therapy is needed to maintain a CD8-mediated response that actually mediates K65R suppression, following a study of four SIV-infected rhesus macaques. [5]

C O M M E N T

Tenofovir was already being included in first-line therapy in the UK prior to change in the EMEA recommendations in June 2003, especially as it was approved for first-line therapy in the US, largely driven by the convenience of a one-pill, once-daily formulation.

Although incidence of K65R is low compared to exposure to tenofovir (2.7%) it is high (almost 25%) in those people whose treatment fails – and the implication for cross-resistance to both existing and pipeline nucleosides means that further research and information in this area will be highly significant.

There may be a reason not to experiment with adherence using once daily regimens based on the tenofovir/ddI combination or to use this combination only once adherence and viral suppression has been obtained. The role of a thymidine-including combination with tenofovir, may be less protective than these studies suggest as some patients using Trizivir+tenofovir in the ESS40013 study reported at the IAS meeting (abstract 42) failed with K65R.

References:

1. Parikh U, Koonz D, Hammond J et al - K65R: a multi-nucleoside resistance mutation of low but increasing frequency. Abstract 136.
2. Winston A, Pozniak A, Gazzard B et al - Which nucleoside and nucleotide backbone combinations select for the K65R mutation in HIV-1 reverse transcriptase? Abstract 137.
3. Miller MD, Margot NA, McColl DJ et al - Characterisation of resistance mutation patterns emerging over two years during first-line antiretroviral treatment with tenofovir DF or stavudine in combination with lamivudine and efavirenz. Abstract 135.
4. Deval J, White KL, Miller MD et al - Drug resistance and viral fitness at a molecular level: the case for viral fitness. Abstract 34.
5. Van Romay KKA, Singh R, Wingfild C et al - Immune-mediated suppression of virulent simian immunodeficiency virus induced by tenofovir treatment. Abstract 70.

Response to STI is determined by virus rather than immunological response

Important findings may explain the different responses that have been reported following treatment interruptions and the results appear to have little to do with the immunological effects that were being closely studied.

Instead, viral characteristics such as *in vitro* replication capacity and infectivity predict control of plasma viraemia after the last cessation of therapy in patients undergoing structured treatment interruptions (STI), according to a group of researchers in Switzerland, California and Oxford.

Low pretreatment *env* diversity in patients controlling viraemia after STI suggests that those viral characteristics were not influenced by STI but were already present years before any therapy was started.

The researchers analysed viral isolates taken from 20 chronically infected patients participating in the Swiss-Spanish Intermittent Therapy Trial (SSITT) which had previously reported no cumulative benefit from several planned treatment breaks. This analysis found that SSITT-baseline neutralising activity but not HIV-specific CTL- or T-help responses were associated with control of viraemia.

Ref: Günthard H, Joos B, Kuster H et al. Virus characteristics predict viraemia control after cessation of antiretroviral therapy. Abstract 56.

Why resistance rarely develops with viral suppression <50 copies/ml

American and Israeli researchers have used a conceptual model to consider the distinct patterns of the virological and immunological response to antiretroviral therapy. They interpret recent data in terms of 'proximal immune activation and virus transmission' (PAT) and believe it may explain why resistance mutations are rarely observed below 50-100 copies RNA/ml despite clear evidence of ongoing viral replication.

The researchers write in their abstract: "We suggest that below this threshold, virus generated in the course of an infection burst rarely sparks new bursts in unrelated target cells, thus precluding gradual increase in the repertoire of infected memory

cells; viral replication remains local and resistant variants that may emerge are prevented from spreading. However, above threshold, HIV-specific memory cells are generated and are capable of spreading new resistant variants within the memory pool. Thus, both direct spreading and anti-HIV response dependent 'mixing' become insignificant when infection bursts are sufficiently reduced. Consistent with mixing, we previously observed that resistance mutations did develop in patients with intermittent viraemia episodes, who showed limited evidence of generalised T cell activation but had large numbers of HIV-specific T cells. Importantly, *PAT* predicts that in the absence of rapid spreading and mixing, wild-type HIV and resistant variants can coexist, actively replicating in relative isolation."

Ref: Grossman Z, Grossman Z, Hunt PW et al. Distinct patterns of the virological and immunological response to antiretroviral therapy interpreted in terms of the dynamics of immune activation and HIV transmission. Abstract 57.

Long-term persistence of distinct mutations in genital tract

Two studies, one using isolates from women and one using isolates from men, show viral mutations in genital tracts that are different to those in blood plasma, and which persisted sometimes for years even without selective pressure of treatment.

Grisselle Tirado and colleagues at the Ponce School of Medicine in Puerto Rico, analysed 45 paired blood and vaginal samples from HIV-1-positive women. Their cross-sectional study suggests that local selective forces allow distinct viral lineages to emerge and evolve independently in the plasma and the vaginal compartment. [1]

They report that delayed clearance of drug resistance mutants was observed in the vaginal compartment and these viruses remained macrophage-tropic despite presence of T cell tropism in plasma and advanced HIV-1 disease "thus suggesting the vaginal tract could serve as a reservoir for M-tropic drug resistant mutants and perhaps contribute to the transmission of drug resistance".

Two patients maintained T215Y in vaginal HIV two and four years after stopping AZT, and a third maintained 184V four years after discontinuing 3TC.

DM Smith and colleagues at the University of California, San Diego, analysed HIV RNA isolates from blood and seminal plasma from two men: a transmission partner pair.[2] The source subject was chronically infected and had a long antiretroviral treatment history. The index subject was acutely infected and naïve to antiretroviral therapy. The researchers found compartmentalisation of 215 revertants in the male genital tract (in this case exclusively 215L), which they conclude may be explained by the isolation of a founding virus or the selection of such variants in the genital tract.

Population sequencing identified a mixture of 215F/L in the source partner (together with high level resistance to NNRTIs and nelfinavir) and length polymorphism analysis of all samples revealed multiple HIV quasispecies but that the blood and plasma samples of the index patient were more similar to the semen rather than plasma sample of the source partner.

They write: "Since antiretrovirals differentially penetrate the blood and male genital compartments, it may facilitate the production and/or selective retention of revertants. This has significant public health implications, as these revertants represent highly fit viruses that can become resistant to zidovudine more readily than wild-type virus."

C O M M E N T

The presence of resistant virus in the genital tract whilst that in the plasma remains wild type has great implications for the sexual transmission of drug resistant HIV, especially when it remains M tropic.

The fact that 3TC resistance persisted in the female genital tract for more than two years in the absence of therapy is quite remarkable and is not something commonly seen in plasma. Similar findings were reported by Taylor et al in ARHR 2003; 19:353-61.

References

1. Tirado G, Jove GR and Yamamura Y. Vaginal HIV-1 shows distinct drug resistance mutation patterns compared to plasma HIV-1 and remain M-tropic despite advanced disease. Abstract 68.
2. Smith DM, Koelsch KK, Wong JK et al. Male genital tract compartmentalisation and transmission of 215L revertant. Abstract 83.

CONFERENCE REPORT

The 5th International Workshop on Adverse Drug Reactions and Lipodystrophy

8-11 July 2003, Paris

Simon Collins, HIV i-Base

The high level of interest in lipodystrophy as a specialist problem was shown by the level of interest in this meeting with around 350 delegates, 25 presentations and 125 additional posters, covering both basic research and clinical care.

Several key plenary lectures with relevance to clinical care (including atherosclerosis, the role of both adipose tissue and adipocytokines in insulin resistance, and pharmacogenomics) will be posted on the internet, although this had not been done as we went to press. This hugely increases accessibility for people unable to attend the meeting, as does the prompt posting of the abstracts from this meeting on the internet. These are available to download as a pdf file from:

http://www.intmedpress.com/pdfs/Lipo_web.pdf

While there were no major breakthroughs at the meeting many studies provided important pieces of information for both mechanism and treatment.

For the underlying mechanism this included the role of adiponectin, TNF-a and adipocytokines in insulin resistance and lipodystrophy and further reports on the role of thymidine analogues in adipogenesis and apoptosis through the mechanism of mitochondrial toxicity.

Clinical reports included switching thymidine analogues of abacavir, use of rosiglitazone (in people with hyperinsulinaemia and LDS) and a report of uridine to treat mitochondrial depletion.

Other reports with clinical relevance covered at the meeting included:

- further reports of increases of IMT
- reduced BMD in HIV-positive women
- rosiglitazone reversed peripheral lipoatrophy in HIV-patients with insulin resistance
- additional benefits of exercise with metformin
- reversal of peripheral fat loss from switching d4T or AZT to abacavir continues over two years
- monitoring facial lipoatrophy
- uridine treatment for mitochondrial toxicity
- breast enlargement in men and testosterone treatment
- treatment interruption can improve lipodystrophy

Jacqueline Capeau, one of the co-chairs of this year's organising committee concluded the meeting confident that the major factors responsible for lipodystrophy have been established "and that we now just have to fit these together and hopefully see the picture next year". If this is true then this will be a very short 12 months.

Underlying mechanisms: adipocytes and cytokines

An excellent overview of the recent basic science presented at the workshop, particularly relating to nucleoside therapy, was provided by Professor Capeau at the subsequent IAS conference. Many of the presentations focused on the effect of HIV treatment on insulin resistance, and altered cytokines that in turn leads to reduced ability to store fat and adipocyte apoptosis. [1]

Several studies focused on the endocrine function of adipocytes in secreting the adipocytokines leptin and adiponectin which control insulin resistance in liver and muscle tissue.[2] Reduced adiponectin was shown to increase insulin resistance and adiponectin partially reversed - and when given together with leptin totally reversed – insulin resistance in lipoatrophic mice.

Adiponectin was also independently and inversely associated with insulin resistance and significantly associated with increased abdominal and reduced peripheral fat in results from a study of 134 HIV-positive patients presented by Khatami and colleagues from UCSF. [3]

Frayn focused on a complementary role of adipose tissue as a 'buffer' to the daily intake of fatty acids in the same way that liver 'buffers' the intake of carbohydrates. In the case of fat accumulation, adipocytes are already swollen and less active than smaller cells and with lipoatrophy there may not be sufficient adipose tissue to cope with incoming fat, and both would account for increased plasma lipidaemia. [4]

A direct effect on fat cells – through altered differentiation (shown with some PIs through interfering with SREBP-1 signalling, and SREBP-1 controls adipogenesis in the liver) or decreased mitochondrial function (shown with nucleosides).

Deveaud and colleagues showed that AZT decreased mitochondrial DNA and cytochrome oxidase levels in subcutaneous fat but not visceral fat in rats, due to slower mitochondrial activity in visceral fat. [5] Other potential mechanisms besides mitochondrial toxicity linked to nucleoside toxicity that were suggested included: certain metabolites of AZT and d4T decrease body fat and increase fatty acid oxidation [6]; altered viability and function of immature (mouse) adipocytes [7]; and decreased lipid accumulation from AZT and d4T (but not abacavir, ddI or 3TC) in cultured cells. [8]

Capeau and colleagues reported increased apoptosis, percentage of fibrosis and number of cells (as a compensatory reaction to apoptosis of fat cells) in ten lipoatrophic patients compared to six HIV-negative controls and that this correlated with increases in cytokines IL-6 and TNF-alpha, and negatively with differentiation markers SREBP-1 and C/EBP-alpha. [9]

More mitochondrial DNA depletion

David Nolan presented updated results form the Western Australian HIV Cohort showing that adipocyte depletion and mitochondrial toxicity are prominent in subcutaneous fat samples from 46 RTI-treated patients, compared to 24 HIV-positive treatment naïve patients and seven HIV-negative controls.[10]

Median mtDNA copies/cell was 1,288 in treatment naïve patients, and reduced by 81% to 240 copies/cell in 28 patients using d4T and by 41% to 726 copies/cell in 29 patients using AZT. Sequential biopsy samples showed significant changes in mtDNA within 2-12 months of initiated nucleoside therapy.

These changes correlated with adipocyte toxicity – reduced size and disorganised tissue architecture and marked macrophage infiltration.

Slides showed the differences between the 'plump normal fatty cells' seen in both HIV-negative and HIV-positive untreated individuals. Lipoatrophy is not a symptom of redistribution of fat – but one on specific fat cell damage in peripheral parts of the body.

Lopez and colleagues reported that HIV antiretroviral naïve patients had 68% mtDNA content with respect to HIV-negative control group, and that HIV itself could be a factor in mtDNA depletion [11] and Tebas and colleagues showed that mtDNA levels doubled on starting treatment, but fell again in patients when using d4T/ddI. [12]

Research on expression of SREBP-1 and apoB, showed increases in the synthesis and secretion of VLDL, and was suggested as an explanation for increases seen in levels of triglycerides and cholesterol. [13]

IMT and cardiovascular risk

Modest increases in carotid intima media thickness (IMT) were reported in a new French study by Mercie and colleagues. [14] IMT increases are a marker for atherosclerosis and a recognised risk factor for cardiovascular disease, but at the 2003 Retrovirus Conference two separate studies reported contradictory results on whether this was occurring.

In this study, 346 patients had IMT measured by ultrasonography at baseline and again at 12 months. They reported a significant increase from 0.57 to 0.59mm but that this also was within the normal range, and that conventional cardiovascular risk factors were associated with the increase (age, gender and smoking). Although antiretroviral treatment was not an associated factor in multivariate analysis, a maximum increase in the general population over this period would be expected to only be 0.01mm.

The Retrovirus study that reported markedly increased IMT (5-fold compared to the previous study) was also presented as a poster at the lipodystrophy workshop. [15]

Hsue and colleagues from San Francisco General Hospital reported higher baselines IMT in 147 HIV-positive patients on HAART (122 male, 25 female) compared to their HIV-negative control group (0.9–0.2 versus 0.7–0.2).

A rate of progression in 87 HIV-positive patients after one year was 0.10mm (–0.1) compared to 0.01mm in published reports of HIV-negative populations. Traditional risk factors but also HIV were predictive in a multivariate analysis of IMT at baseline and age, Latino race and CD4-nadir were predictive of IMT progression.

C O M M E N T

Previously reported increases in IMT in HIV-positive individuals compared to HIV-negative controls was linked to traditional risk factors rather than HIV or HAART (eg Depairon et al AIDS 2001; 15:329-334).

The progression of IMT in this study is again out of proportion to any other study so far or other reports using IMT as a surrogate marker.

Reduced bone mineral density in HIV-positive women

In the last oral presentation at the workshop, Steven Grinspoon presented results from an observational study showing significantly reduced bone mineral density in HIV-positive women compared to BMI and age-matched HIV-negative women. [16]

The study from Massachusetts General Hospital compared results from DEXA and hormonal indices of 84 HIV-positive women to 63 HIV-negative controls (mean age 41, BMI 26-27, 50-60% Caucasian). Bone density and T score were significantly reduced in the HIV-positive women at lumbar spine and hip (p=0.03 and p=0.04 respectively) compared to controls.

Osteopenia was demonstrated in 54% versus 30% (p=0.004) and osteoporosis in 10% versus 5% (p=0.27). 1,25-dihydroxyvitamin D was reduced and urinary NTx and osteoprotegrin both increased in the HIV-positive group but serum calcium, phosphorus, estradiol, FSH, PTH, osteocalcin and 25-hydroxyvitamin D levels were similar in both groups.

Among the HIV-positive women, bone density correlated with body mass and total body fat (both p<0.001) and negatively with urinary NTx.

Increased bone resorption, together with altered nutritional status, hormonal function and body composition may be responsible for these changes and, given that women are at increased risk for osteopenia, suggests that integrating bone density monitoring should be an important part of care for HIV-positive women.

Treatments and clinical effects

Basic research at the lipodystrophy workshop is always a challenge for 'non-scientists' to follow – and one speaker concluded his talk with a quote that 'man is not a good model for rats' – but luckily there were several presentations that had a direct link to clinical care.

Rosiglitazone with insulin resistance

A study of rosiglitazone (a thiazolidinedione agonist of PPAR gamma) at a dose of 4mg/day for three months followed by 8mg/day for a further three months in 28 patients with hyperinsulinaemia and lipoatrophy led to increases in subcutaneous and total body fat, but fasting triglycerides and cholesterol also increased. [17]

Previous studies using rosiglitazone in HIV-positive patients with lipodystrophy have not reported a benefit but this could be an option that helps those who also have insulin resistance.

A separate study from Oette and colleagues reported interaction data on ARVs and rosiglitazone [18] suggesting bioavailability of nevirapine could be reduced (AUC, Cmax and Cmin all by 30-35%) and that individualised dosing using therapeutic drug monitoring was recommended. Rosiglitazone did not produce clinically significant interactions with efavirenz, lopinavir or nelfinavir and no recommendation was given for saquinavir, although these results are limited by the low numbers studies for most of these drugs.

C O M M E N T

Rosiglitazone increases cholesterol and triglycerides whereas pioglitazone does not, however the manufacturer Takeda has no interest in HIV and because of this the data are limited (see pilot study by Calmy, Hirshel et al - AIDS 2003; 17(5):770-772).

Metformin and exercise

Driscoll and colleagues reported that exercise training (one hour of aerobic plus strength training three times a week) together with metformin (850mg BID) significantly improved cardiovascular risk markers (waist-to-hip ratio, resting systolic and diastolic blood pressures and aerobic capacity to exercise) compared to metformin alone.[19]

The study population included 37 HIV-positive patients on HAART with hyperinsulinaemia or impaired glucose tolerance and waist-to-hip ratio >0.90 in men or >0.85 in women. Only 25 people completed the study, which unfortunately did not include an exercise-only arm. Diet did not change during the study.

Mitochondrial toxicity with AZT and d4T – and benefits of switch to abacavir

Two-year follow up data from Australian patients randomised to switching AZT or d4T to abacavir in the MITOX study showed continued benefit, reported Andrew Carr.[20]

Serial DEXA and CT scans previously reported a mean increase of 0.39kg limb fat after 24-weeks compared to controls continuing on thymidine analogues. At this year's meeting follow-up data also presented responses of the control group who switched to abacavir at week 24.

Mean follow-up was 102 weeks with 74/111 patients having imaging data at week 104. Limb fat in the patients who originally switched to abacavir had continued to increase to +1.26kg from a baseline of 3.7kg.

Although these changes may not show great clinical differences, it is very important that lipoatrophy has both stopped progressing and in a limited way also reversed – and that this is documented in measurable changes. It is not know whether the original fat loss had reached a plateau either due to maximal adipocyte depletion or before that level.

The control patients also reported similar improvement once they switch from AZT or d4T at 24 weeks.

Multivariate analysis showed greater increase in limb fat was associated with lower baseline bone mineral density (p=0.006), shorter duration of AZT pre-study (p=0.024) and shorter duration of d4T on study (p=0.004).

Raghavan and colleagues found small but statistically significant differences in the rate of change in BMI, body cell mass, total body fat and circumferences and skin folds between patients using ddI/d4t compared to those using abacavir/3TC in both peripheral and central sites.[21]

BIA and anthropometric measurements (skin-fold and body circumference) were taken every four months over a median of 33 months follow up in 96 patients on their first combination enrolled in a substudy of CPCRA 058.

Facial fat loss – measuring and treatment

Numerous studies reported ways of measuring, monitoring and classifying stages of facial lipoatrophy, much of which is particularly frustrating for patients who clearly have symptoms but no access to treatment.

The most recommended approach in an overview of available treatment provided by Dr Heinz Bull in the final session was using injections of polylactic acid (PLA, New-Fill). This treatment was first reported at the 2nd Lipodystrophy workshop and every year thereafter, and usually is included in other major HIV conferences.

More severe lipoatrophy requires more treatment than mild lipoatrophy, but patient satisfaction is generally high and was reported as improving appearance in 27/30 patients who received New-Fill at St Mary's Hospital in London and who had reported a high level of previous distress from these symptoms. [22]

One poster reported that 4/53 patients, who had undergone autologous fat transfer to treat facial lipoatrophy, had subsequently experienced hypertrophy in their cheeks at the same time as a relapse of their original buffalo hump or central hyperatrophy. Fat was sourced from a buffalo hump in 21/53 cases. Three of these four cases of severely swollen cheeks had involved injected fat removed from a buffalo hump, and one from abdominally collected fat. The study concluded that people undergoing fat transfer should harvest fat for this process from abdomen or groin areas. [23]

Uridine treatment for mitochondrial toxicity

A possible treatment for nucleoside-related mitochondrial toxicity was suggested by Ulrich Walker form University of Freiburg. [24]

Human hepatocytes were exposed to NRTIs with or without uridine for 25 days. Severe depletion of mtDNA, reduction in cell proliferation and increase in lactate and steatosis developed with exposure to ddC and d4T (but not ddI) which was largely reversed in the presence of uridine. It also reversed cell toxicity and lactate of AZT and 3TC-exposed cells.

Interactions with nucleoside were not found and uridine did not affect RTI IC50 or IC90 of any of the nucleosides in resistance assays.

In humans, serum levels of uridine achieved protective levels in the in vitro model following a single 36g dose of a dietary supplement Mitocnol and studies of uridine therapy in HIV-positive patients are now underway. (A website with details if Uridine is at http://www.nucleomaxX.com - see also more detained article below in IAS report).

Male breast enlargement

Breast enlargement in male patients was reported in 28/2,310 patients attending a Barcelona clinic from November 2001 to November 2002 (incidence 1.2%). This was bilateral in just under half the cases and in 57% cases the patients had other symptoms of lipodystrophy. Ultrasound showed gynecomastia in 75% of cases and lipomastia in 25%. Spontaneous regression occurred in only seven (25%) patients and other management approaches including use of testosterone cream or withdrawal of potentially implicating drugs and in one case surgery, produced regression in other patients. (further details not provided in abstract). [25]

Severe efavirenz psychotic events

Mike Allin and colleagues from King's College Hospital in London reported on a small group of six patients who had been referred over a two-year period from a single London hospital with acute severe psychiatric symptoms including suicide ideation out of a total of 200 patients who had started medication with efavirenz. [26]

Suicide was out of proportion to the depressed mood and inner feelings of tension that were also reported and was attempted in two cases with homicide ideation additionally present in one of the six.

All symptoms resolved when efavirenz was withdrawn. Four of six patients had a prior psychiatric history but two did not. Although the factors that predispose patients to severe side effects from efavirenz are not clear, awareness of these extreme reactions that have been previously described and consideration of withdrawal of treatment and specialist referral should be considered by all physicians.

C O M M E N T

Awareness of these uncommon cases is important as both UK and US treatment guidelines include efavirenz-based regimens as one of the preferred first line choices for treatment.

A letter in the 25 July 2003 Issue of AIDS, reported an episode of mania in a patient without previous history of psychiatric symptoms that resolved on discontinuation.

Two case studies of recurrence of post traumatic stress disorder symptoms following initiation of efavirenz-based HAART are reported in the July 2003 Issue of HIV Medicine. Both patients continured efavirenz treatment and reported that symptom resolved to lower levels within four weeks. Both patients were refugees who recounted torture in their country of origin and were receiving treatment in the USA.

Treatment interruption: a real choice

At the end of the last day of the Workshop an important discussion provided a controversial focus concerning clinical management of lipodystrophy.

A presentation from Emmanuel Trenado of results from a prospective cohort study of 725 HIV patients, almost 600 of whom had answered a questionnaire distributed by the French community organisation AIDES, and of the 80% on treatment almost 40% said that on their 'stable' combination they experienced mild to moderate side effects. [27] Sexual dysfunction, sleep disorders, lipodystrophy and fatigue were each reported in 17-20% of the questionnaires.

Perhaps unsurprisingly, people reporting side effects were three times more likely to be interested in taking a treatment interruption, but 10% of the cohort were already taking a break from treatment and half of these people were doing this without consulting their doctors.

Perception of body shape changes in a multivariate analysis from the APROCO cohort was also a significant predictor of adherence failure at month 20 in patients who had previously reported excellent adherence (the only other two factors being daily alcohol use and age).

A summary of management of lipodystrophy by Christine Katlama excluded stopping treatment as an option that clinicians should recommend (for the treatment of metabolic alterations), but this is clearly an approach taken by people in real life. Whatever the exact mechanisms for the body shape changes, HIV treatment is now recognised as a significant contributory factor – and a wealth of studies at every lipodystrophy workshop attests to direct effects on mouse, rat or human cells other than purely targeting of HIV.

Risk factors from a treatment interruption in numerous studies include previous CD4 nadir and history of opportunistic infections, and also perhaps severity of original seroconversion symptoms.

Martinez and colleagues from Barcelona reported effects of a treatment interruption in 10/15 patients with symptoms of lipodystrophy and 5/8 without lipodystrophy. After one year there was a trend to fat gain and fat-free mass loss with minimal change in bone mineral density. Patients who interrupted treatment both with and without symptoms of lipodystrophy had greater increases in weight, BMI, total fat and spine BMD and lower decreases in fat-free mass compared to patients who continued HAART. [28]

While this is not a straightforward option for many patients, that it is always an option that some may choose highlights the real difficulties and urgency of discovering alternative treatment and management options.

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Unless otherwise stated, all abstracts refer to the programme and abstracts from the 5th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 8-11 July 2003, Paris and are published in Antiviral Therapy Volume 8 issue 4.

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23. Guaraldi G, De Fazio D, Orlando G et al - Fat accumulation of the cheeks after autologous fat transfer for treating facial wasting in HIV-related lipodystrophy. Abstract 81.
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25. Garcia M, Martinez E, Domingo P et al – Breast enlargement in male HIV-infected patients. Abstract 82.
26. Allin M, Reeves I, Everal I et al – Frequency of serious psychiatric adverse events with efavirenz. Abstract 129.
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CONFERENCE REPORT

2nd IAS Conference on HIV Pathogenesis and Treatment

13-16 July 2003, Paris

This biannual conference alternates with the years of the International AIDS conference. Location is also planned to alternate between a developed country and one where access to treatment is still not widely available - the first meeting was held in Buenos Aires in 2001 – in order to maintain a balance between new science and the importance of access issues.

The second meeting – this year in Paris – attracted 6,000 delegates from 120 countries. One thousand eight hundred abstracts were received, 180 of which were selected for oral presentations and more than 900 for poster presentations. None of them however were available online as we went to press - although webcasts and other resources for all conference plenaries and selected other sessions are provided by the Kaiser Family Foundation online; they do not include the facility to see the slides being referred to in the lectures:

http://www.kaisernetwork.org

Webcasts include:

Main Plenaries

- Challenges and lessons learned in implementing antiretroviral therapy in the developing world
- Host/virus mechanisms in the molecular pathogenesis of HIV
- New antiretroviral drugs and therapeutic strategies
- HIV vaccine research: the state of the science
- HIV entry: insights into viral tropism, pathogenesis, and antiviral therapy
- Mechanisms and management of metabolic complications associated with highly active antiretroviral therapy

Forum Lectures:

- HIV drug resistance
- The scaling-up of antiretroviral therapy in developing countries
- Mother-to-child HIV transmission

Keynote Lectures:

- 20 Years of HIV Science"
- From Science to Action: Challenges in Managing AIDS

All references are from the programme and abstracts of The 2nd IAS conference on HIV pathogenesis and treatment, Paris, France 13-16 July 2003 unless otherwise stated.

IAS: MOTHER TO CHILD TRANSMISSION

Nevirapine and MTCT: the single-dose backlash

Polly Clayden HIV i-Base

Strategies to reduce mother to child transmission (MTCT) both during labour and through breastfeeding were in the foreground more than ever at this conference.

More than 20 oral presentations and more than 50 posters evaluated various aspects of transmission from mother to child, but as usual data on maternal health before, during or after pregnancy, delivery and breastfeeding was scant.

Notably though, some of the most high profile presentations, not only acknowledged that ideally a woman would receive appropriate treatment for her own health but discussed alternative strategies to single dose NVP given to the mother at onset of labour followed by a dose to her infant.

Presumably an acknowledgement that ease of development of resistance (see report from Mexico Resistance meeting above) and an optimism that through MTCT Plus programmes and various other scaling up initiatives some women will eventually receive treatment, drove – what America likes to call – this "paradigm shift". Anyway as Glenda Gray commented "We seem to be witnessing something of a nevirapine backlash…"

Single dose versus combination therapy "controversy"

As part of a series of sessions entitled "controversies" - two MTCT grandmasters - John Sullivan and Francois Dabis set out to convince us of the benefits of two possible reduction strategies. [1]

Dr Sullivan prefixed his talk with "Of course all these women should be treated with the very best combination therapy," and then argued in favour of a universal application in high prevalence areas of 6mg NVP (post exposure prophylaxis) PEP to the infant (which showed promising results at Barcelona compared to including the maternal dose [2]). He suggested this would avoid both resistance in the mothers and the need for voluntary counselling and testing (VCT).

To avoid MTCT during breastfeeding he proposed using his own (in early trials) infant subcutaneous "controlled delivery system" of NVP prophylaxis or possibly a vaccine.

Dr Dabis then presented the case for more complex therapy, citing his group's DITRAME Plus Trial using three drugs presented at this conference (see below). And the SIMBA study – using two drugs from 36 weeks gestation and infant prophylaxis of 3TC or NVP during breastfeeding (also described later in this article).

Dr Dabis was less concerned about the issue of resistance and more driven by the added potency of combination therapy compared to monotherapy.

Beyond nevirapine

In a state of the art lecture Dr Glenda Gray gave a fascinating overview of where we are with MTCT reduction in resource poor settings. [2]

She reminded us that 1,900-2,200 infants per day are estimated to be infected with HIV and although there have been several large randomised trials addressing this mode of transmission – HIVNET 012, SAINT, PETRA etc – only 3% of pregnant HIV positive women in Africa access an MTCT programme at all.

Although clearly we need better coverage of programmes, better programmes and as she pointed out, "We need not to be happy with transmission rates of around 8-12%", Dr Gray was emphatic that we also need to be worried about NVP resistance. As part of her overview she discussed strategies using both alternative agents and avoiding using nevirapine only for the mother.

She highlighted the BMS: A1455-094 trial– first presented at the Durban conference – that achieved promising results, albeit in a very small study, showing short course d4T/ddI produce transmission rates of less than 5%. [3]

She presented a good case for tenofovir as an attractive possible new candidate for MTCT. This nucleotide reverse transcriptase inhibitor crosses the placenta, does not have to be phosphorylated to be active and has an intracellular half-life of 12-15 hours in activated lymphocytes. It has been shown to remain active against a variety of drug resistant HIV-1 strains in vitro and is less likely than NVP to prejudice future maternal therapeutic options. She explained that, although the PACTG have been working on a protocol for "anything between two and four years and still nothing's happening" and "We need to rapidly translate dispatching new drugs into some kind of intervention."

Strategies to avoid using NVP only are currently underway – the BI 1413 trial utilises what the Boehringer Ingelheim investigators call "functional monotherapy". This three-arm study compares NVP single dose to NVP single dose plus ZDV/3TC (Combivir) for four and seven days in the intrapartum and post partum period to the mother. "Hopefully we will have the results in about a year's time", she explained.

She concluded her talk with a quote from Nelson Mandela from his opening address at this conference: "We have failed to translate our scientific progress into action where it is most needed…this is a global injustice…it is a travesty of human rights."

Short course zidovudine and lamivudine and peripartum nevirapine

In this same session, Francois Dabis presented findings from the ANRS 1201 DITRAME Plus - an open-label non-randomised trial in Abidjan starting in September 2002. [5] In this trial women received ZDV/3TC (Combivir) from 32 weeks of gestation and single dose NVP at the beginning of labour. The maternal treatment (ZDV/3TC) was also continued three days postpartum.

The infant received post-exposure prophylaxis (PEP) for one week of ZDV syrup and a single dose of NVP syrup on day three.

Dr Dabis presented interim results showing a transmission rate of 5%, 5/99 children with 4-6 week follow up. He reported that all HIV-positive infants were infected *in utero* (RNA positive on day seven) and they were born to mothers with CD4 <500mm3. He concluded that this strategy prevents most peripartum transmission from mother to child. This trial is not powered to look at resistance in the mothers.

Breastfeeding

The other issue addressed in this session was transmission through breastfeeding. Dr Ruth Nduati delivered the state of the art lecture and emphasised that intrapartum antiretroviral prophylaxis alone does not work…Breastfeeding diminishes the efficacy of these protocols… Breastfeeding continues to be a reality" [6]

Mortality in breastfed and formula fed children

In an MTCT session the previous day Dr Becquet described a comparison between mortality rates in breast and formula fed children among children born to HIV-positive mothers in the DITRAME Plus ANRS 1202 cohort [7].

Mothers were given the choice between formula feeding (formula provided free) and exclusive breastfeeding for three months then early weaning. Mothers and infants were followed for two years. Of the 398 children enrolled, 201 (51.2%) received formula from birth, 175 (44.5%) were breastfed and 17 (4.3%) were mix-fed. Of the infants 28 children died, among them 11 who were HIV infected at six weeks of age. Among the HIV uninfected children four and two children died in the formula fed (n=187) and breastfed (n=166) groups respectively.

Dr Becquet reported that there was no evidence of a higher mortality in the formula fed HIV uninfected compared to the breastfed.

Mortality among HIV-infected mothers and children's feeding modality

Dr Marie Louise Newell presented data on behalf of the Breastfeeding and HIV Transmission Study Group. She explained

that we know very little about the effect of breastfeeding on the health of HIV positive women themselves and that the two studies to date conducted in Africa have presented conflicting results. One study in Nairobi and Kenya suggested that mortality in breastfeeding women was substantially higher than in non-breastfeeding women and another conducted in Durban suggested there was no difference.

This study evaluated mortality among a multi site cohort of 4,237 African mothers with available data to be eligible for analysis over a period of 18 months following delivery.

Dr Newell reported that the mothers' median CD4 count around the time of delivery was 464 mm3. In the 18 months following delivery, 362 women died and the median time to death was 9.8 months. 3,717(87.7%) women ever breastfed and the median duration of breastfeeding was 8.8 months.

In univariate analysis feeding mode was not associated with mothers' mortality (p>0.11). She reported that independent risk factors were: maternal CD4 count (lower CD4 <200 increased risk of 12 and 18 month mortality [p<0.001]); and child's feeding mode (mothers who ever breastfed had lower risk at 12 moths than mothers of never breastfed children [p=0.033] but not at 18 months [p=0.068]).

She concluded that women who have advanced disease around the time of delivery had a greatly increased risk of dying in the months following, but mortality rates in the first 18 months postpartum were lower in women who ever than those who never breastfed. She suggested that this is because those women are healthy and are able to continue breastfeeding for longer periods. She explained, "This association is likely to be very complex and very difficult to evaluate in observational data but we are trying our best to investigate further".

Formula is safe in a resource poor urban setting

Dr Coetzee, reporting on a study conducted in Khayelitsha, South Africa, described the formula versus breastfeeding issue and in turn appropriate guidelines as "a fierce debate". [9]

Khayelitsha is a township outside Cape Town with approximately 500,000 inhabitants of which 10% are estimated to be HIV-positive and approximately 7,000 HIV positive women deliver each year. Since 1999 there has been an MTCT programme in Khayelitsha implemented by the Western Cape Provincial Health Department. As part of this programme, formula milk is offered free of charge to mothers for nine months (most households in Khayelitsha [71%] have available potable water) and support groups are provided.

Of a sample of 113 women attending the MTCT programme interviewed to evaluate the extent of the uptake of this intervention, 95% of women chose not to breastfeed at all, 3% of women had breastfed for between one and four days or mixed fed for one week. The mothers were also asked whether their children had experienced episodes of diarrhoea and 70% reported that they had not.

Despite the high prevalence Dr Coetzee reported stigma to be still very high and to be seen formula feeding can represent disclosure by bottle, so women have discussed in their support groups how they will lie to their friends and family – TB, hypertension, the milk did not come…"When people ask me why I am formula feeding, what they are really asking me is am I HIV positive?"

Nevertheless, the majority of women chose not to breastfeed and they make the decision themselves. Dr Coetzee concluded: "Formula feeding is safe and feasible in an urban environment where sufficient potable water is available."

SIMBA study shows only 1% breastfeeding transmission rate

The jury is still out though as to whether formula feeding is always possible or even desirable in resource poor settings. Dr Vyankandondera from the SIMBA study – a randomised phase III open-label, multi-centre trial to evaluate the efficacy of prophylaxis with either 3TC or NVP to breastfed children to prevent postnatal HIV transmission – reported promising results in an oral late breaker.

A group of 413 antiretroviral naïve pregnant women were enrolled from centres in Rwanda and Uganda. The mothers received AZT/ddI dual therapy from 36 weeks gestation until one week postpartum and were provided with counselling on exclusive breastfeeding. The median viral load of the mothers at delivery was 2.66 logs copies/ml and median CD4 was 427mm3.

DNA HIV-1 PCR was performed on the infants at birth, six weeks, three months and six months. Three hundred and ninety-seven infants were randomised to receive either 3TC (n=199) or NVP (n=198) syrup. In the 3TC and NVP arms, respectively 90.5% and 86.5% were breastfed exclusively; 7% and 9.6% breast and bottle and 2.5% and 3.5% exclusively bottle-fed. The infants were fed for a median of 107 days in the 3TC arm and 106 days in the NVP arm.

Of the infants that were at risk after four weeks of age, late postnatal transmission occurred in 2/179 (1.1%) in the 3TC arm and 1/179 (0.6%) in the NVP arm. Dr Vayankandondera concluded that infant antiretroviral prophylactic intervention during breastfeeding, and counselling of breastfeeding mothers can reduce postnatal transmission from 15% to an incidence of 1% in the first six months of life. "These are the first data to show that mothers can safely breastfeed children, even in the presence of HIV infection," he explained, and he added: "This strategy could greatly reduce the stigma associated with formula feeding".

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C O M M E N T

Use of 3TC or NVP for breastfeeding prophylaxis has the potential to save hundreds of thousands of newborn babies from contracting HIV via breast milk – after a period of triple combination therapy for their mothers has reduced the initial risk of infection. This was perhaps the most significant and important study presented at the IAS meeting.

Meanwhile a rather confusing decision was confirmed on July 28th by the Medicines Control Council (MCC) of South Africa to deregister nevirapine for use in mother-to-child transmission programmes. This decision is based on a rejection of the HIVNET 012 study, and the patent holders Boehringer Ingelheim has 90 days to provide the MCC with more data before the licence is withdrawn.

Understandably, this has caused an outcry from both the community and healthcare workers in South Africa. In a statement, the Treatment Action Campaign (TAC) explains: "Nurses and doctors in public hospitals have expressed dismay at this decision because it undermines the sustainability of the public sector MTCT programme." They continue: "Nevirapine is not the only drug that can be used to reduce mother to child HIV transmission. AZT and other antiretrovirals can be used as individual drugs or in combination for this purpose. The TAC has for a long time called for hospitals and clinics, where capacity exists to begin using more effective regimens than short course nevirapine, but the reality is many facilities will not be in a position to upgrade their programmes to better regimens for months or even years to come. It is these facilities that will be endangered if the MCC carries out its threat"

The TAC describes the decision as disturbing and confusing, it believes it is politically motivated and threatens to vastly undermine MTCT programmes in South Africa.

At the South African AIDS Conference in Durban, an emergency plenary was arranged to discuss this issue before the closing ceremony. Precious Matsoso from the MCC presented "a regulators perspective" and explained why they found HIVNET 012 to be unacceptable as a pivotal study (for which it was not designed) and the concerns that had led to this decision. In her talk she announced that "combination antiretrovirals are available, they should be used to treat the mother", which most would strongly agree with but it is hard to imagine how this might happen in a country that has no national treatment plan.

Catherine Wilfert the scientific director of the Elizabeth Glazer Paediatric AIDS Foundation and James McIntyre, Director of the Perinatal HIV Unit at the Chris Hani Baragwanath Hospital, Johannesburg presented trial and programme data to defend the use of nevirapine for this indication. Professor McIntyre was clear that: "We cannot compare programme data with randomised clinical trials but we urge the MCC to find ways to consider these data."

Although there is consensus that nevirapine is by no means the best way to reduce mother to child transmission or to benefit maternal health. "We are the first to recognise that we could do even better," Dr Wilfert explained. It is widely accepted that single dose nevirapine has been a central part of developing MTCT programmes that use more complex interventions and provide women with antenatal care. Professor McIntyre was most emphatic: "This would not have been possible without the use of a single dose regimen, this has been the building block of programmes."

In the same plenary, making an impassioned plea for antiretrovirals for her people including nevirapine, activist Prudence Mabale the director of Positive Women Network said: "It is not just the drug - these programmes have changed women's lives."

Links:

Complete statement TAC website:

http://www.tac.org.za

Reports from the South African AIDS Conference will be included in next issue of HTB.

IAS: ANTIRETROVIRALS

Triple nucleoside combinations fail patients again

Simon Collins, HIV i-Base

Two studies at the IAS meetings using triple nucleoside combinations reported very poor results and a third study was closed the week before the meeting on a preliminary analysis of the results. This article will report on all three studies.

Trizivir only arm discontinued in ACTG 5095

In April 2003, the Trizivir arm of the ACTG 5095 study was closed by the trials DSMB (Data and Safety Monitoring Board) because patients receiving the triple nucleoside combination were achieving significantly poorer results than the efavirenz containing arms. The efavirenz arms remain unblended and are continuing. (see HTB April 2003)

These data very quickly resulted in Trizivir unsupported by other drugs being dropped as a preferred option for first line therapy in both the new UK and US treatment guidelines, both produced this summer.

The IAS meeting provided the first opportunity for the results from this study to be presented publicly at a large conference. [1]

ACTG 5085 was a double-blind, placebo trial which randomised 1,147 treatment-naïve patients in 1:1:1 ration to either AZT/3TC/abacavir (Trizivir) or AZT/3TC/efavarenz or the four-drug regimen of AZT/3TC/abacavir/efavirenz.

The study population was 81% male, 40% white, 36% Black, 21% Latin. Eleven percent were IVDUs. Mean baseline viral load was 4.9 log copies/ml and 43% of patients were >100,000 copies/ml. Median CD4 count was 238 copies/mm3.

One hundred and sixty-seven patients reached virological failure at the week 32 analysis (defined as confirmed VL >200 at or after 16 weeks). This occurred in 21% of the Trizivir arm (n=82) compared to 10% in the pooled efavirenz-containing arms (n=85). Time to virological failure was shorter with the triple nucleoside arm compared to the pooled efavirenz arms (P<0.001) and this was true for both baseline viral load > or <100,000 c/ml (P<0.001 for each). It was also shorted for patients who achieved viral load <200 and then rebounded. The proportion of patients with viral load <200 at week 48 in the Trizivir and pooled-efavirenz arms was 74% versus 89% respectively. All analyses are ITT.

Very few patients discontinued due to side effects. After a median 32 wks of follow-up, 93% of patients continued on study and 91% continued study drugs. Grade 3 and 4 signs/symptoms occurred in 12% and 2%, with comparable proportions across study arms, so the main concern focused on efficacy.

Adherence (undefined) was a remarkable 100% but resistance testing of people failing in the Trizivir arm showed 22% failing with wild type virus. About half failing with M184V with or without other RTI mutations. 27% still had <500 copies/ml so were not available for resistance testing.

As the other arms in the study continue, no comparative information is available.

Tenofovir/abacavir/3TC – clearly not recommended

Results from a pilot triple-nuke study of once-daily tenofovir+abacavir+3TC in 20 treatment naïve patients were presented by Charles Farthing. This study was also stopped after the high early failure rate became clear. [2]

The rationale appears to have been based on adding the cumulative antiviral potency of the individual drugs rather a review of previous triple-nucleoside studies – because many of the individuals selected for the study had baseline viral load >100,000. In the Atlantic study and previous Trizivir studies higher baseline viral load has correlated with higher failure rates.

Median baseline viral load was approximately 82,000 (range ,7650-213,000) but 9/20 were >100,000 copies/ml. Median CD4 count was 59 cells/mm3 (range 59-598.

Of 17 patients who remained in the study, nine (52%) had viral rebound: one at week four, six at week eight and two at week 16. Patients were >95% adherent by pill count over this short period.

In the same week these results were presented, GlaxoSmithKline (GSK) announced that they had been running a larger study in the US (ESS 30,009) comparing abacavir/3TC/tenofovir to abacavir/3TC/efavirenz, again all once daily, with approximately 180 patients in each arm. An interim analysis of their data had showed similarly disastrous results – this has got to be one of the worst sets of data on treatment naïve patients presented to a conference for a long time - and they were therefore closing this study. [3]

Baseline viral load levels for patients in this study outlined in a hurriedly called community meeting showed a patient group who arguably should have been even less exposed to this experimental approach. Although baseline statistics were not presented, plotted individual results showed many patients started treatment with viral load well above 100,000 copies/ml and

many with counts into the millions.

Nevertheless, the analysis of the first approximately 200 patients showed that the difference in efficacy again appears early and by week eight only 19% of the triple nucleoside patients had viral load <50 copies compared to 37% of the efavirenz group. By week 16 the difference widened further to 30% versus 95% (though admittedly with small numbers).

At the analysis, 49% of the triple nucleoside group, compared to only 5% of the efavirenz arms, had failed by one or other of the protocol defined definitions of failure. By week eight for example, 31% versus 3% failed to see a 2 log drop in viral load in the triple—nuke and efavirenz arms respectively. Resistance data on seven patients whose genotype was sequenced showed that all seven failed with 184V and three with mixed K65R/K and four with K65R.

This study has now stopped.

Several reasons for the failure of the abacavir/tenofovir combinations were discussed at each meeting.

- one suggestion is purely related to triple-nucleoside single target therapy as a less potent strategy, and previous studies have shown this with other combinations as well as Trizivir. Indeed, Trizivir has always had a caution in treatment guidelines that it is less potent with high viral loads. (Do guidelines not apply to patients in studies?)
- a second possibility is an inherent interaction between abacavir and tenofovir, possible at intracellular level, similar perhaps to that between AZT and d4T.
- a third factor may be several overlapping resistance profiles, compounded perhaps by other factors (ie 3TC and abacavir overlap with M184V and tenofovir and abacavir overlap with K65R)
- a fourth factor may be that these studies used once-daily abacavir and the intracellular and other data supporting this has not yet been approved by either European or US regulatory agencies.

C O M M E N T

This data has been sufficient for the European Medicines Evaluation Agency to issue it's own statement as we went to press: see Treatment Alert on page 3.

It would be important to know whether ongoing studies with Trizivir and tenofovir, or other combinations including both abacavir and tenofovir have raised similar concerns.

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3. Data from GSK presented to EATG community meeting, Paris.

Link:

Previous report of ACTG 5095 Trizivir closure:

http://www.i-base.info/pub/htb/v4/htb4-3/Trizivir.html

Nucleoside-sparing regimens

Simon Collins, HIV i-Base

The increasing link between nucleoside analogues and lipoatrophy and increased potency of ritonavir-boosted protease inhibitors have led to a number of so-called nucleoside sparing strategies, both in treatment naïve and experienced patients. Summary reports from the main studies are included below.

Many of the strategies below are not new in themselves and have usually resulted in poorer results than traditional two-nukes plus either an NNRTI or PI therapies. They are present only limited data, often from open label single arm studies.

Some of the most recently approved drugs (lopinavir/r and tenofovir) have brought expectations for antiviral efficacy to over 90% and provided durable responses and any new approaches have to at least meet this challenge – both in clinical practice and in clinical trials. The 96-week tenofovir study also presented at the meeting showed that this could be done with reduced lipoatrophy compared to d4T and both abacavir and 3TC are generally tolerable, involve a low pill count and are associated less with lipoatrophy than either of the thymidine analogues that were almost universally used and recommended previously.

In dropping both drug numbers and drug potency, certainly in treatment naïve patients, there has to be a very good advantage for why someone who can be adherent with generally more difficult to tolerate ritonavir-boosted BID regimens should be excluded from using generally more tolerable nucleosides - and so far these studies have not provided data to support this.

If you are relying on reduced numbers of drugs, it should be common sense that the drug levels achieved become that much more crucial, because you have additional antiviral activity to buffer and variability. The studies here also highlighted the importance of adequate PK – especially important given the drug-drug interactions between all PIs and NNRTIs.

It is difficult to know what to make of the boosted-indinavir monotherapy study. Patients were carefully monitored throughout and the study due to close if 2/12 patients had confirmed viral load rebound to >400 copies/ml. The results are remarkable, and compartmental penetration is considered within the study, but a patient advantage apart from reduced drug use is not clear, as tolerability of boosted PI regimens is largely related to the boosted-PI component of the therapy.

Lopinavir/r and efavirenz

Ferré presented preliminary 24-week results from the French BIKS single arm 48-week study of open-label lopinavir/r (LPV/r) and efavirenz (EFV) without nucleosides. Because of the interaction between these two drugs the lopinavir/r dose was increased to four capsules twice daily and efavirenz was given at the standard 600mg QD. [1]

Of the 86 patients enrolled, 65 were ARV-naïve and 21 ARV-experienced. Treatment-experienced patients had to be NNRTI-naïve and have fewer than five LPV/r-associated mutations. Mean baseline characteristics included CD4 cell count 307/mm3, mean viral load 4.84 log_{10} copies/ml and was >5 log in 42% of the pts.

Mean viral load reduction at week 24 was –3 logs with 87% of patients <400 cp/ml by ITT analysis and 76% reaching <50 copies/ml (Observed analysis – ITT not given). Mean CD4 increase was +162. Viral rebound occurred in four patients: two patients had blips (HIV RNA <400 cp/ml on subsequent control), one was not compliant and one had confirmed virologic failure.

After a median follow up of 36 weeks, premature discontinuation occurred in 14 pts: CNS side effects (n=3), cutaneous rash (n=3), non compliance or lost to follow up (n=3), others (n=5).

Grade 3/4 clinically relevant adverse events were seen in 34 patients (40%) including CNS symptoms (n=17), diarrhoea (n=11), cutaneous rash (n=4). Grade 3/4 hypercholesterolaemia, hypertriglyceridaemia and asymptomatic hepatic cytolysis have been observed in 29, 13 and three patients, respectively.

Median change in fasting triglycerides and total cholesterol at W24 was +0.88 and +0.62 g/l, respectively. Median increased in LDL/HDL ratio was +0.27 at W24.

Saquinavir/ritonavir plus lopinavir/r

Hellinger and colleagues reported 24 week virological and PK results from a Roche-sponsored pilot study using a dual-boosted PI combination of open label saquinavir/ritonavir 1,000mg/100mg BID together with lopinavir/r at regular dose BID in 20 PI-naïve patients. This study was again without background nucleosides, although two patients intensified treatment at week 12 by adding tenofovir dependent on protocol defined virological response. [2]

Mean baseline viral load and CD4 were 4.4 log and 274 cell/mm3 respectively. Only three women were enrolled, 40% of the patients were African-American and 85% were MSM.

Four patients discontinued (one due to hyperlipidaemia at week 36, on with GI distress at week 4. One case of none adherence and one person moved study centre). 14/16 people remaining on study medications at week 48 achieved viral suppression and two patients adding tenofovir also achieved <50 copies/ml. Plasma trough levels of lopinavir/r and all but one saquinavir level were above the IC50 for wild-type virus (70 ng/ml and 50 ng/ml respectively).

Mean weight gain was 3.9kg and occurrence of central fat accumulation was reported in 66% of the group (increased abdominal girth, and/or chest breast size) although DEXA scan was not included, with only one case of mild to moderate lipoatrophy.

Mean triglycerides increased from 231 mg/dl at baseline to 358 mg/dl, with most of the increase occurring in the first four weeks. Although the study did not report these as extreme, the majority of patients required monitoring and intervention according to NCEP guidelines.

Ritonavir-boosted indinavir plus efavirenz (with and without d4T)

Merck's approach was to use indinavir/ritonavir (dosed at 800mg/100mg BID) together with efavirenz (at 600mg QD) with or without d4T in just under 100 PI- NNRTI- and d4T-naïve patients. Around 30% of the participants were women and 70% male. Mean baseline viral load was around 4.6 log and CD4 count was lower in the d4T-receiving arm 322 –175 versus 407 –234 respectively. [3]

At week 48, by ITT analysis (NC=F) viral load reductions to <400 and <50 were achieved in 34/47 (72%) and 25/47 (53%) for nucleoside-sparing compared to 33/46 (72%) and 28/46 (61%) with additional d4T.

Side-effects for the nuke-sparing and d4T arms respectively were: drug-related (66 and 54%), nervous system (23 and 33%), psychiatric, eg depression (9 and 11%), renal colic/urolithiasis (6 and 9%), and rash (13 and 11%). Discontinuations due to

clinical and laboratory AEs were 15% and 2% for nuke-sparing and 11% and 2% for the d4T group.

Although the study concluded "at 48 weeks IDV/RTV+EFV yielded similar promising efficacy and safety data" p-values were not included in the abstract and, to this reviewer at least, including a nucleoside resulted in both increased viral suppression and fewer side effects. In a clinical setting most physicians would chose a nucleoside associated with fewer side effects.

Lopinavir/r plus saquinavir – PK and efficacy as salvage therapy

Data from using the dual boosted-PI regimen of lopinavir/r plus saquinavir (dosed at 1,000mg BID) without nucleosides (and without additional ritonavir boosting for saquinavir) was also presented from Schlomo Staszewski, this time in 63 heavily treatment experienced patients (13 women, 50 men) from the Frankfurt cohort, whose current regimen was virologically failing. A main focus of the study was intensive PK assessment, included to avoid exposure to suboptimal drug levels through drug-drug interactions. [4]

The rationale for this approach is necessarily very different because of the patient cohort, who had a median age of 42, 6.7 years antiretroviral experience and previous exposure to 10 drugs. Median baseline viral load and CD4 were 5.2 logs and 168 cells/mm3 respectively. Reductive therapy has been suggested to maintain patients with a regimen that has reduced pill burden and toxicity until newer agents become available, but also many if not all of these patients would be expected to have extensive nucleoside resistance**.**

At week 24, 52 (81%) patients were still on therapy. Median viral load was 2.1 log (range 1.0–6.0 log) and median CD4 count was 299 cells/mm3 (range 1–750). PK analysis showed that plasma concentration levels of LPV and SQV were lower in non-responders (AUCss –22%, Cmin –32%; AUCss –47%, Cmin –50%, respectively) compared to responders. Nonresponders also had lower pre-dose levels than responders: SQV 244 versus 903 ng/ml; LPV 3790 versus 4945 ng/ml.

Other factors associated with response were higher CD4 count at baseline (196 cells/mm3 versus 66 for non-responders), fewer PI mutations in the last failing regimen (two versus eight for non-responders) and less prior PI experience.

Boosted indinavir monotherapy maintains durable suppression

Finally, Humfer and colleagues reported remarkable 48-week results from stepping patients down to a single-boosted PI monotherapy by 12 patients with viral load <50 copies/ml. The rationale for the study was that boosted-PI regimens achieve drug levels that are considerable higher than the IC95 for wild-type virus. Indinavir is a drug that is known to penetrate CNS and genital compartments and plasma trough levels were optimised by TDM to 500-2,000 nM/l and adherence support confirmed with MEMS.

At baseline nucleosides were stopped and patients monitored at week two and then monthly for viral load (LQ=20 copies/ml), CD4, and activation markers (CD38 and HLA-DR), and at baseline and week 48 with DEXA. Viral load in semen was tested at baseline and weeks 24 and 48 and seminal mtDNA checked at the start and end of the study. Primary endpoint was either three consecutive viral load measurements >200 or two values >400 copies/ml within four weeks. Premature termination of the study was planned in case two patients would reach a primary endpoint.

Median pre-HAART CD4-count and viral load were 215 cells/mm3 5.0 log (3.6-6.6) respectively. At baseline, median CD4-count was 486/ml and patients had been using HAART for a mean 34 months.

None of the patients reached a primary endpoint. From a total of 138 viral load measurements, 5% were >50 copies (to between 50-100 in seven cases, to 100-200 in four cases (3/4 times was in one patient) and only once to >200 copies/ml). All increases were evenly spread throughout the 48-week study. Mean CD4 increase was 63 copies/mm3.

One patient developed T-cell lymphoma of the brain at week 24 and committed suicide at week 33. Four patients experienced nephrotoxicity despite TDM (three cases of urolithiasis and two increased creatinine).

No changes were detected from DEXA scans, and results from semen viral load and mtDNA that may offer clues for a caution or additional benefit were unfortunately not presented in the poster.

References:

1. Ferré V, Allavena C, Poizot-Martin I et al – BIKS Study (lopinavir/ritonavir plus efavirenz combination): complete 24 week results. Abstract 36.
2. Hellinger J, Cohen CJ, Morris AB et al – A pilot study of saquinavir-SGC (SQV) and lopinavir/ritonavir (LPV/r) twice daily in protease inhibitor (PI) naïve HIV-positive individuals: protease inhibitor concentrations and 24 week results. Abstract 571a**.**
3. Stek Jr M, Hirschel B, Benetucci J et al – Comparison of boosted indinavir with efavirenz plus stavudine regimens in EASIER (European and South American Study of Indinavir, Efavirenz and Ritonavir). Abstract 39.
4. Staszewski S, Dauer B, Von Hentig N et al – The LopSaq study: 24 week analysis of the double-PI salvage regimen containing lopinavir (LPV/r) plus saquinavir (SQV) without additional antiretroviral therapy. Abstract 583.
5. Hupfer M, Wagels T, Kahlert C et al – Pilot study: ritonavir boosted indinavir treatment as a simplified maintenance 'mono'-therapy for HIV infection. Abstract 589.

Dual boosted PIs in salvage therapy

Several studies reported results from dual boosted PIs in salvage setting that included additional background nucleosides.

Lopinavir/r with amprenavir requires additional ritonavir boosting

In France, Raguin and colleagues presented 48 week results of the PUZZLE 1 study (ANRS 104) which looked at an additional 200mg/day ritonavir added to different combinations that included lopinavir/r and amprenavir (with NRTIs) in heavily experienced patients on current failing therapy. [5] While the resistance profile of these two drugs make the combination of interest, both lopinavir and amprenavir levels drop when used together.

Thirty-seven of 40 patients started treatment with median baseline viral load and CD4 of 4.7 log and 207 cells/mm3 respectively. Baseline resistance profile (all median) included seven PI mutations and a phenotypic resistance index of 9.7 for LPV and 2.6 for APV. Average number of antiretrovirals taken prior to randomisation was 7.7.

Twenty-six-week data presented at last year's ICAAC showed that the additional ritonavir produced viral load reductions of –2.5 compared to –1.4 without. Twice as many patients achieved viral load < 50 copies/ml (62% versus 32%). This difference continued to remain significant for the additional ritonavir group with median viral load reduction at week 52 of –2.0 log compared to –1.1 (p=0.05). Undetectable viral load <50 copies was achieved by 39% (7/18) compared to 11% (2/18) in the two groups respectively (P=0.12).

Discontinuation of at least one of the two PIs (APV or LPV) occurred in six and eight patients and grade IV adverse events occurred in seven and 10 patients, respectively.

Ref: Raguin G, Chene G, Morand-Joubert L et al – Salvage therapy with lopinavir/r (LPV/r), amprenavir (APV) – an additional boost with ritonavir (RTV): 1-year results of PUZZLE-1 – ANRS 104 study. Abstract 585.

BMS reports on atazanavir efficacy and safety in treatment experienced patients

Graham McKerrow, HIV i-Base

Two registrational studies were presented to the conference by Bristol-Myers Squibb (BMS) researchers looking at the safety and efficacy of once-a-day doses of the protease inhibitor (PI) atazanavir (ATV, Reyataz) in patients who had experienced virological failure with prior regimens.

L Nieto-Cisneros and colleagues presented the 24-week results of the multinational BMS043 study comparing the efficacy, lipid profile and safety of non-boosted ATV versus lopinavir/ritonavir (LPV/RTV) in combination with two NRTIs in patients who have experienced virological failure with prior PI-containing regimens. [1]

The researchers report significant virological responses for both regimens with a greater decrease in RNA for LPV/RTV versus ATV (mean changes from baseline (SE), HIV RNA (log10 c/ml) –2.11 (0.09) versus –1.67 (0.08) and for CD4 (cells/mm3) +121 (14) versus +94 (13). A post-hoc analysis showed decrease in viral load was comparable between regimens in patients without nucleoside mutations at baseline. Mean lipid changes from baseline (LDL cholesterol, total cholesterol, HDL cholesterol and triglycerides) were lower for ATV (–6%, –2%, +12%, –2%) versus LPV/RTV (+5%, +17%, +18%, +55%). Incidence of side effects was comparable between regimens.

The researchers conclude: "Significant reductions in HIV RNA and robust increases in CD4 cell counts were observed in this PI-failing, ARV-experienced population. While non-boosted ATV demonstrated less antiviral efficacy than the boosted LPV/RTV regimen, ATV had a more favourable lipid profile. ATV may be an option for some ARV-experienced patients, eg, where lipid management is a priority."

R Badaro and colleagues are conducting and ongoing study of ATV/RTV, ATV/saquinavir (SQV) and LPV/RTV in combination with tenofovir (TFV) and another NRTI, in patients who have experienced virologic failure to multiple HAART regimens. The 16-week results of this multinational three-arm study of 350 patients report similar efficacy between ATV/RTV and LPV/RTV, with ATV/SQV having lower efficacy versus LPV/RTV. Mean total cholesterol and triglyceride changes from baseline were favourable for both ATV regimens compared to LPV/RTV. Adverse events were comparable among all regimens.

The researchers conclude: "In this highly ARV-experienced population, the efficacy of ATV/RTV QD is similar to LPV/RTV BID through 16 weeks. ATV, when boosted with RTV or combined with SQV, is safe, well-tolerated and with a more favourable lipid profile than LPV/RTV."

References

1. Nieto-Cisneros L, Zala C, Fessel WJ et al. Antiviral efficacy, metabolic changes and safety of atazanavir (ATV) versus lopinavir/ritonavir (LPV/RTV) in combination with two NRTIs in patients who have experienced virological failure with prior PI-containing regimen(s): 24-week results from BMS AI424-043. Abstract 117.
2. Badaro R, DeJesus E, Lazzarin A, et al. Efficacy and safety of atazanavir (ATV) with ritonavir (RTV) or saquinavir (SQV) versus lopinavir/ritonavir (LPV/RTV) in combination with tenofovir (TFV) and one NRTI in patients who have experienced virologic failure to multiple HAART regimens: 16-week results from BMS AI424-045. Abstract 118.

IAS: TREATMENT INTERRUPTIONS

Unsupervised treatment interruptions are associated with increased risk of AIDS or death

Graham McKerrow, HIV i-Base

An Italian-English study of 'unsupervised' treatment interruptions (TIs), which are common in clinical practice, concludes that TIs of 12 weeks or more are associated with clinically significant increased risk of AIDS or death. A d'Arminio Monforte and colleagues looked at 2,832 patients of the ICONA cohort starting their first HAART. Only TIs of at least 12 weeks were considered.

Over a median follow-up of 148 weeks (IQR: 78–211) 553 patients (19.5%) interrupted HAART for ‡12 weeks and 52 patients (1.8%) interrupted treatment more than once. Patients were generally well and responding well to treatment with median CD4 and viral load at TI of 528 cells/mm3 (IQR: 320–776) and 2.61 log10 copies/ml (IQR: 1.90–3.90) respectively. Over the follow up period 184 patients experienced clinical progression (167 to AIDS and 17 deaths).

The rate of clinical events of patients on therapy was 1.9 per 100 person years (pys) (95% CI: 1.6–2.2) and during TI was 8.7 per 100 pys (95% CI: 6.2–11.8). Crude rate ratio off/on-therapy: 4.55 (95% CI: 3.14–6.48, P=0.0001). In Cox model, TI (RH=2.54 versus continued therapy; 95% CI: 1.54–4.20, P=0.0003), CDC stage B and C versus stage A (RH=1.76; P=0.007 and RH=2.34; P=0.0001), and higher pre-therapy viral load (RH=1.37 per log10 copies/ml higher; 95% CI: 1.12–1.66, P=0.002) were associated with higher risk of progression.

Patients with higher CD4 nadir (RH=0.89 per 100 cells/ml higher; P=0.03), with a greater latest CD4 increase on therapy (RH=0.76 per 100 cells/ml greater increase above nadir; P=0.0001) and with greater latest VL suppression (RH=0.72 per log10 copies/ml greater suppression below pre-therapy; P=0.0001) were at lower risk.

Ref: d'Arminio Monforte A, Cozzi-Lepri A, Murri R et al. The effect of HAART interruptions on clinical progression: evidence from ICONA cohort. Abstract 145.

IAS: SIDE EFFECTS

Uridine as a potential treatment for NRTI related mitochondrial toxicity

Paul Blanchard, HIV i-Base

An intriguing in vitro study was presented at the 2nd IAS Conference in Paris evaluating the potential of uridine to prevent and treat nucleoside reverse transcriptase inhibitor (NRTI) related mitochondrial toxicity. A preliminary pharmacokinetic study was also reported on an extract of sugar cane, which may be used in humans to raise plasma levels of uridine.

Human hepatocytes (HepG2) were exposed in vitro to NRTIs with or without uridine for 25 days and cell growth, lactate production, intracellular lipids, mitochondrial DNA (mtDNA) and the respiratory chain subunits (mtDNA-encoded: COX II, nucleus-encoded COX IV) measured. Uridine serum levels were also followed in individuals for 24 hours after a single dose (36 grams) of Mitocnol, a new dietary supplement derived from sugar cane.

HepG2 cells exposed to 177nM of zalcitabine (ddC) without uridine developed a severe depletion of mtDNA and of COX II. ddC induced a severe reduction of cell proliferation (to 20%), a severe intracellular steatosis and an increase of lactate (350% of untreated control). Uridine fully normalised cell proliferation, lactate and intracellular lipids by adjusting mtDNA-levels to about 65% of NRTI-unexposed control cells. These effects were dose-dependent and maximal at 200mM of uridine. Uridine also rapidly and fully restored cell function despite continued ddC exposure, when added to cells displaying severe mitochondrial dysfunction. Similar results were found in HepG2 cells exposed to stavudine (d4T) but not to didanosine (ddI). Uridine also fully abrogated the increase in lactate and all the cell toxicity of the combination of zidovudine (ZDV) and lamivudine (3TC). All tested concentrations of uridine did not alter the IC50 or IC90 of NRTIs in HIV-resistance assays, suggesting a lack of interference with the intracellular activation, uptake or interaction with HIV reverse transcriptase.

The pharmacokinetic studies revealed that protective uridine levels could be achieved in human serum by oral Mitocnol, an extract from sugar cane, rich in nucleosides. Side effects were not noted.

The researchers concluded that uridine fully abrogates mitochondrial toxicity by NRTI-pyrimidines in a preventive and therapeutic setting and does not appear to interfere with the antiretroviral efficacy of NRTIs. They went on to state that protective levels of uridine could be achieved in humans with Nucleomax^{XT}M, a new dietary supplement containing the sugar cane extract Mitocnol.

Ref: Walker UA, Koch E, Venhoff N et al. Uridine prevents and treats mtDNA-depletion by NRTI pyrimidine analogues and fully restores mitochondrial function. Abstract 745.

Long term exposure to nucleoside analogues and peripheral nerve function

Paul Blanchard, HIV i-Base

Distal sensory peripheral neuropathy (DSPN) is the most common neurological dysfunction experienced by patients with HIV-infection. It is complex in that it may be caused by HIV-infection itself and some antiretrovirals used to treat HIV-infection that may themselves be neurotoxic. It manifests as tingling, burning and other paraesthesias predominantly affecting the feet but also involving the hands in more advanced cases and may be extremely disabling. DSPN is a die back neuropathy of the sensory peripheral nerves whose pathophysiology remains ill defined. Treatment is predominantly symptomatic with analgesics, anticonvulsants and antidepressants often with disappointing levels of efficacy.

This study presented at the 2nd IAS meeting in Paris used quantitative sensory testing (QST) and electrophysiological testing of peripheral nerves to determine infra-clinical alterations of small peripheral nerve fibres in patients who had been exposed long term to nucleoside reverse transcriptase inhibitors (NRTIs). The usefulness of capsaicin topical application for developing optimal QST of heat pain sensation was also evaluated as an additional method to determine the loss of small afferent fibres.

A case control study was performed of 32 patients with HIV-infection who had been exposed to NRTIs for more than 60 months and with mild to moderate symptoms of lipodystrophy. Fourteen untreated HIV-infected or seronegative subjects matched for age and sex were used as case controls.

Nerve conduction velocities and electromyographic examination was performed on both upper and lower limbs. Distal motor latency and motor nerve conduction was also determined on peroneal and median nerves. QST was carried out on the dorsum of the feet in all subjects. Both detection and pain thresholds were determined using nylon calibrated von Frey hairs. Thermal thresholds were tested using standardised thermal sensory testing equipment. Capsaicin was applied to a patch of skin on the dorsum of the foot and thermal stimuli used 15 minutes later in order to produce local activation of c-fibre nociceptors and compared to an untreated area of skin on the contralateral foot. Subjects judged the magnitude of pain sensations on a visual analogue scale (VAS).

Overall the mean duration of exposure to NRTIs was 86.9 months in the 32 patients. Mean CD4 cell count at the time of QST was 619 cells/mL and mean plasma HIV RNA was 5,335 copies/mL. Sensory symptoms in the distal part of the limbs was reported by six patients (19%) the remainder being asymptomatic.

Results of VAS responses to thermal stimuli after capsaicin stimulation showed that NRTI exposed patients experienced less pain compared to the matched controls (mean VAS 0.5 Vs. 1.6, p=0.008). Twenty-one patients (65%) reported no sensory pain (VAS=0) after capsaicin application versus two controls (1.4%).

No correlation was observed between VAS responses and duration of HIV-infection, between VAS responses and plasma viral load or CD4 count at time of QST, or between VAS responses and global duration of exposure to NRTIs.

The researchers concluded that this study demonstrates that HIV-infected patients who are durably exposed to NRTIs show infra-clinical alterations of small peripheral nerve fibres. This adds to the data already accumulated using skin biopsy to assess intraepidermal nerve fibre density, which shows a loss of nerve fibre density in HIV-related DSPN correlated to both symptoms and QST.

They go on to hypothesise that increases in detection and pain thresholds for thermal stimuli demonstrated in both this and previous studies are probably linked to mitochondrial dysfunction induced by a durable exposure to NRTIs and propose to investigate this link by examining the depletion of mtDNA in PBMCs or in SAT.

The researchers further propose that QST after the topical application of capsaicin may be a useful, non-invasive and sensitive method to detect small fibre sensory neuropathies that are not currently well assessed by standard electrodiagnostic studies.

Ref: Jarrousse B, Bouillaguet S, Letoumelin PH et al. Assessment of small peripheral nerve fibres alterations in HIV-infected patients exhibiting lipodystrophy symptoms after long-term exposure to nucleoside reverse transcriptase inhibitors (NRTIs). Abstract 209.

Step-wise intervention eases diarrhoea linked to PI nelfinavir (Viracept) therapy

Michael Smith, HIVandHepatitis.com

Nelfinavir (Viracept) is an HIV protease inhibitor that produces potent and durable activity against HIV when used in combination with other antiretroviral drugs. However, nelfinavir has also been associated with diarrhoea, a limiting side effect of the drug.

Now a simple stepwise programme can help physicians and patients manage the diarrhoea associated with nelfinavir in HIV patients, a Canadian study shows.

The programme can significantly improve symptoms and quality of life, said Anita Rachlis MD, of Sunnybrook and Women's College Health Sciences Centre, in Toronto, Ontario, where the programme was developed. She presented the findings at

the 2nd International AIDS Society Conference on HIV Pathogenesis and Treatment.

"We know that nelfinavir is associated with a lot of diarrhoea," Dr Rachlis said, adding that a survey of eight Canadian clinics revealed "haphazard" treatment patterns. Some physicians prescribed loperamide, some calcium carbonate, and still others suggested psyllium, she said.

The diarrhoea management algorithm, Dr Rachlis said, begins with a three-day washout period in which patients stop any anti-diarrhoea medication they may be using. The idea is to avoid confounding factors and to ensure there is no cause of diarrhoea other than the nelfinavir.The washout period is followed by nutrition consultation, which may include suggestions for dietary changes. The patient may be given lactase (if lactose-intolerance is the issue) or psyllium.If previous efforts have failed, the patient is given 1,500 mg of calcium carbonate twice daily, which can be boosted to 2,500 mg if there is no relief within a few days.

The final step - if the patient still has diarrhoea - is 4 mg of loperamide once daily, plus 2 mg additional doses at the patient's discretion (to a maximum of 16 mg per day.)

The study enrolled 18 patients, Dr Rachlis said, which was fewer than expected, possibly because some potentially eligible patients switched medications, while others may have found their own way of managing diarrhoea.

The study showed statistically significant reductions in frequency of bowel movements, as well as statistically significant improvements in stool consistency, Dr Rachlis said. As well, a quality of life follow-up after nine weeks of the programme showed significant improvements in such measures as dysphoria, overall function, worry over disclosure of HIV status, sexual function, and worries about medication.

Dr Rachlis concluded that the study had found "an algorithm that patients can actually use to deal with diarrhoea related to nelfinavir."

Ref: Rachlis A et al. Step-wise intervention for the management of nelfinavir-associated diarrhoea. Abstract 747. Source: HIVandHepatitis.com

IAS: IMMUNOLOGY AND IMMUNOTHERAPY

First results from ESPRIT study: CD4 response to IL-2 is associated with higher nadir and baseline CD4 and younger age

Graham McKerrow, HIV i-Base

Preliminary results of the multinational ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomised International Trial) showed that CD4 cell count response after the first three cycles of IL-2, used in addition to HAART in patients with baseline CD4 counts >300 cells/ml, at month eight, is associated with higher nadir CD4 count, higher baseline CD4 and younger age.

Of the 1,142 patients who completed three cycles of IL-2 by month eight, 9% were classified as 'non-responders' because they had CD4 counts below their baseline values. There were 4.6% who had a small increase of less than 50 cells/mm3, and 22.4% who had an increase of between 51 and 200 cells/mm3. The remaining participants, almost 70%, were classified as 'responders' because they had an increase of at least 200 cells/mm3 but 27% did not reach the predefined primary endpoint goal, defined as a doubling of the baseline CD4 count or reaching 1,000 cells/mm3 (whichever is lower) and 36% did.

The following factors were associated with CD4 response (>200 cell/mm3 increase or above CD4 goal at eight months): higher nadir CD4 ($P<0.001$), higher baseline CD4 ($P=0.02$), and younger age ($P=0.03$). Odds of response increased by 28% and 11% respectively, for a higher nadir and baseline CD4 count of 100 cells/mm3, and by 19% for 10-year younger age. There was no evidence of an association with viral load <500 copies/ml, hepatitis C or B status, time on antiretroviral therapy, prior progression of disease or gender

Ref: Weiss L, Aboulhab J, Babiker GA et al. Preliminary results of ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomised International Trial): baseline predictors of CD4 T-cell response to Interleukin-2. Abstract 13.

C O M M E N T

Results from this large international study, which has recruited almost 4,000 patients and will follow them for five years, provides evidence that IL-2 can significantly boost CD4 levels in a majority of patients.

It is a concern that almost 10% of patients saw their CD4 count drop and 5% had an increase of less than 50 cells/mm3 given that these

patients are also on background HAART regimens, and also given the significant side effects associated with the weeks when IL-2 is taken.

Data were not presented from the control arm of the study randomised to continue HAART without IL-2.

Lessons learned from early HAART in acute HIV infection

Ross Hewitt, HIVandHepatitis.com

Dr Bruce Walker from Boston discussed his small but provocative cohort of 14 patients who were treated after identification of very early HIV infection (within 90 days). He had previously reported that early treatment of acute HIV infection augments T helper cell responses. In early stages, CD4 cells get activated and infected and rendered dysfunctional. HIV also preferentially infects HIV specific CD4 cells. But, does early treatment enhance immune control?

After initial control, his protocol called for interruptions of HAART followed by restarting it if the viral load rose to greater than 5,000 and interrupting again after viral control was re-established. Three of eight patients went on to control after the first interruption, and have remained off HAART. One patient developed an HIV superinfection and lost viral control but prior to that had controlled the initial HIV infection. For most patients, there is a slow, stepwise loss of control over time that enables them to remain off therapy, some for more than two years. What kind of immune responses are seen?

After treatment interruptions, CD8 cell responses recognise more than 25 epitopes (pieces of HIV) compared to before interruption when only two epitopes are recognised. Only three of 11 patients in follow up were able to control HIV for 1,000 days off therapy and they continue off therapy with viral load <3,000 copies/ml.

When compared to MACS data for progression, 50% of these patients meet the viral parameters of the lowest 25% of the MACS cohort, suggesting that some benefit may be occurring. Genetic factors may also be important. Patients who are HLA B27 positive are more likely to control acute HIV infection and be asymptomatic during acute infection.

The bottom line is that the results of this cohort are intriguing, but do not provide definitive evidence of a significant effect of early treatment with STI.

Ref: Walker BD. Prospects for immunotherapy of HIV infection. State of the art talk. Session 12 . Abstract not submitted.

Source: HIVandHepatitis.com

CD4 cell reconstitution is significantly slower in older patients

Graham McKerrow, HIV i-Base

An analysis of 2,614 antiretroviral naïve people under 50 years of age, and 401 over that age, who started on HAART in France between 1997 and 2001, reveals that patients over 50 exhibit an immune response after HAART, but that their CD4 cell reconstitution was significantly slower than in younger patients. The researchers conclude that this may explain why older patients have a higher risk of clinical progression.

Using information from the French Hospital Database on HIV, patients were divided into two groups: over and under 50. Among patients with baseline HIV viral load below 100,000 copies/ml, in the first six months the CD4 count increase was +17.3 cells/month in the younger group, versus +14.1 cells/month in the older group and thereafter was +11.1 cells/month in the younger group, versus +9.8 cells/month in the older group. Among patients with baseline viral load over 100,000 copies/ml, it was respectively, +42.9 versus +36.9 cells/month in the first six months versus +17.9 cells/month +15.6 cells/month thereafter. All these differences were highly statistically significant (all = $p<0.0001$).

Within a median period of time of 31.5 months, 263 patients had a new AIDS-defining disease and 44 patients died. After adjustments for baseline characteristics, the hazard ratio of clinical progression was significantly higher in the older group as compared with the younger group: HR=1.52, IC95=1.1–2.00.

Ref: Grabar S, Kousignian I, Sobel A et al. Immunological and clinical responses to HAART over 50 years of age, results from the French Hospital Database on HIV. Abstract 85.

IAS: PHARMACOLOGY

Pharmacology studies at the 2nd IAS conference

Ross Hewitt, HIVandHepatitis.com

The 2nd IAS Conference in Paris featured a session on pharmacology that included data on drug transporters and drug metabolism enzymes, the impact of race, gender and co-infections on pharmacology, gender differences in saquinavir concentrations, pregnancy and nelfinavir, and more.

- Drug transporters and drug metabolism enzymes
- Impact of gender, ethnicity and co-infections on antiretroviral pharmacology
- Gender differences in saquinavir concentrations
- Plasma nelfinavir concentrations are significantly lower in pregnancy
- Multidrug resistance transporter in placentas from HIV infected mothers
- MDR and CYP polymorphisms in South Africa

Drug transporters and drug metabolism enzymes

Dr Charles Flexner from Baltimore led the session off by stating that pharmacologists view the body as one big drug metabolising entity. [1] However, this approach does not answer all of the questions that face us. Greater understanding of drug metabolism has come with the discovery of xenobiotic response elements (XREs).

These are genetic binding sites for drug-drug transporter complexes that then induce transcription and ultimately protein synthesis of drug metabolising enzymes. Xenobiotics are foreign substances that our bodies recognise and then attempt to detoxify, treating them as if they were dangerous. An example is induction of cytochrome P450 enzymes (CYP 450) by protease inhibitors (PIs).

How is expression of CYP 450 regulated? At first it was thought that increased transcription was responsible. Drugs bound to a pregnane X receptor (PXR) bind to a retinoid X receptor, which then bind to the transcription XRE. Cell lines that we use to predict drug interactions may not express PXR and thus may not be helpful.

XREs are not only linked to CYP 450 3A4 but also linked to CYP 2D6, GST gene, MDR1 (the P-gp gene), and OATP - a variety of enzymes important for drug transport and metabolism. These have evolved as a result of encountering toxic substances in nature in an effort to survive. This explains how one drug can upregulate many enzyme systems. There are other mediators of pathways such as vitamin D, and bile acids. These provide additional complexity and redundancy in eliminating foreign substances

- Amprenavir (APV) is a moderate CYP 3A4 inhibitor and inducer, ritonavir (RTV) is a major inhibitor and moderate inducer.
- Lopinavir (LPV) may have some effects as well.
- APV and LPV/RTV (Kaletra) have a significant but unpredicted drug interaction. APV trough concentrations increased 4.6 fold versus APV alone, while LPV and ritonavir concentrations decreased by 38% when given in standard doses together. Why does this happen?
- APV induces clearance of RTV. Less RTV means less inhibition of LPV clearance. Possible fixes: give more RTV or increase the LPV/RTV dose.
- Increasing ritonavir did result in a better viral load response in one study.
- One study at this meeting showed that giving five LPV/RTV capsules or three LPV/RTV capsules + two extra RTV capsules twice daily both gave higher LPV levels than standard LPV/RTV. [2]

Some PIs may interfere with RTV's interaction with PXRs was shown with saquinavir (SQV). Because SQV is not an inducer, the interaction would not have been predicted on knowledge of CYP 3A4 alone.

RTV inhibits rifampin induction of PXR/XRE binding. In the absence of ritonavir, a substantial reduction with rifampin alone occurs. When adding RTV, a reduction in the rifampin effect occurs. St Johns wort has been shown to bind and activate PXR, and explains why it is a CYP 3A4 inducer.

Can RTV be given once a day (steady state elimination half-life of three hours)? He studied RTV and SQV given one daily dose every 48 hours. If you give SQV first, four hours before RTV you get very low SQV levels; however, 48 hours later, after the last RTV 400mg dose, SQV concentrations increase 20 to 30 fold. This appears to be a mechanism that provides a rationale

for once daily dosing of boosted PIs.

Finally, there are polymorphisms in these systems, the XREs as well as the genes themselves, that may be the target of future pharmacogenomics studies.

Impact of gender, ethnicity and co-infections on antiretroviral pharmacology

Professor David Back from Liverpool summarised the data on three factors that may influence HIV pharmacology. There is a balance between environmental factors and our own host genetics that interact to create a steady drug level. [3] In patients, PI and other levels can vary quite widely for the same dose. For example, with nelfinavir (NFV) we see a large range of concentrations, and a marked inter-individual variability exists.

Gender differences do exist. Bioavailability is better in females. Males and females have differences in protein binding, distribution of lipophilic and nonlipophilic drugs and glomerular excretion (kidney function). In a Thai study of SQV pharmacokinetics (PK), on average men had a 12 kg higher body weight, with higher SQV concentrations seen with lower weights. There is also a hint of increased LPV concentrations in women. Within a cohort in Liverpool monitored with therapeutic drug monitoring (TDM), women have higher concentrations as a population then men. Atazanavir (ATV) concentrations are also increased by 20% in women. Women also have 20% higher nevirapine (NVP) and 30% higher efavirenz (EFV) concentrations than men in more than one cohort data set. There is an independent effect of gender above and beyond weight.

Pregnancy has effects on drug concentrations as well. In the third trimester, lower indinavir (IDV) concentrations have been observed. SQV levels in pregnancy in the third trimester were also lower than predicted. TDM might be useful in pregnancy to adjust levels, especially as the pregnancy progresses.

Ethnicity encompasses genetic and environment factors. There are ethnic differences in drug metabolising enzymes. Poor metabolisers using CYP 2C19 have been in observed in Chinese subjects to a much greater extent (13% versus 3%) for other Asian ethnicities. CYP 3A4 has also had ethnic differences definitively identified due to genetic polymorphism. Differences have been shown for the MDR1 genotypes T/T versus C/T versus C/C, a difference between Caucasians and Africans exists. Differences were also seen between Malaysians, Chinese and Asian Indians. Black subjects had lower levels than whites in a US study of LPV. There is also a trend of lower clearance of NVP in Blacks. It is impossible to generalise and we need individual drug data to adequately guide treatment and dosing decisions.

Herbal medicines can potentially interact with antiretrovirals, such as aloe vera, cat's claw, echinacea, garlic, milk thistle, St John's wort, and vitamin E, all have potential interactions with HIV medications and antiretrovirals.

Viral co-infection also plays a role in drug metabolism and elimination. Overall, hepatitis C virus (HCV) infected patients had a 50% increase in exposure to NFV, while HCV patients with cirrhosis had a 3-fold increase in exposure. NVP PK also suggest high levels in association with hepatotoxicity. Clearly pharmacologic issues need to be applied to optimise therapy.

Gender differences in saquinavir concentrations

Dr Courtney Flexner from Minneapolis reported gender differences seen in ACTG 359. [4] This was a salvage study that paired SQV with RTV or NFV and combined the dual PI with delavirdine (DLV) or adefovir (ADV) or both. The study was conducted over 24 weeks with an optional 24-week extension. Patient demographics were 53% white, 27% black, 17% Hispanic. SQV median exposures and trough concentrations were higher with RTV and with NFV.

However, unexpectedly ADV decreased SQV levels. Overall, female concentrations were about 25% higher than male concentrations. Week 16 virologic response was associated with higher drug exposure and women also had a greater response rate, reaching undetectable viral loads almost twice as often as men. When accounting for levels, gender dropouts and the levels remain significant predictors of response.

The interaction of SQV and ADV appears to be similar to the atazanavir and tenofovir interaction that has recently been reported. There was a contribution of body weight to higher concentrations with lower weight leading to higher concentrations, however, even when this is taken into account, sex differences still occur. This might be explained by men having a higher concentration of P-gp, the drug transporter, and thus they are pumping the drug out of the cells at a higher rate.

Plasma nelfinavir concentrations are significantly lower in pregnancy

Amsterdam researchers studied NFV PK in pregnancy. [5] Pregnancy induces changes, such as induction of liver metabolism, increase in total water and fat, glucocorticoid levels increase and increased gastrointestinal transit time. Low NFV concentrations have been associated with higher risk of virologic failure. They compared 27 pregnant women with 48 nonpregnant women. Pregnant women were younger in age. Levels were measured during all trimesters. Nonpregnant women had slightly less viral load suppression and slightly higher incidence of hepatitis C (15 versus 0%). NFV levels were 65% lower in the pregnant women. All potential confounders could not be accounted for. Protein binding may change as well. Luckily, the low levels of NFV did not result in either virologic failure or infection in their newborns; however, this finding should raise concern regarding the use of NFV in pregnancy and the potential need for TDM while doing so.

Multidrug resistance transporter in placentas from HIV infected mothers

French investigators studied drug transporter p-glycoprotein (P-gp) in the placenta. [6] P-gp is located on the maternal side of placental cells. They measured MDR1 transcripts (a surrogate for P-gp levels) in the placentas of 28 HIV-negative and 24 HIV-positive women. They isolated chorionic villi from placentas immediately after giving birth. A 3-fold increase in MDR1 expression was seen compared to uninfected women. The increased P-gp levels might result in lower foetal exposure and allow mother to child transmission. This information provides more support for measuring drug levels in pregnant women.

MDR and CYP polymorphisms in South Africa

Researchers from Durban studied genetic differences in South Africa. [7] P-gp is encoded for by the MDR-1 gene. It traverses the cell membrane, allowing it to pump drugs out of the cell. MDR-1 gene can be measured with the SNP at exon 26 (C3435T) polymorphism and it is associated with differential expression of P-gp. P-gp expression is greater in the CC genotype, less in TT and in between in CT group.

CC genotype patients have lower intracellular levels of drugs. CYP 3A4 1B polymorphisms have been linked to decreased metabolism. They studied African, Indian and Caucasian patients from South Africa. Africans had higher CC genotype incidence, Indians had higher CT genotype and Caucasians had higher TT genotype.

These results suggest that antiretroviral drug levels, and thus successful outcomes, could differ in these different ethnic populations.

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7. Chelule PK, Mosam A, Gordon M et al. Preparing for HIV-1 therapy in South Africa: will host polymorphisms in MDR1 and CYP3A4 influence therapeutic outcome? Abstract 131.

Source: HIVandHepatitis.com

IAS: OPPORTUNISTIC INFECTIONS

Studies highlight problems of rectal disease in HIV-positive patients

Graham McKerrow, HIV i-Base

Two studies highlighted the problems of rectal disease in HIV-positive patients, with one study showing anal infection by Human Papillomavirus (HPV) to be almost universal in men infected with HIV. The second study concluded that routine rectal Pap screening is feasible and warranted as part of HIV primary care.

Fortin and colleagues in Montreal, Canada, and at Roche Molecular Systems in California, USA, found anal HPV DNA in 135 (97.8%) of 138 anal samples from 113 men. [1] They also found that anal HPV infection was often caused by multiple HPV genotypes and that high-grade anal intraepithelial lesions (AIN) contained a greater burden of different types.

The most frequent genotypes identified were types 16, 6, 52, 45 and 18 found in 58, 47, 52, 45 and 18 men respectively. Of the newer types studied, four were detected in at least 20 specimens (types 61, 70, 73, 84). HPV-57 was the only type undetected in the cohort. Of 90 men with anoscopy results, 36 were normal, 36 had AIN grade I, and 18 had AIN grade II-III on biopsy. HPV-16 was detected in 12 (33%) of 36 normal men versus 11 (61%) of 18 men with AIN II-III (P=0.05).

All 18 men with high-grade AIN were infected with at least one oncogenic HPV type. A greater number of oncogenic types were identified in specimens from men with high-grade AIN (median of 4, range of 0–9) than normal men (median of 2,5, range of 0–6) (P=0.04, Mann-Whitney).

Norton and colleagues at the Boriken Community Health Centre in East Harlem, New York, recommend routine rectal Pap screening as part of HIV primary care medicine. They say their data support the findings of other groups that have identified a significant prevalence of rectal dysplasia and anal squamous intraepithelial lesions (SIL) among HIV-positive patients, and

conclude from the results of their study that the course of rectal disease among HIV-1 infected patients needs additional characterisation. [2]

Their ongoing study of 115 patients, mostly Latino Hispanic subjects and Black/African Americans, found that 70 (69%) were negative for malignant cells.

Thirty-four patients (30%) were found to have some level of rectal dysplasia. In two patients (1.7%) an inadequate sample was reported by pathology. They found the following levels of rectal dysplasia: five patients had high grade lesions and SIL grade III; seven patients had moderate dysplasia and SIL grade II; 12 patients had mild dysplasia and SIL I; and 14 patients had atypical squamous cells of undetermined significance.

References

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TREATMENT ACCESS

Appointment of industry executive to supervise US AIDS initiative provokes criticism

US President George W Bush has appointed Randy Tobias, former CEO and now Chairman Emeritus of Eli Lilly & Co, one of the world's leading pharmaceutical companies, to supervise America's multi-billion dollar international AIDS initiative.

The appointment has provoked immediate criticism for giving such a senior government role to a high-ranking industry figure amid international arguments over whether public money should spent on generic drugs or on more expensive branded drugs produced by the leading drug companies.

"This decision is another troubling sign that the President may not be prepared to fulfill his pledge to take emergency action on AIDS," said Dr Paul Zeitz, Executive Director of the Global AIDS Alliance. "This raises serious questions of conflict of interest and the priorities of the White House. Both the people of Africa and the people of the United States will lose if the President's AIDS initiative fails to use the lowest-cost, generic medications. Africans will be left with less medicine and more will die."

"We call on the Senate to carefully scrutinise this nomination. Senators from both sides of the aisle should fully investigate the continuing relationship between Mr Tobias and the pharmaceutical industry. Hard questions need to be asked about whether Mr Tobias will continue the Bush Administration's policy of blocking access to lowest-cost generic medicines for the poorest nations."

The Washington Post reports that Tobias and Lilly have been major donors to the Republican Party and to Bush's election campaign in 2000. Later this month, Tobias is scheduled to host a $5,000-per-person dinner for former US budget director Mitch Daniels, a former Lilly executive who is now running for Governor of Indiana.

The White House, after intervention by the pharmaceutical industry, was the only holdout blocking a WTO agreement to allow generic antiretrovirals to be imported into nations facing public health emergencies. The White House position went against the instructions of Congress in the fast-track legislation to respect the Doha Declaration on TRIPS and Public Health.

Patented AIDS medicines can cost upwards of $10,000 per patient each year even though generic prices have dropped to less than a dollar a day. Africa is still waiting for access to medicine to treat AIDS and other infectious diseases.

Source: Global AIDS Alliance

http://www.globalaidsalliance.org

The Global AIDS Alliance has posted on its website a report that reviews the president's unfulfilled promises related to the global AIDS epidemic:

http://www.globalaidsalliance.org/pledge_briefing.html

ANTIRETROVIRALS

T-20 launched in UK

Following approval in the EU on 28 May, T-20 (enfuvirtide, Fuzeon), was launched in the UK on 3 July 2003. It is the first of a new class of entry inhibitors, and results from studies in treatment experienced patients have been closely reported previously in HTB.

Links:

EMEA European Public Assessment Reports

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

Roche press release

http://www.roche.com/med-corp-detail-2003?id=990&media-language=e

Enfuvirtide (T-20): predicting success and modelling survival benefits

http://www.i-base.info/pub/htb/v4/htb4-1/Enfuvirtide.html

US guidelines updated

The latest update of the US Department of Health and Human Services (DHHS) guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents, was released on 14 July.

These guidelines run to around 40 pages of text, 40 pages of tables and 14 pages of references.

Very usefully, changes to the previous guidelines are highlighted throughout the document in yellow. Although dated July 2003 they do don't include recommendations for the recently approved atazanavir and emtricitabine.

This document can be downloaded as a pdf or html file from:

http://www.aidsinfo.nih.gov/guidelines/default_db2.asp?id=50

US approval of FTC (emtracitabine)

On 2 July, the US Food and Drug Administration (FDA) announced the approval of FTC (emtricitabine, trade name Emtriva), a new nucleoside reverse transcriptase inhibitor (NRTI) to be used in combination with other antiretroviral agents for the treatment of patients with HIV infection.

The recommended dose of FTC is one 200 mg capsule daily, with or without food.

The FDA based its approval on data from two 48 week clinical trials. The first trial was a double-blind, active-controlled multicentre study comparing FTC (200 mg once daily) administered in combination with didanosine and efavirenz versus stavudine, didanosine and efavirenz in 571 antiretroviral naïve patients. The proportion of patients who achieved and maintained confirmed HIV RNA < 400 copies/mL (< 50 copies/mL) through week 48 was 81% (78%) for the FTC, didanosine and efavirenz group versus 61% (59%) for the stavudine, didanosine and efavirenz group, respectively. The mean increase from baseline in CD4 cell count was 168 cells/mm3 for the FTC arm compared to 134 cells/mm3 for the control arm.

The second trial was an open-label, active-controlled multicentre study comparing FTC to lamivudine, in combination with stavudine or zidovudine and a protease inhibitor or NNRTI in 440 treatment experienced patients who were on lamivudine-containing triple-antiretroviral drug regimen for at least 12 weeks prior to study entry, and had HIV-1 RNA < 400 copies/mL. The proportion of patients who achieved confirmed HIV RNA < 400 copies/mL (< 50 copies/mL) through week 48 was 77% (67%) for the FTC group versus 82% (72%) for the lamivudine group. The mean increase from baseline in CD4 cell count was 29 cells/mm3 for the FTC arm compared to 61 cells/mm3 for the lamivudine arm.

The most common adverse events that occurred in patients receiving FTC with other antiretroviral agents in clinical trials were headache, diarrhoea, nausea, and rash, which were generally of mild to moderate severity.

Approximately 1% of patients discontinued participation in the clinical studies due to these events. With the exception of skin discoloration, which was reported with higher frequency in the FTC treated group all other adverse events were reported with similar frequency in FTC and control treatment groups.

Skin discoloration, manifested by hyperpigmentation (excess pigmentation) on the palms and/or soles, was predominantly observed in non-Caucasian patients.

The mechanism and clinical significance are unknown.

It is recommended that all patients with HIV be tested for the presence of chronic hepatitis B virus (HBV) before initiating antiretroviral therapy.

FTC is not indicated for the treatment of chronic HBV infection and the safety and efficacy of FTC have not been established in patients co-infected with HBV and HIV. "Flare-ups" of hepatitis B, where the illness can return in a worse way than before, have been reported in patients after the discontinuation of FTC. Patients co-infected with HIV and HBV should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment.

As with other NRTIs, FTC may cause lactic acidosis (buildup of an acid in the blood), serious liver problems called

hepatotoxicity, with liver enlargement (hepatomegaly) and fat in the liver (steatosis).

Source: Gilead Sciences PR
http://www.emtriva.com/

C O M M E N T

FTC has had such a long development programme that its final approval has taken many people by surprise. This one-tablet-a-day drug has a very long plasma and intracellular half-life that may provide protective dosing even in the event of missing a single daily dose. It can be taken with or without food.

On 24 July, the CPMP (the scientific committee of the European Medicines Evaluation Agency) recommended granting marketing authorisation for FTC in Europe and full approval usually takes an additional four months.

This is a drug that should therefore be available in the UK later this year.

RESISTANCE

Resistance summary of new PIs: atazanavir and tipranavir

From PRN Notebook

The following useful summary is taken from 'Understanding Treatment-Resistant HIV' by Veronica Miller, Richard Haubrich and Daniel R Kuritzkes, published in the June 2003 issue of PRN Notebook. The full article can be assess online at:

http://www.prn.org/prn_nb_cntnt/vol8/num2/miller_haubrich_kuritzkes_frm.htm

Atazanavir

Bristol-Myers Squibb's atazanavir (BMS-232,632) is a semi-symmetrical azapeptide protease inhibitor. On13 May, the FDA's Antiviral Drug Advisory Committee recommended that atazanavir be approved. The drug is expected to be approved in June at a dose of 400mg—two x 200 mg tablets once a day with food.

Atazanavir has had an optimistic showing in clinical trials reported to date. For starters, there have been a number of reports indicating that patients receiving atazanavir-based regimens in clinical trials have not experienced significant increases in triglyceride or cholesterol levels - an encouraging observation in light of the metabolic complications that have been seen in patients taking any of the currently approved protease inhibitors. In terms of its effectiveness, a pair of phase II clinical trials comparing atazanavir and two NRTIs to nelfinavir and two NRTIs found that both regimens yielded comparable results (Cahn, 2001; Sanne, 2001). And in a phase III study reviewed in the March 2003 issue of the PRN Notebook, an atazanavir-based regimen was comparable to an efavirenz-based regimen in terms of HIV-RNA suppression and CD4+ cell count increases after 48 weeks (Squires, 2002).

Important data regarding atazanavir's resistance profile were reported by Dr Richard Colonno of Bristol-Myers Squibb at the XI International HIV Drug Resistance Workshop (Colonno, 2002). Dr Colonno's group reviewed data involving 76 isolates obtained from patients who were failing an atazanavir-based regimen in clinical trials. Seventeen of these patients had evidence of resistance to atazanavir, nine of whom were treatment-naïve prior to receiving atazanavir. The remaining eight patients were antiretroviral-experienced and were combining atazanavir with another protease inhibitor, most notably saquinavir (Fortovase).

A novel mutation˜I50L˜was identified in 8/9 resistant isolates from the patients who were initially naïve to antiretroviral therapy. Five of these eight patients also carried the A71V mutation. Interestingly, viruses carrying I50L remained susceptible or showed hypersusceptibility to other protease inhibitors, particularly amprenavir. It was also demonstrated that I50L substantially reduced viral RC and that the addition of the A71V mutation partially restored RC.

In the antiretroviral-experienced patients who took atazanavir in combination with saquinavir, the I50L mutation was not observed. Instead, the I84V mutation was documented, which ended up conferring broad cross-resistance to almost all of the protease inhibitors (with the exception of amprenavir, which is not affected by the I84V mutation).

The observed mutation at codon 50 in the protease gene is intriguing. Patients taking amprenavir who develop a different mutation at the same codon ˜I50V˜ develop resistance to amprenavir but remain susceptible to other protease inhibitors,

including atazanavir. Conversely, an I50L mutation that arises during therapy with atazanavir results in hypersusceptibility to amprenavir. “We’re talking about a tiny difference between a leucine substitution and a valine substitution,” Dr Kuritzkes explained. “It appears that atazanavir and amprenavir select for drug resistance mutations by mutually exclusive pathways. There’s a dichotomous relationship at work here.”

Tipranavir

Tipranavir is a nonpeptidic dihydropyrone, a new class of protease inhibitors believed to have greater flexibility in conforming to enzyme variants resistant to current protease inhibitors. The compound was originally developed by Pharmacia & Upjohn and has since been taken over by Boehringer Ingelheim. In February, BI announced the launch of the Phase III RESIST clinical trial program designed to further study the efficacy and safety of tipranavir as a component of HAART. The RESIST 1 and 2 trials - along with their accompanying companion studies - will evaluate tipranavir in antiretroviral-experienced patients in more than 280 clinical trial sites worldwide.

An initial glimpse into the in vitro activity of tipranavir against multiple-protease inhibitor-resistant HIV strains was published three years ago by Dr. Brendan Larder and his colleagues (Larder, 2000). Studied by Dr. Larder’s team were 134 clinical viral isolates documented to be highly cross-resistant to currently available protease inhibitors. Of 105 isolates with more than tenfold resistance to three or four protease inhibitors - with an average of 6.1 key protease mutations per sample - 95 (90%) were susceptible to tipranavir; eight (8%) had four- to tenfold resistance to tipranavir, and only two (2%) had more than tenfold resistance.

Data presented at the 9th CROI helped shed some light on baseline susceptibility to tipranavir in the setting of various protease mutations (Schwartz, 2002). In the reported analysis, the genotypic patterns of 41 protease inhibitor-experienced patients participating in a dose-finding study of tipranavir (BI 1182.2) were analyzed. At the start of the study, all patients had HIV-RNA levels above 5,000 and had failed two previous protease inhibitor-based regimens.

At baseline, 40/41 (97%) clinical isolates were considered to be susceptible to tipranavir (defined as a less than tenfold reduction in IC50) despite decreases in susceptibility to a mean average of 2.9 currently available protease inhibitors. There was no association between the number of protease mutations at baseline and the magnitude of viral load reduction. For example, individuals with fewer than five baseline protease mutations experienced reductions in viral load of -2.39 log at week 48, compared to a reduction of -2.24 in patients with more than five protease mutations at baseline. Decreased tipranavir susceptibility was associated with a mean of 16 mutations including two or three universal protease inhibitor-associated mutations (UPAMs) - mutations that commonly arise during therapy with current protease inhibitors and are often associated with broad cross resistance - at positions L33I/V/F, V82F/L/T, I84V, and L90M.

Investigators have recently taken a closer look at baseline phenotypic and genotypic sensitivity to tipranavir in patients with multiple protease inhibitor experience (Cooper, 2003). In a phase IIa dose-optimization study of tipranavir (BI 1182.52), patients who had tried at least two protease inhibitors in the past and had strains of HIV harboring at least one UPAM were randomized to receive one of three tipranavir doses in combination with ritonavir (500/100 mg, 500/200 mg, and 750/200 mg).

According to phenotypic analyses of 157 isolates collected at the start of the study (216 patients were enrolled), the median fold increases in IC50 ranged from 7.0 to 94.2 for all of the currently approved protease inhibitors, compared to a 1.1-fold increase in the tipranavir IC50 against these highly resistant isolates. Tipranavir’s IC50 increase was onefold or less in 42% of the isolates, between onefold and twofold in 27% of the isolates, between twofold and fourfold in 18%, and greater than fourfold in 12%. Among patients harboring HIV strains with twofold or less resistance to tipranavir, viral load decreased, on average, by 1.23 log copies/mL during the first month of the study. Among patients with greater than twofold resistance to tipranavir, median viral load decreases were less than 0.25 log copies/mL. In other words, a greater than twofold increase in tipranavir’s IC50 appeared to be a breakpoint for the drug.

Also of interest are data analyzing the number of UPAMs at baseline and viral load responses after 14 days of tipranavir therapy. Looking at the patients who received 500 mg tipranavir plus 200 mg ritonavir - the dose that is currently being explored in phase III clinical trials - a median viral load reduction of 1.15 log copies/mL was seen in patients with one UPAM, a viral load reduction of 1.40 was seen in patients carrying virus with two UPAMs, and a viral load reduction of 0.33 was seen in patients with three UPAMs. “In the phenotypic analysis, patients with three UPAMs had a 2.2-fold increase in tipranavir IC50, which doesn’t appear to be much of a shift,” Dr. Kuritzkes said. “However, when looking at the impact of these UPAMs on viral load, we see that there is a loss of activity when three UPAMs are present.”

Source: PRN Notebook
http://www.prn.org/prn_nb_cntnt/current.htm

SIDE EFFECTS AND OPPORTUNISTIC INFECTIONS

Bone mineral metabolism and HIV-infection

Paul Blanchard, HIV i-Base

Alterations in bone mineral metabolism leading to osteopaenia and osteoporosis have been observed in HIV-infection. It remains unclear, however, to what extent HIV-infection itself, or various antiretrovirals might be contributing to such disturbances.

A recent report published in AIDS investigated the influence of HIV-infection on osteocalcin plasma levels in Brazilian patients. Santos and colleagues performed a cross sectional analysis on 69 patients with HIV-infection before the initiation of any antiretroviral therapy. Matched controls consisted of 50 age and sex matched healthy seronegative adults.

Although the role of osteocalcin in the bone metabolism is still unknown, it is a specific and sensitive marker for bone formation.

Overall, reduced osteocalcin plasma levels were present in 43.5% of HIV-infected patients and in 16% of healthy controls (p=0.0001; odds ratio 4.04; 95% confidence interval 1.68 - 9.69).

The study authors hypothesised that the direct interaction of HIV with cells of the bone marrow microenvironment could induce chronic T-cell activation and abnormal cytokine production affecting osteoclast and osteoblast function. They also suggest that the reduced osteocalcin levels seen in these patients may, over time, lead to clinically significant bone loss.

It now remains to determine the relative contributions of HIV-infection itself and antiretroviral drugs to the bone mineral abnormalities observed in HIV-infected patients. If the osteocalcin reduction induced by HIV-infection itself is of primary importance you would expect antiretroviral treatment to correct this and perhaps negate its effects. The reports of a number of research teams, however, suggest that bone mineral loss may actually be accelerated once antiretroviral treatment is initiated leading to suspicions that at least some antiretroviral agents may interfere directly with bone mineral metabolism.

Ref: Silva Santos Jr AC, Lopes Crisostomo LM, Olavarria V et al. Alterations in bone mineral metabolism in Brazilian HIV-infected patients. AIDS. 2003 Jul 4;17(10):1578-1580.

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db= PubMed&list_uids=12824805

Protease inhibitors and Kaposi's sarcoma (KS): KS relapse seen after switch from PI to NNRTI

Paul Blanchard, HIV i-Base

Kaposi's sarcoma (KS) is the most common malignancy experienced in the context of HIV-infection. Although the aetiology and pathogenesis of KS remains ill defined it is known to be an angio-proliferative disease characterised by angiogenesis, endothelial spindle-cell growth, inflammatory cell infiltration and oedema. KS in HIV-infection is also associated with coinfection with human herpesvirus 8 (HHV8), KS development and aggressivity is highly associated with reactivation and viral load of this particular herpesvirus.

Chemotherapy of KS with cytostatic drugs as well as radiotherapy has been found to have variable response rates and has also been associated with an increase in the frequency of opportunistic infections. Recent reports have described both a reduced incidence and regression of KS in HIV-infected patients treated with combination antiretroviral therapy including at least one HIV protease inhibitor (PI). [1] It is unclear, however, if PIs are an essential component of combination antiretrovirals required to bring about such protection or regression of KS. There remains a lack of evidence to conclude if alternative regimens such as those based on non-nucleoside reverse transcriptase inhibitors (NNRTIs) or triple nucleoside analogue (NA) alone offer the same benefits as PIs in terms of KS regression or protection. A single study did, however, identify three patients whose HHV8 viral load and KS showed a reduction after initiation of NNRTI-based regimens. [2]

The KS regression observed with the use of PI based antiretroviral regimens is thought to occur primarily due to the immune reconstitution that occurs after such regimens are initiated. Other studies have indicated that the evolution of AIDS-related KS is greatly dependent on the HIV-1 burden, and the ensuing degree of immunodeficiency. However, both in vitro and animal model studies have also shown that PIs may have a direct anti-KS and/or anti-angiogenic effect that may enhance their potency against KS when used in this setting over and above other classes of antiretroviral agents. Recently Sgadari and colleagues reported data showing that PIs have direct anti-angiogenic, anti-KS and anti-tumour effects. [3]

A report in the journal AIDS by doctors from the Hospital Saint Louis, Paris, appears to be the first publication to identify a relapse of KS in five HIV-infected patients switching from a PI to an NNRTI based antiretroviral regimen. [4] All five patients had experienced widespread KS prior to the use of PI based antiretroviral regimens and had all received treatment with various

regimens of cytotoxic chemotherapy and/or radiotherapy. Under PI treatment they had experienced a median duration of complete KS remission of 32 months.

PIs were discontinued due to virological failure in three cases and a wish to simplify therapy in the other two. Substituted therapy consisted of two nucleoside analogues and efavirenz in four patients and two nucleosides and nevirapine in one patient. Overall the median CD4 count did not change significantly after the switch and HIV viral load remained well suppressed. KS relapse was diagnosed within a median of 11 months post-switch and at a median CD4 cell count of 499 cells/mL.

Bani-Sadr and colleagues comment: "Of significance is the fact that the KS relapse was not explained by the immunological or virological failure of NNRTI-based HAART." They go on to suggest that the relapse may be explained by the antineoplastic effects of PIs, which are independent of their ability to inhibit HIV protease or induce CD4 cell recovery.

A final caution is given that: "A switch from PI to NNRTI should be performed with caution in patients with a history of KS, even though the new regimen is fully active in maintaining HIV viral suppression and high CD4 cell counts."

References:

1. Cattelan AM, Calabro ML, Aversa SM et al. Regression of AIDS-related Kaposi's sarcoma following antiretroviral therapy with protease inhibitors: biological correlates of clinical outcome. Eur J Cancer. 1999 Dec;35(13):1809-15.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10673996

2. Gill J, Bourboulia D, Wilkinson J et al. Prospective study of the effects of antiretroviral therapy on Kaposi's sarcoma-associated herpesvirus infection in patients with and without Kaposi's sarcoma. J Acquir Immune Defic Syndr. 2002 Dec 1;31(4):384-90.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12447008

3. Sgadari C, Barillari G, Toschi E et al. HIV protease inhibitors are potent anti-angiogenic molecules and promote regression of Kaposi's sarcoma. Nat Med. 2002 Mar;8(3):225-32.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11875492

4. Bani-Sadr F, Fournier S, Molina JM. Relapse of Kaposi's sarcoma in HIV-infected patients switching from a protease inhibitor to a non-nucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy regimen. AIDS. 2003 Jul 4;17(10):1580-1.
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12824806

OTHER NEWS

UK highest rate of new infections at over 5,000 cases

Figures from the Health Protection Agency show 5,338 people were diagnosed with HIV last year compared to 4,965 in 2001. There has been a significant increase in the number of heterosexuals being infected abroad - especially in Africa. More than 41,000 people living in the UK are now believed to be HIV positive. One in three of these do not know they have the virus.

Medicines Control Agency slated by Commons committee

Debashis Singh, BMJ

The former Medicines Control Agency has received a damning blow from the House of Commons Committee of Public Accounts.

The committee's report, Safety, Quality, Efficacy: Regulating Medicines in the UK, criticises the agency for its "lack of dynamism" in improving public health and for its "non-existent" public profile, which made it difficult for it to function as a provider of safety information.

The agency was, until earlier this year, responsible for protecting public health by ensuring the safety, quality, and efficacy of the one billion medicines that are prescribed and sold over the counter in the United Kingdom each year. It inspects manufacturing and supply facilities and monitors the risks and benefits of existing medicines.

The agency was set up in 1989. In April 2003, it merged with the Medical Devices Agency to form the Medicines and Healthcare Products Regulatory Agency, which now inherits the responsibilities of the Medicines Control Agency.

The committee looked at the Medicines Control Agency's performance against its key objectives of promoting and safeguarding public health through the regulation and provision of information on medicines, and its service to stakeholders.

The report was critical of the poor quality of information leaflets and labels, designed to alert patients and doctors to potential risks of medication, and the low level of reporting of adverse reactions to medicines by doctors. These were cited as evidence of the lack of dynamism to drive further improvements in the protection of public health.

The report added that the widespread but unmonitored practice of prescribing drugs to children that, although licensed, were not specifically approved for paediatric use was also cause for concern.

The committee also highlighted the irony that an agency whose mission was to put across safety messages to the public had a non-existent public profile. Even doctors had little awareness of its role. Unlike the US Food and Drug Administration, the agency failed to embrace advertising and awareness campaigns necessary for developing a relationship with the public, says the report.

The committee hopes that the creation of the Medicines and Healthcare Products Regulatory Agency will be a good opportunity to rectify some of the failings of its predecessor. It wants to see the new body develop training for doctors on monitoring the safety of medicines, as well as establishing an effective communications and awareness strategy for conveying safety messages both to the public and to health practitioners.

Edward Leigh MP, chairman of the Committee of Public Accounts, said: "It is simply unacceptable that the agency's efforts to drive improvements in the protection of public health have been so lacklustre."

Safety, Quality, Efficacy: Regulating Medicines in the UK (26th report of session 2002-3) is available at:
http://www.parliament.uk

Source: BMJ 2003; 327:10 (5 July)
http://bmj.com/cgi/content/full/327/7405/10

ON THE WEB

Conference reports and abstracts:

XII International HIV Drug Resistance Workshop

Abstracts from the XII International HIV Drug Resistance Workshop: Basic Principles and Clinical Implications, Los Cabos, Mexico, 10-14 June 2003, are now available for download.

http://www.mediscover.net/journals.cfm

IAS report from the Resistance Workshop: Sex, drugs, and viral escape - by Mark Mascolini

http://www.ias.se/pdf/625.pdf

A thorough and very readable review of this important workshop.

5th Workshop on Adverse Drug Reactions and Lipodystrophy in HIV

A report of highlights from the Workshop by Andrew Carr MD, for HIVandHepatitis.com, includes sections on:
- Cardiovascular disease
- Lipodystrophy
- Insulin resistance and diabetes
- Body composition
- Safety of hepatitis C therapy
- Mitochondrial dysfunction
- Other toxicities

http://www.hivandhepatitis.com/2003icr/5thadverse/main.html

2nd IAS Conference on HIV Pathogenesis and Treatment

13–16 July, Paris

Although the programme for the meeting is posted to the IAS, together with the late breaker abstract, the full abstracts were not posted on the IAS site as HTB went to press.

A pdf file of the abstracts has been posted to the AEGiS website:

http://ww2.aegis.org/conferences/2ndIASHIVPT/ias.pdf

A limited selection of abstracts is posted to the HIVandHepatitis.com website as html pages:

http://www.hivandhepatitis.com/2003icr/2ndias/main.html#anti

The IAS report by Mark Mascolini: Key Clinical Studies at the 2nd IAS Conference on HIV Pathogenesis and Treatment is posted as a pdf file:

http://www.ias.se/pdf/632.pdf

Daily reports all the above meetings and conferences are also posted to the NATAP website:

http://www.natap/org

Past IAS International AIDS Conference abstracts

Selected abstracts from 5th through 13th biannual International AIDS Conferences are available on-line on the AEGiS website.

http://www.aegis.org

Medscape articles:

Medscape requires one-time free registration.

Immune reconstitution and immunotherapy in HIV infection

Bruce D. Walker, MD

http://www.medscape.com/viewprogram/2435

New Perspectives on CMV and other viruses in the Immunocompromised Patient

W. Lawrence Drew, MD, PhD; Ajit Limaye, MD; Nina Singh, MD

http://www.medscape.com/viewprogram/2255

Genital herpes and the primary care practitioner

Author: Stephen Brunton, MD

http://www.medscape.com/viewprogram/2366

Strategies for concurrent treatment of HIV and HCV: a practical approach for managing coinfected patients

Robert L. Murphy, MD and others

http://www.medscape.com/viewprogram/2233

Transcripts and slides of presentations delivered at a symposium held in Chicago, October 2002.

Newletters and reports:

Forum report: Quality of HIV care – closing the gap

Report and presentations from a workshop organised by the Forum for Collaborative HIV Research: Quality of HIV Care – Closing the Gap in December 2002 are now available to download.

Participants were asked to better define the components of quality care for persons with HIV, with special emphasis on how this relates to low-volume settings of HIV care. This report summarises the key themes that emerged focusing on the systems of care and support that need to surround both the individual clinician and the individual person receiving HIV care.

http://www.hivforum.org/projects/closing-the-gap.html

PRN Notebook – June 2003 now online

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

Bioterrorism and smallpox vaccination: experience and considerations - by Isaac Weisfuse, Kent Sepkowitz, and Yehuda Danon

Understanding treatment-resistant HIV- by Veronica Miller, Richard Haubrich, and Daniel Kuritzkes**.**

HIV AIDS in resource-poor settings - by David H**o**

Advancing HIV prevention: new CDC strategies for a changing epidemic - by Tim Hor**n**

The Hopkins HIV Report - July 2003

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

- Review of ACTG 5095
- Atazanavir: clinical use
- HIV and solid organ transplant
- Treatment of chronic HBV in coinfected patients

GMHC Treatment Issues - June 2003

http://www.gmhc.org/living/treatment/ti1706/ti1706.html

- Researching alternatives: a talk with Donald Abrams
- 'Alternative' treatment activism
- Moving forward with integrative AIDS research
- HIV/AIDS and people with disability
- Atazanavir (Reyataz) dosing options discussed

HIV Knowledge Base – updated chapters

Updated chapters in June 2003 from this thorough online HIV medical reference manual on the HIV-insite website.

Initiating antiretroviral therapy

E.M. Kojic, MD and Charles C.J. Carpenter, MD

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03-02-05

Herpes simplex virus and HIV

Kim S. Erlich, MD

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-05-03-02

Treatment of HIV-associated Kaposi's Sarcoma

Jamie H. Von Roenn, MD

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-06-02-04

Neurologic manifestations of HIV

Dawn McGuire, MD

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-04-01-02

Antiretroviral drug overview: Atazanavir (Reyataz)

Susa Coffey, MD

http://hivinsite.ucsf.edu/InSite.jsp?page=ar-03-07

MEETING ANNOUNCEMENTS

EACS Advanced HIV Course

27-29 August 2003

The European AIDS Clinical Society will organise its first course on Antiretroviral Therapy and Comprehensive Care for people living with HIV/AIDS, focused on the clinical management of HIV, in Montpellier, France, from 27 to 29 August 2003.

The application form can be download it from the EACS website.

http://www.eacs.ws

For further information contact Sylvie Chatelin at the EACS Office, Tel: +33 1 44 24 17 96

sylvie-chatelin@psl.ap-hop-paris.fr

9th European Conference on Clinical Aspects and Treatment of HIV Infection (ECCATH)

26- 29 October, 2003, Warsaw, Poland

Some community scholarships are made available for this bi-annual European meeting. Press registration is also encouraged.

http://www.eacs-conference2003.com/

UK Resistance and PK Workshops

27-28 November 2003

An interactive educational workshop on resistance testing and pharmacological assessment in HIV, principally aimed at consultants and specialist registrars.

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

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

Please contact Mediscript on 020 8446 8898 for further details.

PUBLICATIONS AND SERVICES FROM i-BASE

Treatment 'Passports'

These new, handy booklets for recording health and treatment history have proved so popular that we have distributed the entire 8,000 print run in the first month they have been available. So, of course, we have ordered a reprint so you can still order them for your personal use or, in the case of professionals, for clients.

Treatment 'passports' are for HIV-positive people – whether newly diagnosed or positive for a long time - to keep a record of health and treatment history. Such a record is useful when talking to different health care workers, changing clinics and changing treatments. Like all i-Base publications, it is 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).

Guide to Changing Treatment – now in Greek

Our guide to second line and salvage therapy has now been translated into Greek by the Athens-based organisation Synthesis. You can download the pdf file from our website (see below). Further information in Greek is available at the Synthesis site:

http://www.hiv.gr

The information in our guide was updated in January 2003. Our treatment guides are reviewed every six months to ensure the latest information is available. Many factors contribute to whether a combination works and in salvage therapy it is

important to look at all of these together.

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

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

- T-20 has reported clear benefits for people resistant to current drugs – and has just received marketing approval in Europe.
- Atazanavir appears to increase cholesterol and triglycerides less than other protease inhibitors and is available in an expanded access programme for people with raised lipids on current PIs.
- Tipranavir, a PI with activity against currently resistant HIV, will be available during 2003 in a limited emergency access programme.

For additional free copies, including bulk orders see below

Guide to Avoiding and Managing Side Effects- now in Italian

The i-Base Guide to Side Effects has now been translated into Italian by colleagues in Milan. You can download the pdf file from the i-Base web site (details below). 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.

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

UK-Community Advisory Board: new 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.

The programme, reading material, reports and powerpoint slides from the presentations from the fifth meeting, held on 2 May, are posted to the i-Base website.

This meeting focused on:

- Access to treatment for UK visitors, refugees and asylum seekers - Linda McDonald
- TB and HIV coinfection - Dr Anton Pozniak
- T-20 - meeting with Roche

http://www.i-base.info/ukcab/may03/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

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

The i-Base web site

Our web address is:

http://www.i-Base.info

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

our archives and an incomparable range of links.

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

Translations of 'Introduction to Combination Therapy'

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

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

For Latvian and Slovak copies please contact the i-Base office (contact details on page 2).

Printed versions of this booklet are also available in English, French, Italian, Spanish, Chinese and Macedonian. The guide explains what combination therapy is, how well it works, who can benefit from it, when to start taking it, some differences between treating men and women, side effects, the best combinations, changing treatment, taking part in drug trials, your relationship with your doctor, the importance of adherence, and drug resistance and how to avoid it. To order copies, see below

Positive Treatment News (PTN)

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

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

HIV Treatment Bulletin (HTB)

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

http://www.i-base.info

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

Treatment information request service – 0808 800 6013

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

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

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

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

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Positive Treatment News (PTN) *from Spring 2003*

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

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