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EDITORIAL

The end of the financial year is upon us!

HIV i-Base receives no statutory funding and yet we provide all our publications free of charge and delivery to individuals and NHS clinics all over the country. If your organisation has any spare funds in its coffers that it needs to spend before the end of the financial year, then please think of making a donation to HIV i-Base so that we can continue providing all our services free of charge.

We can submit an invoice for publications! If you think you may be able to help and want to know more, simply give us a call on 020 7407 8488 or fax us on 020 7407 8489.

HIV i-Base is a registered charity (number 1081905) and any amount would be gratefully received.

Thanks...

TREATMENT ALERT

Risk factors for severe, life-threatening and fatal hepatotoxicity with nevirapine

Recent research by Boehringer Ingelheim into risk factors for liver toxicity in patients using nevirapine found that women with a baseline CD4 count >250cells/mm3 and men with a count >400 cells/mm3 were at a significantly increased risk of rash-associated liver toxicity compared with patients who started treatment with lower CD4 counts. These data were reviewed and approved by both the European and US regulatory agencies, and finally letters have been released in Europe and the US to clarify this issue for doctors. This is the full text of the European letter:

Dear Healthcare Professional,

It is well known that severe and life-threatening hepatic and cutaneous reactions constitute the major clinical toxicity of nevirapine. In agreement with the European Medicines Evaluation Agency's scientific committee, the Committee for Proprietary Medicinal Products (CPMP) and the IMB, Boehringer Ingelheim is now writing to inform you of important new information concerning patient management and risk factors for these reactions that have been recently introduced to the Summary of Product Characteristics of Nevirapine (date of Commission Decision 4 February 2004). This new information is the result of recent analysis of post-marketing surveillance data and of the expanding nevirapine clinical trial database.

Specifically we wish to draw your attention to the following:

The first 18 weeks of therapy with nevirapine are a critical period which requires close monitoring of patients to disclose the potential appearance of severe and life-threatening skin reactions (including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis) or serious hepatitis/hepatic failure. After this period, monitoring should continue at frequent intervals throughout treatment.

The greatest risk of hepatic events and skin reactions, including severe and potentially fatal events, occurs in the first six weeks of therapy.

Women and patients with higher CD4 counts are at increased risk of hepatic adverse events, often associated with rash. Especially women with pre-treatment CD4 counts > 250 cells/mm^3 are at considerably higher risk of hepatic adverse events, often associated with rash.

Nevirapine should not be administered to patients with severe hepatic impairment or pre-treatment ASAT or ALAT > 5 x ULN until baseline ASAT/ALAT are stabilised < 5 x ULN.

If patients present with a suspected nevirapine associated rash, liver function tests should be performed. Patients with moderate to severe elevations (ASAT or ALAT > 5 x ULN) should be permanently discontinued from nevirapine.

Patients with chronic hepatitis B or C and treated with combination antiretroviral therapy are at an increased risk for severe and potentially fatal hepatic adverse events.

Patients should be advised that occurrence of symptoms suggestive of hepatitis, severe rash or hypersensitivity reactions should lead them to contact promptly their physician. Nevirapine treatment should be permanently discontinued in these patients.

The main changes to the Summary of Product Characteristics are highlighted in the attachment to this letter, and a copy of the revised full Summary of Product Characteristics for nevirapine 200 mg tablets is enclosed with this letter for your information.

Any suspected cases of hepatotoxicity associated with the use of nevirapine should be notified to the company and/or the IMB, in the usual way.

I trust that the enclosed is satisfactory. However, please do not hesitate to contact me or Medical Information on 01 295 9620 should you require any further information.

Yours sincerely, C.S. de Wet

Medical Director UK & Ireland, Boehringer Ingelheim Ltd

Source: Boehringer Ingelheim

Guidelines for the management of hepatic and rash events with nevirapine and a copy of the US letter are available at:

http://www.viramune.com/

C O M M E N T

Few patients start treatment at these CD4 levels in the UK unless they are using HAART treatment in pregnancy to reduce viral load prior to birth. The data in the revised SPC for nevirapine states that women with CD4 counts above 250 when starting nevirapine therapy had an 11% risk compared to 0.9% for women with CD4+ cell counts <250. The risk for men with CD4 counts > 400 was 6.3% compared to 2.3% in those starting at a lower level. This risk only relates to baseline CD4 count when starting treatment. Subsequent increases in CD4 count does NOT increase this risk.

Patient management guidelines from Boehringer Ingelheim at the above link also include the following information:

• The recommended 14-day, 200 mg once-daily lead-in dose, prior to escalation to 200 mg twice daily, has been shown to reduce the frequency of rash and must be strictly followed

• Don't increase the lead-in dose of nevirapine in the presence of rash

• If nevirapine is interrupted for more than seven days, reintroduce with the 14-day, 200 mg once-daily lead-in dose

• It is suggested that nevirapine and other medications that often cause rash (eg abacavir, trimethoprim-sulfamethoxazole) should not be started simultaneously

• Prednisone should not be used to prevent rash. Prednisone administration during the first two weeks of therapy with nevirapine appears to increase the incidence of rash. Antihistamines do not appear to be effective in preventing rash with nevirapine.

Nevirapine should not be used for PEP, eg needle stick injury, except for the prevention of fetal-maternal transmission.

CONFERENCE REPORTS

11th Conference on Retroviruses and Opportunistic Infections (CROI)

8-11 February 2004, San Francisco

About 3,500 doctors, researchers, healthcare workers, journalists and community advocates attended the 11th Conference on Retroviruses and Opportunistic Infections held in San Francisco from 8-11 February, 2004. This meeting is one of the most important annual meetings, and is prioritised by many researchers as the first choice platform for their research.

There is always more to report from this meeting than we can summarise in HTB and links to recommended sites that provide a wide range of additional reports are included in our 'On The Web' section at the end of HTB.

Many of the overview presentations are available as audio and video webcasts from the conference website, and include slide presentations from these talks, and is accessible from both Mac and PCs. The conference website also has access to searchable abstracts online and many of the full posters are posted as pdf files.

http://www.retroconference.org

Unless stated otherwise, all references in the following articles are to the Programme and Abstracts of the 11th Conference on Retroviruses and Opportunistic Infections, 8-11 February 2004, San Francisco.

CROI: ACCESS

Treatment with generics: tolerability, safety and resistance

Simon Collins, HIV i-Base

As antiretroviral treatment becomes more widely available, through reduced prices and generic combinations, it is important that lessons learned in the first countries to use treatments are not ignored for patients in resource poor countries.

Many access programmes focus on providing treatment, often without the support of viral load or even regular CD4 tests, so it is important to follow the effect of treatment when such studies are presented. This is particularly important as the WHO first-line regimen of generic d4T/3TC/nevirapine based on fixed-dose combinations (FDCs) produced in single formulations is not only the most widely-used but is often the only combination available. This may result in little or no choice for patients accumulating d4T-associated toxicity.

Of note, many studies reported at the Retrovirus meeting included use of this generic combination.

Saple and colleagues from Mumbai reported results from an observational study using generic combinations of efavirenz+3TC-based HAART plus rifampicin-based TB treatment in 60 patients with HIV/TB coinfection. [1]

The third drug was AZT in 24 patients (regimen cost $1/day) and d4T in 36 patients (regimen cost $1.5/day). Response was assessed in monthly clinical visits and CD4/CD8 results were available every six months. Median increases in CD4 count increase were comparable in the two groups.

CD4 increases (cells/mm3):

	d4T (n=36)	AZT (n=24)
Median baseline (range)	160 cells/mm3 (93 to 343)	194 cells/mm3 (160 to 310)
6mo	+ 53 (n =36, p <0.001)	+ 69 (n = 24, p <0.001)
12 mo	+ 92 (n = 34, p <0.001)	+ 85 (n = 24, p <0.001)
18 mo	+148 (n = 29, p <0.01)	+ 130 (n = 23, p <0.001)
24 mo	+163 (n = 32, p <0.001)	+ 197 (n = 22, n <0.001)

AZT-associated side effects (anaemia) was reported in three patients whereas in the d4T arm, six patients reported peripheral neuropathy. Lipoatrophy in the d4T arm was reported in 12 and 26 patients at week 48 and 72 respectively. This small study concluded that although d4T provided a less costly regimen, the high level of subsequent lipoatrophy limited long-term use.

An observational study from India of more than 1,100 patients using either efavirenz (n=254) or nevirapine (n=857) based combinations reported median CD4 increases from baseline levels of 100 and 115 cells/mm3 to 425 and 377 cells/mm3 respectively at week 24. [2]

Side effects were sufficient to show the importance of alternative regimens for adequate patient management: peripheral neuropathy in 18% patients using d4T, almost 10% of rash or hepatotoxicity in patients using nevirapine and 20% CNS side effect in patients using efavirenz.

These high levels may be associated with excessive d4T doses (especially with low body weight) and not using the lower 200mg/day induction dose for nevirapine for the initial two weeks. The range of baseline CD4 counts was 2-613 cells/mm3 and 32-741 cells/mm3 in the efavirenz and nevirapine groups respectively, indicating that some people in this study started at much earlier stages of HIV than would be recommended in Europe or the US.

Studies from Thailand, Uganda, Zimbabwe and Nigeria also reported on the more usual reality of patients starting treatment with more advanced HIV including many with baseline CD4 counts <50 cells/mm3. Response rates were generally encouraging and similar to those observed in industrialised countries. [3, 4, 5, 6] Treatment works well – as most optimistic doctors would expect – but higher mortality occurs with when treatment is started with the most advanced HIV disease.

The Nigerian group reported access only to baseline CD4 and hemogram, and no subsequent monitoring available over 18 months follow up in over 70% of patients. Less than 10% of patients had access to regular CD4 or full blood count tests. The study also reported high OI and HIV burden for treating physicians, low experience with antiretroviral treatment and 42% informed consent for patients in the trial.

C O M M E N T

Patients are at last accessing generic-based combinations. None of these countries provided any significant market for any brand manufacturers and the Western pharmaceutical industry has not collapsed as a result. Future access is threatened by US-determined

changes to new trade agreements coming into effect in some countries as early as 2005.

There is a clear need for alternative choices to prevent short-term access to life-saving medications resulting in permanent and debilitating painful neuropathy – as occurred in many patients who continued to use neuropathy-related nucleosides for too long in Western countries. Protease inhibitors are more complex and costly to produce than nucleosides - for example generic nelfinavir is more expensive than the most discounted Roche price, and even this discounted price costs m ore than $800/year. The need for a generic formulation of tenofovir seems compelling.

The importance of use of lower doses of d4T, and increasing patient awareness of early symptoms of neuropathy will also be crucial.

References:

All references are to the Programme and Abstracts of the 11th Conference on Retroviruses and Opportunistic Infections, 8-11 February 2004, San Francisco.

1. Saple D, S Vaidya. Generic AZT vs d4T in HIV/TB co-infection in clinical practice in India: an observational study. 11th CROI 2004, Abstract 583
2. Patel AK, Pujari S, Patel KK, et al. Nevirapine- vs efavirenz- based antiretroviral treatment in naïve Indian patients: Comparison of effectiveness in a clinical cohort. 11th CROI 2004, Abstract 584.
3. Sungkanuparph S, Vibhagool A, Kiertiburanakul S et al. Initiation of HAART in advanced HIV-infected patients with CD4 <50 Cells/mm3 in a resource-limited setting: efficacy and tolerability. 11th CROI 2004, Abstract 587.
4. Bhattacharaya D, Kadzirange G, Zijenah LS et al. Clinical monitoring of cotrimoxazole, Duovir, and Nevimmune (Generic HAART) among men and women with AIDS in Zimbabwe. 11th CROI 2004, Abstract 591.
5. Munderi P, C Kityo Mutuluuza C, Reid A. CD4 response to HAART in previously untreated adults with HIV infection in Africa: the DART trial. 11th CROI 2004, Abstract 592.
6. Ekong E, Idemyor V, Akinlade O et al. Challenges to antiretroviral drug therapy in resource-limited settings: the Nigerian experience. 11th CROI 2004, Abstract 596.

CROI: PK AND DRUG INTERACTIONS

Drug levels can persist for more than two weeks after stopping efavirenz

Simon Collins, HIV i-Base

How to stop treatment safely is arguably as important a management issue as how to correctly initiate treatment, but it has been the focus of far less research. As antiretroviral drugs have different plasma and intracellular half-lives, a strategy to safely discontinue treatment may be essential in order to avoid resistance.

Indeed, several treatment interruption studies have reported cumulative risk for developing NNRTI resistance with each interruption when using efavirenz (EFV, Sustiva, Stocrin) based regimens, when all drugs have been stopped at the same time. Other regimen-switching or cycling studies have shown greater virological benefits when efavirenz is included, and residual antiviral activity may be a plausible explanation for the improved results in those arms.

Steve Taylor from Birmingham Heartlands Hospital presented results from patients who were either stopping or switching efavirenz due to treatment failure or toxicity, or after a planned short course of treatment. Drug elimination takes five times the half-life of a compound and as the plasma half-life of efavirenz is estimated at 40-55 hours this theoretically risks monotherapy with a drug with a low genetic resistance barrier for a significant time.

Ten patients (six Caucasian men, four African women) were followed in an intensive PK study with EFV plasma levels measured at days 0, 4, 7, 14 and 21 by HPLC. A second group of 25 patients who were stopping a short course of antiretroviral therapy initiated following seroconversion, stopped efavirenz five to seven days prior to the other drugs in their regimen. Resistance testing was used at different times for each group.

In this small group, the calculated half-life in the eight patients in the PK study actually ranged from 32-100 hours. Values >1000ng/mL were considered therapeutic and those between 100 to 1000ng/mL sub therapeutic but sufficient to produce selective pressure on replicating virus. Efavirenz concentrations after discontinuation are shown below:

	Median (ng/mL)	Range (ng/mL)
Baseline	3004	894 – 8216
Day 7	310	<40 – 4478
Day 14	149	<40 – 1845
Day 21	62	<40 – 637

Individual cases included in the oral presentation at the conference showed this extreme variability between patients. A 64-year-old Caucasian man retained levels of efavirenz >100ng/mL three weeks after stopping efavirenz (he continued to take Combivir plus tenofovir) and showed a plasma half-life close to 150 hours. The other four Caucasian men had expected half-lives of 40-50 hours.

The four African women in the study had considerably longer half-lives than the expected mean ranging from 116 –115 hours. Two of these women were found to have extremely high baseline concentrations close to 10,000 ng/mL at baseline and three of the four women maintained 'therapeutic' levels of efavirenz (>1000ng/mL) two to three weeks after stopping treatment.

The 25 patients stopping treatment in the virologic study (23 Caucasian men, one Black man, one Black woman) continued Combivir for one week after discontinuation of efavirenz. No new resistance was detected between baseline and week 4 in this group.

The study concluded with a reference to the BHIVA (British HIV Association) guidelines, which recommend, when stopping an NNRTI, to either continue nucleoside for a further week, or to switch the NNRTI to a PI and use three drugs with similar (short) half-lives when stopping all drugs at the same time. A suggestion from the audience was that ritonavir could be used to speed up elimination, but this was unsupported by research.

On the basis of these data, even further caution may be necessary in many individuals, and the results from ACTG 5095 below suggest this is true for Black women in particular, if efavirenz is to be stopped without risk of developing resistance.

Ref: Taylor S, Allen S, Fidler S et al. Stop study: after discontinuation of efavirenz, plasma concentrations may persist for two weeks or longer. 11th CROI 2004, Abstract 131.

Race affects absorption and clearance of efavirenz

Simon Collins, HIV i-Base

Heather Ribaudo followed the UK efavirenz study with particularly supportive results from a sub-study from ACTG 5095 that randomised patients in a double-blind placebo controlled trial to either efavirenz (EFV, Sustiva, Stocrin) + Trizivir (AZT+3TC+abacavir) or to Trizivir alone. This sub-study looked at efavirenz-related toxicity over the first 24 weeks of treatment. Plasma levels of efavirenz at 1, 4, 12 and 24 weeks obtained from 190 patients (36 women and 154 men) were analysed in relation to toxicity and virological response. [1]

Race distribution was 53% Caucasian, 32% Black and 15% Hispanic. Median weight was 75kg (range 46-186kg).

Caucasian non-Hispanic patients had a 32% increase (95 CI, 15 - 51%; p <0.001) in clearance compared to Black and Hispanic subjects. Both clearance and volume of distribution were associated with weight (p<0.001). There was no apparent association with gender (p >0.26) or HCV coinfection.

There was some evidence of an increasing rate of EFV discontinuation with decreasing clearance (p=0.052) and increasing Cmax (p=0.048). Sixteen percent of patients discontinued efavirenz during the first 24 weeks (n=31) due to CNS symptoms (n=5), rash (n=5), other toxicity (n=4), subject/clinician decision (n=6), and non-compliance (n=6). There was no apparent association between EFV pharmacokinetics and rates of first CNS toxicity or viral load of <200 copies/mL (for clearance, p=0.99, p=0.46, respectively).

In a second presentation from the same ACTG sub-study Haas and colleagues looked for a genetic basis of efavirenz clearance by identifying single nucleoside polymorphisms in CYP2B6, 3A4, 3A5 and MDR1 enzymes using real-time PCR. [2]

The functional G to T change at position 516 that identifies CYP2B6 *6 and *7 haplotypes was found in 20% of Black patients compared to only 3% of Caucasian patients, and was associated in higher efavirenz concentrations and lower clearance in all populations.

	G/G	G/T	T/T
number of patients	78	60	14
Median AUC24 ug.h/L	44	60	130

The CYP3A4 1B (A392G) G/- genotypes were also associated with higher EFV levels (p <0.001) although A/A genotype was rare among non-whites. The CYP3A A392G genotype was also associated with AUC24h. The CYP2B (G516T) T/T genotype was significantly associated with adverse CNS symptoms (p = 0.04). None of the genotypes studied showed significant associations with initial or short-term virologic or immunologic response to treatment.

C O M M E N T

The PK case studies showing therapeutic efavirenz levels three weeks after discontinuation of the NNRTI shows that extremely slow clearance may not be so unusual. The genetic research from the US studies supports particular caution in African patients.

References:

1. Ribaudo H, Clifford D, Gulick R et al. Relationships between efavirenz pharmacokinetics, side effects, drug discontinuation, virologic response, and race: results from ACTG A5095/A5097s. 11th CROI 2004, Abstract 132.
2. Haas D, Ribaudo H, Kim R et al. A common *CYP2B6* variant is associated with efavirenz pharmacokinetics and central nervous system side effects: AACTG Study NWCS214. 11th CROI 2004, Oral abstract 133.

Triple PI interactions: atazanavir increases saquinavir levels in ritonavir-boosted once-daily combination

Simon Collins, HIV i-Base

Marta Boffito and colleagues from the Chelsea and Westminster Hospital in London reported a synergistic boosting interaction between 300mg atazanavir (ATV, Reyataz) and 1600mg saquinavir hard gel capsule (SQV, Invirase) when both boosted by 100mg ritonavir (RTV, Norvir) in a once daily combination.

Twenty HIV-positive patients (two women, 18 men), mean age 41 years, median CD4 442 cells/mm3, were administered SQV/RTV 1600/100mg once daily with a 20g fat meal. Atazanavir 300mg once daily was added to the regimen on day two for 30 days, and intensive PK testing was performed at day one and 11 days after atazanavir was added.

Pharmacokinetic results for saquinavir and atazanavir are shown below:

	Geometric mean [95% CI]		
	SQV (+ RTV)	SQV (+ATV/RTV)	ATV (+SQV/RTV)
Ctrough (ng/mL)	87 [72–139]	184 [140–311]	767 [577–1427]
Cmax (ng/mL)	2756 [2219–4551]	3923 [333–5350]	4982 [4432–6235]
AUC0-24 (ng.h/mL)	18,270 [14,951–30,357]	29,445 [24,986–40,348]	51,036 [44,369–64,591]

Geometric mean ratios (GMR) showed statistically significant increases in SQV levels with, compared to without, atazanavir of 112% in Ctrough (GMR 2.12; 95%CI: 1.72 to 3.50), of 42% in Cmax (GMR 1.42; 95%CI: 1.24 to 1.94) and 60% increases in AUC (GMR 1.60; 95% CI 1.35 to 2.43). ATV concentrations were similar to those seen in ritonavir-booted atazanavir regimens without saquinavir.

No significant changes in ALT, AST, glucose, total cholesterol and triglycerides were observed. Total and indirect bilirubin increased by five times after 10 days of atazanavir therapy (median, range: 36, 11-139, and 32, 9-128 mol/L, respectively. Four patients developed scleral icterus and two developed jaundice.

Ref: Boffito M, Kurowski M, Kruse G et al. Atazanavir enhances saquinavir hard gel concentrations in a ritonavir-boosted once daily regimen. 11th CROI 2004, Abstract 607.

Triple PI interactions: fosamprenavir and Kaletra interaction is difficult to overcome

Simon Collins, HIV i-Base

Previous reports have highlighted that the interactions between fosamprenavir and Kaletra are problematic, including a study from last year's ICAAC conference. [1, 2] Normally, two pills of fosamprenavir are combined with ritonavir either once or twice daily for boosting; lopinavir/ritonavir (Kaletra) is normally dosed as three pills twice daily.

Two studies at this meeting reported that the interaction is not overcome by increased doses of either drug or of additional ritonavir. Even when increased doses of Kaletra were tolerated, fosamprenavir levels remained lower than those used without lopinavir, and most patients using dual-boosted-PI combinations are also likely to be looking for higher levels to overcome earlier levels of resistance.

Corbett and colleagues from the University of North Carolina looked at whether separating each PI by four or 12 hours improved the pharmacokinetics compared to giving all three drugs together. Patients with separated doses used an additional 200mg ritonavir. This strategy corrected the drug levels of lopinavir, but did not improve the levels of amprenavir. [2]

The second study from Wire and colleagues at GSK looked at pharmacokinetics of both fosamprenavir and lopinavir in two different dosing strategies in two crossover studies in HIV-negative subjects. [3]

The first regimen increased the dose of Kaletra, using 1400mg fosamprenavir (two pills) with 533/133 mg of lopinavir/ritonavir

(four pills) all taken twice a day. The second added an additional dose of ritonavir to standard doses of each drug: 1400mg fosamprenavir (two pills) with 400/100 mg of lopinavir/ritonavir (three pills) with an additional 100mg of ritonavir (one pill), all taken twice a day.

The discontinuation rate due to toxicity was high with 13/36 and 16/36 subjects discontinuing in the first and second study respectively and elevations in cholesterol and triglyceride levels were frequent in all study arms. Both of the increased dosing strategies increased amprenavir levels, but not to the levels seen in other boosted-amprenavir studies. Based on the PK results the study could make specific recommendations about the dosing of fosamprenavir and lopinavir/ritonavir.

C O M M E N T

These results are in good agreement with the previous findings for amprenavir, the parent drug. In the UK, individualising drug dosing with therapeutic drug monitoring (TDM) is recommended for interactions for which there are insufficient data to recommend a particular dosing strategy. TDM appears warranted to determine the safest approach to any dual-boosted or triple-PI combination.

Although GSK covers the cost of TDM for interactions involving fosamprenavir, [4] in this particular example it seems likely that gastrointestinal toxicity as well as the huge interindividual variation in plasma levels limit the utility of this combination, and that co-administration should only used in exceptional circumstances.

References:

1. Kashuba A, Tierney C, Downey G et al. Combining GW433908 (fosamprenavir; 908) with lopinavir/ritonavir (LPV/R) in HIV-1 infected adults results in substantial reductions in amprenavir (APV) and LPV concentrations: pharmacokinetic (PK) results from adult ACTG protocol A5143. 43rd ICAAC, September, 2003; Abstract H-855a.
   http://www.i-base.info/pub/htb/v4/htb4-9/Interaction.html
2. Corbett AH, Davidson L, Park JJ. Dose separation strategies to overcome the pharmacokinetic interaction of a triple protease inhibitor regimen containing fosamprenavir, lopinavir, and ritonavir. 11th CROI 2004, Abstract 611.
3. Wire MB, Naderer OJ, Masterman AL et al. The pharmacokinetic interaction between GW433908 and lopinavir/ritonavir (APV10011 and APV10012). 11th CROI 2004, Abstract 612.
4. For details of individual TDM programmes see http://www.hiv-druginteractions.org/
5. Blanchard P. Combinations of lopinavir/r and amprenavir in heavily treatment experienced patients. HTB Vol2 No9.
   http://www.i-base.info/pub/htb/vol2/htb2-9/htb2-92.html
6. Mauss S, Scholten S, Wolf E et al. A prospective, controlled study assessing the effect of lopinavir on amprenavir concentrations boosted by ritonavir. HIV Med. 2004 Jan;5(1):15-7.

Ribavirin (RBV) does not alter intracellular levels of AZT, 3TC or d4T

Simon Collins, HIV i-Base

In a late-breaker oral presentation, Gries and colleagues presented results from a PK sub-study of the APRICOT trial. This study randomised more than 800 patients coinfected with HIV and HCV to either standard interferon-alfa + ribavirin, pegylated interferon (Pegasys) + placebo or Pegasys + ribavirin. Results from the full APRICOT study are reported in detail later in this issue of HTB.

The PK study only included patients receiving pegylated interferon +/- ribavirin 800mg/day or placebo. Stable background HAART included either AZT+3TC or d4T+3TC for more than six weeks prior to the study.

Serial blood samples were collected at 0, 2, 4, 6, 8 and 12 hours at baseline and after 8-12 weeks of therapy. Plasma concentrations of RBV, d4T, AZT and 3TC were determined by LC/MS/MS and triphosphate metabolites in PBMCs by template primer extension assays.

No significant differences were found in either the mean plasma or intracellular AUC levels between baseline and week 8-12 in the 48/55 patients who completed the sub-study. The study concluded that coadministration of ribavirin does not alter the intracellular phosphorylation or the plasma pharmacokinetics of AZT, d4T or 3TC in coinfection patients after 8-12 weeks.

C O M M E N T

For historical reasons, the main concern at the time when this sub-study in APRICOT was designed was the inhibition of the phosphorylation of pyrimidine-analogues by ribavirin.

However, today the toxicity of ddI which may be increased by a promotion of phosporylation by ribavirin is of a much greater relevance. Unfortunately data on this interaction are not provided by this study.

Ref: Gries J-M, Torriani FJ, Rodriguez-Torres M et al. Effect of ribavirin on intracellular and plasma pharmacokinetics of nucleoside reverse transcriptase inhibitors in patients with HCV/HIV co-infection: final results of a randomised clinical study. 11th CROI 2004, Abstract 135LB.

CROI: ANTIRETROVIRALS

COLATE study shows no clinical benefit from continuing 3TC to maintain M184V mutation

Simon Collins, HIV i-Base

For many years there have been few data on whether maintaining the 3TC-associated M184V mutation can have an impact on viral fitness that translates into any clinical benefit. The theoretical basis for this was first suggested in early 3TC studies and several small studies have supported this.

The COLATE study planned to randomise 160 patients to either drop or continue 3TC when switching a failing combination following at least two consecutive viral load counts >1000 copies/mL. This study first enrolled patients in June 1999 and despite being an international European study with 18 sites it took almost three years to enroll 76 patients failing their first combination and 55 patients failing their second or higher combination. The study was terminated early by the trial's data and safety monitoring board on the basis of futility. Nevertheless, the results presented from the 133 patients followed for at least 48 weeks still had sufficient power to detect any significant difference between the two arms.

No differences were seen in the proportion of patients with renewed viral suppression to <50 or <400 copies/mL and HIV RNA reduced by 1.4 log copies/mL in both arms. Primary efficacy calculated by average under the curve changes in viral load from baseline also found comparable results in each arm when adjusting for baseline CD4 count. Most patients adhered to their study arm. Discontinuation rates and numbers of drugs used in the subsequent regimen were both similar in each arm. There was no difference in the time to protocol-defined failure of less than 0.5 log drop compared to baseline or an increase of >1 log compared to nadir response. There were also no differences in change of CD4 count or time to increase of >100 cell/mm3.

The M184V mutation was present in most patients at baseline and was maintained in those who continued to take 3TC, but generally became difficult to detect after six months in patients who discontinued 3TC.

Ref: Dragsted U, Fox Z, Mathiesen L et al for the COLATE trial group. Final week 48 analysis of a Phase IV, randomised, open-label, multi-centre trial to evaluate safety and efficacy of continued 3TC twice-daily versus discontinuation of 3TC in HIV-1-infected adults with virological failure on ongoing combination treatments containing 3TC: the COLATE trial. 11th CROI 2004, Abstract 549.

C O M M E N T

This is the first randomised study looking at clinical results from maintaining M184V. It is disappointing that this easy to use strategy resulted in no apparent clinical differences. Viral fitness remains an intriguing and plausible factor in response to therapy that is proving difficult to link to practical benefit.

Studies of new pipeline drugs

Mike Youle, NATAP.org

The Retroviruses Conference this year appeared to have a greater than usual emphasis on basic science and the clinicians were left feeling that a lot was in the pipeline but not much new around the corner. This was certainly true of new antiretroviral agents where exciting data were shown on a range of novel agents especially targeting the various steps required for attachment of HIV to the cell, a potentially very attractive proposition since the likelihood of toxicity from these compounds is low.

Compounds covered in this report include:

- Reverset (NRTI)
- SPD-754 (NRTI)
- GW678248 and GW695634 (NNRTIs)
- TMC 114 (PI) and TMC 125 (NNRTI)
- GW873140 (CCR5 receptor antagonist)
- SCH-D (CCR5 receptor antagonist)
- BMS-488043 (attachment inhibitor)

The main session on new drugs on Wednesday morning was opened by Dr Rob Murphy, from Northwest University in Chicago, who showed a study of Reverset, a novel nucleoside analogue (D-D4FC) with potent in vitro activity against many resistant strains of HIV, although it appears the drug is unlikely to act against the Q151M or 69 insertion mutants [1].

It has been difficult to select for resistance in vitro although after more than 20 passages several viruses with <15-fold resistance have been produced which include K65R and K70N along with 4-5 other RT mutations. Favourable single dose data was presented at the Paris IAS meeting last June and in this study, conducted at the Charité-University Hospital in Berlin, 30 subjects in three cohorts of eight treated and two placebo patients were given 50mg 100mg or 200mg of drug for 10 days. Subjects had >50 CD4 cells/mm3 (median 468 cells/mm3), >5,000 copies/mL HIV RNA (median 4.29 log10 copies/mL) and included six women. Study drug was given in blinded manner and after 10 days of dosing day 11 viral load was reduced by 1.32, 1.54 and 1.77 $\log^{10}$ copies/mL in each dose group respectively. With increasing dose the Cmax also rose from 2.3 to 5.4 to 9.8 ng/mL and the AUC increased from 11.9 to 31.7 to 74.6ng/mL.

Despite this, no serious adverse events were reported and there appeared to be no differences between drug and placebo in terms of minor adverse events, most of which consisted of flu-like symptoms, common at the time of the year the study was undertaken. During the treatment phase CD4 cell levels rose, but these declined after cessation of therapy and HIV RNA returned to baseline. No genotypic changes occurred during the study and specifically no new mutations appeared.

Further studies are now underway to evaluate the effects of this novel nucleoside analogue in 180 treatment experienced individuals. Questions to the speaker included whether the drug passed the blood brain barrier, for which no data exist, and whether in vitro mitochondrial toxicity has been seen of which none has been reported. Pigmentation of the nose, which appears in female dogs, has not yet been reported in human studies. Murphy said no mitochondrial toxicity has been observed yet, but no data to support this were shown and this remains to be seen.

A second nucleoside analogue, the deoxycytidine analogue SPD754 from Shire Pharmaceuticals, was presented next [2].

This drug also appears to have no laboratory induced mitochondrial toxicity and is additive or synergistic with most available nucleoside agents. The aim of this study was to evaluate the interaction due to phosphorylation between SPD754 600mg BID and lamivudine (3TC) 150 mg BID. In a study of 21 HIV-negative volunteers who were given each drug separately or in combination in a three-way study of four days treatment with seven days washout, no effects were seen on plasma concentrations. However, when the intracellular drug levels were examined there was six-fold reduction in SPD754 levels by the co-administration of 3TC, which did not occur, in the opposite direction. These data suggest that it is imperative to evaluate tri-phosphate concentrations of agents to assess drug-drug interactions prior to commencing clinical efficacy studies if the active moiety could potentially be affected by co-administration. The speaker pointed out, however, that since SPD754 is targeted at viruses that are already resistant to 3TC, this particular interaction should not, per se, affect the development of the compound.

A study of SPD75, at dose from 400mg to 1600mg daily, in 63 patients, some of whom had baseline thymidine analogue mutations, showed no evolution of new resistance mutation after 10 days monotherapy and substantial viral load reductions [3]. In addition, a 52 week safety study in cynomolgus monkeys demonstrated no significant toxicity, although some hyperpigmentation developed as well as mild gastrointestinal side effects [4]. This was in contrast to the racemate of the drug, BCH-10652, which was associated with significant degenerative skin disease.

Several other new compounds were presented as in vitro studies suggesting that the hunt for new drugs that target the reverse transcriptase enzyme has not yet reached saturation.

GlaxoSmithKline showed their new non-nucleoside agents, GW678248 and GW695634, both of which seemed to work well against panels of NNRTI resistant strains of virus [5]. In addition, the compounds were examined for evidence that they could reduce the primer unblocking reaction that has been proposed to contribute to AZT resistance and using a filter paper binding assay these agents seemed to reduce it significantly.

Boehringer Ingelheim (Canada) also presented new versions of nevirapine with quinolone moieties, which appeared to abrogate the effect of some of the mutations known to affect the efficacy of the parent compound [6]. No clinical data are yet available.

The team from Tibotec and Janssen Pharmaceuticals produced yet more potential agents with a study of diarylpyrimidines and diaryltriazines, which appeared more potent than available NNRTIs, and to have favourable pharmacokinetics [7]. Sadly Paul Janssen the doyen of Janssen Pharmaceuticals died recently and one hopes that his work will continue unabated since he was a great champion of HIV within the pharmaceutical industry and a formidable chemist, as well as a fascinating raconteur.

A clinical study of the new protease inhibitor TMC114 boosted with ritonavir was presented: TMC114-C207 [8].

This was a randomised three-arm study of 300mg, 600mg or 900mg twice daily with 100mg ritonavir as a pharmacokinetic booster in subjects failing on a PI-containing regimen. Thirty-five subjects were randomised to receive active drug or placebo and the median viral load decline was -1.2, -1.3 and -1.5$\log^{10}$ copies/mL in the three groups respectively although there was no statistical difference across the arms. The reduction in viral load was unaffected by phenotypic resistance to all licensed

PI's or baseline viral load. This drug seems promising although no tolerability data were presented. A further poster presentation on TMC114 examined the resistance profiling of the drug against 1600 PI clinical resistance isolates [9].

The isolates were grouped as >4-fold resistant to 1, 2, 4, 5, 6 or 7 currently available PIs and TMC114 performed well in vitro against all of these isolates, demonstrating at most a <4-fold change to isolates resistant to all seven drugs or with three major PI mutations. A similar study also examined the activity of TMC125, the Tibotec NNRTI that is now in Phase III studies. Four single mutants, one double and one triple mutant showed reduced susceptibility to TMC125 although these mutants were at low levels in the population. Mutations at positions 101, 179, 181 and possibly 227 and 230 may play a role in decreased susceptibility to the drug and the triple mutation K103N, L100I with either Y181C or T386A appears to produce >10-fold resistance to TMC125.

Moving from inside the cell to the surface, Steve Piscatelli from GlaxoSmithKline presented exciting data on GW873140, a CCR5 receptor antagonist which joins SCH-D from Schering and UK427,857 from Pfizer in the race to see who can first bring one of these receptor blocking agents to the clinic [10]. This drug has an IC50 of 1-5nM and a unique binding profile to the CCR5 receptor. A double blind randomised placebo controlled study was conducted in 70 fasted subjects (57 men and 13 women). Subjects received single doses of 50, 200, 400, 800 or 1200mg fasted or 400mg with a standard breakfast in cohorts of 10 subjects (eight treated and two placebos). Thereafter a multiple dose phase was conducted with a seven-day dosing of 200, 400, 600 and 800mg twice daily. Initial data suggested the drug was well tolerated with some mild to moderate side effects of abdominal cramping, diarrhoea and nausea. No changes occurred in ECG measures, specifically not QT prolongation, which has been a potential side effect (in other drug development programmes) and no serious or grade three or four adverse events were seen. The AUC increased from 130 to 479 ng/ml from the 200 to 800mg dose level and food increased the AUC by 1.7-fold and the Cmax by 2.2-fold. In the single dose arms the viral load had returned to baseline in 50% of the subjects by 24 hours with 66-84% occupancy of the receptor whereas in the multiple dose arms occupancy at two and 12 hours post dose was 93-99%. This agent unfortunately appears to have minimal CNS penetration, but looks set to advance through the development process apace with such favourable safety and viral load decline data. As with the other CCR5 inhibitors under evaluation, the question of whether the drug can be given once daily needs clarification in further clinical trials.

Mark Laughlin from Schering-Plough then showed their latest information on the second CCR5 receptor antagonist inhibitor the company has developed, SCH-D [11].

This has a better in vitro potency than SCH-C and improved bioavailability. A study evaluating SCH-D in subjects with CD4 >250 cells/mm3 and HIV RNA 5,000-200,000 copies/mL evaluated three dosage levels (10mg, 25mg and 50mg BID) in cohorts of 16 subjects (14 treated and two placebo). The viral load decline at 14 days was 1.0, 1.2 and 1.5 $\log^{10}$ copies/mL respectively for the three doses. One subject who was of mixed CCR5 and X4-virus showed a 0.5 log10 copies/mL drop in viral load with no change in susceptibility over the treatment phase. A further individual with >1.5 $\log^{10}$ copies/mL showed a transient detection of X4 virus following cessation of the drug. The percentage rates at each dose level (20, 50, 100mg/day) for >1log decline was 55%, 69%, and 81%, and for >1.5log decrease in HIV RNA 27%, 46% and 45% respectively. To date, 275 individuals have received this agent and no significant toxicity has been seen. There appears to be a good correlation between in vitro activity and in vivo efficacy, which will allow correlation of potency to be evaluated. It would appear also that this drug is extremely difficult to select resistant viruses for, which bodes well for the durability of efficacy. However, this will only be clear when prolonged dosing has been undertaken.

The earliest step in the entry of the virus into the host cell is the attachment of gp120 on the virus coat to the CD4 receptor on the cell surface.

Bristol Myers Squibb have a stable of potential agents that they are developing to block this interaction. Last year they showed data on BMS-378806, a forerunner for the new molecule BMS-488043 they presented at this conference [12].

Both of these are small molecules that have activity against viruses using all co-receptors, and in vitro and in animal studies appear non-toxic with no cross-resistance to currently available agents. The EC50 for the new compound is 36.5 compared to 61.5 for BMS-378806 and it has a superior half-life.

The latest study, AI430-003, is a proof of concept trial involving subjects not receiving antiretroviral therapy and with a T4 count >250 and a viral load between five and 500,000 copies/mL. Subjects were randomised 4:1 to receive active drug or placebo and two cohorts of 15 subjects were given 800mg or 1800mg twice daily with a high fat meal. There were two women in the lower dose cohort and one in the 3600mg cohort. Baseline median viral load was 4.77 and 4.65 $\log^{10}$ copies/mL and medianT4 count 413 and 372 respectively. Viral load decline at day eight was 0.72 and 0.96 $\log^{10}$ copies/mL for the two dosage groups and maximal median decline was 1.01 and 1.23 $\log^{10}$ copies/mL. T4 cell rises were seen of 106 cells (range -214 to +272) for the 1600mg arm and 48 cells (range -177 to +191) for the 3600mg arm. The percentage rates at the two dose levels was for >1log decline 58 versus 67% and for >1.5log decrease 24 compared to 42%. No serious adverse events or discontinuations occurred and apart form mild fatigue in four subjects and headache in two, no side effects were reported. The optimisation of exposure-response relationship is ongoing for this drug and it appears a very promising new agent.

Overall, there is a rosy picture emerging of antiretroviral opportunities for the next couple of years with the drugs acting outside

the cell holding promise for effective non-toxic drugs that could dramatically alter the way HIV is treated.

Source:

http://www.natap.org

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Little benefit seen for treatment during acute infection

Keith Henry, thebody.com

Bruce Walker walked across the hall from the immune response session (featuring four Walker-linked studies) to present an update on his highly visible and often-presented small study of patients treated during primary infection who subsequently underwent several sequential treatment interruptions (STIs). The initial results from the study (3/8 maintained <5,000 copies HIV RNA after the first STI and 5/8 maintained <5,000 copies/mL after the second STI) suggested that very early antiretroviral therapy during primary infection, followed by a series of brief treatment interruptions, could lead to improved immune control of HIV off therapy. Those results have stimulated the practice of treating primary infection and spawned enthusiasm that immunologic interventions (such as therapeutic vaccination) could also be utilised in chronic infection.

Dr Walker then presented the longitudinal data for 14 patients (all had acute retroviral syndrome) followed for an average of 5.3 years including for up to three years after the last STI. Only 1/14 of the patients had maintained control of viraemia (defined as <5,000 copies RNA/mL). The second and third STI failed more quickly, with the fourth STI providing no observable benefit.

The rate of CD4 count loss when antiretroviral therapy was stopped was quite high and it was not much different from the CD4 loss observed when stopping antiretroviral therapy in the setting of chronic infection. Dr Walker then discussed what factors could be identified that could predict the control of viraemia. They had looked at HLA type, CCR5 status, GBV-C infection, time of treatment since onset of ARS symptoms, viral load at seroconversion, and anti-HIV immunity from CD4+ or CD8+ T-cells. None of those factors predicted control of viral rebound.

Particularly disappointing was the observation that, although anti-HIV immunity appeared to be enhanced with the STIs, this did not translate into observable clinical benefit. These results were interpreted to indicate that durable maintenance of low-level viraemia might be difficult to achieve. The CD4 declines were substantial with immune escape at even low viral loads sufficient to be a problem.

In a question to Dr Walker, Joe Eron made the comment that the window to perhaps protect anti-HIV immunity during primary infection may be vanishingly short. Another questioner pointed out that the definition of failure (confirmed viral load >5,000 copies/mL or one level >50,000) made it difficult to perhaps see some attenuation in the true magnitude of viral rebound. Although Dr Walker stated that randomised clinical trials of early treatment and immune interventions are needed, the enthusiasm about the potential for this to achieve much has waned.

In all, the different presentations on acute infection suggested that we could do much better in finding and preventing recent infections. Although discussed a lot, superinfections still seem to be relatively unusual but are a growing problem. And it's still unclear how helpful treatment during acute infection is.

Source: www.thebody.com

Ref: Kaufmann D, Lichterfeld M, Altfeld M et al. Limited durability of immune control following acute HIV infection. 11th CROI 2004, Oral abstract 24.

CROI: RESISTANCE

Summary of resistance studies at Retrovirus

Many of the oral presentations provided a higher profile for research than was first presented at the XII International HIV Drug Resistance Workshop, Los Cabos, Mexico, held in June 2003.

These studies, based on the same data are reported in our report from that meeting in September/August 2003 issue of HTB.

http://www.i-base.org.uk/pub/htb/v4/htb4-7/index.html

Summary conclusions from these important studies included:

- the persistence of transmitted drug resistance including 9/11 patients including no PI-reversion to wild-type after more than three years. [1] Similar duration of transmitted resistance was also reported by a UK group in a new study at the meeting. [2]
- that efavirenz-exposure correlated more strongly with treatment failure than the absence of evidence of genotypic NNRTI-resistance and that most currently available resistance assays are insufficiently sensitive to detect this low-level resistance. [3]
- discussions about the K65R mutation and the possible protective benefit from using thymidine analogues in tenofovir-containing regimens. [4, 5]

Several studies also provided updated information on the incidence of NNRTI resistance in mother to child transmission programmes using single-dose nevirapine and these are covered in detail by Polly Clayden in this issue of HTB.

A study from the UK presented for the first time at this meeting indicated that response to first-line treatment in patients who have been infected with single-class associated drug-resistant virus can be similar to response in treatment naïve individuals. The researchers commented that the response to future treatments is likely to be where the impact of the transmitted resistance becomes clinically significant through reduced treatment options. [6]

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CROI: SIDE EFFECTS

Update on peripheral neuropathy in HIV-infection

Paul Blanchard, HIV i-Base

A major plenary session at this year's CROI was devoted to the important issue of distal symmetrical polyneuropathy (DSPN) in HIV-infection [1]. This formed part of an oral session devoted to neuropathogenic manifestations of HIV-1 infection, which together with additional poster sessions provided a useful forum for presenting advances in the field.

David Simpson, professor of neurology at Mount Sinai Medical Center, New York, gave an update on DSPN, which focused on issues of epidemiology, diagnosis and misdiagnosis, the toxicity of antiretrovirals to the peripheral nervous system and pain and the management of pain.

Since the widespread introduction of HAART the incidence of DSPN in the HIV-infected population appears to have increased - from 17.3 per 1000 person years in 1994 to 31.1 by the year 2000 (John Hopkins HIV Clinical Cohort).

New assessment tools

NARC, a sub-study in ALLRT (Adult Longitudinal Linked Randomised Trials) looked at the sensitivity and specificity of a brief peripheral neuropathy assessment (BPNS) carried out by a nurse coordinator and how these correlated with a total neuropathy screen (TNS) performed by neurologists [2]. Patient population used was a subset of subjects (n=301) enrolled in studies to assess the impact of HAART on neurological disease in HIV.

The rate of neuropathy diagnosed using the BPNS was 20% vs 32% using a TNS. This gives the BPNS a sensitivity of 46% and a specificity of 91%. The investigators conclude that this brief peripheral neuropathy assessment provides a quick, simple and low-cost screening tool with acceptable diagnostic efficiency. These characteristics should allow for easy incorporation into large scale clinical trials.

Why aren't all of us diagnosing DSPN in a third of all our patients?

Many patients with DSPN can be asymptomatic at the time of presentation. Using an earlier form of BPNS 71% of patients with HIV-infection diagnosed with DSPN had no neuropathy symptoms [3]. In support of these figures a separate study (Manhattan HIV Brain Bank) found that 71% of cases meeting a neurologist evaluation for DSPN had not been diagnosed previously or mentioned in patients' case notes [4]. Unsurprisingly, of the asymptomatic cases newly diagnosed, 86% were undiagnosed previously. This highlights the fact that many clinicians will not attempt to diagnose the disease when patients are not complaining of symptoms. Of more concern, however, is that 63% of symptomatic cases had not been diagnosed by clinicians prior to this study.

Risk factors for neuropathy

Over the years, attempts have been made to determine the risk factors associated with the development of DSPN. It is now well established that an increased risk of development occurs with increasing immunosuppression.

The DANA Consortium study also established risk factors for incident DSPN [5].
Patients entered the cohort with a CD4 cell count <200 cells/mL. Using neurological assessment it was found that by 12 months after entry 25%, and at two years over 50%, had evidence of symptomatic neuropathy.

Much of the data on incidence and risk factors comes from the pre-HAART era so an attempt has been made in the last couple of years to determine how this data may have been modified by HAART. It has been established that the higher the viral load at baseline prior to HAART, the higher the risk for the development of DSPN [6]. In a sub- study of the ACTG nerve growth factor trial the severity of neuropathy, both by intensity of pain and degree of abnormality of quantitative sensory testing (QST), also correlated with plasma viral load [7].

Does treatment of HIV make PN better?

Here there appear to be very few data so far. At least with QST, thermal threshold has been seen to improve with effective control of plasma viral load [8]. It has also been established that intraepidermal nerve fibre (IENF) loss at the distal leg is associated with increased neuropathic pain, lower CD4 counts, and higher plasma viral load in HIV-DSPN [9]. Early results presented at this meeting also suggest that reductions in IENF density may be reversed with effective HAART therapy and/or modification of didanosine and stavudine components of regimens [10].

A major study expected to improve on the available (mostly retrospective) data was introduced by Professor Simpson. ACTG 5117 is a DSPN study of 100 subjects with CD4 <300 cells/mm3 looking at the risk factors for the development and progression over 48 weeks using an intensive neurological evaluation:

- sensory and motor signs and symptoms
- QST (vibration, heat and cooling)
- nerve conduction
- intraepidermal skin biopsy (IENF)
- lymphocyte MtDNA

Data are currently being analysed and should be available within the next few months.

Nucleoside analogue related DSPN

Clinicians frequently encounter DSPN related to the use of dideoxynucleoside agents (stavudine, didanosine, zalcitabine). This form of DSPN is clinically indistinguishable from HIV-related DSPN in any given patient and in many patients they may often overlap. Pain when therapy is stopped should resolve within 8 – 16 weeks, although the signs of neuropathy may remain much longer. Additionally there are likely to be additive or synergistic effects between the impact of both HIV and dideoxynucleosides on nervous tissue. As Professor Simpson stated: "The more bad things you do to the peripheral nerve the less happy it gets".

Up to a 28-fold increase in the incidence of DSPN over and above HIV alone has been seen with a variety of nucleoside or nucleoside plus hydroxyurea (HU) regimens. These side effects have been a major factor in the reduction in prescribing of certain regimens (eg. ddI+d4T, ddI+HU).

Pathogenesis of distal polyneuropathy

The pathogenesis of DSPN in AIDS is currently unknown even though the pathology is relatively well characterised.

Justin McArthur and colleagues have shown "deposition" of TNF-alpha in peripheral nerves correlating with neuropathy [11]. There are also neurotoxic byproducts of HIV replication such as gp120 [12]. At this meeting Keswani and colleagues presented data demonstrating that application of gp120 to dorsal root ganglia (DRG) culture leads to a reduction in the length of neuritic outgrowth with the nociceptive DRG neuronal population being particularly vulnerable [13]. Similarly when various nucleoside analogues (ZDV, ddI, d4T, ddC) are introduced to neuritic cell cultures the potency with which each NRTI inhibits neuritic outgrowth parallels the potency of each drug in causing peripheral neuropathy in HIV positive patients, ie ddC > ddI >d4T [14]. An intriguing question that remains is why different nucleoside analogues have different organ system toxicities?

The whole issue of mitochondrial toxicity and its potential pathogenetic role in numerous organ system toxicities has been a matter of great discussion and debate. Similarly, there are questions about the effects of dideoxynucleosides on mitochondria as a potential mechanism for the pathogenesis of both DSPN and another neurological disease - the ascending neuromuscular weakness syndrome.

What do we know about drugs and mitochondrial function?

Serum lactate, a presumed marker of mitochondrial dysfunction, has been measured in a study by Bruce Brew and colleagues in various groups of patients with and without neuropathy who were either receiving or not receiving d4T [15]. A significant elevation of serum lactate was seen in those patients with DSPN receiving d4T compared to those receiving d4T without DSPN and those with purely HIV-related PN. Additionally, it has been shown that ddC induces a mitochondrial neuropathy with depletion of the nerve's mtDNA. These findings are consistent with the ability of ddC to selectively inhibit the gamma-DNA polymerase in neuronal cell lines [16]. However, Professor Simpson suggested that caution must be exercised in ascribing mitochondrial toxicity just to the presence of mitochondrial abnormalities in patients with HIV-infection receiving dideoxynucleosides. Similar, although less severe, mitochondrial abnormalities were seen in neuronal culture with the addition of gp120 alone [17], raising the possibility that there may be synergistic effects between HIV and the dideoxynucleosides on mitochondria.

HIV-associated neuromuscular weakness syndrome

This newly described syndrome also points to the role of mitochondrial dysfunction in DSPN. Sixty-nine patients have been identified in a retrospective series (Simpson et al. In Press, AIDS 2004). The syndrome is characterised by a rapidly progressing motor weakness that superficially mimics Guillain-Barre syndrome. In many of these patients, this syndrome is associated with lactic acidosis. It is hypothesised that there is a potential combined mitochondrial/immunological pathogenesis occurring through the interplay between HIV and dideoxynucleosides.

Management of DSPN

One of the most challenging aspects for physicians is the consideration of what to do with patients experiencing DSPN who are also receiving neurotoxic antiretrovirals.

Unfortunately, there is no black and white answer and Simpson suggested that consideration be made of the following factors;

- identify and attempt correction of metabolic or nutritional causes
- optimise HIV virological control
- assess risk of progressive neuropathy
- assess the risk to virological control of modifying antiretrovirals
- availability of active non-neurotoxic antiretrovirals for a given patient.

In some patients, a stop-and-switch strategy may be employed, while in others there may be no choice but to continue a regimen that includes dideoxynucleosides.

Pathophysiology of neuropathic pain

When one begins to address pain there is a complex set of mechanisms that we do not completely understand which may be going on within one particular patient. These pathophysiological mechanisms may have a huge bearing on the mechanism and efficacy of treatment. Among the processes contributing to the generation of pain the following are thought to be the most significant:

- chemical excitation of nociceptors
- recruitment of nerves outside of site of injury

- excitotoxicity
- sodium channels
- ectopic discharge
- deafferentation
- central sensitisation (maintained by peripheral input)
- sympathetic nervous system involvement
- antidromic neurogenic inflammation
- loss of neurotrophins (NGF)
- neurotoxins (gp120, cytokines: TNF, IL-1, IL-6)

Pain interventions may be directed at one or many of these contributing processes. Similarly, interventions may be targeted at anatomical sites of pain generation and transmission (periphery to cortex) or some of the physiological pathways of pain perception (transduction, transmission, modulation, perception, interpretation, behaviour). Such guided therapy has become known as a mechanism or pathogenesis based approach [18].

Under-treatment of pain in AIDS and cancer

Pain is a huge and challenging problem in HIV-infection. Eighty-four percent of ambulatory patients with AIDS have been found to be receiving inadequate analgesia according to the WHO criteria compared to 42% of patients with cancer [19]. Why is this? Barriers to the effective management of pain in HIV-infection have been explored by Breitbart [20, 21] and may be:

i) patient related
   - stoicism - a reluctance to report pain
   - fear of substance abuse and associated stigma

ii) health care provider related
   - fear of addiction
   - fear of being conned (diversion of controlled drugs)

iii) health care system related
   - restrictions and bureaucracy of prescribing controlled substances.

Neuropathy clinical trials

A wide range of clinical trials over many years has attempted to determine effective treatment for HIV related DSPN. These may be divided into those attempting to address the symptoms and those that attempt to modify the pathogenesis of DSPN, restoring nerve function and thereby reducing symptoms.

Simpson highlighted some of these in this meeting update.

Lamotrigine

Lamotrigine is an anticonvulsant that has generated interest as a potential treatment for DSPN. It has been explored most recently in a multicentre, double blind, placebo controlled trial of 11 weeks duration [22]. Patients with DSPN were stratified according to exposure to neurotoxic antiretrovirals versus no exposure. A significant benefit on pain of lamotrigine over placebo was seen in those patients receiving neurotoxic antiretrovirals. Interestingly, and somewhat paradoxically, no benefit was seen in patients not exposed to neurotoxic antiretrovirals.

Opioids

Opioids can be an effective management strategy in neuropathic pain. Numerous controlled studies (in postherpetic neuralgia, phantom limb pain, diabetic neuropathy, but not yet in HIV) establish them as an important part of the treatment armamentarium.

Topical treatments for neuropathic pain

These have received increasing attention over the last couple of years with lidocaine and capsaicin being the prime candidates. A topical agent has the advantage of being delivered at the sensory level of the skin rather than as another systemic agent on top of the many systemic agents delivered by pill that the patient is already likely to be receiving.

Capsaicin

This is the most active chemical constituent in chilli pepper (Capsicum sp.) - a volatile compound that is closely related to vanillin, a component of vanilla. It acts on a known receptor – the VR1 receptor and is mostly available as a low concentration cream (0.075% capsaicin), which is of questionable efficacy. However, high concentration patches are now being investigated

in experimental studies.

McArthur, using skin biopsy, has shown a mechanism of action of capsaicin. Forty-eight hours after a single application of capsaicin, virtually complete depletion of IENF has taken place. Twenty-seven days later, there is regeneration and repletion of these fibres. This effect is thought to be mediated by capsaicin stimulating the depletion of substance P, neurokinin, somatostatin, and calcitonin from peripheral nerve fibres, particularly C-fibres [23].

It may be asked if this strategy is safe. You are taking away important fibres at the level of the skin, albeit temporarily. Are you removing important aspects of sensation? QST shows a change in a couple of degrees C for detection of thermal threshold – probably not clinically significant, but no change in mechanical sensitivity.

A study of the efficacy of high concentration capsaicin patch versus low concentration patch has been performed in post herpetic neuralgia (Backonja et al. AAN 2003). Significant pain reduction was achieved in 33% of high concentration patch recipients versus 4% of low concentration patch recipients over one month.

High concentration capsaicin patch in HIV-associated DSPN

An open label study performed in painful HIV-associated DSPN was presented by Simpson et al. at this meeting [24]. Twelve patients received a single application and were then followed for three months. Topical anaesthesia was used before the application of capsaicin and over 40% pain reduction was achieved lasting for three months after this single application. Eight of 12 patients were responders based on thresholds of greater than or equal to 30% pain reduction from baseline. Overall, good tolerability was observed although exposure to high concentration capsaicin did lead to a significant increase in pain, but of short duration. Local dermal changes were limited to a transient erythema. Simpson concluded that further research in controlled studies is now needed as such local treatments are attractive as an alternative or complement to centrally acting agents.

Standard concentration capsaicin patches normally contain 10–40 mg/cm^2 whereas those used in this study contained 640 mg/cm^2. The pain and discomfort induced by application of such a high concentration should not be underestimated and although 100% of subjects completed the one application it is unknown if any would subject themselves to the procedure a second time. Previous studies have been performed with high concentration capsaicin for patients with intractable pain [25]. Here, capsaicin concentrations of 5–10% were used after the administration of regional anaesthesia by epidural or peripheral nerve block and sedation with midazolam. After nerve blocks wore off, intravenous fentanyl was required for pain relief and oral morphine after discharge. Only four of the original 10 patients in this study went on to receive additional applications.

Future directions for the research of DSPN highlighted by Professor Simpson at the end of his update included diagnostic criteria, risk factors, antiretroviral toxicity and both symptomatic and pathogenesis based treatments.

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Smoking marijuana provides analgesic effect on HIV neuropathy

Graham McKerrow, HIV i-Base

A nine-day pilot study of 16 patients carried out by researchers at the University of California, San Francisco, found that smoking marjuana had an analgesic effect on HIV neuropathy.

Sixteen patients (14 men, median age 43) with previous experience of smoking marijuana, but who had not done so for 30 days prior to the study, and with an average of six years duration of neuropathy, were enrolled in the open-label, in-patient study. Neuropathy was related to HIV alone (3), nucleoside therapy (8) or both (5). After a two-day lead-in period, patients smoked one 3.56% THC containing joint three times a day for seven days. A heat capsaicin model induced experimental pain. Patients experiencing a greater than 30% reduction in their 24-hour neuropathy pain scored on a 0-100 visual analogue scale were assessed as responders.

The mean baseline average daily pain value was 47/100 but this dropped to 40/100 following the two-day lead-in. The smoking of marijuana caused a drop in mean pain score to 20/100, with 10/16 patients experiencing a greater than 30% reduction in average daily pain.

The researchers report: “Excellent correlation was seen in response to the heat capsaicin model where 14/16 patients experienced a greater than 30% reduction in the area of secondary hyperalgesia after smoking.”

In an attempt to confirm these preliminary results, the researchers have initiated a 50-subject, seven-day randomised placebo-controlled trial.

Ref: Jay C, Shade S, Vizoso H et al. The effect of smoked marijuana on chronic neuropathic and experimentally induced pain in HIV neuropathy: Results of an open-label pilot study. 11th CROI 2004, Abstract 496.

CROI: METABOLIC COMPLICATIONS

Two D:A:D updates: cardiovascular risk from HAART, and predictors of hypertension and changes in blood pressure

Simon Collins, HIV i-Base

The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study is the largest cohort study initiated to investigate whether HAART was linked to increased risk of cardiovascular disease (CVD). At the 2003 Retrovirus conference an analysis from the first 123 incidents of myocardial infarction (MI) predicted a cumulative relative rate of 1.26 with every year of HAART. While the absolute risk remained low, and was still clearly outweighed by the benefits of HAART, it was clear that health advice given to the general population was equally if not more important for HIV-positive patients.

Two posters were presented at this year’s meeting that included new information from the same study.

In poster 737, an analysis based on other predictors of CVD (rather than just MI as in last year’s analysis) confirmed previous cumulative risk associated with HAART and suggested that the causal mechanism was similar for this composite endpoint. [1]

The observed rates of MI seen in D:A:D were also compared to the rates that would have been predicted from the Framingham equation. Best predictions of MI rates assumed a five-fold increased risk of MI with previous CVD with upper limits assuming that features of metabolic syndrome (lipodystrophy, BMI >30kg/m2 and triglycerides >2.3 mmol/L) carried a similar increased risk as pre-existing diabetes in the general population; and lower limits assuming that these metabolic changes contribute no clinical risk over five-10 years.

Patients not receiving HAART had fewer events than predicted (three observed vs 7.6 predicted). Patients on HAART had slightly higher numbers of MI than best predicted rates but generally lower than the upper limit predictions. The trend for higher events related to duration of HAART was similar to those that would have been expected based on known risk factors. The study concluded that the observed increase in risk of MI could largely be explained by HAART-induced changes in

conventional CVD risk factors. On these data there is no cause to change last year's recommendations concerning diet, exercise and smoking cessation.

A second study analyses longitudinal changes in blood pressure (BP) from just over 16,000 patients on the D:A:D database. More than 43,000 BP measurements were included (median three per patient over a median of 1.5 years [IQR 0.8-1.7]. [2]

Risk factors significantly associated with a higher predicted increase in systolic BP (>/= 5mmHg) were older age (+12.8 and 14.5 mmHg at baseline and month 24, respectively, for 60 years old versus 30 years old), male (+7.0 and +6.6 at baseline and month 24, respectively, male versus female), higher BMI (+16.4 and +15.6 at baseline and month 24, respectively, for those with BMI>30kg/m_ versus <18) and blood pressure-lowering drugs (+8.3 mmHg at baseline and month 24 for those treated with an antihypertensive treatment).

In 8,341 patients with normal BP at baseline, 487 developed hypertension providing an incidence of 35.8/1000 patient years. Factors associated with hypertension were similar to those in the general population: older age, male gender and higher BMI. Cumulative exposure to any individual drug class or type of treatment at baseline was not associated with change in BP or risk of hypertension.

C O M M E N T

Because of the fortunately small number of events even such a large cohort as D:A:D is not powered to allow a subanalysis of the association of cardiovascular events and antiretroviral classes or even specific drugs. Evidence-based recommendations cannot therefore be made for specific antiretroviral drugs.

In addition, due to the huge variability as a result of the low number of events and the limited data base in some aspects D:A:D is not able to exclude additional less pronounced risk factors, which may explain the rapid rise in cardiovascular events after only one year of exposure to antiretrovirals.

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Low-dose rHGH maintains reductions in abdominal fat for 60 weeks

Simon Collins, HIV i-Base

Although several studies have shown that recombinant Human Growth Hormone (rHGH) can reduce abdominal fat accumulation and buffalo hump, the benefits have been reported to be transitory, and to reverse when treatment is discontinued. In an oral presentation, Donald Kotler presented results from using a maintenance dose of rHGH in patients who had previously responded to rHGH in the earlier STARS trial.

This extension study randomised 127 patients to 1mg or 2mg daily maintenance therapy for 24 weeks, after having used 4mg rHGH on alternate days for at least 12 weeks. One hundred and nineteen patients completed 36-60 week follow up from start of initial rHGH treatment.

Significant reductions from the start of the STARS trial (baseline) to week 60 were found in both the 1mg and 2mg maintenance groups for trunk fat measured by DEXA scan (-1.1, -1.4 kg from 9.5 and 9.8 kg), non-HDL cholesterol (-21.2, -23.8 from 175.6 and 172.1 mg/dL), and total cholesterol (-16.9, -18.5 from baselines of 213.0 and 209.2 mg/dL); all $p<0.05$.

Oral glucose tolerance testing revealed no change from baseline to week 60 in insulin area under the curve. There were no between-group differences in any parameters from baseline to weeks 36 or 60 among patients who received 1mg or 2mg, nor differences in incidence of most common adverse events, except for arthralgia (5.7% on 1mg vs 12.5% on 2mg) during the 24 weeks maintenance period.

Kotler concluded that based on a more favourable safety profile, the 1mg daily r-HGH dosage merits additional investigation as a maintenance therapy for HIV patients who have benefited from abdominal fat reduction at a higher r-HGH dose.

C O M M E N T

The main problem with this trial is the lack of approval of r-HGH in Europe. It is still unclear which endpoints will be accepted by the EMEA or FDA for approval of drugs that are able to change the course of lipodystrophy.

Ref: Kotler DP, Grunfeld C, Muurahainen N et al. Low-dose maintenance therapy with recombinant Human Growth Hormone sustains effects of previous rHGH treatment in HIV+ patients with excess centre fat: treatment results at 60 weeks. 11th CROI 2004, Oral Abstract 80.

Rosiglitazone shows no benefit for lipoatrophy

Simon Collins, HIV i-Base

Several research groups have already reported that rosiglitazone (RSG) is not an effective agent to treat lipoatrophy, [2, 3] and this was confirmed in an oral presentation of a new study from Andrew Carr. [1]

This study randomised 108 patients with lipoatrophy to either 4mg rosiglitazone twice-daily (n=53) or placebo (n=55) for 48 weeks. The study was powered to detect a 0.5kg difference in limb fat by DEXA scan.

Limb fat increased by 0.14 kg in the RSG group and 0.18 kg in the placebo group (mean difference, -0.04 [95%CI, -0.29, 0.21] kg; *p*= 0.74 by rank-sum test). There was no benefit of RSG on: subcutaneous thigh or abdominal fat, or visceral fat or objective or subjective assessment of lipodystrophy severity (p= 0.99 and p= 0.42 respectively).

There were significant increases in plasma adiponectin (4.1 mmol/L [101%]; p<0.0001), which was the theoretical rationale behind the study, but not leptin (0.2 mmol/L [6%]; p= 0.33), and significant (p= 0.01 - 0.02) decreases in three markers of insulin resistance with RSG. No subgroup, defined by PI use, thymidine NRTI use, limb fat mass, or insulin resistance at baseline, derived benefit for limb fat with RSG.

The key adverse effects of RSG were asymptomatic hypertriglyceridaemia (mean peak increase, 1.5 mmol/L [58 mg/dL; 40%] at week 8; +0.9 mmol/L [35 mg/dL] at week 48; p=0.007) and hypercholesterolaemia (mean peak increase 1.9 mmol/L [170 mg/dL] at week 8; +1.5 mmol/L [132 mg/dL; 16%] at week 48; p= 0.0001). There was no significant effect on viral load or CD4 counts.

C O M M E N T

Previous studies showing that rosiglitazone does not improve lipoatrophy, even at higher doses than used in this study, were presented at the 5th International Workshop on Lipodystrophy in Paris last year, and at the Retrovirus Conference in 2002. [2, 3]

These results are in contrast to data reported from non-HIV associated lipodystrophy and NIDDM type-2 patients from glitazones. These patients showed a partial reversal of central fat accumulation and in the first group a trend for an increase in subcutaneous fat. Dyslipidemia in this study seems to be the same as reported from patients with diabetes mellitus type-2.

In March 2003, a study published in AIDS showed some return of fat with pioglitazone, which also did not increase cholesterol or triglycerides. However this was an uncontrolled case study in 11 patients which limits the conclusions to be drawn from this study. Takeda, the manufacturer of pioglitazone, apparently has no interest in HIV and because of this the data are limited. [4]

References:

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CROI: WOMEN'S HEALTH

Hypertension related to HAART in HIV-positive women

Polly Clayden, HIV i-Base

A poster reporting data from the US Women's interagency HIV study (WIHS), an ongoing, prospective, multi site cohort study of HIV positive and at risk HIV negative women, evaluated the occurrence of hypertension and its association with HAART. [1]

In this analysis, data from 2,057 HIV-positive and 569 HIV-negative women enrolled in 1994 and 1995 were evaluated. Study visits occurred every six months and the evaluations were performed at visit 16.

Hypertension was defined as elevated diastolic blood pressure >90 mmHg or elevated systolic blood pressure >140 mmHg on physical exam during a routine study visit or the taking of antihypertensive medications.

The investigators found the baseline prevalence rate of hypertension to be 19% for both HIV-positive and HIV-negative women. The overall incidence rate was not significantly different between the HIV-positive (47%) and HIV-negative women (46%).

In both univariate and multivariate analyses they reported: increasing age, African American race, lower education level, smoking, increasing body mass index (30+), and use of HAART (RR 1.26, 95% CI: 1.10 to 1.48, p=0.01) to be significantly associated with hypertension. They also found that both current pregnancy, and AZT monotherapy (RR 0.50, 95% CI: 0.35 to 0.72, p=0.0001) offered protection from hypertension.

Lower CD4 count and higher viral load were associated with a reduced risk in univariate analysis for developing hypertension, although neither was found to be significant in multivariate analysis. The investigators also reported a time-dependent relationship between duration of therapy and hypertension (RR 1.32, 95% CI: 1.11 to 1.58, p=0.02 for one six-month interval on HAART; RR 1.36, 95% CI: 1.12 to 1.65, p=0.02 for 12 months; and RR 1.51, 95% CI: 1.30 to 1.75, p<0.0001, for more than 18 months on HAART).

The investigators concluded that after controlling for risk factors such as age, race and body mass index an increased RR of developing hypertension was found in HIV-positive women on increasing duration of HAART. However, they reported that this did not correspond with the overall incidence rate or with incidence across visits in which no difference was found between the HIV-positive women receiving and not receiving HAART, nor between the HIV-positive women and at risk HIV-negative women. They also noted a possible protective use of AZT monotherapy although not AZT as part of a HAART regimen.

C O M M E N T

One interpretation of these data could be that treating HIV infection restores the normal risk of hypertension. There was also informal discussion of this as a possible explanation for reported pre-eclampsia in pregnancy and HAART. [2]

The mechanism is obscure but then so is the cause of essential hypertension but perhaps some involvement of the immune system is needed for essential hypertension as it is for pre-eclampsia.

References:

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2. Coll O, Suy A, Martinez E et al. Increased risk of pre-eclampsia and foetal death in HIV-infected pregnant women receiving highly active antiretroviral therapy. 11th CROI. Abstract 921.

Testosterone therapy for women with low androgen levels or body weight

Polly Clayden, HIV i-Base

Dr Dolan from the Massachusetts General Hospital, Boston, USA, presented findings from a double blind, placebo controlled study to evaluate the safety, efficacy and tolerability of testosterone administered to women with reduced androgen levels and low body weight.

A group of 57 HIV-positive women whose free testosterone was less than the median of the normal reference range, and whose weight was less than 90% of the ideal body weight (or whose weight loss was greater than 10%), were randomised to receive transdermal testosterone (4mg per patch) twice weekly (n=29) or placebo (n=28) for a period of six months.

The effect of the treatment was assessed in two ways: muscle mass was assessed by urinary creatinine excretion and muscle function was assessed by the Tufts Quantitative Muscle Function Test.

The investigators reported that at baseline all women had low weight (body mass index = 20.6+/-0.4 kg/m 2), significant weight loss from pre-illness maximum (18.7+/-1.2%), and reduced muscle function.

Among the women receiving the testosterone treatment there was significant rise in testosterone levels (total testosterone: 37+/-5 vs –2+/-2 ng/dL, p<0.0001; free testosterone: 3.7+/-0.5 vs -0.4+/-0.3 pg/mL, p<0.0001, testosterone and placebo arms respectively). The investigators observed that the testosterone was well tolerated, without adverse effects on immune function, lipids, glucose, liver function, body composition, or hirsuitism.

They also reported an increase in muscle mass (1.4+/-0.6 vs 0.3+/-0.8 kg, p=0.082). Muscle function in shoulders (0.4+/-0.3 vs -0.5+/-0.3 kg, p=0.023), elbows (0.3+/-0.4 vs -0.7+/-0.4 kg, p=0.036), knee extension (0.2+/-1.0 vs -1.7+/-1.3 kg, p=0.019) and knee flexion (0.7+/-0.5 vs 0.3+/-0.7 kg, p=0.036) increased in the women receiving testosterone compared to the women receiving placebo.

Dr Dolan concluded: "Testosterone administration is well-tolerated and increases muscle strength in low-weight HIV-infected women. Testosterone administration may be a useful adjunctive therapy to maintain muscle function in symptomatic HIV-infected women, but we need to find the optimal dosing strategy."

C O M M E N T

In general, steroids should be combined with regular physical exercise to improve the lean weight gain. This may explain the non-significant difference in muscle mass.

Ref: Dolan S, Wilkie S, Aliabadi N et al. Effects of testosterone administration in HIV-infected women with low weight: A randomised, placebo-controlled study. 11th CROI 2004, Abstract 151.

CROI: PREGNANCY, MATERNAL HEALTH AND MTCT

Nevirapine, pregnancy and adverse events

Polly Clayden, HIV i-Base

There have been legitimate concerns that the serious adverse events associated with nevirapine - including rash and hepatitis - which women are at greater risk of experiencing compared to men, may be heightened in pregnancy. Due to this agent's widespread use in pregnancy, there is potential for serious risk both to the pregnant woman and to her foetus were a serious event to develop. Three posters evaluate tolerability and toxicity of nevirapine use during pregnancy.

Kramer and colleagues from the University of Southern California, Los Angeles, performed a case note review of 125 pregnancies during the period March 1996 to November 2002 - in which women received nevirapine-containing HAART - to determine the tolerability of nevirapine in HIV-positive pregnant women according to ethnicity, CD4 and viral load [1]. Additionally the investigators analysed use in women with underlying risk factors for hepatotoxicity: chronic hepatitis B or C and alcoholism, according to duration of therapy and gestational age at initiation.

Of the group 76 (61%) were Latino and 36 (29%) were Black; 7 (6%) were co-infected with HCV and 18 (15%) with HBV. At baseline, the median CD4 count was 395 cells/mm3 and 86 women (66%) had CD4 counts <500 cells/mm3. Median HIV viral load was 4382 copies/mL with 57 (46%) women having <4000 copies/mL HIV RNA. 76 (63%) of women received nevirapine within the first 24 weeks of pregnancy with a median length of nevirapine therapy of 14 weeks (range 1 to 40); 29% were receiving nevirapine at conception. Of the 125 pregnancies, there were no transmissions (this in itself is an exciting finding).

Toxicities occurred in 17/125 (13%) women: rash in 8, elevated liver function in 6 and both in 3. The investigators reported no difference in mean baseline CD4 count between those women with or without toxicity (420 cells/mL for both, p=0.99). However, those women with CD4 >500 cells/mm3 had more frequent toxicity than those with CD4<500 cells/mm3, but this was not statistically significant (19%: 8/42 vs 11%: 9/82 p=0.22). Toxicity occurred more frequently within first eight weeks of nevirapine use, but again this did not reach statistical significance (7/ 37, 19% vs 10/87, 11%, p=0.27).

In multivariate logistic analysis, the investigators found no significant association between toxicity and ethnicity (p=0.22), baseline CD4 (p=0.14), baseline HIV RNA level (p=0.37) and duration of nevirapine use (per week increase: p=0.71 or longer than eight weeks: p=0.48). They also noted that there was no additional nevirapine toxicity among women taking nevirapine at the time of conception and who continued during pregnancy.

They concluded: "Nevirapine containing regimens provided effective treatment of our pregnant patients and contributed to our lack of perinatal transmission over the last seven years."

A second case note review from Bershoff-Matcha and colleagues at the University of Washington was performed to investigate this group's observation: "We anecdotally noted fewer serious adverse events among women who were initiated on nevirapine during pregnancy." [2]

Both pregnant (n=41) and non-pregnant (n=222) women receiving nevirapine at two clinics between September 1999 and July 2003 were evaluated in this study. Demographic data, CD4 counts, viral loads, concurrent medical therapies, and serious adverse events were reviewed.

The pregnant women were younger than the non-pregnant women (mean age 28.7 years for pregnant women vs. 38.0 years for non-pregnant women). The mean CD4 counts and viral loads for the two groups were 474 cells/mm3 (range 93 to 1,290) and 52,209 copies/mL (range 49 to 296,056) for the pregnant women and 289 cells/mm3 (range 3 to 1490) and 379,119 copies/mL (range 49 to >750,000) for the non-pregnant women respectively.

Only one pregnant woman (0.4%) and 38 non-pregnant women (14.5%) from this group developed any adverse event after

initiating nevirapine (OR = 8.26, 95% CI: 1.10 to 62.0, p=0.0153). The investigators reported mild adverse events (grades 1-2) in one (0.4%) pregnant woman and 21 (8.0%) non-pregnant women (p=0.1365) and serious adverse events (grades 3-4) in none of the pregnant women and 17 (6.5%) non-pregnant women (OR=7.07, 95% CI: 0.41 to 119.87, p=0.0675). They found risk of rash to be independent of race, age, CD4 count, viral load, or other medications including hormonal contraceptives, antihistamines and corticosteroids.

The investigators concluded**: "**Although our results are limited by small sample size, women in our study were significantly less likely to develop an adverse reaction to nevirapine when the drug was initiated during pregnancy."

Finally the FDA presented a report of a search of their Adverse Event Reporting System (AERS) database following reports of six deaths (three in 2003) of pregnant HIV-positive women receiving antiretrovirals, due to hepatic failure [3].

This study found hepatic adverse events most commonly associated with 3TC (35 reports), AZT/zidovudine (ZDV) (34), and nevirapine (28) and to be less common with protease inhibitors (7 nelfinavir, 6 saquinavir and 5 ritonavir). There were no reports for more recently approved antiretrovirals (tenofovir, emtricitabine, atazanavir or enfuvirtide).

Rash, fever, or jaundice with increased transaminases were reported with the use of nevirapine (9), 3TC (7), and ZDV (6). Hepatic failure was reported with the use of nevirapine (6), ZDV (4), ddI (4), and d4T (4).

Five deaths were reported due to hepatic failure during pregnancy and one in the immediate postpartum period: 3 women were receiving ZDV/3TV/NVP, 2 ddI/d4T/NVP and 1 ddI/d4T/NFV. The deaths in women receiving ZDV/3TV/NVP were due to hepatic necrosis while the deaths in women receiving ddI and d4T were associated with lactic acidosis.

The investigators concluded: "The majority [of adverse events] of were reported in patients receiving ARV commonly prescribed during pregnancy (ZDV, 3TC, NVP) … Severe hepatotoxicity, including hepatic failure and death, was reported with ZDV/3TC/NVP and with regimens containing ddI and d4T. Due to limitations of AERS, it is difficult to determine if this is due to increased toxicity during pregnancy or reactions to one of the ARV or combinations of ARV."

C O M M E N T

The findings of Kramer et al mirrors the published experience of nevirapine use in pregnancy in London (Edwards et al, HIV Medicine 2001) in which 4/30 women (13.3%) starting nevirapine during pregnancy experienced rash (2 women) or biochemical hepatitis (2 women) but otherwise nevirapine was well tolerated. It is also very encouraging to see no transmissions among the group of 125 pregnant women in this study.

The difficulties with the FDA data are the lack of numerator, potential for reporting bias and a lack of causal association. However there is real concern that nevirapine toxicities are more common in women with CD4 counts greater than 250 cells/mm3, a profile that frequently matches pregnant women receiving short courses of antiretroviral therapy to reduce the risk of mother to child transmission.

In comparison to the experience with zidovudine, lamivudine, nevirapine and nelfinavir, there is relatively little experience with other antiretroviral therapies. The benefits for the mothers and babies should not be underestimated but all antiretroviral therapy should be prescribed with care and closely monitored in pregnancy.

References:

1. Kramer F, Stek A, Du WB et al. Nevirapine tolerability in HIV-infected women in pregnancy. 11th CROI 2004, Abstract 923.
2. Bershoff-Matcha SJ, Mundy LM, and Henry JV. Adverse events to nevirapine therapy during pregnancy. 11th CROI 2004, Abstract 939.
3. Baylor M, Truffa M, and Gibbs N. Hepatic toxicity of antiretrovirals in HIV-infected pregnant women: a review of the FDA's adverse event reporting system. 11th CROI 2004, Abstract 944

Prior nevirapine exposure for pregnant women can contribute to treatment failure

Polly Clayden, HIV i-Base

Oral abstracts evaluating levels of nevirapine (NVP, Viramune) resistance following a single dose to reduce mother to child transmission, greater efficacy with a more complex intervention and the effect of nevirapine resistance on subsequent nevirapine containing HAART, unsurprisingly reported both high levels of resistance, better efficacy with two drugs and compromised subsequent therapy following single maternal dose.

Dr Neil Martinson presented findings from a study assessing nevirapine induced genotypic resistance in women exposed to single dose NVP to reduce mother to child transmission [1].

A group of 623 HIV-positive mothers from two South African hospitals were enrolled late in their third trimester of pregnancy (32 to 38 weeks). Dr Martinson reported preliminary genotypic findings at baseline and at a scheduled six weeks follow up, for which data were available for 455 (73%) of the women. The study investigators defined high-level nevirapine resistance as having acquired the K103N, V106A/M, Y181C, YI88C, and G190A mutations.

The women had a median baseline CD4 and viral load of 392 cells/mm3 and 28,700 copies/mL respectively. All but four were clade-C and no previously unexposed women had baseline resistance. Follow up visits were at a median of 7 weeks postpartum (IQR between 6.3 and 10.3 weeks). Dr Martinson reported 38.8% of mothers and 42.4% of their infants as having genotypic nevirapine resistance. There was a decline in detectable resistance in mothers with longer time to follow up: 43% in the first analysis (4 to 6 weeks postpartum), 44% in the second (6 to 7 weeks), 44% in the third (7 to 10 weeks) and 24% in the fourth (10 to 36 weeks) (test for trend p=0.006).

Mutations reported in the mothers included K103N (31%), Y181C (12%), and Y188C (8.1%); 21% had a single mutation, 13% had two, and 5%, three or four mutations. The babies' mutations included Y181C (32%), K103N (12%) and Y188C (5%). The K103N was the most frequent in both mothers and babies.

At 10 weeks the overall mother to child transmission rate was 8.6% (95% CI: 6.0 to 11.2). The investigators found an association between maternal nevirapine resistance and transmission (OR 2.9, 95%CI: 1.4 to 6.1) in univariate analysis but not after correcting for viral load. Dr Martinson cited baseline CD4, baseline viral load, the time from labour to the nevirapine dose to the postpartum blood draw and the total number of times a mother took nevirapine during her pregnancy (51% had taken one or more prior doses in pregnancy due to false labour) as being statistically significantly associated with development of resistance. In multivariate analysis only maternal viral load was significant. Mode of delivery was not important.

Dr Martinson concluded his talk with some recommendations from the authors which included: limiting nevirapine exposure ie avoiding multiple doses in pregnancy; nevirapine to the baby only and nevirapine plus two nucleosides to reduce mother to child transmission. He said: "ARV rollout must include MTCT," and added that the effect of nevirapine single dose on subsequent HAART and subsequent pregnancies must be considered. There are concerns about transmission of nevirapine resistant virus and for women exposed to single dose nevirapine, protease containing regimens may be more appropriate than the WHO recommended first line NNRTI containing HAART.

Two drugs are better than one…

Two late breakers in the same session presented results from a Thai study - PHPT-2 - designed to evaluate whether greater mother to child transmission efficacy could be gained by adding single dose nevirapine to standard AZT prophylaxis [2].

In this study 1,844 women were enrolled and mother and infant pairs were randomised to three arms: single 200mg nevirapine dose to the mother in labour and 6mg to the baby within 72 hours of birth (the nevirapine-nevirapine arm); nevirapine dose to the mother and placebo to the infant (nevirapine-placebo) and both mother and baby receiving placebo (placebo-placebo). Additionally all mothers received AZT from 28 weeks of gestation and infants one week of AZT and formula feeding. The study endpoint was HIV infection of the infant.

Presenting author Dr Marc Lallemant reported that the placebo-placebo arm was discontinued following the trial's first interim analysis due to the highly significant reduction in transmission among those receiving the additional drug: 1.1% in the nevirapine-nevirapine arm and 6.3% in the placebo-placebo arm, an 80% reduction (p=0.00026). Transmission rates between the nevirapine-nevirapine and the nevirapine-placebo arms did not differ dramatically: 2.0% and 2.8% respectively.

He reported that in these findings, although transmission was also associated with viral load and CD4 count and slightly associated with prematurity and onset of ZDV prophylaxis, the effect of nevirapine was observed across most sub groups, and that such a reduction "…was much higher than we had hypothesised when the study was designed".

…But subsequent treatment response is compromised

A second late breaker from the same group presented by Dr Gonzague Jourdain assessed the effect of nevirapine exposure in PHPT-2 on subsequent NNRTI containing HAART regimens.

Dr Jourdain reported that a 12 day postpartum sample was assessed for genotypic nevirapine resistance, this was first performed in a random sample of 90 women of which 18% of those tested were found to have NNRTI mutations (K103N, G190A, or Y181C). In a PK analysis the investigators also found that 77% of women had detectable blood plasma levels of nevirapine at 5 to 15 days post partum and one woman at 19 days postpartum. Of the women who participated in the PHPT-2 study 25% needed treatment and subsequently received an NNRTI containing regimen - nevirapine/3TC/d4T - and those for whom viral load could be assayed at 3 and/or 6 months were also assessed.

Of these 255 women starting HAART, 42 had not, and 213 had, been exposed to nevirapine. Six percent of the women switched to efavirenz.

At six months, 75% of the unexposed, 53% of the exposed but with no detectable mutations and 34% of the women exposed and with mutations were below 50 copies. Later initiation of therapy six months or more after exposure was associated with a modest improvement in virological response at six months duration of therapy (although this was not statistically significant).

Comments from the floor after the presentation included Dr John Mellors who remarked that these findings echoed those from his group from ACTG 398 – presented as an oral abstract in the same session [4], and first reported at the XII Resistance meeting in Mexico in 2003 [5], in which patients receiving efavirenz containing regimens had responded less well if previously

exposed to an NNRTI even without detectable resistance. This report concluded that prior NNRTI exposure could select minor resistant variants that are not detected by standard genotype assays and can contribute to failure of NNRTI containing regimens. Another speaker added: "Don't you think the time has come to abolish the use of suboptimal regimens and use generic HAART?"

C O M M E N T

These studies confirm the efficacy of nevirapine to reduce mother-to-child transmission and to rapidly select resistance mutations. The novel finding that single dose nevirapine exposure can impact future outcome to such a dramatic extent must lead to a rapid change in policy especially in those countries rolling out combination therapy. The potential of NNRTIs as subsequent therapy for the mother must be protected with their use restricted to effective combinations only and with due consideration to their prolonged clearance which varies considerably between individuals.

On 5th and 6th February the World Health Organisation (WHO) convened a technical consultation in Geneva to review the experience with programmes and evidence to date on safety and efficacy of antiretroviral use in the reduction of mother-to-child transmission. Prior to this consultation the WHO had issued a draft set of recommendations for public comment, this is now under revision in view of comments received and the recommendations made at the technical consultation.

Summary of the key recommendations:

• Women who need ARV treatment for their own health should receive it. The use of ARV treatment when indicated during pregnancy will improve maternal health and reduce the risk of transmission of HIV to the infant.

• Women who do not need treatment for their own health, or do not have access to treatment, should be offered ARV prophylaxis to reduce mother to child transmission using one of a number of ARV drug regimens known to be safe and effective.

• The most efficacious regimen among those recommended for reduction of MTCT for women with HIV who do not need ARV treatment is zidovudine (ZDV) from 28 weeks with single dose nevirapine (NVP) at onset of labour for the mother and single dose NVP plus one week ZDV for the infant.

• Alternative but less efficacious regimens include one based on ZDV alone (from 28 weeks of pregnancy and through labour for the mother and for one week for the infant), one using the combination of ZDV plus lamivudine (3TC) (from 36 weeks of pregnancy, through labour and one week postpartum for the mother, and for one week for the infant), and a regimen comprising a single dose of NVP to the mother and to the infant (which does not need to be initiated until labour).

• The selection of the ARV drug regimen should be made at national level, based on issues of efficacy, safety, drug resistance, feasibility, and acceptability.

This consultation included a review of available maternal and infant resistance data and the Lallemant et al. findings were taken into account in developing the above recommendations. The WHO press release states: "Consultation participants felt that the implications of these preliminary data on subsequent treatment options for women were unclear and require further study…Until further evidence is available it was the group's expert opinion that the ZDV plus single-dose NVP regimen can be recommended for the prevention of MTCT because of its considerable efficacy in reducing MTCT (by 80%, from the transmission rates observed with short-course ZDV alone, down to an absolute level under 2%), its simplicity and its safety profile for mother and infant. In view of these results, the government of Thailand is implementing this regimen nationwide for the prevention of MTCT, alongside its efforts to scale up ARV treatment for all in need."

References:

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1. Martinson M, Morris L, Gray G et al. HIV resistance and transmission following single-dose nevirapine in a PMTCT cohort. Abstract 38.
2. Lallemant M, Jourdain G, Le Coeur S et al. A randomised, double-blind trial assessing the efficacy of single-dose perinatal nevirapine added to a standard zidovudine regimen for the prevention of mother-to-child transmission of HIV-1 in Thailand. Abstract 40LB.
3. Jourdain G, Ngo-Giang-Huong N,Tungyai P et al. Exposure to intrapartum single-dose nevirapine and subsequent maternal six-month response to NNRTI-based regimens. Abstract 41LB.
4. Mellors J, Palmer S, Nissley D et al. Low frequency NNRTI-resistant variants contribute to failure of efavirenz-containing regimens. 11th CROI 2004, Abstract 39.
5 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. XII International HIV Drug Resistance Workshop, Los Cabos, Mexico, 10-14 June 2003. Abstract 134
6 WHO press statement.

Conflicting findings with HAART use in pregnancy and prematurity

Polly Clayden, HIV i-Base

Two oral abstracts presented conflicting and worrying findings on the association of prematurity and HAART use during pregnancy.

Dr Claire Thorne from the Institute of Child Health in London presented data from the European Collaborative Study in which HIV-positive pregnant women and their infants are followed up prospectively in 25 clinics in nine European countries [1].

As of January 2004, 4,377 HIV-positive women and their children had been enrolled in the study. Dr Thorne evaluated data from 1994 to 2003 and reported an increase in prematurity associated with more widespread use of HAART in pregnancy.

The authors found that during the period 1994 to1997, 54% of women had received ART during pregnancy. This increased to 88% in 1998 to 2000 and 90% in 2001 to 2003 (p<0.0001). Only 11% of women delivering in the earliest time period were already receiving ART when they became pregnant, increasing to 19% in 1998 to 2000 and 34% in 2001 to 2003 (p=<0.0001).

In the later period they also noted that there had been a decline in the rate of elective Caesarean section – generally seen to add no benefit with the use of complex therapy - from 73% in 1999 to 62% in 2002, and therefore a rise in vaginal deliveries.

During the period 1995 to 1997, 17.1% of infants were born prematurely (defined as before 37 weeks of gestation) which rose to 35.2% and 46.1% during 1998-2000 and 2001-2003 respectively (p=0.0001). There was also an increase in very premature infants (defined as before 34 weeks of gestation): 5.94%, 16.1% and 21.2% in the same three time periods respectively (p=0.0001).

Low (defined as below 2,500 grams) and very low (defined as below 1,500 grams) birth weight incidence also increased:

	Low (<1,500g)	Very low (<2,500g)
1995 to 1997	14.9%	0.48%
1998 to 2000	29.4%	4.7%
2001 to 2003	36.9%	8.05%

(trend p<0.0001)

The authors cited maternal age 35 years and above (OR 2.24, p=0.002), maternal IDU (OR 2.52, p=0.001), maternal CD4 below 200 cell/mm3 (OR 2.26, p=0.0001) and HAART use in pregnancy (OR 3.41, p=0.0001 without protease inhibitor and 4.17 p=0.0001 with protease inhibitor) as risk factors for prematurity.

Additionally they reported a high rate of neonatal mortality (defined as dying within 28 days of birth) from 1999 to 2000, 21.00 per 1,000; and from 2001 to 2002, 24.5 per 1,000. The range in the general population in Western Europe is 4.4 to 9.2 per 1,000. However, this finding is hard to interpret as data on pre-labour caesarean section were censored in this study, and general population data excluding pre-labour caesarean section is not available.

There were too few deaths to perform a multivariate analysis, but in univariate analysis the authors found prematurity to be associated with infant death: 74% who died were born prematurely vs 21% who survived (0.0001). Protease inhibitor containing HAART was moderately associated with an increased risk but the association did not reach statistical significance.

The authors concluded: “Although the benefits of HAART in reducing MTCT vastly outweigh the increased risk of premature delivery and possibly in perinatal and neonatal mortality, monitoring for adverse pregnancy outcomes should be recommended in ART programmes.”

A presentation in the same session from Dr Karen Beckerman from New York University used data from the Antiretroviral Pregnancy Registry (APR), an ongoing registry since January 1989 [2].

The objective of this study was to examine the association between prematurity, low and very low birth weight (defined differently from the European Collaborative Study: 32 weeks in the APR and 34 weeks in the ECS) and the use of combination ART. The authors compared women receiving monotherapy with those receiving combination ART. Additionally, protease inhibitor containing HAART was compared with combinations that did not.

Of the 3,782 evaluable pregnancies, 440(13%) received monotherapy, 1,368 (41%) received HAART with no protease inhibitor and 1,539 (46%) received protease inhibitor containing HAART. Dr Beckerman reported no significant differences in prematurity between the various treatment groups (see table elow).

	Mono (N=440)	Any Combo (N=2907)
Gestation Age		
<37 weeks	55 (13%)	353 (12%)
<32 weeks	9 (2%)	57 (2%)
Birth Weight		
<2500 g	57 (14%)	443 (16%)
<1500 g	7 (2%)	53 (2%)

However, the study did find a modest increase in low and very low birth weight among women receiving protease inhibitor containing HAART particularly in the first trimester: low birth weight - 258 (17%) vs 185 (14%) and very low birth weight - 34 (2%) vs 19 (1%) for protease inhibitor containing and not containing HAART respectively.

Dr Beckerman hypothesised that other risk factors such as viral load, disease stage and prior premature delivery, which could not be controlled in this analysis, could be responsible for this effect. She explained that women with more advanced HIV, may be more likely to receive a protease inhibitor (women with CD4 counts of less than 200 cells/mm3 were 2.8 times more likely, and women exposed in the first trimester were 2.4 times more likely to receive a protease inhibitor) and more likely to have low birth weight babies.

C O M M E N T

Neither study resolves this issue, but despite the differences in emphasis, both support earlier observations that antiretroviral therapy in pregnancy can increase obstetric risk for babies. This does not however diminish the considerable benefit of antiretroviral therapy for mothers and their babies.

The data from the ECS, which overstate the risk of pre-term delivery by excluding deliveries by pre-labour Caesarean section, need to be re-evaluated with all deliveries included (with the understanding that elective pre-term Caesarian sections will also bias the data).

Conversely the data from the Anti-retroviral Pregnancy Register may underestimate any effect, as only women exposed to any antiretroviral therapy are included.

In both studies an effect of antiretroviral therapy on severe pre-term delivery should be analysed according to the time of starting therapy ie including women starting therapy later than 32 weeks will reduce the likelihood of detecting a genuine effect of antiretrovirals on severe pre-term deliveries and severe low birth weight.

References:

1. Thorne C, Newell M, and European Collaborative Study. Pregnancy outcome in ART-treated HIV-infected women in Europe. 11th CROI 2004, Abstract 98.
2. Beckerman K, Covington D, Garcia P et al. Association between antiretroviral therapy during pregnancy and prematurity/low birth weight. 11th CROI 2004, Abstract 98.

Antiretrovirals, mode of delivery and transmission risk

Polly Clayden, HIV i-Base

In an oral abstract presentation Dr David Shapiro presented data from the PACTG study looking at mother to child transmission rates among pregnant women with low viral loads. Data were collected from 3,081 women at 72 US centres between 1998 and 2002 and use of antiretrovirals, mode of delivery and viral load were evaluated in association with transmission risk.

In this study, 97% of women were in antenatal care, 61% of women already knew their status before their pregnancy and 88% began antiretrovirals in the first or second trimesters.

Dr Shapiro noted that between 1998 and 2002 there had been an increase in the use of combination therapy in pregnancy, and by 2002 the transmission rate was less than 1%. The rates for women receiving no antiretrovirals, monotherapy, dual therapy and three or more drugs were: 18.5, 5.1, 1.4 and 1.3 respectively.

At a viral load of less than 1,000 copies/mL and using multi therapy, the transmission rate overall was 0.6% and an elective caesarean section did not appear to offer any advantage.

Dr Shapiro concluded: “Transmission rate among women with plasma HIV RNA<1000 copies/mL did not differ significantly according to delivery route but was significantly lower with multi- versus single-agent ART.”

Responding to a question about transmission rate at less than 50 copies/mL, Dr Shapiro explained that at this viral load the rate was practically zero. “Is that data likely to be published?” the speaker asked, “We have been waiting for this for years.”

C O M M E N T

These findings shift emphasis on concerns about mode of delivery to careful maintenance of maternal health during pregnancy.

Ref: Shapiro D, Tuomala R, Pollack H et al. Mother-to-child HIV transmission risk according to antiretroviral therapy, mode of delivery, and viral load in 2,895 US women (PACTG 367). 11th CROI 2004. Abstract 99.

CROI: PAEDIATRICS

Tenofovir studies in children

Simon Collins, HIV i-Base

Kearny and colleagues from Gilead and the Albert Einstein School of Medicine in New York evaluated the PK of a single dose of an investigational oral suspension of tenofovir (TDF, Viread). [1]

Seven boys and five girls aged between two and eight years received a single 8mg/kg dose, selected based on results of previous studies in older children. All children were already on HAART regimens with either undetectable or low level viraemia (range 1.69-4.31 $\log^{10}$ copies/mL).

As a group, the children produced a similar mean concentration-time profile to the adult 300mg dose. Although there were only small numbers in this study (n=3 aged 2-4; n=5 aged 5-6 and n=4 aged 6-8) lower mean concentrations correlated with lower age, and as with adults there was a range of interpatient variability (AUC24hr range approx 1125-4125 ng.hr/mL in children vs 1875-4500 ng.hr/mL in adults).

Cmax and Tmax were similar to mean adult values and no treatment related side effects or laboratory abnormalities were reported.

In a second study, Hazra and colleagues from Bethesda MD reported 48-week results from using tenofovir plus optimised background regimen in 19 treatment experienced children median age 11.9 years (range 6.2 to 16.2) in a Phase I paediatric study. Safety monitoring included routine laboratory studies and additional monitoring for bone toxicity by dual-energy x-ray absorptiometry (DEXA) of the lumbar spine. [2]

Median time of prior ARV therapy was 9.7 years (range 4.8 to 13.5). Baseline resistance testing showed median of 9 (range six to 14) major RT mutations and eight (two to 10) major protease mutations. Baseline CD4 and viral load count was 206 cells/mm3 (0 to 766) and 5.4 $\log^{10}$ copies/mL (4.1 to 5.9) respectively.

At week 48 (n=14) median increase in CD4 count was 4 cells/mm3 (-274 to 768) and decrease in viral load was -1.52 logs (-4.0 to 0.52). HIV RNA was <50 copies/mL in four children (<400 copies/mL in six children).

Four subjects discontinued TDF for elevated transaminases (one before TDF dosing, two during the TDF monotherapy phase, and one at week 18). One child died at week 34 from an intracranial haemorrhage unrelated to TDF; one child was removed from study at week 43 for disease progression. At week 24, the median (range) decrease BMD Z-score was -0.38 (-1.2 to 0.52); 10 subjects had decreases in BMD from baseline, seven of whom were virologic responders (viral load decreases from -1.57 to -4.0). At week 48, the median (range) decrease in BMD Z-score from baseline was -0.31 (-2.9 to 0.21); five subjects had decreases in BMD from baseline, and all five had virologic responses (from -2.15 to -4.0).

C O M M E N T

The authors concluded that TDF-containing combination antiretroviral therapy is virologically active for at least 48 weeks in heavily treatment-experienced children, but can be associated with decreased bone mineral density. Further efficacy, toxicity, and tolerability studies are ongoing. The relationship between lower BMD and virologic response should also be studied. Substantially reduced BMD in children has already been reported (Vignano et al) and been linked to HAART therapy and should be taken very seriously.

References:

1. Kearney BP, Abadi J, Rosenberg M et al. Pharmacokinetics (PK) of tenofovir DF (TDF) oral suspension in HIV-1 infected children between two and eight years of age. 11th CROI 2004, Abstract 935.
2. Hazra R, Gafni R, Maldarelli F et al. Safety, tolerability, and clinical responses to tenofovir DF in combination with other antiretrovirals in heavily treatment-experienced HIV-infected children: data through 48 weeks. 11th CROI 2004, Abstract 928.

CROI: OPPORTUNISTIC INFECTIONS

Increase of non-AIDS defining cancers in HOPS cohort

Simon Collins HIV i-Base

An oral presentation of an analysis from Patel and colleagues looked at the age-, race-, smoking-, and gender-adjusted relative rates of five cancers that are not traditionally associated with AIDS (lung, head/neck, Hodgkin's disease [HD], anorectal [ARC], melanoma) in 7,900 patients treated at two large Chicago HIV clinics with those observed in the 20 million County and 92 million State cancer registry patients. A second group of around 4,050 HIV-patients from the HOPS (HIV Out-Patient Study) cohort was compared with 334 million patients from the general population. The study period covered 1992 to 2002. [1]

The incidence of the five non-AIDS malignancies was much higher in the HOPS population than in the general population.

	Chicago		HOPS	
	Adj. RR	95% CI	Adj. RR	95% CI
Lung	3.63	2.18–6.05	2.13	1.06–4.27
HD	77.43	19.37–309.55	4.58	3.10–6.77
Anorectal	5.03	4.76–5.33	10.13	7.48–13.72
Melanoma	4.10	9.39–152.70	2.99	1.71–5.22
Head/neck	9.96	2.49–39.79		

The study noted that while the incidence of KS and cervical cancer have reduced in the HAART era, these five malignancies appear to be increasing. The incidence of other common cancers such as breast, colon and prostate cancer were not significantly increased in either the HIV-positive or general population groups.

In a discussion session, Joel Palefsky provided an overview of incidence and treatment of HPV (human papilloma virus)-associated anal cancer, in reference to two other studies presented at the conference. [2]

Palefsky also highlighted previous research from his group that showed that the risk for HIV-positive gay men of developing HPV-associated anal cancer is around 35-fold higher than for men in the general population and twice as high as HIV-negative gay men. Although the absolute risks for anal cancer are reported as 35/100,000 incidence in HIV-positive men he noted that this was comparable to rates of cervical cancer prior to the introduction of effective screening and treatment programmes. These programmes have successfully been able to reduce rates of cervical cancer down to 8/100,000. Early detection and treatment of anal cancer significantly improves prognosis.

Patrick Sullivan and colleagues from the US Centres for Disease Control and Prevention (CDC) in Atlanta looked at incidence and risk factors for anorectal cancer from 1990-2002 in a cohort of more than 58,000 HIV-positive patients and compared this to the NCI general population dataset. [3]

During more than 231,000 patient years of follow-up, 150 patients were documented as having anorectal cancer. Among HIV-positive cases, 92% were male, 44% were aged 35 to 44 years, and 79% were exposed to HIV through male-male sex. The age-standardised anorectal cancer rate was 84.9 cases per 100,000 person-years (95% CI: 52.4 to 117.5); the age- and sex-standardised rate was 66.1 per 100,000 person-years (CI: 38.0 to 94.2). The general population rate was 21.8 per 100,000 person-years (CI: 21.6 to 22.0).

Incidence of anorectal cancer was associated with:

	adjusted odds ratio	95% CI
HIV exposure MSM vs MSW	5.6	1.8 to 17.3
Age ‡ 45 yrs vs <35 yrs	2.5	1.6 to 3.9
Age 35 - 44 yrs vs <35 yrs	1.7	1.1 to 2.5
Clinical AIDS diagnosis	1.5	1.1 to 2.2
CD4 count <200 vs >500	4.0	1.9 to 8.4
CD4 counts 200-499 vs >500	2.4	1.1 to 5.1

The study concluded that these data suggest that clinicians must be vigilant for ARC during periodic examinations of HIV-infected persons, especially men with a history of male-male sex, older persons, and those at more advanced stages of disease.

Diamond and colleagues from the University of California performed a match between the AIDS and cancer registries for San Diego County from 1988-2000.

They identified 39 cases of anal squamous cell carcinoma. All were men and 38 (97%) were men who have sex with men (MSM). The median age was 42 years (range 25 to 59); 28 (72%) were Caucasian, two (5%) were Black, seven (18%) were Latino, and two (5%) were of unknown race/ethnicity.

The median CD4 count was 120 cells/mm3 (range 2 to 551). Among the 36 patients diagnosed with HIV prior to or simultaneously with their anal cancer diagnoses, the median duration of known HIV infection was 78 months (range 0 to 175). No cases of anal cancer were diagnosed before 1992.The median duration of HIV infection in the pre-HAART era (1992 to 1995) was 29 months while post-HAART (1996 to 2000) it was 84 months (p = 0.01).

Eight cases (21%) were diagnosed pre-HAART, while 31 (79%) were diagnosed post-HAART. The number of cases increased from 2.8/1000 AIDS cases in 1992 to 24.7/1000 in 2000 despite a declining incidence of AIDS (r = 0.83, p = 0.005). However, the study reported 3/8 (38%) and 8/31 (26%) in pre- and post-HAART period were in-situ which many clinicians would not count as a registered cancer and would remove rather than treat.

Twenty-eight patients received surgical treatment, one received radiation therapy, one received chemotherapy, 16 (41%) received both, and 21 received neither. At most recent follow-up, 20 (51%) were alive. Among the 19 deceased, six died of HIV/AIDS, six died of anal cancer, and seven died of other/unknown causes.

The study concluded that increased incidence could be related to increased screening for anal cancer or increased longevity with the use of HAART but that the fewer in-situ tumors in the post-HAART era argue against a screening phenomenon. The longer duration of HIV infection post-HAART suggests that HAART increases the time at risk for the development of anal cancer.

C O M M E N T

Screening availability is general by specialist referral in HIV clinics in the UK. However, cost effectiveness should be higher than for cervical screening as the population at risk is easily defined.

Although the natural history can lead to regression, this is only in younger men and rarely in men over 30 years old.

References:
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4. Diamond C, Taylor TH, Culver HA. Dramatic increase in anal cancer diagnoses in the era of Highly Active Antiretroviral Therapy. 11th CROI 2004, Abstract 778.
   http://www.retroconference.org/2004/cd/PDFs/778.pdf

CROI: HEPATITIS COINFECTION

HIV/HCV coinfection: superiority of pegylated interferon plus ribavirin, but lower response rate compared to mono-infected patients, especially for genotype-1

Simon Collins, HIV i-Base

Coinfection with HIV and hepatitis C presents an increasingly pressing challenge because around 20-50% of patients in European cohorts are coinfected with HCV and are at an increased risk of liver-related mortality. [1]

Three major coinfection trials reported results in oral presentations at the conference, two of which were late breakers, using various approaches to pegylated interferon plus ribavirin. The following article will briefly report on each study. Comments specific to new data in coinfection together with the implications of and differences between the three studies are made together at the end of the article.

Although the baseline characteristics and treatment arms limit cross-study comparisons, they clearly show poorer sustained virological response (SVR) rates to those achieved in mono-infected patients, although this was known prior to final 72-week results. In the UK PEG-interferon + ribavirin is already NICE (National Institute for Clinical Excellence) - approved standard of care for treatment of HCV.

APRICOT

The AIDS PEGASYS Ribavirin International Co-infection Trial (APRICOT) randomised 868 co-infected subjects in 19 countries to 48 weeks of treatment with standard interferon-alpha-2a (IFN) 3-MIU three times a week plus 800 mg/day ribavirin (RBV), peginterferon-alpha-2a (40 kD) 180 mg weekly plus placebo, or peginterferon-alpha-2a 180 mg weekly plus 800 mg/

day RBV. PEGASYS is pegylated interferon manufactured by Roche Laboratories. [2]

Eligible subjects had compensated liver disease, a CD count >100 cells/mm3, and stable HIV disease, with or without antiretroviral therapy (ART). The primary endpoint was SVR, defined as HCV RNA <50 IU/mL at the end of 24 weeks of treatment-free follow-up (week 72). Response rates were stratified by geographical region, genotype and CD4 count.

Approximately 285 patients were included in each arm - about 80% men, 20% women, 80% Caucasian, mean age 40 +/-7. Mean CD4 count was > 530 cells/mm3 and only around 5% patients had CD4 counts <200 cells/mm3. Eighty-five percent of patients were on HAART, and 60% had undetectable viral load.

Final week-72 results are presented in Table 1 below:

Table 1: APRICOT trial results

	(A)	(B)	(C)
	IFN/RBV + placebo	PEGASYS +RBV	PEGASYS
Baseline Characteristics			
Mean HCV RNA (10^3 IU/mL)	5208+/-5954	6354+/-6429	5616+/-6434
Mean ALT (IU/L)	87+/-53	88+/-57	85+/-50
Genotype-1	60%	61%	61%
Cirrhosis (%)	16	16	15
Median HIV RNA (log)	5.2	6.3	5.6
Mean+/-SD CD4+/- (cells/mL)	542+/-270	530+/-265	520+/-277
HCV Virological Outcome (%)			
SVR:			
Overall %	12 %	20 % p=0.0078 vs A	40 % p<.0.0001 vs A & B
Genotype-1 %	7 %	14%	29 %
Genotypes 2&3	20 %	36 %	62%

Treatment discontinuations overall occurred in 39%, 31% and 25% of patients in arms A, B and C respectively. Adverse events or lab abnormalities occurred in about 15% of patients in each arm. Serious adverse effects related to the treatment occurred in 5%, 10% and 8% of arms A, B and C. Deaths (treatment related) occurred three (1), five (0) and four (1) in each group. Neutropenia (<0.5 x 10^9/L) occurred significantly less in the standard interferon arm (<1%) compared to 13% in the PEG/placebo and 11% in the PEG+ribavirin arm.

Median CD4 decreased comparably in each arm over the 48 weeks of treatment and returned to baseline levels by week 72. Over the treatment period, the median HIV viral load reduced by about 0.8 log in both the PEG arms in patients who had detectable viral load at study entry, and returned to baseline during weeks 48-72 off-treatment.

ACTG A5071

ACTG A5071 randomised 133 coinfected patients to peginterferon-alpha-2a (PEG) (180mg weekly for 48 weeks) to interferon (6MIU three times weekly for 12 weeks followed by 3MIU three times weekly for 36 weeks). This study used the Roche PEGASYS formulation. Both arms received ribavirin in a dose-escalation schedule from 600mg/d to 1000mg/d. [3]

Table 2: Treatment response in ACTG A5071 by genotype

	IFN/ribavirin	PEG/ribavirin	p
End of Treatment VR	12%	41%	p = 0.0001
Genotype-1	6%	29%	
Genotype-2/3		80%	
SVR week 72 (24 wks after Tx)	12%	27%	p < 0.03
Genotype-1	6%	14%	
Genotype-2/3	33%	73 %	

Independent predictors of sustained virologic response included receipt of PEG/ribavirin, HCV genotype non-1, no prior injection drug use, and a detectable HIV-1 RNA at entry.

Histologic response was observed in 36% of virologic non-responders and in 52% of virologic responders who underwent liver biopsy. Both regimens were well tolerated. Similar frequencies of flu-like symptoms, depression, and laboratory abnormalities were observed in each arm, and premature discontinuation rates were 12% in each arm.

Failure to achieve >2 log HCV RNA reduction at week 12 uniformly predicted failure to accomplish sustained virologic response (100% negative predictive value). After 12 weeks treatment, 41% (n=43) of patients had either >2 log drop in HCV-RNA or an undetectable HCV-RNA viral load. Among these 43 patients, half went on to achieve SVR at week 72 and half did not. None of the 63 patients who were not responding virologically after 12 weeks of therapy achieved an SVR at week 72.

RIBAVIC

The French ANRS RIBAVIC study compared a 48-week course of the standard (IFN-alpha-2b: 3 MIU x 3/week, n = 207; INF group) to the pegylated (PEG-IFN-alpha-2b: 1.5 m/kg x 1/w, n = 205) interferon; PEG group) both combined with ribavirin (800mg/d, approximately 12mg/kg/d). Primary endpoint was sustained virologic response (SVR) defined as loss of detectable serum HCV RNA at week 72 of follow-up. PEG Interferon in this study was made by Shering Plough. [4]

The population was similar to the APRICOT study - 40 years old, 74% male, 79% injection drug users [IDU]), 82% on HAART with 66% with controlled HIV viraemia <400 copies/mL. Mean CD4 cell count was 514 +/- 229 cells/mm3. HCV genotypes were 1 or 4 in 58%, 3 in 34%, and others in 8%. Mean HCV viral load at baseline was 5.9 + /- 0.7 logs. Baseline variables at entry were not different between groups.

Patients in RIBAVIC may have had more advanced HCV disease than patients in either ACTG A5071 or APRICOT. The mean pre-treatment Metavir score was A 1.8 + 0.7, F 2.3 + 1.0, 24% of patients had F3 (bridging fibrosis) and 16% F4 (cirrhosis).

Treatment discontinuation occurred in 167 patients (42%; 86 IFN, 81 PEG) and severe adverse events in 127 patients (31%) (64 IFN, 63 PEG), including six cases of symptomatic hyperlactataemia and five of acute pancreatitis.

A decrease was observed at week 12 of treatment, in INF and PEG groups respectively, significant for Hb (-1.4 g/dL vs -1.8, p = 0.002) and platelets (-19,000 vs -33,000, p = 0.04), not significant for neutrophils (-692 vs -1071), lymphocytes (-543 vs -662), or CD4 cells (-116 vs -124). A summary of response rates is shown below:

	IFN+RBV	PEG+RBV	
Responders wk 12	34%	41%	
Responders wk 48	34%	52%	
SVR week 72 (ITT)	18%	26%	p = 0.031

Virologic response at week 12 predicted SVR with 87% Positive Predictive Value and 87% Negative Predictive Value. SVR varied with genotypes 1 or 4 (11%) vs 3 or others (43%).

Table 3. Summary of Sustained Virologic Responses (SVR) to PEGinterferon in HIV/HCV-coinfected patients

	No. of pts	Response (%)	Genotype-1 (%)	Non-Genotype-1 (%)
ACTG A5071 *(approx 22% cirrhotic)*				
Standard IFN + ribavirin*	67	12	6	33
Pegasys + ribavirin*	66	27	14	73
APRICOT *(approx 16% cirrhotic)*				
Standard IFN + ribavirin	285	12	7	20
Pegasys + placebo	286	20	14	36
Pegasys + ribavirin	289	40	29	62
RIBAVIC *(approx 40% cirrhotic)*				
Standard IFN + placebo	207	19	5**	41
Peg-Intron + ribavirin	205	27	15**	44

* Escalating dose of ribavirin was used in AACTG 5071. Patients started at a dose of 600 mg/daily, which was then increased by 200 mg/daily every four weeks for a maximum total of 1,000 mg/day. Both Apricot and Ribavic used 800 mg/day ribavirin throughout.

** Included patients with HCV genotypes 1 and 4.

C O M M E N T S

Although HCV-monoinfected patients with an HCV genotype of 1 can expect a 40–45% chance of an SVR using pegylated interferon/ribavirin, HIV/HCV-coinfected patients with genotype-1 are looking at an SVR of 14% (ACTG) to 29% (Apricot). The results in co-infected patients with genotypes 2/3 infections were encouraging with 45% (Ribavic) to 62% (Apricot) SVRs. However, it is important to note that all patients received 48 weeks of therapy. It is likely that, in order to achieve an optimal response, all genotype 2/3 HIV/HCV co-infected patients should receive 48 weeks of treatment with pegylated interferon/ribavirin.

HCV-RNA was associated with treatment outcome in Apricot, but not Ribavic. Analysis, especially for patients with genotype -1 co-infections, by baseline viral loads were not available. It is likely that those with high HCV viral loads (800,000 iu/l) will have poor responses. Although, baseline CD4 counts have been shown to affect response to therapy, patients in both Ribavic and Apricot had median CD4 counts above 500 cells/mm3, and included very few patients with CD4 counts less than 200.

The higher proportion of African Americans in the ACTG study and dose escalation of ribarvirin could also contribute to the poorer response. The high discontinuation rate in Ribavic may also have affected thse trial results.

Although, these three studies show slightly different results, it is difficult to make cross-study comparisions, since the patient populations were different, and in the case of ACTG 5071, a lower starting dose of ribavirin (600mg/day) was employed.

In Ribavic, approximately 40% were Metavir grade F3 (24%, bridging fibrosis) or F4 (16%, cirrhosis). In Apricot, approximately 16% of patients had cirrhosis, and in AACTG 5071, no more than 11% of patients, in either treatment group, had cirrhosis before beginning therapy.

The clinical importance of histologic improvement, even without SVR, is unclear, especially as in HCV-monoinfected patients viral response was associated with histological improvement (Camma et. Al. EASL 2003).

There are two different molecules of pegylated interferon, the 12kD Viraferon-PEG (Schering-Plough) and the 40kD Pegasys (Roche). These two molecules have different pharmacokinetics. The 40kD molecule has a slightly longer half-life and a smaller volume of distribution. Although, studies in singular HCV infection has not shown a significant difference interms of SVRs between these two pegylated interferons, a head-to-head study is underway. In terms of HIV/HCV co-infection (where patients have higher HCV viral loads and, in theory, lower viral-specific immune responses) the pharmacokinetics, and the resultant HCV viral kinetics, may play an important role in determining the optimal dose and length of therapy.

Newer viral life cycle inhibitors are still at least 4-5 years away from approval. Research also needs to address how to optimise the safety and tolerability of treatment for coinfected people - for example, dose adjusting or using EPO to maintain adequate dosing of ribavirin, and possibly extending treatment for longer periods (Apricot and Ribavic treated people with genotype 2/3 for 12 months rather than six, and saw a very low relapse rate). Beyond that, half-dose long-term maintenance therapy with pegylated interferon is being studied as a strategy to reduce further liver damage.

References:

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2. FJ Torriani, Rockstroh J, Rodriguez-Torres M et al. Final results of APRICOT: a randomised, partially blinded, international trial evaluating peginterferon-alfa-2a + ribavirin vs interferon-alfa-2a + ribavirin in the treatment of HCV in HIV/HCV co-infection. 11thCROI 2004, Oral abstract 112.
3. Chung R, Andersen J, Volberding P et al. A randomised, controlled trial of PEG-Interferon-alfa-2a plus ribavirin vs interferon-alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-co-infected persons: follow-up results of ACTG A5071. 11thCROI 2004, Oral Abstract 110.
4. Perronne C, Carrat F, Bani-Sadr F et al. Final Results of ANRS HC02-RIBAVIC: A randomised controlled trial of pegylated-interferon-alfa-2b plus ribavirin vs interferon-alfa-2b plus ribavirin for the initial treatment of chronic hepatitis C in HIV co-infected patients. 11thCROI 2004, Oral abstract 117LB.

Epoetin-alfa improves interferon/ribavirin-associated anaemia

HIVandHepatitis.com

Anaemia is the most common haematologic disorder in HIV-infected patients. Combination IFN/RBV therapy for chronic HCV infection is known to induce anaemia as well; therefore, co-infected patients may be at higher risk for developing anaemia. It has been demonstrated that anaemia in HIV and HCV mono-infected patients can be treated with epoetin-alfa (EPO, Procrit). This is the first prospective, randomised study to evaluate the effect of EPO in anaemic HIV-HCV co-infected patients.

An open-label, randomised, parallel group study was conducted in 52 anaemic HIV-HCV-co-infected patients receiving IFN/RBV. Patients who had Hb £12 g/dL or who experienced an Hb decrease of at least 2g/dL from the start of IFN/RBV therapy

were randomised to receive either EPO 40,000 IU subcutaneously once per week or no EPO (standard of care) for 16 weeks. The primary objective of this study was to evaluate the Hb response between EPO and standard of care groups at week 16.

An interim analysis was conducted in 41 patients (n = 22 [EPO], n = 19 [standard of care]). Baseline characteristics were similar between the two groups: mean age, 46.4 years; 83% men; mean weight, 80.1 kg; 10% no ARV; 90% on HAART; 54% on AZT-containing regimen; mean CD4+, 404.1 cells/mL [range 51 to 1062]. The mean duration from start of IFN/RBV therapy to randomization was 12 weeks.

The mean change in Hb from baseline to week 16 was 2.8+/-0.3 g/dL in the EPO group vs 0.4+/-0.3 g/dL in the standard of care group ($p < 0.001$; table). AZT patients receiving EPO had a similar Hb response compared with non-AZT patients receiving EPO.

Serious adverse effects occurred in one EPO patient (constipation) and two standard of care patients (substernal chest pain, psychosis). A total of five (23%) EPO patients and seven (37%) standard of care patients dropped out within 16 weeks due to: IFN/RBV discontinuation (five EPO, three standard of care), patient request (three standard of care), lost to follow-up (one standard of care).

The authors conclude: "Anaemic HIV-HCV co-infected patients receiving IFN/RBV therapy demonstrated significant increases in Hb at week 16 with EPO compared with standard of care. Similar Hb increases have been demonstrated in HIV and HCV mono-infected patients treated with EPO."

Ref: Dieterich D et al. Epoetin-Alfa administered once weekly improves anaemia in HIV-HCV co-infected patients treated with interferon/ribavirin therapy: a prospective, randomised study. 11th CROI 2004, Abstract 824 (poster).

C O M M E N T

Erythropoietin (EPO) for ribavirin induced anemia is off label in Europe, but in the UK and Germany some doctors use it, and will try to avoid dose reductions if at all possible.

G-CSF is approved for treating leukopenia in HIV-positive patients, but this is minor issue in HCV-treatment, because severe infections are rare. There is a larger study in HCV-monoinfected patients showing a good effect on haemoglobin and a clear improvement in physical performance and QoL (AASLD 2003).

ANTIRETROVIRALS

Gilead discontinues DAPD development

Gilead Sciences has announced that the company, for strategic reasons, is ending its licensing agreement with Emory University and the University of Georgia Research Foundation for the development and commercialisation of amdoxovir.

Also known as DAPD, amdoxovir is an investigational guanosine nucleoside analogue currently in Phase II development for the treatment of HIV. Amdoxovir has also been tested in humans for the treatment of chronic hepatitis B infection and is currently in Phase II clinical trials under a US IND [investigational new drug exemption]. Gilead will meet its ongoing obligations with respect to existing clinical trials and is committed to cooperating with the universities during the transition of this technology to a new licensee.

In March 1996, Triangle Pharmaceuticals Inc. entered into a licensing agreement with Emory University and the University of Georgia Research Foundation for worldwide rights to amdoxovir. In January 2003, Gilead acquired Triangle Pharmaceuticals. In accordance with the licensing agreement, Gilead will transfer toxicity, efficacy and other data including the IND to the universities.

"Gilead remains committed to developing novel compounds to fight HIV," said John C Martin, president and CEO of Gilead Sciences. "We continue to focus resources on the development of other promising candidates in our pipeline, including the co-formulation of Viread (tenofovir disoproxil fumarate) and Emtriva (emtricitabine) into a single fixed-dose combination tablet, and two investigational agents, GS7340, an amidate prodrug of tenofovir, and GS 9005, a protease inhibitor."

"Amdoxovir has great potential for salvage therapy in HIV infected individuals," said Mary L. Severson, chief technology officer at Emory University. "Emory and the University of Georgia Research Foundation are committed to the continued development of this drug and the ongoing NIH-sponsored clinical trials ACTG 5118 and ACTG 5165."

Source: Gilead Press Release

Ritonavir US price increase: update

Simon Collins, HIV i-Base

Pressure from community and medical organisations continues for Abbott to retract the 400% increase in the US price of ritonavir (see HTB Vol 5 No 1/2). Although a short-term commitment has been made not to increase the price in Europe, it is feared that the new US price may reflect the target price for the new formulation of ritonavir that is expected in 2005-6.

Abbott has made a series of concessions to counter the disruption and poor press publicity generated by the increase – largely related to opportunistic greed and anti-competitive pricing - but the company has failed to grasp the reasons for patient anger.

Illinois' attorney general has launched an investigation into Abbott Laboratories' decision as an example of unfair pricing that may violate the Illinois Consumer Fraud and Deceptive Business Practices Act.

The price of Abbott's protease inhibitor Kaletra, which includes ritonavir, was not increased but the cost of all other boosted regimens has increased, leaving Kaletra as the cheapest boosted protease inhibitor.

After considerable effort and extensive loss of good faith from the medical and patient community, Abbott still has not made any reduction in the 400% price increase.

Links:

Illinois Attorney General launches investigation into Abbott

http://www.ag.state.il.us/pressrelease/20040206c.html

ATAC community response

http://www.atac-usa.org/Abbottpricehike.html

Abbott February response to community and care providers

http://www.abbott.com/hiv/hiv.html

TREATMENT ACCESS

International community meeting on drug pricing

Bob Huff for HIV I-Base

During the past year and a half, people living with HIV/AIDS (PLWHA) and HIV community advocates from around the world have begun meeting to discuss how they can advance treatment literacy and increase PLWHA input into decisions by the commercial, research, educational and care programmes that affect them. In Europe and the US, community advisory boards (CABs) have long been an important vehicle for representing the needs of PLWHA to drug companies, researchers and government regulators.

In February 2004, for the first time, a World CAB was convened to enable PLWHA from the developing world to voice their concerns about drug pricing in their regions to senior representatives of the multinational pharmaceutical industry. Twenty-eight individuals from 21 countries gathered in San Francisco, California, in advance of the annual Retrovirus Conference, the year's most important scientific conference on HIV, to meet with officials responsible for marketing and global pricing policies at Roche, GlaxoSmithKline, and Boehringer Ingelheim. The participants, from South America, Eastern and Western Europe, South and Southeast Asia, and North America, are active in treatment advocacy and literacy efforts in their own countries; many had first met during the First International HIV Treatment Preparedness Conference, held in Cape Town in March 2003.

During the three-day World CAB meeting, participants questioned company representatives about pricing and research policies and asked the pharmaceutical companies to:

1. Review pricing policies within low and middle income countries:

- the economic development criteria used to set prices are often unrealistic
- rigid pricing structures produce inequitable outcomes
- disparities between regions are often not justified
- the continued relevance of Accelerating Access Initiative (AAI) pricing agreements is questionable
- the gap between no-profit prices and prices in middle income countries is too wide

2. Halt corporate activism to win trade advantages in excess of those provide by TRIPS:

- do not undermine the Doha world trade agreement language

- do not lobby for bilateral trade agreements with US (FTAA)
    - extension of patent terms to 30 years
    - research data as intellectual property

3. Conduct relevant, responsible and ethical research in developing regions:

- publish details of clinical trials being conducted in the developing world
- assure usefulness and rationale of these trials to their particular settings
- assure informed consent in local languages
- assure continued availability of tested drugs at affordable prices after research is concluded
- perform long-term side effects research among diverse ethnic groups
- perform interaction studies with opiates and amphetamines

4. Incorporate PLWHA involvement at all levels:

- in the design and conduct of clinical trials in developing world settings
- in discussions with governments, NGOs and drug companies
- in the design of treatment literacy programmes for patients and professionals

5. Promote product availability and utility:

- drugs need to be registered and marketed in middle income countries with small markets
- explore simplifying regimens, including co-formulating and co-packaging with drugs from other manufacturers, including generic makers
- guarantee the development and distribution of paediatric formulations
- extend shelf-life of products for tropical regions
- halt promotion of suboptimal therapies (eg Trizivir in Moldova)

World CAB participants agreed to follow up on these action items:

- ask UNAIDS to review AAI assumptions for relevance in 3 by 5 era (the WHO target of treating .three million people by 2005)
- initiate community contacts with WHO staff in-country
- arrange future CAB meetings with generic manufacturers
- plan follow-up meetings for the International AIDS Conference in Bangkok.

The World CAB pricing meeting was organised by HIV i-Base of London and GMHC of New York. We will be producing a full report from the meeting.

Bob Huff is the editor of GMHC Treatment Issues, the HIV treatment research and policy publication of Gay Men's Health Crisis (GMHC), New York

Global Fund halts $92 million grant for Ukraine after problems

Graham McKerrow, HIV i-Base

The Global Fund to Fight AIDS, TB and Malaria has halted a $92 million five-year grant for Ukraine because of irregularities and a lack of progress in the work it was meant to finance – and the fund has since appointed another body to take on the work of treating 4,000 people in the former Soviet state.

It is the first time the Global Fund has withdrawn funding. The Fund suspended the grant after concluding the project was poorly managed and behind schedule. Some reports said that money intended to pay for medicines "was likely to be inappropriately diverted". The Fund said it did not suspect embezzlement. The three principal recipients for Ukraine were the Ministry of Health, a charity called the Ukrainian Fund to Fight HIV infection and AIDS, and the United Nations Development Programme (UNDP). The Fund was dissatisfied with the performances of all three. Evidence of the problems was brought to light by the Fund's staff and PricewaterhouseCoopers, the Fund's local fund agent in Ukraine as well as two external government sources.

More than $7 million dollars was given to Ukraine and of this about $1 million has been spent. The Fund is asking for the remainder to be returned. In the meantime the Global Fund has appointed the international NGO, the International HIV/AIDS Alliance, to take on the role of Principal Recipient of its funding in the Ukraine. The Alliance was a sub-recipient of the previous agreement.

The agreement is still being finalised but it seems the Alliance will receive $15 million to take charge of the programme for one year, with future funding dependant on performance. The money is to pay to increase the number of people receiving antiretroviral treatment in the Ukraine from fewer than 60 to 4,000.

Global Fund says it needs $5 billion during 2004-2005

Global Fund Observer

The Global Fund to Fight AIDS, TB and Malaria projects that it will need to receive $5 billion during 2004 and 2005. This is based on two major assumptions. First, that Rounds four, five and six grants will be launched and approved during these two years, and that the cost of the first two years of the grants approved in each of these Rounds will be $1,000 million. (The first two years of Rounds one, two and three cost $613 million, $884 million and $623 million respectively.) Second, that money for years three to five of all Round one and two grants and a few Round three grants will also need to be received during those years.

The breakdown of the $5 billion needed is that $1,560 million will be needed in 2004 and $3,580 million will be needed in 2005.

If the United States gives the full $547 million that it has conditionally approved for 2004, the Fund expects to receive at least $1,532 million during 2004, based on current pledges. This is only $28 million short of the Fund's goal for 2004, and makes it likely that there will be sufficient funding for Round four. However, US legislation says that its $547 million pledge for 2004 is not a guarantee, but is a maximum donation. Specifically, the US says it will give one third of the total amount received in cash (or, possibly, promissory notes) by the Fund between 1 January and 31 July 2004, up to a maximum of $547 million (the US has one third of the world's GDP.) This places considerable pressure on other donors not only to increase their total pledges for the year by about $110 million, but also to pay all their 2004 pledges by 31 July.

That will be challenging enough for the Fund, but the greater challenge will be to raise the needed $3,580 million during 2005.

Timing of Round five

Round five will, in theory, be launched some time between October 2004 and January 2005, but the financial situation puts this timing in doubt.

The secretariat's budgetary projections are based on the assumption that one Round will be approved every second board meeting in the board's three-meetings-per-year schedule. (This means that Rounds five and six would be launched in about October 2004 and June 2005, and approved at the March 2005 and November 2005 board meetings.) And the board has resolved to have at least one Round per year (meaning that Round five should be launched by January 2005, one year after the launch of Round four).

However, the board has also resolved that paying for new grants will take second place behind paying for renewal of existing grants. Thus, Round five cannot take place until pledges have been received sufficient to pay for renewal of many Round one, two and three grants, as well as for new grants from Round five. It is believed that some countries are racing to complete a Round four application because if they wait until Round five, they might have to wait longer than expected.

Non-payers

Countries that as of 24 February 2004 had not paid their pledges for 2003 are Barbados ($100,000), Belgium ($7.5 million), Cameroon ($100,000), Iceland ($216,000), Mexico ($100,000), Nigeria ($1 million), South Africa ($2.9 million), and Zimbabwe ($842,000).

New pledges

The Global Fund has only received $163 million in firm new pledges during the eight months since just before the "International Meeting to Support the Global Fund" held in Paris on 16 July 2003. Those new pledges represent just 10% of the amount required during 2004, or 5% of the amount required during 2005.

This weak performance is slightly offset by the fact that currency fluctuations caused the value of existing pledges to increase by $107 million during this period.

Beyond this, the USA has increased its existing $200 million pledge for 2004 by up to an additional $347 million, but as discussed above, it will limit its 2004 payment to one third of the total money received from all sources during the first seven months of 2004. Thus, the increase cannot be regarded as a firm pledge.

During this period, the new pledges by foundations total a mere $11,600 (barely more than the pledge from the Treatment Action Campaign in South Africa), and the pledges by corporations have actually decreased by nearly $100,000, due to the non-payment of a $100,000 pledge from Statoil, a Norwegian oil and gas company. Foundations and corporations each have one seat on the Global Fund's board.

Australia has announced its first pledge to the Global Fund. This is for US$18.9 million, spread out over three years. The Australian foreign minister stated that Australia had delayed contributing to the Global Fund because it wanted to "wait and see how the Global Fund would work out." He added: "In those two years, we have been pretty impressed with the Global Fund. I think it's done an excellent job."

Relative to the sizes of their economies, every developed country in the world that has made a pledge to the Fund for 2004 has pledged more than Australia - from 1.5 times as much by each of Germany, Japan and Spain, to 11 times as much by Sweden. Oxfam and Medecins Sans Frontieres in Australia issued a statement saying that based on the size of its economy, Australia should be contributing US$25 million for 2004 alone, rather than US$19 million over three years.

Reproduced from the Global Fund Observer Newsletter (www.aidspan.org/gfo), a service of Aidspan. To receive the GFO newsletter send an email to receive-gfo-newsletter@aidspan.org

Link:

Global Fund

http://www.theglobalfund.org/

South African minister of health in line to chair Global Fund

Graham McKerrow, HIV i-Base

The governments of eastern and southern Africa have chosen the South African minister of health, Manto Tshabalala-Msimang as their representative on the board of the Global Fund to Fight AIDS, TB and Malaria. Next year the Fund has to choose a new chair to succeed Tommy Thompson, of the United States. Dr Tshabalala-Msimang will have served as a board member of Alternate for longer than most and will be in line for the top job.

This has caused some surprise among observers because Dr Tshabalala-Msimang has attracted a lot of criticism in South Africa and internationally for her views on HIV/AIDS and her government's reluctance to provide treatment for its people.

Thai ddI patent case serves as example to other developing countries, Lancet viewpoint piece says

Kaiser HIV Report

Thai AIDS advocacy groups' successful lawsuit against drug maker Bristol-Myers Squibb, in which BMS was forced to return to Thailand the patent for its antiretroviral drug didanosine, has "set an important precedent that essential drugs are not just another consumer product but a human right, and that patients are injured by patents," Nathan Ford, David Wilson, Onanong Bunjumnong and Tido von Schoen Angerer of Medecins Sans Frontieres write in a Viewpoint piece in the 14 February issue of the Lancet.

In October 2002, Thailand's Central Intellectual Property and International Trade Court ruled in favour of the AIDS Access Foundation, the Thai Network for People Living with HIV/AIDS and two AIDS patients and ordered BMS to amend its Thai patent on didanosine.

Although BMS originally appealed the case, it dropped the appeal in January, according to the Lancet. As a result, BMS in January reached an agreement with the AIDS advocacy groups to return its patent for the antiretroviral drug didanosine to the country's Department of Intellectual Properties, which granted the patent in January 1998. In exchange, the Foundation for Consumers and three HIV-positive people agreed to settle a legal suit filed against the drug maker in 2002.

The opinion piece calls for all developing countries to implement by 2005 the Trade-Related Aspects of Intellectual Property Rights agreement in full because "[w]ithout the effective use of safeguards to ensure generic competition, the cost of all new medicines will largely depend on price setting by the patent holder." The authors add that developing countries will need assistance implementing TRIPS and "meeting their obligations under the Doha declaration ... in a way that protects public health and promotes access to medicines for all." The authors conclude: "Thailand's example can only be encouraged."

Source: Kaiser Foundation

http://www.kaisernetwork.org/dailyreports/hiv
http://www.kff.org/hivaids/index.cfm

UK gives £3 million to WHO's '3 by 5' treatment goal

Graham McKerrow, HIV i-Base

The United Kingdom has announced that it is giving £3 million ($5 million) towards the World Health Organisation's (WHO's) "3 by 5" initiative to treat 3 million people in developing countries by the end of 2005.

The gift comes as some observers are questioning whether the target will be met and just after the resignation of the Director of the WHO's HIV Department.

The British announcement was made in March by Gareth Thomas, parliamentary under secretary of state at the Department for International Development (DFID). He commented: "We have no time to waste in the fight against HIV/AIDS, which is why we are supporting the 3 by 5 initiative. Teachers in dozens of poor countries are dying of HIV/AIDS faster than they can be trained so if we cannot tackle the scourge of HIV/AIDS we cannot lift people out of poverty."

The money will help to pay for additional staff, most of whom will work overseas with national Ministries of Health and training health service staff to provide antiretroviral therapy to people living with HIV/AIDS. DFID said the UK's bilateral expenditure on HIV/AIDS programmes has risen from £38 million in 1997/8 to £270 million in 2002/3.

Dr Paulo Teixeira resigned in March as director of the WHO's HIV department citing health and personal reasons. He has been replaced Dr Jim Yong Kim, formerly adviser to the WHO's director-general. Before Dr Teixera became director of the WHO HIV department, he ran the National AIDS Programme in Brazil and earned acclaim and awards for defending the free and universal distribution of antiretrovirals. He will continue to work with the 3 by 5 initiative, advising on the emergency deployment of staff and continuing to focus on work in developing countries.

Dr Kim is an infectious disease physician-anthropologist, an expert on treating poor people in several countries, who is currently on leave from his position as associate professor of medicine and medical anthropolgy at Harvard Medical School.

HEPATITIS COINFECTION

International panel issues new guidelines for the care of HIV-HCV coinfected patients

New consensus guidelines from a panel of international experts cover the most relevant and currently conflicting topics in the management of chronic viral hepatitis in the setting of HIV infection. The statements are graded according to the Infectious Diseases Society of America scoring system.

Full text available online at NATAP or Medscape:

http://www.natap.org/2004/jan/012604_04.htm

http://www.medscape.com/viewarticle/467365

An interview on management of coinfected patients following Retrovirus presentations is available on the Medscape website. Medscape requires one-time free registration:

http://www.medscape.com/viewarticle/469674

Ref: Soriano V, Puoti M, Sulkowski M et al. Care of patients with hepatitis C and HIV co-infection: Consensus Panel Recommendations. AIDS: Volume 18(1) 2 January 2004 pp 1-12

NICE approves pegylated interferon plus ribavirin in UK

Britain's National Institute for Clinical Excellence (NICE) has issued guidance on the use of interferon alpha, peginterferon alfa – a newer, longer-acting version of interferon alfa, which doesn't need to be taken as often – and ribavirin for the treatment of chronic hepatitis C within the National Health Service in England and Wales.

NICE has made the following recommendations:

- Combination therapy with peginterferon alfa and ribavirin should be used to treat people aged 18 years or older who have moderate to severe chronic hepatitis C if they:
  - have not been treated before with either interferon alfa or peginterferon alfa, and/or
  - have been treated before with interferon alfa but not with peginterferon alfa, and/or
  - have been treated with peginterferon alfa monotherapy but it did not work, or the virus came back after treatment
- The length of the treatment depends on the HCV genotype and how well a person initially responds to the drugs.
- People who are currently being treated with interferon alfa may be switched to peginterferon alfa.
- People who cannot take ribavirin, or have bad side effects from it, should be treated with peginterferon alfa monotherapy.
- People who are likely to have complications from the procedure do not need to have a liver biopsy to find out how extensive their liver damage is before treatment is started.

Source: NICE press release. PDF file of guidelines:

http://www.nice.org.uk/pdf/TA075guidance.pdf

OTHER NEWS

New HIV cases in England and Wales increase by 20% in past year

Stephen Pincock, BMJ.com

The number of new cases of HIV diagnosed in England and Wales rose by 20% between 2002 and 2003, triggering anxiety among public health authorities. "The year on year increase we are observing in the number of newly diagnosed HIV infections is a cause for considerable concern," said Dr Barry Evans from the Health Protection Agency, which released the figures last week. "HIV is an infection that is here to stay."

So far, 5,047 new HIV diagnoses have been recorded for 2003, compared with 4,204 at the same time last year. This follows the 26% increase that took place from 2001 to 2002. When all reports have been counted, the 2003 total for new diagnoses is expected to exceed 7,000 — the highest ever level — and unsafe sex was "undoubtedly the driving force," said the agency.

"We've got no vaccine, we've got no cure, but people have got accustomed to HIV in many respects," Dr Evans told the BMJ. "The chances of having an HIV infected partner have never been greater in the UK." The rising trend was seen in both homosexuals and heterosexuals.

Among gay men, reports received so far show there were 1,414 new diagnoses during 2003 compared with 1,195 at this time last year for 2002, although some of this is due to more prompt reporting from some centres. When the counting is over, 2,000 new cases are expected—the highest number since testing began.

A 27% hike has also been seen among heterosexuals. So far, 2,785 new heterosexual cases have been identified for 2003, compared with 2,199 at this point last year for 2002. Heterosexual infections contracted in England and Wales increased to 254, but some 80% in this group were contracted in Africa and elsewhere.

Dr Evans said the rise in other sexually transmitted infections could be behind the increase in HIV reporting. It could also be partly due to people coming forward for HIV testing who may have been infected for some time.

Nevertheless, almost a third of the estimated 49,500 people who are HIV positive in Britain are thought to be unaware of their infection. Figures like this mean that the rising trend is liable to get worse before it gets better, Dr Evans said. They also mean that more needs to be done to stem the tide, says the agency.

"In the third decade of HIV, we're in it for the long haul," Dr Evans said. "Somehow we've got to reinvigorate health promotion, and we've got to get people practising safe sex . . . and the scare tactics of the 1980s aren't going to work."

Source: BMJ 2004;328:425 (21 February)

More information can be accessed at:

http://www.hpa.org.uk

Micronutrient supplements may enhance survival; research has implications for poor countries

Graham McKerrow, HIV i-Base

Multiple micronutrient supplementation may enhance the survival of HIV-infected individuals with CD4 <200 cells/mm3 say researchers who conducted a randomised trial that enrolled 481 HIV-positive people in Thailand.

Sukhum Jiamton and colleagues in Bangkok, London and Quebec, conducted a randomised, placebo-controlled trial to examine the impact of high dose commercially available, multiple, micronutrient supplementation on survival and disease progression. Participants received either the supplement or a placebo for a period of 48 weeks, were examined clinically at 12-week intervals and CD4 counts were conducted at 24-week intervals. A subset had their plasma viral load recorded at 48 weeks.

Seventy-nine (16%) were lost to follow up and 23 (5%) died. The death rate was lower in the micronutrients arm with the mortality hazard ratios [95% confidence interval (CI)] of 0.53 (0.22-1.25; P = 0.1) overall and 0.37 (0.13-1.06; P = 0.052) and 0.26 (0.07-0.97; P = 0.03) among those with CD4 cell counts < 200 /mm3 and < 100 /mm3 respectively. The researchers report that there was no impact on CD4 cell count or plasma viral load.

The supplement used was a mix of vitamins and minerals in amounts higher than recommended daily allowances for healthy individuals, and consisted of vitamin A, betacarotene, vitamin D3, vitamin E, vitamin K, vitamin C, vitamin B1, vitamin B2, vitamin B6, vitamin B12, folacin, pantheothenic acid, iron, magnesium, manganese, zinc, iodine, copper, selenium, chromium and cystine.

The study said that since micronutrients are inexpensive and easily tolerated, their effect on the progression of HIV is an important public health question. The researchers concluded that the findings could have important public health implications in the developing world where access to antiretrovirals remains poor.

Ref: Jiamton S, Pepin J, Suttent R et al. A randomised trial of the impact of multiple micronutrient supplementation on mortality among HIV-infected individuals living in Bangkok. AIDS. 2003 Nov 21;17(17):2461-2469.

Durex withdraws N-9 condoms

The maker of Durex has ceased production of condoms containing the spermicide lubricant, nonoxynol-9 (N-9). Recent studies showed that it may actually increase the risk of HIV infection and was highlighted by the World Health Organisation and UNAIDS.

N-9 was originally developed as a detergent, and has been used for nearly 50 years as a vaginal cream that rapidly kills sperm cells. N-9 can also act to break up or irritate the cell lining, or epithelium, of the rectum and the vagina - and can make it easier for a virus or other infective organism to invade. The danger in anal sex is especially significant because the rectum has only a single-cell wall. The vagina has a wall that is about 40 cells thick.

Source: BBC News - Tuesday, 20 January, 2004

See: UK campaign to remove Nonoxynol-9 from condoms and lubricants, HTB Vol 4 No 5.
http://www.i-base.info/pub/htb/v4/htb4-5/Nonoxynol.html

ON THE WEB

Conference reports:

11th Conference on Retroviruses and Opportunistic Infections (CROI)

8-11 February 2003, San Francisco, CA

Extensive coverage including summaries of selected presentations, news stories and links to conference coverage are available on several other useful sites.

The Body
http://www.thebody.com
NATAP
http://www.natap.org
HIV InSite
http://hivinsite.ucsf.edu/InSite.jsp?page=cf11croi-00-00
HIVandHeptitis.com
http://www.HIVandHeptitis.com
Medscape
http://www.medscape.com
Clinical Care Options
http://clinicaloptions.com/croi

HIV InSite Knowledge Base

Integrating HIV prevention into the care of people with HIV - February 2004

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-07-04-17

Prophylaxis following nonoccupational exposure to HIV - February 2004

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-07-02-07

Sexual transmission of HIV: related resources

Features journal articles, reports and presentations, patient and provider fact sheets, and links. February 2004

http://hivinsite.ucsf.edu/InSite?page=kbr-07-02-01

Patient material in Asian languages

Several materials on HIV/AIDS and STDs are now available in Asian languages from the CDC National Prevention Information Network (NPIN).

http://www.cdcnpin.org/scripts/pubs/matlpubsearch.asp

- Living with HIV/AIDS
- HIV and AIDS: Are You at Risk?
- Ten Things You Should Know: For You and Your Baby
- Teens and HIV and other STDs: At Risk? Get Tested!
- Learn About HIV Testing

PUBLICATIONS AND SERVICES FROM i-BASE

The i-Base website

Our web address is

http://www.i-Base.info

All i-Base publications are available at our website, which is accessed by people all over the world; in February 2004 we had more than 5,000 successful page requests per week from 78 countries on all continents.

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

Introduction to Combination Therapy

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

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

Italian treatment guides

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

Guide to HIV, Pregnancy & Women's Health

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

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

http://www.i-base.info/pub/guides/pregnancy03/index.html

Guide to Changing Treatment: second-line and salvage therapy

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

Guide to Avoiding & Managing Side Effects

This is a comprehensive 36-page guide that is aimed at helping anyone using HIV drugs to get the most out of their treatment, the most out of their relationships with their doctor and other health professionals, to get better medical care to improve their health and, most importantly, to enjoy a better quality of life.

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

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

Treatment information request service – 0808 800 6013

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

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

For details, call the i-Base treatment information free phone line on 0808 800 6013. The line is usually staffed by positive people and is open Mondays, Tuesdays and Wednesday from 12 noon to 4pm.

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

UK-Community Advisory Board: reports and presentations

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

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

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

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

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

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

Treatment 'Passports'

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

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

Copies can be ordered using the form on the back page or by visiting our website (details below).

HIV Treatment Bulletin (HTB)

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

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.

Find HTB on AEGiS

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

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

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

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

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

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

h-tb

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

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

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