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SPECIAL ISSUE: Reports from the 10th Conference on Retroviruses and Opportunistic Infections, Boston

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EDITORIAL

The annual Conference on Retroviruses and Opportunistic Infections (CROI) remains one of the most important scientific meetings for presentation of new research and this year's meeting in Boston from 10-14 February was no exception.

As such, we have focused most of this issue of HTB on reporting from that meeting including reports on new agents, antiretroviral strategy, gender studies, generics, treatment in resource-poor settings, metabolic side effects and lipodystrophy.

Two of the bigger general news stories this month, appropriately included in 'other news', were the results from the VaxGen vaccine trial, and the approval (in the USA) and pricing (in Europe) for Roche/Trimeris fusion inhibitor T-20.

The VaxGen results are undoubtedly disappointing but did not come as a surprise to most researchers. The impressive logistical difficulties of running a large preventative vaccine trial, including ethical barriers, were nevertheless overcome. This was somewhat overshadowed by the company's emphasis on benefits shown in the small numbers of African-American and Asian people in the study. The tiny numbers involved, and indeed the calculation of statistical significance that has since been challenged, were effectively highlighted by community reports. We are left to wait until the results of the Thailand study expected in a few months time, to see whether this leads to any benefit in practice.

T-20 is the first 'new-class' drug to be approved since 1996 and the significant scientific and medical advances implicit in its development have been largely overtaken by the issue of cost - at $20,000 per year this is at least three times higher than the most expensive current drugs.

Development costs were undeniably high, and if Roche hadn't partnered early with Trimeris and run with the many uncertainties of a subcutaneously administered drug, we wouldn't have seen the compound introduced into clinical care for many years.

T-20 will work against all virus resistant to current treatments, but like all drugs, for long-term benefit requires support from other active agents in a combination. Strictly speaking, this implies use earlier in treatment failure and at least in third-line therapy.

The UK has been relatively sheltered from individual drug costs for HIV, and also thankfully sheltered from National Institute of Clinical Excellence (NICE), but there is no guarantee that this will continue. Restructuring healthcare through Prmary Care Trusts is likely to mean that everything now comes from the same pot and there has still been no government recognition that increasing numbers of new infections and reduced mortality in itself requires an increasing annual drug budget.

Although still easily justifiable by health economic analysis, there is a concern that cost may be used as a factor to delay use of T-20. In practice, instead of becoming a possible drug for many patients to successfully control viremia and reduce further resistance, it may become used only sparingly and in salvage situations.

The implications for other markets, notably the USA where many ADAP and Medicaid programmes already have closed waiting lists are unclear but indications of the concern from patients dependent on these programmes are provided in linked articles for this story.

CONFERENCE REPORT

10th Conference on Retroviruses and Opportunistic Infections (CROI) 10-14 February, 2003. Boston, USA

The 10th Conference on Retroviruses and Opportunistic Infections (CROI) was held from 10-14 February in Boston, USA, and was attended bw˚Óearly 4,000 delegates. This conference is one of the most important annual scientific HIV meetings.

Abstracts, including all abstracts referred to in references to the following reports, as well as many of the full posters, and webcasts from the symposium sessions and special lectures together with accompanying slides, are available at:

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

CROI: ANTIRETROVIRALS

Pipeline compounds in Phase2/3 Studies

Simon Collins, HIV i-Base

Early data was presented on several new agents at the first of the opening oral sessions on new antiretrovirals. Many of these new molecules included new targets and mechanisms of action, but were also still only in pre-clinical stages of development. These included pyranodiprymidine integrase inhibitors, AK605 CCR5 inhibitor and TAK-220 and UK-427,857 CCR5 agonists and PA-457, a new budding inhibitor (see abstract 9, 10, 11, 12 and14).

There were also important new results from compounds already in Phase 2/3 studies in HIV-positive people that are likely to be available to treatment-experienced patients in the UK in clinical trials, expanded access or as licensed drugs over the next year.

TMC-114

TMC-114 is a protease inhibitor developed by Tibotec that has strong antiviral activity against a broad range of protease-resistant virus. In a Phase II, open label dose finding study, 50 multiple treatment experienced patients were randomised to one of four arms - adding BID doses of 300, 600 or 900mg TMC-114, with 100mg ritonavir BID for 14-days to their regimen (arms A, B, C), or to continue their existing combination (arm D). [1]

Baseline median viral load and CD4 counts were 4.3 log and 297 cells/mm3 median number of three primary PI mutations (0-5) and six additional PI mutations (2-11) between the four arms. Almost half the patients were resistant to all PIs at baseline, with approximately 25% sensitive to only one PI and 25% sensitive to ‡2 PIs.

Median viral load change from baseline to day 14 was -1.24 (-0.51 to –2.06), -1.50 (-0.47 to –2.49), -1.13 (0.49 to –2.13) and +0.02 (+0.37 to –0.41) in the 300, 600, 900 and placebo arms respectively. 69%, 92%, 69% and 17% had at least a >1log reduction and in the TMC-114/r groups 97% of patients had at least a 0.5 log reduction.

One patient in the 900mg arm discontinued treatment due to GI discomfort and one patient in the 600mg arm due to hepatitis. Grade 3/4 ALT, AST or GGT enzymes occurred in two, two, and one of arms A, B, and C respectively with one Grade 3 ALT in the control group. One patient had a G4 rash. Grade ‡2 triglycerides and cholesterol increases occurred in eight and 12 of the TMC-114 group compared to three and one of the control group respectively.

T-20 and T-1249

The next antiretroviral agent to be licensed will be T-20 (long expected in Europe to be in June or July, but possibly now delayed to December). The TORO 1 and TORO 2 studies showed clear benefit of using T-20 over optimised background therapy alone when previously presented individually at the Barcelona, ICAAC and Glasgow conferences, so it was no great surprise that the pooled data presented at CROI showed similar results. [2]

One poster focused on the injection site reactions associated with T-20 administration and reported pathological changes following biopsy from seven patients. T-20 was detected in all samples and concentration correlated positively with areas of greatest inflammatory response. [3]

Other findings reported that this response, consistent with a localised hypersensitivity reaction, was seen in all patients, including patients with erythema without nodules, palpable nodules or no clinical reaction; that the pattern of eosinophil and histiocyte proliferation and collagen degeneration resembled that of granuloma annulare and the recently described interstitial granulomatous drug reaction, and that there was no relation between the clinical reaction and the degree or localisation of inflammation, or the depth of injection.

Patients on early studies have reported that nodules are very slow to disappear, and although Roche suggests that they have been seen less frequently since the introduction of a more recent formulation that requires less preparation time (nodules may be associated with a drug that was not entirely constituted), the poster concludes: “Due to the high incidence of this adverse reaction, clinical dermatologists should become familiar with the findings in this study prior to caring for HIV-infected patients undergoing this new mode of therapy.”

It is also becoming clear that like all other drugs, T-20 has limited benefits unless supported by activity of additional drugs in the combination. People receiving T-20 in early studies or the expanded access programme who are not able to achieve maximal viral suppression accumulate resistance to T-20, and derive limited benefit.

Preliminary data on efficacy of the second generation fusion inhibitor T-1249, which binds to a slightly different sequence of gp41 than T-20 in T-20 resistant patients, were presented as a late-breaker oral session on the second generation fusion-inhibitor from Trimeris/Roche. [4]

Fifty patients who had already developed resistance to T-20 were enrolled in the first T-1249 Phase II study, receiving 192mg QD for 10 days. Planned interim analysis was presented for the first 25 patients. Mean viral load and duration of previous T-20 therapy at study entry was 5.1 logs and 70 weeks, with mean time on T-20 with a viral load >5,000 copies was 56 weeks (range 28-136 weeks).

Median viral load change at day 11 was -1.12 (1.50-0-83, 95% CI). Fifteen patients had >-1 log drop and 19 had a drop >0.05 log. When analysed by time on previous (failing) T-20 regimen, patients with least exposure to a failing regimen (24-48 weeks) whilst only 8/17 people who had continued >48 weeks achieved >1 log drop.

One patient who had pre-existing severe chronic obstructive pulmonary disease at baseline developed an upper respiratory tract infection and died of pneumonia before the end of the trial. The two other significant adverse events were one case of elevated liver enzymes and one case of acute bronchitis.

This study demonstrates antiviral activity of a once-daily fusion inhibitor prior to the approval of T-20 and access to similar roll-over studies is essential for patients unable to derive sustained benefit from the first programme, especially as response to the new agent is limited by previous time on a failing T-20 regimen.

Atazanavir

Longer-term efficacy and safety data were presented for atazanavir, particularly important as the profile for this once-daily azapeptide protease inhibitor has promised a kinder metabolic profile and consequent hope for a reduced risk of lipodystrophy than has yet to be seen in clinical studies.

This prospective open-label roll-over study (BMS-044) assessed the longer-term efficacy and safety of ATV beyond 72 weeks and the efficacy and safety in patients switched from nelfinavir (NFV) to atazanavir (ATV) in the earlier Phase II study (BMS-008). [5]

A total of 346 patients (63% male, 37% female) were enrolled and treated in AI424-044; the median cumulative time on therapy was approximately 108 weeks (72 weeks in 008 and 36 weeks in 044).

Viral load, CD4 and lipid effects are summarised in the table below:

	ATV 400 mg (n = 139)		NFV to ATV (n = 63)	
	044 Entry	Week 24	044 Entry	Week 24
Response Criteria†		Observed/Evaluable (%)		
< 400 c/mL ITT	-	111/139 (80)	-	54/63 (86)
< 50 c/mL As treated	63/129 (49)	80/133 (60)	30/60 (50)	37/62 (60)
< 50 c/mL ITT	-	80/139 (58)	-	37/63 (59)
Median CD4	472	556	543	584
Total Chol *	180 (129)	176 (128)	202 (56)	169 (56)‡
Fasting LDL-C *	110 (60)	105 (86)	132 (33)	99 (40)‡
Fasting TG *	105 (103)	104 (110)	127 (47)	102 (52)‡

* Median mg/dL (n)

†As treated analysis, results maintained through 108 weeks from start of AI424-008. ITT analysis for 008/044 selected cohort

‡p < 0.0001, NFV to ATV, mean % change, week 24 vs entry

Discontinuations due to adverse events were infrequent and comparable across cohorts (ATV 400 mg, 1%; ATV 600 mg, 2%; NFV to ATV, 3%), and no new safety issues were identified after approximately 108 weeks of cumulative ATV treatment. Asymptomatic elevation in indirect bilirubin (without hepatic transaminase elevation) was the most frequent laboratory abnormality.

ATV treatment did not produce clinically relevant increases in TC, fasting LDL-C, or fasting TG. After 24 weeks of ATV, patients switching from NFV, experienced significant decreases in TC, fasting LDL-C, and fasting TG towards pre-antiretroviral treatment levels.

Tipranavir

The Phase II study used to select the dose for development programme for tipranavir (see also January/February issue of HTB) was presented at the conference.

Gathe and colleagues presented results from an international, blinded, multicentred trial of three investigational doses of tipranavir/ritonavir dose regimens in 216 patients experienced to all three classes, and at least one primary PI mutation. [6]

The three doses of tipranavir/ritonavir (TPV/RTV) used were 500mg/100mg, 500mg/200mg and 750mg/200mg added to existing therapy for the first two weeks to assess change in viral load. Background therapy could then be optimised.

Median baseline CD4 count and viral load were 153 copies/mm3 and 4.5 log copies/mL respectively and previous PI use ranged from 37.5% for lopinavir to 79.6% for indinavir.

Median decreases in viral load by intent-to-treat analysis were -0.9 log in the 500/100mg arm, -1.0 log in the 500/200mg arm, and -1.2 log in the 750/200mg arm.

The most common adverse events associated with tipranavir were diarrhoea, nausea, fatigue, headache, vomiting and elevated liver transaminases.

A second poster analysed baseline PI susceptibility with median baseline fold WT IC_{50} in 157 isolates to tipranavir of 1.1 (range

0.3–100.2). This was 76.5 (0.5–165.3) for lopinavir, 8.7 (0.3–150.7) for amprenavir, 7.0 (0.1–108.9) for saquinavir, 12.2 (0.4–197.4) for indinavir, 36.8 (0.3–96.4) for nelfinavir, and 94.2 (0.2–808.5) for ritonavir. [7]

Viral isolates from 200/216 (93%) patients had >10 protease gene mutations at baseline and 41/216 (19%) patients had genotypes indicative of resistance to all currently marketed PIs. Twenty-two per cent of patients had virus with three universal protease inhibitor-associated mutations (UPAMs) - L33I/V/F, V82A/F/L/T, I84V, L90M.

The distribution of TPV susceptibility in these isolates was 42% £ 1-fold WT, 27% >1 to 2-fold WT, 18% >2 to 4-fold WT, and 12% >4-fold WT. The overall median viral load changes after initial two weeks were -1.23 log, -1.24 log, -0.21 log, and -0.19 log, respectively. This indicates a strong antiviral response for TPV IC_{50} £ two-fold WT, and a lesser response for TPV IC_{50} >two-fold WT.

As indicated by the clinical results, baseline phenotypic susceptibility to TPV was maintained in the majority of isolates that were highly resistant to available PIs. The reduced response to TPV susceptibility at an IC50 approximately two-fold WT required the accumulation of 16-20 protease gene mutations including three UPAMs.

The 500/200mg dose has been selected to take forward to Phase III RESIST 1 and 2 studies, which were planned to start enrolment from February 2003, but which have still not been approved at UK clinics.

FTC

FTC (emtricitabine, Coviracil), is a nucleoside (cytosine) analogue similar to 3TC, that was recently acquired by Gilead following a protracted development programme with Triangle Pharmaceuticals. Several posters were presented showing comparable or similar efficacy to d4T or 3TC in treatment naïve and experienced adults and children, perhaps with advantages of an improved resistance profile and once-daily dosing.

In FTC-301, 571 patients were randomised to receive FTC or d4T (285 d4T, 286 FTC) with background ddI and efavirenz. Median BL VL was 4.9 log10 and the mean BL CD4+ was 318 cells/mm3. [8]

The proportion of patients having virological failure through week 48 was 5.3% in the FTC arm and 12.7% in the d4T arm ($p < 0.05$). The mean increase from baseline to week 48 in CD4+ was significantly greater in the FTC arm (153 cells/mm3) than the d4T arm (120 cells/mm3) ($p < 0.05$).

Genotypic analysis performed on 46 of the 49 confirmed virological failures showed 32 (97%) patients had mutations in the d4T arm compared to 69% (9/13) from the FTC subgroup ($p < 0.05$). The M184V mutation was observed in 46% (6/13) of the FTC group while TAMs were observed in 8% (1/13) of the FTC subset and 21% (7/33) of the d4T subset. Both the ddI-associated mutations and the NNRTI mutations were less prevalent in the FTC subset, 0% and 69% (9/13) as compared to the d4T subset, 12% (4/33) and 88% (29/33), although these differences did not reach statistical significance.

Longer-term efficacy and safety results were presented by Wakeford and colleagues for 215 patients who continued to receive FTC after 48-week successful treatment in FTC-303. Of these, 152 of 294 (51%) maintained suppression of HIV-1 RNA £ 400 copies/mL and 139 (47%) £ 50 copies/mL through week 120 (2.3 years). Median time on FTC was 140 weeks and the Kaplan-Meier probability of virological failure at four years was 11%. [9]

Most adverse events were mild or moderate; the annual incidences of drug-related severe or potentially life threatening adverse events were 3% and < 1%, respectively. The annual incidences of Grade 3 and Grade 4 laboratory abnormalities were 11% and 10%, respectively. Of these, asymptomatic and transient elevations in CPK accounted for more than two-thirds of the overall Grade 4 events.

Although the cumulative virological failure in patients switching to FTC appears high (49% failure between weeks 48 and 120) understanding this is frustrated by the focus on results based on suppression to only <400 copies/ml - as partial suppression to only 50-400 copies/ml is already well understood to lead to virological rebound. The long-term safety data from this long-awaited drug is nevertheless encouraging.

Molena and colleagues reported benefits from randomising 355 patients already on treatment (with viral load <400 copies) to a once daily regimen of FTC, ddI and efavirenz or continuing existing therapy over 48 weeks. [10]

The proportion of patients with plasma HIV RNA < 50 copies/mL at week 48 was significantly higher in the once-daily arm than in the continuation arm (95% versus 87%, $p = 0.01$). Median CD4 count increase was similar between arms (+21 and +13/mm3) as were rates of treatment discontinuations (10.1% and 12.4% respectively).

FTC is also formulated for paediatric dosing as a palatable flavoured syrup and results from two paediatric studies were also presented.

Fifty-one naive and 31 experienced children (median four years prior ART), reported results from using FTC at a FTC dose of 6mg/kg QD in children of all age groups (range three months-17 years old) produced similar plasma levels to adults receiving 200 mg QD. [11]

In the NP group, at week 20, the median changes in HIV-1 RNA and CD4 were -2.6 log10 and +213 cells/mm3 respectively. Naïve patients received FTC with lopinavir/r and d4T and treatment experienced children substituted FTC for 3TC similar to

the protocol for the adult 303 study described above.

Across both groups, by Non-Completer=Failure analysis, at week 24, 89% (73/82) of evaluable patients achieved a VL <400 copies/ml.

Virological response at week 24:

Efficacy endpoint	ARTnaïve (n=51)	ARTexp (n=31)	Total (n=82)
%< 400 copies/mL (NC=F)	47 (92.2%)	26 (83.9%)	73 (89.0%)
%< 50 copies/mL (NC=F)	32 (62.7%)	22 (71.0%)	54 (66.0%)
Median change from B/line RNA	-3.09 (-4.03, -0.07)	-0.00 (-0.81, 0.96)	-2.52 (-4.03, 0.96)

Grade 3/4 lab abnormalities were reported in 17% (14/82) of patients. Three patients discontinued the study, one for SAE (anemia), one for virologic failure, and one withdrew consent.

The incidence of serious adverse events was 13.7% (7/51) in ART-naïve patients and 16.1% (5/31) in ART-experienced patients. There were five events of at least moderate severity that were possibly or probably related to study drug (one case each of pancreatitis, vomiting, leucopenia, anaemia and pleural effusion).

Grade 3/4 lab abnormalities were reported in 6% (5/82) of patients; 2% (1/51) ART-naïve and 13% (4/31) ART-experienced patients.

PACTG 1021 is an ongoing Phase I/II study of once-daily FTC in combination with ddI and efavirenz in minimally treated or treatment naïve children. [12]

Thirty children were enrolled at 15 sites into two cohorts (three-12 years, 13-21 years), and were stratified as either therapy naïve or < six weeks of perinatal prophylaxis. At baseline, median age: 10.5 years (17 <12 years old; 13 13-21 years). Median CD4 count and percentage was 302 cells/mm3 and 16.5%. Median viral load was 50,000 copies/ml. FTC was dosed were FTC 6 mg/kg.

Viral results (ITT, discontinuation = failure): at week 16 (n = 23), 87% < 400 copies/ml, 74% < 50 copies/ml. For children >12 yrs old (n = 13), 92% < 400 copies/ml.

Three patients permanently discontinued therapy (one viral failure, one voluntary withdrawal, one Grade 3 rash). At week 16 (n=19), median CD4 increase was 220 cells (9%) with all children showing a CD4 increase from baseline.

Fosamprenavir

Updated results from two Phase III studies of fosamprenavir (908) were presented at the meeting.

Nadler and colleagues reported 48-week results from an open-label randomised (2:1) study comparing 1400mg 908 BID to 1250mg nelfinavir (NFV) BID, conducted in the USA, Panama, Puerto Rico and South Africa. [13]

251 treatment naïve individuals in closely matched arms had baseline values (all approximated) including: median CD4 210 (range 2-1000) with 45% <200 cells/mm3 and 20% <50 cells/mm3; median viral load 4.8 log with 45% > 100,000 copies/ml; median age 38; approximately 30% women; 50% heterosexual; 24% White, 32% African-American, 44% Hispanic.

At week 48, by intent-to-treat analysis, 58% and 42% patients had achieved and maintained viral load reductions to <50 copies/ml in the 908 and NFV arms respectively. Analysis by stratified baseline viral load showed 56% vs 57% <100,000 and 60% vs 24% when >100,000 copies/ml in the 908 and NFV arms respectively.

The overall incidence of drug related Grade 2–4 adverse events was comparable; with only greater incidence of diarrhoea in the nelfinavir arm showing significantly different AE being higher on NFV (18% vs 5%, p = 0.002).

In practice, and in previous studies (ie the SOLO study), fosamprenavir is co-administered with low-dose ritonavir. DeJesus and colleagues randomised 315 PI-experienced patients to either 908/RTV 1400mg/200mg once daily, 908/RTV 700mg/100mg BID or to lopinavir/ritonavir BID (1:1:1) together with two sensitive RTIs, with the aim of showing non-inferiority of the 908 arms. [14]

With low baseline median baseline viral load of only 4.14 log (range not provided) efficacy was assessed by measuring time-averaged change in vRNA from baseline (AAUCMB) at both 24 and 48 weeks. At 24 weeks this was, by a confusing 'intent-to-treat observed' analysis, -1.46, -1.48 and -1.63 log in the 908 QD, 908 BID and LPV/r arms respectively. The upper limits of both CIs were below the pre-specified 0.5 non-inferiority margin, although these are both very short-term and limited data.

Finally, MacManus and colleagues presented data on resistance for people experiencing treatment failure on the SOLO and NEAT studies. The SOLO study (48-week results were presented as a late breaker in Glasgow) compared boosted 908 QD to NFV BID with an abacavir + 3TC background in 660 treatment naïve individuals. All failures showed evidence of ongoing replication, but a statistically significant difference in patient incidence of both PI and NRTI-associated mutations in favour of 908 (0% vs 56% and 9% vs 57% respectively). [15]

In contrast, patients failing on non-ritonavir boosted, fosamprenavir regimens in the NEAT study showed mutations characteristic of development of APV resistance in virus from 5/29 (17%) 908 treated subjects analyzed (3% subjects exposed) and included I54L/M, V32I + I47V and M46I. NFV-selected mutations (D30N, N88D/S, or L90M) were detected in 6/26 (23%) NFV-treated subjects analysed (7% subjects exposed).

Anti-CD4 mAb (TNX-355)

Finally, interesting results were shown from using a novel entry inhibitor, TNX-355, a humanised IgG4 anti-CD4 domain 2 mAb, that showed potent anti-HIV-1 activity following a single dose of TNX-355 in HIV-positive subjects. [16]

Five sequential cohorts of six HIV-1-infected subjects received single iv doses of TNX-355 in an open-label dose-escalation study (0.3, 1, 3, 10, and 25 mg/kg). Mean baseline CD4 count was 354 cells/mm3 and viral load was 5.1 log10 copies/mL. All were HAART-experienced and 19/30 were on failing HAART at entry.

Mean peak decreases in VL of 0.2, 0.68, 1.48, and 1.09 log10, occurred on days two, four, 14, and 21 for the 1, 3, 10, and 25 mg/kg dose cohorts, respectively. The number of patients achieving >1.0-log10 decrease was nought out of six, two out of six, five out of six and five out of six for the 1, 3, 10, and 25 mg/kg cohorts, respectively. Duration of complete CD4 cell coating with TNX-355 ranged from one to two days at 1 mg/kg to 15–27 days at 25 mg/kg, and correlated with day of VL nadir. TNX-355 was well tolerated. No serious adverse events were reported. CD4 cell depletion was not observed in any cohort.

Further assessment of therapeutic potential awaits data from longer duration trials; a phase 1b multiple- dose study is planned.

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3. Ball RA, Kinchelow T. Pathology of injection site reactions with enfuvirtide. Abstract 714.
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15. Macmanus S, Yates P, White S et al. GW433908 in ART-naive subjects: absence of resistance at 48 weeks with boosted regimen and APV-like resistance profile with unboosted regimen. Abstract 598.
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96-week results show tenofovir-including regimen has side-effect advantages over d4T regimen in treatment naïve patients

Graham McKerrow, HIV i-Base

Scientists in Germany, the USA, London and Brazil reported in a poster the 96-week preliminary interim results of a blinded, randomised study looking at the safety and efficacy of tenofovir disoproxil fumarate (TDF, Viread) vs stavudine (d4T, Zerit) when used in combination with lamivudine (3TC, Epivir) and Efavirenz (EVF, Sustiva) in ARV-naïve patients.

The researchers, including Dr A Cheng of Gilead Sciences, who produce TDF, concluded that high proportions of patients in both arms of the study achieved HIV RNA <400 and <50 c/mL as well as significant increases in their CD4+ cell count.

They further concluded that the TDF arm showed significantly fewer toxicities associated with mitochondrial dysfunction, a better total fasting lipid profile, lower use of lipid lowering agents and more limb fat and weight gain. Both arms showed a similar renal safety profile.

Six hundred ART-naïve patients were randomised into the two treatment arms for a 144-week study.

The mean (95% CI) change in the fasting lipid profile for triglycerides was more than 100mg/dL in the d4T arm, but only 5mg/dL in the TDF arm (p<0.001). The mean (95% CI) weight change from baseline was more than 6lbs in the TDF arm and only about 1lb in the d4T arm (p=0.002). Total limb fat (DXA) was more than 17lbs in the TDF arm compared with about 11lbs in the d4T arm (p<0.001).

Selected toxicities associated with mitochondrial dysfunction through week 96

All Grades	TDF+3TC+EFV	d4T+3TC+EFV
Patients (%) with Events	n=299 11 (4%)	n=301 61 (20%)
Peripheral Neuritis/Neuropathy	8 (3%)	29 (10%)
Lipodystrophy*	3 (1%)	35 (12%)
Lactic Acidosis**	0	3 (1%)
Pancreatitis	0	0

Relative risk (95% CI) for toxicity (d4T/TDF) 5.5 (3.0, 10.3)

*Investigator defined

**p value <0.001

Ref: S Staszewski et al. Efficacy and safety of tenofovir DF (TDF) versus stavudine (d4T) when used with lamivudine and efavirenz in antiretroviral naive patients: 96-week preliminary interim results. Abstract 564b.

2NN results – nevirapine and efavirenz in prospective randomised head-to-head study

Simon Collins, HIV i-Base

Among the most anticipated study results were those from the IATEC run and Boehringer sponsored 2NN study, and these were presented in the last session of oral poster presentations at the conference.

2NN is the first large randomised study to compare nevirapine (NVP, Viramune) and efavirenz (EFV, Sustiva) in a head-to-head study, and it was planned and run long after both drugs had been licensed. Such studies are generally rare and it is commendable that several important patient-centred questions were answered in one study.

The study also included a dual-NNRTI arm using both drugs together to look at whether similar benefits as dual-PI strategy were possible. A fourth arm was added and enrolment size significantly increased very early in the study to include once daily nevirapine. All four arms used a nucleoside backbone of stavudine (d4T, Zerit) and lamivudine (3TC, Epivir).

The multicentred international study enrolled 1,216 treatment naïve patients from 67 sites in 17 countries including from Europe, South Africa, Australia, Thailand, South America and the USA. Primary endpoints were the percentage of patients with treatment failure, defined as >1 log drop in viral load at week 12; virological failure after week 24, disease progression or change in assigned treatment. Secondary endpoints included percentage of patients with viral load <50 copies/ml; change in CD4 count and incidence of clinical or laboratory adverse events. All analyses were intent-to-treat (ITT) for all randomised patients at week 48. The four planned pair-wise comparisons were: NVP bd vs EFV; NVP bd vs NVP qd; NVP qd vs EFV+NVP and EFV qd vs EFV+NVP.

All arms were well matched and patient characteristics were relevant to people starting treatment today. Baseline median characteristics for the whole study included CD4 cell count just below 200 cells/mm3 (range 70-330), plasma viral load of 4.7

log (4.4-5.5), age 34 (29-40), 21% CDC class C. Over one third of patients were women, almost 60% acquired HIV heterosexually, and 5.3% and 9.5% were coinfected with hepatitis B and C respectively.

Results at 48 weeks

% of pts	NVP QD	NVP BID	EFV QD	NVP+EFV
n (randomised)	220	387	400	209
n (completed)	83% (182)	83% (332)	84% (337)	84% (175)
Rx success (ITT)	56.4	56.3	62.3	46.9
Change Rx	29.1	22.0	20.0	34.5
Virologic failure	11.4	18.9	15.3	16.3
<50 copies ITT	70.0	65.4	70.0	62.7
virol. success:	65.0	63.6	67.8	61.7
baseline <100k	71.1	68.2	71.1	64.0
baseline >100k	51.5	53.7	61.3	57.1

The only statistically significant difference by efficacy was between EFV QD and NVP+EFV arms (p<0.001).

CD4 increases for patients completing the study increased similarly and were 170, 160, 160 and 150 cell/mm3 at 48 weeks in the NVP QD, NVP BD, EFV QD and NVP+EFV arms respectively, with no statistically significant difference between arms.

As expected, differences were recorded in treatment arms when assessing side effects and grade 3/4 toxicities are shown below:

Clinical events

% of pts	NVP QD	NVP BID	EFV QD	NVP+EFV	p value
N	220	387	400	209	
Hepato-biliary	1.8	2.6	0.5	1.0	0.082
hepatotoxicity	1.4	2.1	0.3	1.0	
Cutaneous	4.1	3.6	3.8	5.7	0.619
rash	4.1	3.1	1.8	3.8	
CNS / Psychiatric	1.4	3.6	5.5	7.7	0.001
Miscellaneous:					
diarrhoea	0.5	0.8	1.0	1.9	
vomiting	0.9	1.0	1.0	1.4	
pyrexia	0.9	2.1	0.8	1.0	
Total % patients *	15.0	20.4	18.0	24.4	0.077
Total % pts discont.†	24.1	21.2	15.5	29.7	<0.001

* patients with at least one grade 3/4 event.

† patients temporarily or permanently discontinuing treatment (Rx) because of AE (any grade)

Laboratory events

Hepatobiliary lab. toxicity *	13.2	7.8	4.5	8.6	0.002
Non-hepatobiliary lab. tox	8.2	12.9	8.8	9.6	0.161
neutropenia	2.3	3.9	1.8	5.3	
amylase	1.8	3.1	3.5	1.4	
triglycerides	1.4	1.3	1.3	0.5	
alkaline phosphatase	0.5	1.3	0.8	1.9	

* elevated ASAT and/or ALAT

Twenty-five patients died during the study. Of these two were attributed to NVP use (one case of toxic hepatitis from Argentina without evidence of hepatic co-infection and one case of Steven's Johnson syndrome from South Africa who died of MRSA septicaemia while recovering in hospital); one death was from lactic acidosis attributed to d4T; 11 deaths related to HIV-disease; 11 deaths non-Rx and non-HIV related.

The clearest conclusion achieving statistical significance was that dual NNRTI therapy results in statistically poorer virological response compared to efavirenz, and significantly greater grade 3/4 clinical toxicity than efavirenz. NVP once daily is associated with significantly greater grade 3/4 liver lab toxicity than efavirenz, which may have been a surprise, and that efavirenz is associated with greater CNS toxicity which wasn't.

However the take home message stressed by the investigators, and in the many reports of this study, is that nevirapine and efavirenz both performed similarly with no statistical difference in potency or serious toxicity and that they should be considered equally when planning antiretroviral choices.

Lipid sub-study

A sub-study looked at the lipid samples obtained after a mandatory ‡3-hour fast with primary outcome being absolute change in plasma lipid concentrations adjusted for baseline value between start of treatment and week 48. The analysis was limited to patients who continued their randomised treatment for 48 weeks.

This showed a small but statistically significant benefit in favour of the patients receiving nevirapine alone over efavirenz alone. Change in plasma lipid concentrations over 48 weeks showed a larger increase in HDL-c (+0.37 vs + 0.24), larger decrease in TC:HDL-c ratio (-0.36 vs 0.04), both p<0.001; and a smaller increase in TG (+0.12 v +0.37), p=0.01.

The percentage of patients with dyslipidemia defined as TG>2.3mmol/l, TC >6.2mmol/l, LDL-c>4.1mmol/l, HDL-c <0.9 mmol/l and TC:HDL-c ratio >6.5 tended to be very slightly higher for efavirenz but in this analysis there was no significant statistical difference between treatment arms.

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C O M M E N T

Is there any importance to the several numerical differences between arms that showed greater EFV efficacy generally at >100k even though these were not statistically significant? P-values were not provided in order to comment on the importance of any trend and some questions are not answered as they were not included in the pairwise comparisons (ie NVP QD vs EFV QD)?

Absolute success rates were not high, but definition of failure was very strict and devised to show real-life results from each drug (ie switch = failure). This study certainly provides clinicians with data to support use of NVP-based combinations in first line therapy, although in the UK this is already common practice.

This study may not provide the clinical answer for when to choose one NNRTI over another as this will be guided by the approach to management of side effects, but for such a substantial non-registrational study it is as good as we are likely to see.

NIH/NIAID study of generic drugs shows results consistent with stringent manufacturing standards

Polly Clayden, HIV i-Base

This conference had a strong emphasis on international issues and treatment in resource limited settings. Production of generic antiretrovirals by generic manufacturers has reduced the cost of HAART to as little as $1 a day. Several sessions included reports of programmes using these affordable drugs in their treatment strategies, including data from Malawi using Triomune [1] and India and Mozambique using nevirapine (NVP)-containing generic HAART regimens [2, 3].

However concerns have been raised (with varying agendas) that generic medications may contain little or no active ingredient or may not be bioequivalent to originator products. A poster from Dr Penzak and colleagues from the NIH and NIAID compared the NVP content of several generic and originator formulations as part of a pilot, quality control investigation [4].

The authors explain that "There are currently no publicly available data describing the integrity (drug content vs. label claim) of these preparations." These data are essential to enable governments and healthcare providers to make decisions as to which antiretroviral formulations will provide the greatest benefit to the 90% of HIV positive people who currently have no access to these medications.

Tablets containing NVP (alone or in combination with other ARVs) were obtained from six international sources and the NVP content of the six products was determined by HPLC. In total, six chromatographic analyses were performed for each individual

Table for article:
NIH/NIAID study of generic drugs shows results consistent with stringent manufacturing standards by Polly Clayden,

Nevirapine products analysed for drug content

Manufacturer/ Product	Country where product was obtained	Date of manufacture (expiration)	Mean nevirapine content (cv [%])
Cipla - Triomune 30 Nevirapine 200 mg Stavudine 30 mg Lamivudine 150 mg	Kenya	Not provided (1/03)	194.2 mg (3.1)
Viramune -Boehringer Nevirapine 200 mg	Lithuania	Not provided (Not provided)	201.9 mg (3.0)
Viramune -Boehringer Nevirapine 200 mg	South Africa	Not provided (12/01)	196.6 mg (2.2)
Cipla - Triomune 40 Nevirapine 200 mg Lamivudine 150 mg Stavudine 40 mg	Zambia	12/01 (05/03)	191.4 mg (2.1)
Cipla - Nevimune Nevirapine 200 mg	Zambia	8/01 (07/03)	197.8 mg (3.0)
Nevirex -Aurobindo Pharma Ltd. Nevirapine 200 mg	Zambia	11/01 (10/03)	205.5 mg (2.1)

tablet. The NVP content and demographic data for the individual products are listed in the table below.

All products in this study were labeled as containing 200 mg of NVP drug. The average NVP content among the tested preparations was 197.9 mg. Average accuracy of nevirapine content in the tested preparations versus labeled amounts was 99.0%.

The investigators concluded that: "The results are encouraging and consistent with stringent manufacturing standards (– 3% of labeled drug amount); these data are particularly reassuring given the widespread use of nevirapine-containing products in the developing world."

Studies are currently in progress to analyse all currently available generic antiretroviral products at the NIH and UAB.

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CROI: TREATMENT STRATEGIES

Treatment interruptions: cycles, pauses, or just plain stopping?

Dr David Margolis, University of Texas, for NATAP.org

Interruption of antiretroviral therapy occurs every day as part of clinical practice, and as part of everyday life for many with HIV infection. Over the past several years prescribed interruptions of therapy have been proposed to accomplish a variety of goals: to improve the immune response via auto-vaccination with HIV, to diminish the proportion of circulating drug-resistant HIV and improve the response to salvage therapy, or to reduce the exposure to antiretrovirals and ameliorate drug-related toxicities.

A great deal of data was presented at the 10th CROI around this issue, and well summarised by Guenthard for those with the stamina to stay and listen to the meeting's final symposium. Little support was found for an auto-vaccination effect of STI, as cytotoxic T cell responses (CTL) returned upon interruption, but without the appearance of a new, broader, or more potent response. Further, several studies showed that viral load rebounds were not significantly different after STIs, suggesting a lack of improved immune control. In the special case of HAART given upon acute HIV infection or shortly thereafter, several small studies of cycled or prolonged interruption [1, 2, 3, 4] came to differing conclusions as to the benefit of therapy in acute infection and its interruption. These differences may reflect small or disparate samples.

There are many potential drawbacks to treatment interruptions. Resistance, particularly to drug with low genetic barriers (M184V resistance for 3TC, and K103N resistance for efavirenz) has developed during STIs. CD4 declines, relapse of an acute retroviral syndrome, and opportunistic infections have all been reported during STIs. On the other hand, some patients have remained stable following long interruptions. There is clearly short-term amelioration of some drug-related toxicities following treatment interruption, long-term cumulative benefits of cycling interruptions have not yet been demonstrated. Clearly the devil is in the detail as to when therapy is interrupted, and how.

A study of intermittent therapy following the one week on/one week off model was initially piloted by the NIAID Clinical Center group [5]. It was performed in Thailand in a group of patients with a history of dual NRTI therapy followed by treatment with two NRTIs and a PI in several clinical studies. Three cohorts of such patients, approximately 25 patients per group, were then randomised to continued HAART therapy interruption until CD4 counts dropped below 350 cells/mm^3, or one week on/one week off intermittent therapy. At entry CD4 counts were in the 500-700 cells/mm^3 range; 75% of the subjects were men. At 48 weeks of study, 13% of the subjects in the CD4-guided interruption arm had suffered CD4 declines to < 350 cells/mm^3, but all but one patient in the other arms had CD4 counts > 350 cells/mm^3. However, in the week on/off arm seven patients had virological failure, one had CD4 < 350 cells/mm^3, and two were lost to follow-up. Only 35% of patients in the on/off arm had HIV RNA < 50 copies/ml, while 96% of the subjects in the continuous arm were < 50 copies/ml. Of nine patients from whom genotypes were available in the on/off arm, four had resistance mutations (three in RT and one in PR). The Swiss Cohort also found evidence of significant viral replication within one week of an interruption. [6]

Overall the one week-on-one-week-off strategy appeared to be an unmitigated disaster. No evidence of decreased toxicity or improved immune control was reported, at the cost of a striking incidence of virological failure and the appearance of resistance when compared to continuous therapy. The CD4-guided arm appeared to have done well, but the median CD4 count at reinitiation of therapy was 536 cells/ul, suggesting that therapy was re-initiated after small declines in CD4.

Further support for the use of prolonged interruptions without cycling to spare toxicity or cost was provided by a preliminary report of CD4-guided therapy from the Barcelona group [7]. Of 120 patients with a median CD4 count of cells/mm^{3}and HIV RNA < 50 copies/ml for a median of 40 months, half were randomised to interrupt therapy. Therapy was restarted if HIV RNA

> 100,000 copies/ml or CD4 count dropped < 350/ul. Forty-four per cent of subjects stayed off therapy for 48 weeks, and almost all of the 56% who restarted did so because of viral rebound > 100,000/ml at a median of eight weeks after stopping. Those who restarted also had a steeper CD4 decline slope and a lower nadir CD4 cell count. Those who remained off therapy for 48 weeks lost 33 CD4 cells/mm^3 per month.

Stefano Vella reported on 56 week results of longer cycled interruptions from an Italian cohort [8]. One hundred and thirty-seven patients continued therapy, while 136 underwent one month on/three months off cycles. Two-thirds of subjects used NNRTI-based HAART; median CD4 at entry was 691 cells/mm^3. Due to the long half life of NNRTIs, in those on NNRTIs the NNRTI was stopped several days before the NRTIs to reduce the chance of NNRTI resistance. While patients on cycled therapy generally suppressed to < 400 copies/ml on reinitiation, a disturbing trend towards increased resistance mutations, particularly NNRTI mutations, in patients undergoing cycling gives pause. No metabolic data was yet available, and given that there is therefore no data to show the benefit of this strategy, such cycling should be left to the clinical investigator for now.

Conflicting evidence was presented with regard to the benefit of interruptions in the setting of salvage therapy. A large and careful study, CPCRA 064, studied patients failing therapy with long drug experience and multidrug resistance [9]. Salvage therapy was guided by genotypic and phenotypic resistance tests done at study entry, and patients randomised to immediate salvage or salvage therapy after a four month interruption. This population with advanced disease had a mean CD4 count of 180 cells/mm^3, 26% had CD4 counts below 50 cells/mm^3, a mean baseline viral load of 100,000, and exposure to five NRTIs, 4.2 PIs, and 1.5 NNRTIs. Forty-eight per cent had three class drug resistance on testing. There was no difference in the number of active drugs prescribed to the two groups (2.7 vs. 2.8).

STI in this study was inferior to immediate salvage therapy. There were 22 primary endpoints (progression of disease or death) in the STI group and 12 in the no-STI group (hazard ratio = 2.57, 95% CI = 1.2, 5.5, p = 0.01). Events in the STI arm included seven esophageal candidiasis, four PCP, three cryptosporidiosis, two lymphomas, and one CMV. Mean difference in CD4 favoured the no-STI arm by 85 cells/mm^3 (p < 0.001) for months one to four (STI phase), 47 cells (p < 0.001) for months five to eight, and 31 cells/mm^3 (p = 0.11) for months 12-20. The study closed to accrual as recommended by the DSMB based on data before full accrual.

In stark contrast, this strategy appeared to be successful in a study performed by Katalama and collaborators in France [10]. Patients with multiple failures of therapy and very advanced HIV disease (HIV VL > 50,000cps/ml and CD4cells < 200 cells/mm^3) were randomised to either immediate therapy or therapy after eight weeks of STI. Therapy consisted of three to four NRTI and one NNRTI – hydroxyurea (500 mg bid) and ritonavir (400 mg bid) and amprenavir (600 mg bid) or lopinavir and a third PI (indinavir 400 mg bid or saquinavir 600 mg bid or nelfinavir 1,250 mg bid). Seventy patients were randomised, 68 started study drugs, and 63 were evaluated at weeks 12 and 24, and 64 at week 48. At baseline, median plasma HIV RNA was 5.3 log copies/ml (200,000), CD4 27/_l, duration of ARV therapy was 6.6 years with a median of 11 antiretroviral drugs. By ITT missing equal failure analysis, the percentage of patients with HIV VL decrease > 1 log from baseline was 26% at week 12, 24% at week 24 if immediately salvaged, versus 62% at week 12 and 50% at week 24 in the STI group (p = 0.007 and p = 0.043, respectively). Median decrease in HIV RNA from baseline was -0.37 at week 12, -0.29 at week 24, and -0.37 at week 48 in the immediate group versus -1.91, -1.08, and -0.79 in the STI group (p = 0.008 at week 12, p = 0.013 at week 24). Percentage of patients with HIV RNA < 400 cp/ml was 15% at week 12, 12% at week 24 in immediate salvage vs 38% and 32% in the STI group (p = 0.053 and p = 0.077, respectively). Median increase in CD4 cell count from baseline was +7 cells/mm^3 at week 24 and week 48 in immediate salvage vs +51 cells/mm^3 and +69 cells/mm^3 in the STI group. Two subjects died in each arm. Twenty-two per cent and 47% of patients were still on treatment with more than six drugs at week 48. Three major factors were associated with virologic success: treatment interruption with reversion of resistance, adequate drug concentration, and the use of lopinavir.

It was difficult to reconcile the success of this extraordinarily intense regimen with the poor outcome of CPCRA 064. Possible explanations include the longer STI in CPCRA 064, and unique, ineffable characteristics of the French patient population. Many investigators at CROI felt that it was likely that the CPCRA experience was more likely to reflect the success of this strategy in general clinical practice.

The other side of interruptions: when to continue failing therapy and why?

Several presentations addressed the continued immunological and clinical benefits of therapy that is continued despite loss of complete (that is, for the time being, <50 copies/ml) suppression of viral replication. A synthesis of the insights into the benefits of antiretroviral therapy, the still-emerging long-term risks of therapy, and the risks and benefits of cycled or intermittent therapy is probably the most important immediately clinically applicable insight to be gained from the 10th CROI.

Steve Deeks provided complex and provocative insights during his symposium discussion of 'When to Switch' [11], and important details were available in his poster with Bob Grant and the ViroLogic group [12]. Deeks himself expressed concerns after the presentation that his studies, meant to be an experiment to explore the relative immunological benefits of different components of antiviral therapy, will be misinterpreted as a prescription for inappropriate use of HAART.

It was hypothesised that among treated patients with multi-drug resistant HIV, interruption of all drugs from a single therapeutic class ('partial treatment interruptions') might (1) maintain partial viral suppression and its associated immunologic benefit, (2) prevent overgrowth of wild-type HIV, (3) delay viral evolution, and (4) reduce drug-toxicity and drug costs. Twenty subjects were studied in this non-randomised, open-label pilot study. Subjects actually chose which drug class they would interrupt. The median baseline viral load was 3.9 log [8,000] copies/ml (IQR 3.6 - 4.5) and the median CD4 T cell count was 336 cells/mm^3.

Fifteen volunteers interrupted all PIs and continued all NRTIs; in these subjects viremia and CD4+ T cell counts were stable over 24 weeks. As expected after interruption of PIs, fasting triglycerides and non-HDL cholesterol improved. Genotypic and phenotypic resistance remained stable in all patients interrupting PI therapy through week 16-24; however, PI mutations waned and replicative capacity and viremia increased in two patients after week 24. The conclusion from this finding in this brief, small, uncontrolled study should be the insight that continued PI therapy in the presence of MDR HIV contributes to the control of viral replication, and may confer a potential clinical benefit. This is not surprising as many studies have suggested this in the past, but this experiment offers strong evidence that patients are benefiting from PIs despite resistance and viremia. The conclusion should not be that sub-optimal nucleoside therapy is acceptable in patients with MDR virus.

Five other volunteers interrupted NRTI therapy and continued PI therapy. In contrast, immediate and sustained increases in viremia (+0.03 log copies/week, $P < 0.001$) were observed. This is not surprising to virologists, as many studies have suggested the maintenance of RT mutations results in a virus that grows more slowly, and that this may confer a clinical benefit. Of note, three of five subjects interrupting NRTI therapy exhibited a delayed loss of M184V, which was temporally associated with a rise in viremia. This finding should provide satisfaction to Mark Wainberg and others, as it is the first clear and direct validation of their contention made in the 1980s that the maintenance of the 3TC resistance mutation confers a clinical benefit.

Deeks et al concluded that interrupting PI therapy in patients with multi-drug resistant HIV is associated with stable viremia, reduced toxicity, and halted accumulation of drug resistance (which may preserve future PI options). However this effect may not hold for more than 24 weeks, as illustrated in a handful of their cases. On the other hand, clinical benefits may be gained by a drug holiday of a few months. In contrast, interruption of NRTI therapy was associated with rapid rises in viremia, indicating that NRTIs may have continued antiviral effects against drug resistant HIV. Partial treatment interruptions may be appropriate for maintaining partial virologic responses in persons with limited treatment options. The critical caveat to these conclusions is the specific patient population in whom this clinical strategy might be considered. The patients in this study all had preserved CD4 counts (366 cells/mm^3) and many PR and RT mutations. Such a manoeuvre is unlikely to work without a virus significantly impaired by MDR mutations and without a partially intact immune response. However, the findings of this group should give us pause for careful consideration in making therapy changes or interruptions, and identifies important questions to be explored in careful clinical trials.

Another important data set with regard to the decision to interrupt or continue therapy was presented by the PLATO collaboration [13]. This is a prospective observational study following patients from 13 cohorts in Europe, North America, and Australia. Data from 2,448 patients with 3-class drug failure was obtained, and CD4 counts were used to determine CD4 slopes during treatment failure. CD4 counts were excluded from the analysis if the concurrent viral load was not 'stable'. That is, if the VL blipped up and subsequent VLs returned to the prior 'stable' level, the CD4 count at the time of the blip would not be analysed. It appeared that if the VL 'reset' to a stably higher level, CD4 counts would be used in this analysis. 2,596 CD4 counts were obtained to obtain CD4 slope during failure from 628 patients in whom baseline pretreatment CD4 counts were known. These patients were 90% male, 60% MSM, CD4 median 170/ul, mean VL 4.5 logs (32,000), and on any therapy for a median of 4.1 years, on HAART for a median of 2.2 years, and exposed to a median of eight antiretrovirals. The take-home message was that for any VL at failure, the CD4 slope was greater if the subject was off antiretrovirals, and that despite failure the mean CD4 slope per year was still positive (CD4 gain) if the VL was less than 4.0 logs (10,000). Further, even when failing with VLs of 4.5 logs or greater, the CD4 slope was roughly 20 cells/year, less than the 70 cells/yr seen in untreated infection. Further, when examining the delta viral load from setpoint (eg. 5 logs prior to therapy - 4 logs at failure = 1 log delta VL), a delta VL of 2 logs or more predicted a positive CD4 cell slope (CD4 gain).

Numerous studies have shown the gradual accumulation of drug-resistance mutations when viremia is detectable. This process occurs more rapidly for single point mutations that confer high-level drug resistance, and when the level of viremia at failure is higher. However, decisions about when to change therapy should take into account the continued benefit of partial suppression of viral replication (delta viral load).

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Link:

http://www.natap.org/2003/Retro/day11.htm

C O M M E N T

There is a reluctance to accept the findings from the GIGHAART study in the US, and this study was actually submitted, but not accepted, for last year's Retrovirus conference. Some of the comments in this article still reflect this. However, the STI in the GIGHAART study not only selected a shorter STI period but reported success only when patients retained phenotypic drug sensitivity and optimal drug levels were achieved. Other multiple drug regimens have also produced greater sustained levels of viral load reduction than regular three or four drug rescue therapies.

Stopping antiretrovirals in patients with low CD4-cells may result in a higher risk of having an AIDS defining event and a longer period with lower CD4 than on a plain switch. Some cohort studies (e. g. EUROSIDA) have shown that ART may have a partially protective effect despite virological failure in patients with <100 CD4-cells. These facts should be discussed with a patient before interrupting treatment.

Reductive therapy to two nucleoside reported by Deeks may only be appropriate with a sufficiently protective CD4 count (in this study >300 cells/mm3. Individual patient histories may hold some of the reasons for this success, rather than the strategy itself. Maintenance dual therapy was originally suggested as the alternative arm to megaHAART in the OPTIMA study, though this was not adopted due to caution for accumulation of nucleoside mutations.

CROI: WOMENS STUDIES

Conference has strong emphasis on women

Polly Clayden, HIV i-Base

The conference had a surprisingly strong emphasis on women and these sessions were extremely well attended. This in turn was much commented on – session chair Professor James McIntyre from Soweto chairing the "lone session on women and paediatrics" remarked that "I thought I'd be sitting here alone."

However, there was still only limited data reported on women over and beyond their role in mother to child transmission. Chairing the session on HIV and Women, Dr Judith Currier emphasised: "Half of the new infections in the world are in women, yet we spend so little time discussing issues unique to prevention, pathogenesis and treatment as it pertains to their health."

Women and HIV in India and Africa

Dr Suniti Solomon painted a grim picture of the position of women - and in particular HIV positive women - living in India [1]. She discussed the limitations of prevention strategies in a society where infanticide is not uncommon following the birth of a girl, every 34 minutes a woman is raped, every 93 minutes a woman is burned to death over a dowry and 1,000 child marriages were still reported in a single day in the year 2003.

Their vulnerability to HIV can only be enhanced by beliefs such as that sex with a virgin can cure sexually transmitted diseases and by a system where monogamy is often unilateral (in one study 95% of HIV positive women were married, 81% housewives and 88% report monogamy). Lack of economic autonomy and job opportunities means that women are frequently forced to remain in a marriage where they are at risk or to support themselves through sex work.

Dr Solomon described their prevention needs, which include: empowering women, encouraging men to admit that they are vulnerable; gender sensitising programmes; engaging men in the process of changing gender norms and initiating structural changes. In other words reconstructing the culture in which, as Dr Solomon pointed out at the beginning of her talk, the "social construct of gender has evolved for several hundred years." In a society where, she estimates, seroprevelance is greater than

5% among women of chid bearing age within a population of over a billion, the potential threats and challenges seem insurmountable. “How on earth does she get out of bed in the morning to all that?” wondered my colleague.

Leaving her audience completely stunned, Dr Solomon concluded that: “It is not flattering that it takes a ruthless epidemic to awaken the world to the needs and condition of her women.”

In a session on international strategies Dr Dorothy Mbori-Ngacha from Kenya outlined the situation for women in Africa where “as the epidemic has matured the vulnerability of women has come to the fore.” [2] Current UNAIDS figures indicate that women constitute 58% of all people living with HIV on the continent of Africa and women are more vulnerable to HIV acquisition for a variety of social, cultural, economic and biological reasons.

In the USA

Dr Ruth Greenblatt from the Women’s Interagency HIV Study (WIHS) and Dr Kate Squires from the University of Southern California both described the current situation in the USA [3,4]. Here HIV is still the greatest cause of death among women of colour between 25 and 44 years old, and women living with HIV, and those at high risk, remain a demographically distinctive group.

Dr Squires gave an overview of sex/gender differences, and both speakers emphasised how little we actually know and the need for more trials that address these differences and women specific research programmes. Dr Greenblatt was emphatic that “we need to address research related to women much more aggressively.’

And there were a few reports addressing women’s health presented at this meeting…

Osteopenia and fat redistribution

There is no current consensus of the effect of HIV and/or antiretroviral use on the prevalence or course of osteopenia in HIV positive women, particularly older women.

Two oral presentations evaluated bone mineral density in HIV positive women [5,6]. Dr Jacobsen and colleagues from Tufts University, Boston looked at the association between HAART use and other demographic variables on bone mineral density in a cohort of 141 women over nine-18 months and 21-27 months of follow up (42 women were followed for two years). This cohort is 33% Caucasian, 52% African American, and 22% other with a median age of 39 years.

The median total BMD at first DXA scan was 1.09 gm/cm2 (25th% 1.04; 75th% 1.16). After adjusting for age and weight, neither HAART use nor demographic variables were significantly associated with total BMD.

In this study the median BMD was not found to change over two years. The investigators report: “However, in individuals loss of BMD is associated with loss of lean body mass.”

They also found that “osteopenia is prevalent in HIV-positive Caucasian women”, and that “smoking and injection drug use may increase the risk of osteopenia”.

Dr Arnsten from the Montefiore Medical Centre evaluated the incidence of osteopenia in a cohort of 284 older (above 35 years, median 45 years) peri- and post menopausal HIV positive (n=144) and negative women (n=140)

Using DXA, they analysed BMD of the lumbar spine, hip, and total body, and in addition they also analysed the impact of protease-inhibitor (PI) use on BMD.

Controlling for race, physical inactivity, smoking, and HIV status, the researchers found that osteoporosis was more prevalent in post-menopausal (OR = 6.8, $p < 0.001$), physically inactive (OR = 3.9, $p = 0.04$), and white (OR = 3.5, $p = 0.04$) women. HIV infection was not associated with either osteopenia or osteoporosis.

In contrast with previous studies, the investigators also reported that women who had used PIs for more than one year were significantly less likely to have osteopenia than women who had used PIs for less than one year or not at all (OR = 0.3, $p < 0.01$). They concluded: “PI use among older HIV-infected women may protect against bone mineral loss by modifying cytokine-mediated disturbances in the synchronised bone-remodelling process.”

A poster from Dr Yin and colleagues evaluated the prevalence of osteoporosis and HIV associated risk factors for low bone density (BMD) in 32 postmenopausal HIV-positive women [7].

The mean age of this cohort was 56 years, and mean time since onset of menopause 10 years. Eighty-eight per cent of women had used HAART for a mean of five years. Thirty-six per cent had experienced all three classes of drugs, 36% to nucleosides plus PIs and 7% to nucleosides plus NNRTIs. Seventy-two per cent were Hispanic and 25% African American.

An assessment by DXA was conducted at the lumber spine and femoral neck.

In this small study the investigators found the prevalence of osteoporosis to be considerably higher among African American and Hispanic women with HIV than in comparable HIV-negative women. They reported that lower BMD was more strongly associated with generally accepted osteoporosis risk factors (higher weight, time since menopause and use of HRT) but not with HIV and treatment related factors. They noted that “Hispanics and African Americans account for over 80% of HIV-positive

women over age 50 in New York. As the female HIV population increases and ages, diagnosis and treatment of osteoporosis should play a more prominent role in their long-term management."

A poster from Dr Howard and colleagues from the Montefiore Medical Centre evaluated fat distribution in a cohort of HIV-positive (n=105) and negative (n=120) women and evaluated the impact of antiretroviral use and demographic factors on regional adiposity [8]

Of this group the mean age was 45 years; 45% were African American, 36% Hispanic and 15% white. HIV-positive women were younger and more likely to be African American and obesity was greater in HIV-negative women. Regional body composition was measured by DXA scan. Among the HIV-positive women studied 129 (66%) were using PIs for a median duration of 27 months and 110 (56%) used d4T for a median of 24 months.

The investigators found that in this group of older, predominately obese women after controlling for age, CD4 and PI use in a multivariant analysis, HIV was associated with decreased body mass index (BMI) and percentage of body fat but not with fat redistribution. Amongst the women with HIV, d4T use was associated with an increase in truncal fat and decreased extremity fat, but PI use was not.

Cervical cancer

Likewise there is still no consensus on the effect of HAART use on the course of HPV (human papillomavirus) related cervical pathology in HIV-positive women. In response to contrasting reports in the literature Dr Ubert-Foppa and colleagues from Milan assessed the long-term (mean 36.4 months + or – 10.4 months) effect of HAART on persistent HPV infection and histological cervical lesions in 154 HIV-positive women (mean age 37.3 years) receiving two nucleosides, HAART or no treatment [9].

Women were assessed every six-12 months using PAP smear and coploscopy (with biopsy if indicated) and high grade cervical lesions were treated with loop electrosurgical incision.

Unsurprisingly CD4 levels significantly increased in the HAART-receiving women ($p = 0.017$) and in those switching to more potent HAART ($p = 0.0001$), but this was not associated with a decreased persistence of HPV. A significant reduction of positive biopsies though was found only in women on long term HAART ($p = 0.00006$).

However, the investigators found that in this cohort they could establish no beneficial effect of long term HAART on HPV persistence and related cervical disease and that these conditions persisted in a high proportion of women. They explained that HPV-related histological lesions are significantly reduced only in women with stable clinical and virological picture including those untreated or treated with two NRTIs or with HAART. HPV pathology persists particularly in those with the longest history of HIV infection, suggesting that, regardless of antiretroviral regimen and its effect on HIV replication, the crucial aspect is the number (and probably the competence) of CD4 cells.

They recommend continued monitoring and "strict surveillance of patients is still the best preventive scheme for HPV-related cervical lesions, also in the era of HAART."

A poster from the WIHS describes the magnitude of incidence of cervical cancer in this cohort of HIV-positive and at risk women (n= 2,133 women - 463 HIV-negative, 1,662 HIV-positive, and eight seroconverters) followed prospectively from October 1994 through September 2001. Women with a history of cervical cancer or hysterectomy were excluded.

Cervical cytology was obtained at six-month intervals and cervical disease treatment was individualised. They found cases of invasive cervical cancer were observed in the HIV-negative women during 2,380 years of observation - an incidence rate of 0/10,000 woman-years. During 8,260 woman-years of observation, eight cases of cervical cancer were identified in HIV-positive women but only two were confirmed. They found no significant difference in incidence rates between HIV-positive and negative women.

The investigators noted that this low incidence could not be generalised to women who are not under a regular screening and prevention programme or to women not receiving HAART.

Neurological Disease

Finally, a poster from Dr Hall and colleagues, in response to previous chart review data suggesting a higher incidence of HIV neurological disease and differences in progression in women and men, reported findings from a longitudinal study evaluating gender differences in nervous system decline [11].

In this prospective longitudinal study of 48 HIV-positive, 48 HIV-negative women and 52 HIV-positive men undergoing standard neurological exams by a neurologist and controlling for factors such as antiretroviral use, the investigators found no evidence that nervous system decline was more likely in one gender than the other.

References

1. Solomon S. Stopping HIV infection before it begins in women. Abstract 114
2. Mbori-Ngacha D. Prevention and care of HIV-infected women in Sub-Saharan Africa. Abstract 47
3. R M Greenblatt Natural history of HIV-1 infection in women—findings from the Women's Interagency HIV Study. Abstract 115

4. Squires K. The impact of sex/gender and antiretroviral therapy and its complications. Abstract 117
5. Jacobson D, Knox T, Shevitz A. et al Low bone mineral density in HIV-infected women. Abstract 102
6. Arnsten JH, Freeman R, Santoro N, et al. HIV infection and protease inhibitor use are not associated with reduced bone mineral density in older HIV-infected women. Abstract 103
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8. Howard AA, Freeman R, Santoro N et al. Body composition and antiretroviral use in older HIV-infected women. Abstract 735
9. Uberti-Foppa C, Ferrari D,. Lodini S. Long-term effect of highly active antiretroviral therapy on histological cervical squamous intra-epithelial lesions among HIV+ women. Abstract 767
10. Massad LS, Seaberg E, Bitterman P et al. Incidence of invasive cervical cancer among women with HIV. Abstract 768
11. Hall C, Robertson W, Fiscus S et al. No gender differences in progression of HIV-related neurological disease. Abstract 703

CROI: SIDE EFFECTS

Tenofovir and renal tubular dysfunction

Simon Collins, HIV i-Base

Tenofovir DF (TDF, Viread), the most recently approved reverse transcriptase inhibitor has rapidly become widely prescribed since approval last year. In the USA the indication is for use in both ARV naïve and experienced patients, and although originally indicated in Europe for treatment of experienced patients the European Medicines Evaluation Agency has just given a positive indication that it will expand this to include use in first-line therapy. (see page XX).

At the Retrovirus conference 96-week data was presented showing similar antiviral potency to d4T (stavudine) and although it is still not clear whether resistance implications are more complicated for people who fail TDF during first line therapy, it's popularity has developed due to formulation (one pill, once daily) and generally low toxicity profile, including indication for low mitochondrial toxicity. Two posters at the conference included case studies of renal tubular dysfunction related to tenofovir.

Although tenofovir is closely related to other nephrotoxic drugs (adefovir and cidofovir have both previously involved renal tubular dysfunction), this was not highlighted as a toxicity in the registrational studies. With widespread use however, it is important to be aware of any rare complications that may be discovered.

Reynes and colleagues from Centre Hospitalier Universitaire, Montpellier, France, reported three cases of renal tubular injury and hypophosphoremia (Fanconi Syndrome).

Common characteristics included low body weight (all <60kg, BMI 14.5, 20.7 and 22.4). Two patients had low calculated creatinine clearance prior to TDF therapy (65 and 73ml/min) despite normal creatinine levels. Two patients had symptoms of myalgia and/or paresthesia possibly related to hypophosphoremia which resolved one week after stopping TDF. Biological signs of tubular injury resolved within three months of discontinuation of TDF.

All patients were on four-drug therapy that included a ritonavir boosted PI and other drugs used included 3TC, ddI, efavirenz, lopinavir/r, amprenavir. Duration of TDF therapy was eight to 11 months and two patients had undetectable viral load <20 copies and one had 122,000 copies (with a CD4 count of 64 cells/mm3).

The range of serum abnormalities observed at the time of renal tubulopathy included phosphoremia (0.39, 0.47 and 0.41mmol/l); increased creatinine (100, 78 and 101umol/l); reduced creatinine clearance (41, 64 and 59 ml/min) and uricemia (73, 96 and130 umol/l), all of which resolved after tenofovir interruption.

The study observed that all symptoms were consistant with a Fanconi syndrome – a generalised defect in proximal tubule transport – and that periodic screening including phosphoremia, glycosuria, proteinuria and serum creatinine may be useful in patients receiving tenofovir, especially those with low weight or pre-existing renal dysfunction.

Blick and colleague from New York Medical College reported three further cases of hypophosphatemia, all in patients using tenofovir but who had previously experienced grades 2-3 renal tubular acidosis and hypophosphatemia during earlier adefovir studies, Patients who had used adefovir were excluded from the development and registrational studies for TDF.

All three patients were highly treatment experienced and developed symptomatic grade 2-3 hypophosphatemia (1.0-2.4 mg/dl) three to seven months after introducing tenofovir into their regimen. Potassium phosphate (KPhos) 1500mg BID or TID was used to replete phosphorus when TDF was discontinued, but levels fell again when TDF was restarted. Continuing a maintenance dose of KPhos (1000-1500mg BID) while restarting TDF prevented recurrence in the patients when TDF was restarted for a second time.

The study noted that in addition to serum abnormalities, grade 1-3 hypophosphatemia can result in CNS symptoms (malaise, ataxia, irritability), generalised muscle weakness, altered red cell function, haemolytic anaemia and bleeding tendency, osteomalacia, bone resorbtion, glycosuria, metabolic acidosis, proteinuria and transient hyperbilirubineamia.

References:

1. Reynes J, Peyreiere H et al. Renal tubular injury and severe hypophosphoremia (Fanconi Syndrome) associated with tenofovir therapy. Abstract 717.

2. Blick G, Greiger-Zanlungo P et al. Tenofovir may cause severe hypophosphoremia in HIV/AIDS patients with prior adefovir-induced renal tubular dysfunction. Abstract 718.

C O M M E N T

Caution over TDF toxicity in patients with existing renal dysfunction has been reported and in the USA Gilead has recommended increasing dosing intervals related to levels of creatinine clearance (CLcr) for patients with various degrees of renal failure (dosing every 48hrs if CLcr 30-49 mL/min, every 72-96 hours if 10-29 mL/min, every seven days if <10 mL/min or every seven days following dialysis or after a total of approximately 12 hours haemodialysis), though this has not yet been approved by the European Medicines Evaluation Agency.

The symptoms listed for Grade 1-3 hypophosphataemia are only likely with prolonged or severe cases. In the 903 study the incidence of mild abnormalities was similar in the TDF and non-TDF arms and indicated that at low levels discontinuation of treatment was not necessary.

Increased pharmacovigilence is always important when newly approved drugs roll out to general use and common factors for cases reported in the UK often include co-administration of other nephrotoxic agents. Physicians who experience similar cases should report this to both Gilead and the appropriate safety agency so that an accurate understanding of the incidence of this side effect can be obtained.

Asymptomatic hypophosphotemia is relatively frequent and clinical consequences (e. g. bone) are not known yet. Clinical cut offs from treatment guidelines for asymptomatic hypophosphatemia do not exist, so clinical management of this symptom has still to be defined.

The observation that maintenance treatment with potassium phosphate may allow continued use of TDF is important given the reliance many patients have to place on TDF in salvage therapy, and this warrants further study.

Approaches to treatment of lipodystrophy

Simon Collins, HIV i-Base

Few presentations added much to the understanding of the causes of lipodystrophy and although the most relevant presentations for clinical care included treatments that have previously been reported these studies are still important to inform the generally limited access that patients have to these options.

New-Fill for Lipoatrophy

Two poster presentations, both from Paris, reported almost identical positive results from using New-Fill, a hydrogel of polylactic acid, to treat facial lipoatrophy.

Additional safety and efficacy results from the VEGA study were presented by Camille Aubron-Olivier and colleagues from the Hopital Pitie Salpetriere in Paris.
This open label, single arm pilot study enrolled 50 patients between June 2000 and January 2001. All had severe facial lipatrophy and had lost almost all facial fat (median facial fat thickness at baseline measured by ultrasonography was 0mm, range 0.0-2.1mm). Patients received four courses of injections at nought, two, four and six weeks and results were measured at six, 24, 48, 72 and 96 weeks. Each course of injection requires approximately 20-40 deep injections into each check. Anaestetic is applied locally, often mixed with the compound, and careful massage immediately post treatment is critical to achieve best results.

Results showed cumulative benefit over the first six months of treatment that have so far been sustained over the follow-up period. The mean total cutaneous thickness increased by +5.1mm (range 2.2-8.6) at week six, +6.4 mm (3.1-9.1) at week 24, +7.2 (4.2-9.6) at week 48, +7.1 (3.5-9.6) at week72 ($p<0.001$) and +6.8 (3.9-10.1) at 96 weeks ($p<0.001$). Total cutaneous thickness remained >10mm in 43% patients at week 96.

No serious adverse events were reported during the study, with minimal swelling at injection sites reported in 15 patients, which resolved within one to two days. In 22 patients (44%) palpable but non-visible subcutaneous micronodules were observed which spontaneously resolved in six patients by week 96. Visual improvements from the treatment were clear in the photographs presented and in the patient quality of life questionnaires.

A second study, from the St Louis Hospital, Paris, involving 40 patients (four women) reported benefits measured by three-dimensional photography and an analogue visual scale satisfaction index (AVSSI). Mean age was 43 (40-58), mean CD4 525 cells/mm3, viral load <50 copies in 44% patients (two patients were not on ARV treatment) at baseline.

Patients received a mean 4.4 injections (–0.7) with a mean injected volume of 2.7ml PLA, mixed with lidocaine, per cheek.

Mean AVSSI increased significantly from 3.3 –2 after two injections to 7.2–1.5 two months after the end of treatment which was sustained six months after the end of treatment. Mean increase in dermal thickness six months after treatment was 3.4–1.8mm and 2.2–1.2 in the right and left checks respectively.

No serious side effects were reported. Grade 1-2 pain was noted in 76% patients.

References:
1. Valantin M, Aubron-Olivier C, Katlama K et al. Polylactic Acid implants (New-Fill) in the correction of facial lipoatrophy in HIV-infected patients (VEGA Study): Results at 72 weeks. Abstract 719.
2. Lafaurie M, Dolivo M Molina J. Treatment of facial lipoatrophy with injections of Polylactic Acid in HIV-infected patients. Abstract 720.

C O M M E N T

This treatment has received a lot of attention over the last two years and the 24-week results from this study were presented at the i-Base meeting on facial lipoatrophy just over a year ago. Since then, several clinics have expanded provision of this important corrective procedure within the NHS. Many other patients have paid for treatment privately.

Clinics currently providing New-Fill emphasise that this service is currently for their regular patients. However, establishing specialist clinics will also mean that later they will be available for referrals from other hospitals. It is estimated that between 5% and 10% of patients currently using antiretroviral treatment may have lipoatrophy that could benefit from New-Fill.

Brighton has treated approximately 50 patients over this year. The main hospitals in the North Thames region (Chelsea and Westminster, Ealing, St Mary's and West Middlesex) have already carried out a needs assessment programme and trained specialists to provide treatment. Although patients have yet to benefit from this, the programme is expected to open shortly. The Royal Free Hospital obtained funding for a limited course of treatments, and Manchester General continued to treat patients over the year.

Although there is still no clear etiology for facial lipoatrophy, this treatment appears to provide a safe and minimally invasive repair procedure that can minimise the social and psychological distress that these symptoms cause.

In the VEGA study in the poster the decrease in patients with >10 mm cutaneous thickness over time was paralleled by a decrease in QoL rating on visual analogue scales suggesting the need for repetition of the injections at least in some patients. In addition not all patients respond well to the injections (range of dermal thickness) stressing the need for safe alternative procedures.

Surgery for buffalo hump shows variable results depending on method

Simon Collins, HIV i-Base

It has been suggested that there may be a higher incidence of buffalo hump in the USA compared to Europe, but it has still been reported as a side effect in the UK and referrals for surgical removal on the NHS is appropriate. Three posters at the conference presented results from various surgical operations to remove cervical fat pads across the shoulders, buffalo hump (BH), dorsal fat pads (DFP) and lipohytrophy of face and neck (submandular fat, often referred to as 'moon face').

The case examples shown in these studies all had severe symptoms, involving a significant change in appearance, serious restriction of normal movement, prevention of normal sleep and sometimes pain.

Gervasoni and colleagues from L Sacco Hospital, Milan reported on 14 men and four women who had BH, and two patients who additionally had DFP enlargement. At time of first diagnosis of BH, 16 patients were on PI-containing regimens (indinavir, saquinavir or nelfinavir), with two previously naïve patients on a first combination that was NNRTI-based. No improvement was reported in the 11 patients who switched the PI to an NNRTI for a median 14 months prior to surgery (range 10-24).

Fifteen patients underwent liposuction (preceded by local infiltration of saline solution, cold adrenaline 4 C and lidocaine using the wet technique) and three had classical surgical removal. No surgical or local complications were reported. ARV therapy was continued in all patients after surgery, five including PIs. After a follow-up of a median 12 months (range 8-30) BH returned in only one patient (on an efavirenz/3TC/d4T combination), occurring three months after surgery.

DeWesse and colleagues from St Francis Memorial and Kaiser Permanente Hospitals in San Francisco reported less successful results from 28 patients (median age 47; 23 men, five women) with dorso-cervical fat accumulation (DC), 16 of whom also had submandibular (SM) fat accumulation who were treated with ultrasound-assisted liposuction (UAL) of dorso-cervical, submandibular, trapezio-occipital and mastoid fat deposits.

Liposuction was performed under general anaesthetic and tumescent technique was used. This involves injecting a large volume (two to three litres) of dilute anaesthetic into the area to be treated. The liquid causes the compartments of fat to become swollen and firm or 'tumesced' and the expanded fat compartments allow the liposuction cannula to travel more smoothly beneath the skin as the fat is removed. Standard ultrasonic equipment is used to liquefy the fat by cellular fragmentation at a frequency that targets fat cells leaving other tissue and nerve structures intact.

Results were measured by change in patient symptom score, surgeon assessment of pre- and post-operation photographs and patient post-op satisfaction.

Mean symptoms scores (0= no pain 10=greatest severity) improved from 5.3 pre-op to 3.1 at 2-3 months and 2.8 at > 6months.

Mean patient satisfaction score (0=dissatisfied, 5=most satisfied) post op (time not specified) was 3.8. Surgeon assessment DC reduction as >75% reduction in 75% cases, and 25-75% reduction in a further 18% of operations, but 7/25 (28%) recurrences were reported. Reduction of SM was less successful with no patients achieving >75% reduction, 29% patients achieving 25-75% reductions and 71% patients achieving <25% reductions.

Of concern was the rate of major complications in 5/28 operations and minor complications in 10/28 operations. Patient photographs on the poster which can often show the most encouraging results for lipodystrophy treatment included three men with severe DS, two of whom showed partial recurrence at one and two years, one of whom showed very successful and encouraging result out to one year.

Piliero and colleagues reported retrospectively evaluated results from 12 ultrasound-assisted liposuctions, similar to that described above, performed on 10 patients (six men, four women; mean age 46, range 37-60) treated at Albany Medical College, New York. Fewer details were provided for the evaluation of results in this study, and although no patient had full resolution of buffalo hump all had initial partial reduction in size. Buffalo hump returned to pre-treatment levels in five patients. Two subjects developed pneumococcal bacteremia at one and three months post-UAL, both despite having received vaccinations twice in their lifetime.

References:

1. Gervasoni C, Vaccarezza M, Galli M et al. Long-term efficacy of buffalo hump surgical treatment in patients continuing antiretroviral therapy. Abstract 723.
2. DeWesse J, DeLaney A et al. Surgical treatment of HIV lipohytrophy of head and neck. Abstract 721.
3. Piliero P, Hubbard M, King J et al. Ultrasound-assisted liposuction of HIV-related buffalo humps. Abstract 724.

C O M M E N T

Liposuction to remove buffalo hump is the preferred method for removal as the scarring is minimal, and this is always important, particularly so around the neck and face. However, a common complication of any liposuction is contour deformity – the degree of "bumpiness" - which is difficult to avoid completely and which could also be seen in some of the examples presented. This is almost impossible to correct.

Problems regarding using "dry-wet-suprawet-tumescent" techniques have generally been solved and there is wide acceptance that tumescent techniques generally have fewer complications. Also, more local anaesthetic can be used if local anaesthetic is diluted (wet technique) or very diluted in tumescent technique. Superdilution of local anaesthetic keeps lidocaine longer in the tissues (a lot of it is also "sucked out" together with fat). Adding adrenalin not only causes vasoconstriction helping thus to prevent local haematomas, but also delays absorption of local anaesthetic. It is known that it is possible to inject more than maximum dose of local anaesthetic with the tumescent technique because of this effect. However, it remains unclear exactly how much of the injected local anaesthetic gets into circulation and how much is removed together with the fat. Lidocaine is metabolised by the hepatic cytochrome P450 enzyme, and although all these patients remained on antiretroviral treatment over the period of surgery, the risk from excessive lidocaine dosing was not addressed.

In general lidocaine can cause hypersensitivity reaction as the most common side effect. Cardiac arrhythmia is a potential complication of high doses of lidocaine. In addition fat embolism may be a complication of liposuction itself, particularly if large amount of fat are removed.

A limitation in injecting large volumes to the nape of the neck involves avoiding any circumferential or semi-circumferential injecting to avoid pressure on the neck structures. For this reason it would be expected for these patients to have the posterior and anterior part of the neck done at separate sessions, which again was not the case in these studies. Fat around the neck in Madelung's disease, which more surgeons are familiar with, is very well vascularised, so bleeding, haematomas and subsequent delayed healing is not that uncommon, and it is unusual that surgical or local complications were not reported here.

Ultrasonic liposuction is more efficient in fibro-fatty tissue (which is the case for buffalo hump), than standard liposuction. But risk of burning or other damaging of skin is higher. Equipment is expensive and because the difference is not significantly noticeable, many plastic surgeons returned to the classical liposuction method.

Liposuction is a specialised area of medicine and even the poster presentations for these studies provided few details of the actual procedures used. Different techniques may or may not be appropriate for HIV-related lipodystrophy and use of more recent techniques involving greater fluid volumes may also be related to the greater complications seen in the UAL studies. The sooner specialised HIV-associated lipodystrophy clinics are established, the sooner effective treatment can be determined.

Comment prepared with the assistance of Lada Lysakova, Charing Cross Hospital.

Links:

A brief summary of different liposuction techniques is available at:

http://www.liposuction.com/basic_liposuction_techniques.html

Other studies – nucleosides and switching to abacavir; importance of lipoatrophy and buffalo hump

Simon Collins, HIV i-Base

Several Australian research groups that have reported on studies of switching to abacavir continued to show interesting results. Switching d4T to abacavir has previously been reported to reverse limb fat loss and even lead to slight fat increase (approx +10%).

Thompson and colleagues from Melbourne, Australia in a GlaxoSmithKline-supported study, looked at the effect on fat apoptosis in 12 patients who switched to abacavir (and one who switched to AZT) after >two years use of d4T. Increases in arm, leg and trunk fat of 25%, 15% and 23% respectively were reported from DEXA results 48 weeks after the switch. Adipose mitochondrial (mT) DNA/fat cell levels increased from 214 at baseline to 462 at week 48 in the eight patients measured, and this compared to 863 for a control group of 20 HIV-negative individuals. Median adipocyte apoptosis, assessed semi-quantitatively by terminal deoxynucleotidyl transferase dUTP-digoxigenin nick end labeling (TUNEL), decreased from 2.0 (IQR 1-2.5) at baseline to 1.25 (IQR 0.5-2.5) at week 48. Although one patient in this study switched to AZT, and given that AZT has also been implicated in lipoatrophy, it is more appropriate the study be mainly observed as the result of the abacavir switch. [1]

A second study from Hoy and colleagues assessed mitochondrial DNA cells/copy in PBMCs from 39 patients in the MITOX study who switched to abacavir and 55 controls who remained on d4T or AZT. Mean (SD) changes in mT DNA copy number at four, 12 and 24 weeks were 54.8 (350.4), 76.6 (414.2) and 48.8 (431.61) for the switch group compared to –38.0 (267.7), -15.3 (344.7) and –85.3 (390.4) in those who continued on d4T or AZT. There was a trend to increased mt/DNA in the switch group but there was no correlation between change in mT DNA and change in peripheral fat measured by DEXA and the study concluded that there is currently limited utility in quantifying mT DNA in PBMCs to access nucleoside toxicity. [2]

To add further weight to the contribution nucleosides play in lipodystrophy, limb and VAT fat were found not to change significantly over two years in 45 male patients who switched from a PI containing regimen but who continued using nucleosides. Lifetime duration of d4T or AZT use independently and significantly correlated with reduction in limb fat at week 120 with a decrease of 0.72kg (CI –1.18 to –0.26) and 0.29kg (CI –0.52 to –0.06) with d4T and AZT respectively. [3]

Finally, Boyd and colleagues reported improvements in lipoatrophy in 61 patients (38 male, 23 female) who switched to nuke-sparing indinavir/ritonavir (800/100 BID) plus efavirenz combinations and increases in percentage body fat by DEXA, increases in thigh and abdominal subcutaneous fat (p=0,04) and abdominal visceral fat (p=0.05) at 48 weeks after the switch. [4]

The finding that buffalo hump was not in itself an HIV-associated condition statistically related to lipodystrophy syndrome was, together with a similar suggestion for abdominal fat accumulation, one of the controversial conclusions presented by Carl Grunfeld in the preliminary data from the FRAM study last summer at the Barcelona International AIDS Conference. Posters 732 and 733 from this study at CROI further elaborated on the finding that compared to matched controls, lipoatrophy (fat loss) in both limbs and/or abdomen were the predominant link to HIV-related fat loss, and maintained that fat accumulation was not statistically associated with the same syndrome. [5, 6]

A more detailed analysis of buffalo hump from the same study (BH was found in 8% of HIV-positive men and 11.3% of HIV-negative controls in the US population) revealed, as many people suspected at the time, the importance of a qualitative analysis, finding that NH averaged 2.5 times higher in HIV+ (9.0x8.2cm) compared to controls (5.5x5.4cm); each dimension p<0.001. [7]

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HAART to HEART: cardiovascular risk in HIV

Judith Aberg MD, for NATAP.org

The debate at the CROI over whether HIV and its therapy are associated with the development of coronary heart disease (CHD) was as prominent as it was at last year's conference. Again we heard conflicting data as the studies are either retrospective with many confounding factors or prospective with short duration thus making it impossible to know how much, if any, HIV and its therapies are contributing to the development of CHD. In fact the New England Journal of Medicine (20

February 2003) contained an editorial by Drs Dan Kuritzkes and Judith Currier debating this same issue as they reviewed the results of a retrospective study of the VA database by Dr S. Bozzette and colleagues. [1, 2] I agree with their conclusions that longer follow-up of the VA cohort and other cohorts is needed before cardiac risk can be ascertained.

Dr Friis-Møller presented the results of the prospective observational D:A:D study of 23,468 subjects from 11 cohorts in three continents [3]. Subjects were enrolled from July 1999-April 2001 with final data collection/analysis August 2002. Although the subjects were since followed prospectively starting July 1999, the investigators entered data based on years subjects were started on HAART (PI or NNRTI), which varied from none to greater than six years. It is unclear if they truly have source documentation of all 23,468 subjects' first date of HAART or whether they derived this data from the subjects' history as documented in a chart. Data on HIV disease, risk factors for myocardial infarction (MI) and incident MI were collected. The median age of this cohort is 39 years, 24% female, 60% smokers and 30% had elevated triglycerides (TG). During 36,479 person years, a total of 126 subjects had a MI - a subgroup comprised of 90% men and median age 48 years. Thirty-six (25%) of the subjects had a fatal MI. Traditional risk factors such as age, male sex, previous history of CHD and smoking remained independent predictors of developing a MI. Other important risks included diabetes and hypertension. The relative risk per year of exposure to HAART was 1.26. Interestingly, lipodystrophy was a protective risk (RR 0.6). However this term was defined by subjective measures and needs to be further studied before any conclusions can be drawn. The investigators concluded that HAART use was associated with a 26% relative increase in the rate of MI per year of exposure over the first seven years. As Dr. Friis-Møller noted, the risk of MI at this point is low and the obvious benefits of HAART outweigh concerns over potential CHD. Nevertheless, it remains important to consider all aspects of health care for HIV infected individuals including modification of traditional CHD risk factors if possible as well as treating the complications of HAART as they arise.

This database has many of the same limitations that other databases have that collect information retrospectively and then follow subjects prospectively. Hopefully, over time as they follow this cohort, particularly the many subjects who entered the study naive to ART or on their initial regimens, we can begin to sort out those factors contributing to CHD from HIV and its therapies versus traditional risk factors. The investigators are to be commended for developing such a large cohort and collecting data from various international centres. This has taken enormous effort and will be a very valuable cohort to follow long-term.

Dr Lucas presented the results from the Johns Hopkins database, another large cohort that has been followed longitudinally since 1990, regarding the incidence of CHD and cerebrovascular disease (CVD) among their patients infected with HIV [4]. A nested case control study was designed to assess factors associated with CHD and CVD. Subjects without CHD and CVD risks were randomly selected as controls. Five controls per case were identified and matched on cohort enrolment date and duration of follow-up. Of 2,671 patients followed for 7,330 person-years (PY) after 1 January 1996, there were 43 CHD and 37 CVD events for an incidence rate of 5.9 events/1000 PY and 5.0 events/1000 PY, respectively. Factors associated ($p < 0.05$) with having a CHD or CVD event included age (mean = 46 years-cases, 41 years-controls), cholesterol (mean 186 g/dl cases, 156 g/dl controls), prior diabetes (15% cases, 7% controls), prior hypertension (43% cases, 17% controls), CD4 (mean 351 cells/mm3 cases, 251 cells/mm3 controls). There was no difference between cases and controls in race, injecting drug use, or HIV-1 RNA. Cases were significantly more likely than controls to receive protease inhibitors (PI) (59% vs 43%) and D4T/3TC (63% cases, 43% controls); however, no differences were found for other nucleoside RTIs, NNRTIs, or any individual PI. The risk factors were similar for CHD and CVD when assessed separately. The investigators did not adjust for smoking or lipodystrophy. Also given the limitations of this database, they could not account for nadir CD4 count or duration of HIV infection. The incidence of CHD and CVD is significantly higher than one would have expected for the same age-sex-race population rates of 2/1000 PY for CHD and 3/1000 PY for CVD as reported from the National Health and Nutrition Examination Survey (NHANES). However, it is difficult to compare historic controls to the current database plus given the many confounding factors and lack of reliable information (smoking, metabolic syndrome, HIV duration, CD4 nadir), it remains unclear if HIV and its therapies are independent risks for the development of CHD. In contrast to these two large population studies, Dr Bozzette reported no change or a slight decrease in incidence of CHD among an even larger cohort of 39,766 HIV infected persons followed at Veterans Affairs facilities in the USA. The answer to these question will take time and further study.

Carotid artery intima thickness test in HIV-infected individuals on HAART, first study

Dr Judith Currier, University of California, Los Angeles presented the baseline results of the trial evaluating 'Carotid artery intima thickness (IMT) in HIV-infected and uninfected adults'. [5]. The AIDS Clinical Trails Group 5078 team carefully designed a study limiting the high-risk confounding factors and having matched HIV seronegative controls to really focus on the contribution of HIV and its therapies unlike other trials we have seen.

Carotid IMT has been shown to be predictive of clinical cardiac events in individuals with and without cardiac symptoms. All seven sites were trained by a standard protocol, performed in duplicate and sent to a central reader at the Cleveland Clinic. All subjects were evaluated at baseline and at weeks 24, 48, 72 and 96. Each site enrolled a triad at a time consisting of one HIV infected individual on a protease inhibitor (PI) for at least two years, one HIV infected individual not on a PI, and one HIV seronegative control. All three subjects were matched for age within five years, race/ethnicity, sex, blood pressure status, smoking status and menopausal status for women. Subjects with high-risk CHD risk factors such as diabetes, history of CHD either by the subject or a first degree relative and uncontrolled hypertension were excluded from the study to limit the number

of confounding factors. A total of 45 triads (patient groupings) were enrolled and one subject in the PI group of one triad discontinued prematurely. The median duration of PI use was 216 weeks. Each of the triads was well matched and the HIV groups were equally matched for CD4 and HIV viral load. The median CD4 was 530 in the PI group and 482 in the no PI group. The nadir CD4 count was unavailable as was duration of HIV seropositivity. The cohort was predominantly male (90%) and white (76%) with a median age of 42 years and 56% non-smokers. All subjects were normotensive. The ACTG 5078 team defined smokers as per the guidelines for the American Cancer Society, which is used for most cardiology studies. The median value of the labs were similar between the groups except for triglycerides (TG) and total cholesterol (TC) were slightly higher in the PI group at 219 and 192 mg/dL respectively compared with 142, 107 mg/dL TG and 179, 187 mg/dL TC in the no PI and uninfected groups. There was also an increased weight to hip ratio among the PI group compared with the other two, however there was no difference in respect to the body mass index or waist circumference.

The 5078 team reported that there was no significant difference in the measurements of the carotid IMT among the three groups. When one controls for the known CHD risk factors, the PI group did not have increased carotid IMT measurements compared with the no PI or HIV seronegative matched controls. Factors associated with an increased carotid IMT were low HDL, elevated TG (more pronounced when HDL is low), older age and increased BMI. This by itself is very interesting as low HDL is associated with HIV itself and was among the first lipid abnormalities described prior to the introduction of HAART. HAART, particularly ritonavir containing regimens, have been implicated as a cause of hypertriglyceridemia. Although the 5078 team did not find a significant difference among the groups now, it may be too early to detect any differences. CHD may take decades to develop and it will be critical to follow this extremely well matched cohort for years, in fact longer than the team has initially planned.

Carotid artery intima thickness test in HIV-infected, second study

On behalf of investigators from San Francisco General Hospital (SFGH), Dr P Hsue presented longitudinal results of measuring carotid IMT in 106 HIV-infected subjects on ART. [6] Similar to the ACTG 5078 study reported above, this group of investigators sought to determine the predictors of carotid IMT in subjects infected with HIV and to follow IMT progression over time. The mean age of the 106 subjects was 45 years and 88 (83%) were male. The duration of HIV infection was 11 + 5 years, median CD4+T-cell count was 354 cells/mm3 and the median duration of PI use was four years prior to enrollment. Compared to historic controls, the baseline mean carotid IMT was 0.90 + 0.27 mm was thicker than expected. Multi-variable predictors of increased IMT at baseline were age, LDL, hypertension and nadir CD4 <200. C-reactive protein, fibrinogen, HDL, triglycerides, lipodystrophy and duration of HIV were not predictive of increased baseline carotid IMT. The investigators followed the first 22 subjects enrolled over a year. The mean rate of carotid IMT progression was 0.1 + 0.1 mm/yr, which the investigators noted was increased compared to that reported in previous published studies of the general population. Age and duration of PI use were associated with carotid IMT progression. Interestingly, 41% of the 22 subjects had hypertension.

In contrast to the findings by the 5078 study, the investigators of this study concluded that HIV and its therapy in addition to traditional risk factors may contribute to the development of CHD. So, why the difference between the two studies? There was some debate over the methodology used by the ACTG 5078 team in comparison to one done by investigators at SFGH. The 5078 team chose to measure the carotid IMT at a specific site on the far wall on the internal carotid artery where there is laminar flow and this method has been reported to be a very precise and reproductive measurement. The SFGH chose to measure six sites near the bifurcation on each internal carotid artery for a total of 12 measurements and used the mean. I am unaware of any head to head comparisons of these two methodologies but I think the most important aspect will be following these cohorts long term using the same method to determine the longitudinal differences within each cohort.

The difficulty in interpreting the SFGH results is that there is no HIV seronegative control group. The investigators compared their results to historic controls who may not be representative of our current population, plus the equipment may be different with results being very operator dependent. Just this past year, there were national headlines stating that more than 20% of Americans met the definition for the metabolic syndrome compared with <10% ten years ago. And even more disturbing is that over 6% of 20 year olds met the criteria for the metabolic syndrome. Given the marked improvement of technology plus the changing demographics, I think it is imperative that these trials have HIV seronegative matched controls. I encourage the investigators at SFGH to increase their sample size and enrol controls as they continue their studies. Let's see what next year's results tell us.

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Source: NATAP.org

http://www.natap.org/2003/Retro/day19.htm

C O M M E N T

Of the two IMT studies, the SFGH is methodologically by far the inferior study: it is cross sectional with a small number of patients and no control of the traditional risk factors is made in the subjects who were followed longitudinally. The increase in IMT is a log greater than associated with any other cardiovascular risk factor. The low number of patients creates the problem of multiple testing, i. e. to have a statistical positive results by chance with no real meaning. The ACTG study balances the risk factors by a valid design and is excluding only patients with existing cardiovascular disease who will have a rapid progression, probably due to high risk constellations in the past most probably before ART.

D:A:D like all the other cohort studies has the critical problem that it does not have good data on the duration of HIV-infection which may be a risk factor by itself. The low number of events makes establishing high-risk profiles difficult at the time being including the use of different antiretroviral agents, but most identified variables point in the direction of traditional cardiovascular risk factors. However it would be interesting to know if different lipid changes result in different risks. A hint in this study that different lipid profiles due to ART may translate into different risks is the observation, that triglycerides are not associated with an increased risk in myocardial infarction.

Neither the D:A:D nor the Hopkins study can control for the duration of HIV-infection. Antiretroviral treatment may simply be a surrogate marker for being HIV-positive for a longer time. In addition the replication rate of HIV may matter as a proatherogenic factor. Again a higher replication rate of HIV will lead to immunosuppression and earlier treatment with ART. This dilemma is impossible to solve in both studies due to their design. This should not mean that hypercholesterolemia may not be a risk factor, but it may be more complicated than it seems. In both studies HIV-negative controls are missing.

Alendronate, vitamin D and calcium are safe and effective treatment for HIV-associated bone loss

Graham McKerrow, HIV i-Base

Researchers who conducted a study of 31 HIV-positive subjects on ART suffering from osteopenia or osteoporosis conclude that treatment with alendronate, vitamin D and calcium is safe and effective.

These bone conditions are frequent complications of HIV infection and/or its treatment and alendronate is the only bisphosphonate approved to treat them in men and women. Dr P Tebas and colleagues at Washington University, St Louis, conducted a 48 week prospective, randomised, open label study to evaluate the treatment on bone mineral density in HIV-positive patients.

Thirty-one subjects who had been on ART for at least six months and who had lumbar spine BMD *t* scores less than –0.1 were randomised to receive 70mg of alendronate (n=15) or not (n=16) weekly for 48 weeks. All subjects also received 1,000mg of calcium carbonate daily and 400IU vitamin D daily. The study was powered to detect 3% changes in bone mineral density (BMD) in the lumbar spine within arms. The researchers report that the increase in lumbar spine BMD was 5.2% at 48 weeks in the alendronate arm, compared with 1.3% in the non-alendronate arm.

These results were reflected in other sites in the body with the BMD in the neck being increased 2.4% on baseline in the alendronate arm, compared to 1.6% in the non-alendronate arm; and in the hip BMD being increased 2.3% in the alendronate arm compared with 1.7%. They report that there were no serious side effects.

Dr Tebas and colleagues conclude: “Alendronate, vitamin D and calcium are safe and effective in the treatment of osteopenia/osteoporosis associated with HIV infection... These results are consistent with the results observed in HIV individuals. These data provide the basis for sample size calculations and support the evaluation of alendronate in larger randomised trials.”

Ref: Mondy K, Powderly W. Tebas P et al. Alendrolate, vitamin D and calcium for the treatment of osteopenia/osteoporosis associated with HIV infection. Abstract 134.

C O M M E N T

This is a short term study with low numbers, and although the results are very interesting this limits the conclusions on safety. When to treat is an important question. Routine monitoring of bone density in patients without fractures is currently limited by healthcare and insurance providers in many countries, but with prevalence of low BMD shown at 40-60% HIV-positive studies this will need timely reviewing.

Bone loss and fat loss are closely related in HIV patients on HAART

HIVandHepatitis.com

A number of previous studies have demonstrated that HIV positive individuals on HAART regimens are at increased risk for developing lipoatrophy (fat loss) and bone loss. The aim of the present longitudinal cohort study was to determine whether there is a direct association between the fat mass and bone changes.

The study population consisted of 86 HIV positive patients (73 males, 13 females; 44 PI-experienced, 42 PI-naive) aged 37.3 –8.6 years. Whole body composition was determined by DEXA; bone mineral content (BMC), fat (FAT), and lean body mass (LEAN) were evaluated for whole body as well as regionally. Two body-composition analyses were obtained for each patient. The second measurement was performed 30 months after the first. The degree of association between the bone and fat mass changes was tested using the Pearson's correlation coefficient.

Mean BMI on study entry was 24.40 –3.17 kg/m2, and mean CD4+ count was 362 –228 cells/mm3. Patients exhibited a significant decrease in their body weight. Weight loss was due exclusively to FAT, while LEAN was not affected.

Fat loss was statistically significant in the arms and legs, but not in the trunk. A significant decrease in the whole body BMC was also evident. Analysis showed a statistically significant positive correlation between the fat and bone mass changes ($r = 0.357$, $p < 0.001$).

Conclusions: "In a cohort of HIV-infected individuals receiving antiretroviral treatment, a positive correlation between the bone and fat mass loss was observed. This finding possibly suggests that common pathogenetic mechanisms contribute to lipoatrophy and osteopenia/osteoporosis in HIV-infected patients."

Ref: G Tsekes et al. Bone loss is closely related to fat loss in HIV-infected patients receiving antiretroviral treatment. Abstract 764.

Source:
http://www.hivandhepatitis.com/2003icr/10thretro/docs/022103c.html

CROI: HEPATITIS COINFECTION

Low dose 200/100 IDV/RTV managed by TDM in substudy of co-infected patients

Graham McKerrow HIV i-Base

A substudy of six patients coinfected with HIV and either chronic hepatitis B (HBV) or chronic hepatitis C (HCV) concludes that low dose treatment with indinavir (IDV, Crixivan) and ritonavir (RTV, Norvir) appears to be effective and safe.

The poster presentation by Dr G Peytavin on behalf of colleagues in Paris, looked at six patients from the larger GEOPHAR study, which is evaluating the benefits of therapeutic drug monitoring (TDM) in association with genotypic resistance testing to optimise treatment in multi-experienced patients.

In five patients with HCV, one with HBV and a control group of 16 without chronic hepatitis, treatment with IDV/RTV low doses (400/100 mg bid) combination plus two NRTIs was selected upon results of the resistance genotyping test, treatment history, and drug tolerance. A month after starting the new regimen, HIV-1 RNA level was measured and IDV Cmin was performed by using an HPLC assay. The researchers considered plasma concentrations as adequate if values of IDV Cmin determined 12 hours after the last intake were in the therapeutic range of 150 to 675 ng/mL.

In the six patients with chronic hepatitis, IDV plasma concentrations were very high, and all Cmin but one were < 675 ng/mL (median value: 1,440 ng/mL; range: 650 to 2,310 ng/mL). In all patients, a viral load < 200 copies/mL was achieved. Despite high IDV Cmin in these patients, no side effects were noted. After a therapeutic adjustment within a month (IDV/RTV 200/100 mg bid), adequate IDV Cmin were obtained and remained stable in five patients until the end of the study (at week 24: median value: 277 ng/mL; range: 150-320 ng/mL). The patient with HCV, who had an adequate Cmin, was lost to follow-up. HIV-1 RNA level remained undetectable until the end of the study.

The researchers conclude: "The results of this study suggest that the IDV/RTV low dose (200/100 mg bid) appears to be effective and safe in patients co-infected with HIV and HCV or HBV. The benefit of TDM in association with genotypic resistance testing and expert advice to optimise subsequent therapy in HCV or HBV co-infected patients receiving the combination IDV/RTV appeared crucial in this GENOPHAR substudy."

Ref: P. Bossi, G. Peytavin, C. Lamotte et al. High indinavir plasma concentrations in HIV-1 patients co-infected with hepatitis B or C virus receiving indinavir and ritonavir low dosages: a GENOPHAR substudy. Abstract 546

C O M M E N T

There is no report in the abstract on what stage of liver disease these six patients were at. Did they have advanced disease where the liver might be less functional thus leading to higher IDV drug levels or did they have earlier stage disease where the liver may be more functional leading to more normal IDV drug levels?

This small study exemplifies the role of the liver in clearing certain classes of anti-HIV drugs, particularly the PIs and NNRTIs. Most NRTIs are cleared by the kidneys (and hence dose adjustments in renal impairment). Unlike renal impairment, where creatinine clearances can be easily calculated or measured, hepatic clearance of drugs is difficult to predict or measure. Thus, therapeutic drug monitoring may be the only way of ascertaining drug levels of PIs and NNRTIs in patients with hepatitis co-infections and advanced liver disease and such drug dose adjustments need to be made on an individual basis. No data on co-medications was provided in this study.

The authors' conclusion that low doses of ritonavir-boosted indinavir is safe and effective in co-infected patients may not be valid for all patients and indeed, may not apply to other liver cleared anti-HIV drugs. Safe and effective dose-reduction is only possible by TDM on an individual basis.

12-week response predicts which HIV-HCV coinfected patients will not benefit from continued pegylated interferon plus ribavirin

Ronald Baker PhD, HIVandHepatits.com

Treatment with pegylated interferon plus ribavirin is producing an average 60% 'cure' rate among HCV-monoinfected individuals. At the same time, liver disease caused by HCV infection is a growing cause of concern among HIV-HCV coinfected patients and their caregivers.

The response rates to combination therapy with pegylated interferon/ribavirin appear to be lower in HIV-HCV coinfected patients, while the side effects of treatment are more frequent. This may be due to the interaction between ribavirin and the nucleoside analogue drugs.

In HCV-monoinfected patients, the treatment response at 12 weeks or 'early virological response' (EVR) predicts which patients will not benefit from continued therapy with pegylated interferon/ribavirin. A reduction in HCV RNA > 2 logs at 12 weeks predicts a continued benefit.

No data among coinfected patients are available on the validity of this approach.

In the present study, investigators evaluated 89 HIV-HCV coinfected patients who completed a course of anti-HCV therapy. Pegylated interferon was administered to 63 and standard interferon to the remaining patients, all at standard doses. All received ribavirin 400 mg twice daily.

Overall, sustained virological response (SVR) occurred in 29 patients. End-of- treatment response with further relapse was seen in 15. The remaining 45 were non-responders.

A drop in HCV RNA > 2 logs occurred in 38 (43%) and 52 (58%) of patients at four and 12 weeks, respectively. Of those subjects, only 18 (48%) and 29 (56%), respectively, reached SVR. In contrast, SVR occurred in 11 (38%) and 0 patients who did not show a > 2 log drop In HCV RNA at weeks four and 12, respectively.

Thus the negative predictive value (NPV) was 100% at week 12. There were no significant differences between HCV genotypes, baseline HCV RNA and use of either pegylated or regular interferon.

In patients with HCV genotype 2-3, a high rate of relapse in early responders was noted, which suggests that extending treatment beyond six months might have provided a higher SVR rate for them.

The investigators conclude: "The use of an early time decision point at 12 weeks to identify which subjects will not benefit from continuing anti-HCV treatment is valid for HIV positive patients. However, a delayed clearance of HCV RNA in early responders with HIV might account for a higher relapse rate when treatment is stopped prematurely, eg six months in genotypes 2-3."

Ref: M Perez-Omeda et al. Predictive value of early virologic response (12 weeks) to pegylated interferon plus ribavirin in HIV-HCV co-infected patients. Abstract 842.

Source:
http://www.hivandhepatitis.com/2003icr/10thretro/docs/021403a.html

C O M M E N T

This study makes two very important observations in the treatment of chronic HCV in HIV co-infection. Firstly the low rates of SR compared to HCV mono-infected patients even with Pegylated IFN and Ribavirin and secondly the importance of EVR (12 week response) in predicting overall SR.

Two large RCTs presented to date, ANR HCO2-RIBAVIC study (AASLD, 2002) and Voigt et al (Glasgow 2002) have shown overall ETRs of 45% and 38% respectively with PEGIFN-alpha 2b and Ribavirin in HCV/HIV co-infected patients. In both these studies treatment was given for 12 months and ETRs for genotypes 2/3 were much higher at 55% and 72% respectively. The final results from these studies and the multinational APRICOT study (Pegasys and Ribavirn) will give us a better idea of overall SR in co-infected patients and predictors of response (pre-treatment HCV viral loads, CD4 counts, HAART and drug interactions, stage of liver disease etc). It is likely that even in patients with genotype 2/3 HCV co-infection 12 months therapy may be recommended to prevent virological relapse.

These results also confirm the importance of the 12 week response in predicting ETR and SVR. This has been confirmed as a predictor of response with IFN and Ribavirin in co-infected patients (Soriano 2002). High drop-out rates due to intolerance and side-effects are common with IFN and Ribavirin (20-30% in most studies with co-infected patients), and a non-response, or < 2 log drop in viraemia at 12 weeks is predictive of treatment failure. For these reasons it is currently good practice to stop treatment at this stage.

The benefit of possible inhibition of fibrosis progression in (non responding) advanced patients by interferon maintenance has been suggested, but the data supporting this approach are not conclusive and the studies are still ongoing.

Pegylated interferon associated with eye disorders

Brian Boyle MD, HIVand Hepatitis.com

Ophthalmologic (eye) disorders have been recognised as potential side effects of interferon-alpha (IFN). These disorders include reports of retinal vascular occlusions, retinal hemorrhages, and cotton wool spots (CWS) and, uncommonly, potentially sight threatening optic neuropathy.

In an open-label prospective trial conducted at the National Institutes of Health (NIH), HIV/HCV co-infected patients were treated with PEG-Intron (Pegylated-IFN alfa-2ß) and Rebetol (ribavirin) 48 weeks. These patients had ophthalmologic evaluations at baseline and at least every three months, which included visual acuity, threshold visual field testing, colour vision exam, and indirect ophthalmoscopy.

The investigators found that seven of the 16 patients enrolled in the study (44%) developed ophthalmologic pathology. Six developed cotton wool spots (CWS) on their 12 week follow-up funduscopic examination, which 'waxed and waned' while PEG-Intron therapy was continued.

In addition to CWS, one of these patients was found to have bilateral cataracts at 12 weeks, while another patient subsequently developed a unilateral cataract. Finally, one patient developed a 50% decrease in colour vision requiring cessation of PEG-Intron therapy. This patient's colour vision improved over the four weeks following PEG-Intron discontinuation, but did not return fully to normal.

The authors conclude: "The incidence of serious ocular pathology associated with treatment with anti-HCV therapy may be very high and is likely associated with peg-IFN. While HIV, hypertension, and diabetes mellitus are associated with these ocular lesions, incident cases of CWS and cataracts occurred in patients with high CD4+ T-cell counts and developed soon after beginning peg-IFN therapy.

"As with patients treated with ethambutol, medications toxic to retinal ganglion cells can cause lesions such as optic neuropathy and result in colour blindness or loss of vision. "Our findings suggest a need for increased vigilance in monitoring patients treated with peg-IFN for visual changes. Colour vision testing should be a routine component of the standard examination, as loss of colour vision may be a harbinger of serious optic neuropathy."

Ref: C Farel et al. Serious ophthalmologic pathology with visual compromise in HIV/HCV co-infected patients treated with Pegylated Interferon Alpha-2b and Ribavirin. Abstract 844.

C O M M E N T

A number of ophthalmic complications, including retinal vein thrombosis, retinal artery occlusions, haemorrhages, cotton wool spots, proliferative retinopathy and acute loss of vision have been reported with Pegylated interferon-alpha therapy. All of these are a very rare

class effect of these drugs. In the APRICOT and RIBAVAC studies this was rarely reported, if at all.

Cotton wool spots (CWS) are relatively common in patients with advanced HIV disease (up to 60% of patients) and in symptomatic HIV disease. They do not have any impact on visual acuity and do not usually require any dose modification. They have not been associated with any long-term ophthalmic events but this needs to be checked and confirmed in a larger study before giving any general conclusions. Six to seven patients with ophthalmic complications had CWS.

The occurrence of cataracts and loss of colour vision each in a single patient is of concern. Best clinical practice is a baseline ophthalmic assessment for all patients pre-Pegylated interferon alpha therapy and further assessments only if visual symptoms are reported. In light of this report clinicians may need to consider colour vision testing as part of the pre-therapy assessment.

Data on use of cocaine or opiods which may be other drugs involved, were not available.

CROI: RESISTANCE

Nevirapine resistance – the cautionary tales continue

Polly Clayden, HIV i-Base

…following labour

Two posters from Susan Eshleman's group reported further analyses of nevirapine (NVP, Viramune) resistance from the HIVNET 012 trial in Uganda in which it was famously demonstrated that single dose NVP given as prophylaxis to a mother in labour followed by a single dose to the infant can reduce mother to child transmission. However following analyses of NVP resistance in 111 of the women, 21 (19%) had detectable mutations at six to eight weeks post dose, most commonly K103N.

In an expanded evaluation of the rate of NVP resistance, paired samples collected at seven days and six to eight weeks were compared [1]. NVP mutations were detected in 66 (24%) out of 271 women and a similar number had mutations at both time points. However patterns of mutations were different.

Y181C was detected in 13 (87%) of 15 women with NVP resistance at seven days, but in only four (22%) of 18 women with NVP resistance at six to eight weeks. In contrast, K103N was detected in six (40%) of 15 women with NVP resistance at seven days, but was detected in all 18 women with NVPR at six to eight weeks. Analysis of paired samples suggests that of the most common mutations associated with NVP resistance Y181C is selected early, but fades from detection in most women by six to eight weeks. By contrast, K103N is more likely to be detected at six to eight weeks than at seven days.

The investigators noted that "the pattern of NVPR mutations detected after single-dose NVP depends on the timing of sample collection". And they explained that "more rapid emergence and fading of Y181C vs K103N may reflect differences in the NVP susceptibility and fitness of HIV-1 with these mutations. Analysis of cloned variants reveals that diverse populations of HIV-1 variants with NVPR mutations are selected as early as seven days following single dose NVP".

A second poster from the same group evaluated the samples by subtype using a univariate analysis and their findings suggest that the rate of NVP resistance was higher in women infected with subtype D than with subtype A HIV-1 [2]. Unsurprisingly high baseline viral load and low CD4 were associated with likelihood of acquisition of NVP resistance. The authors speculated that "the rate of NVPR following single dose NVP prophylaxis may vary from region to region, depending on which subtypes are prevalent."

In addition a Thai poster assessed the development of resistance in pregnant HIV-infected women and their infants receiving both short-course zidovudine (ZDV) therapy and single-dose intrapartum/newborn NVP [3]. The authors reported that amongst 133 ARV-naive women receiving both prophylaxis strategies, 20 demonstrated NVP and one a ZDV genotypic resistance mutation at one month postpartum and of the three HIV-infected infants tested, one demonstrated NVP resistance.

…and breastfeeding

Breastfeeding may account for as much as a third of mother to child transmission (MTCT) with estimated transmission rates at 0.5%-2% per month. MTCT breastfeeding interventions have included a second dose of NVP to the mother (conferring a threefold increase in incidence of resistance from 19-67% women receiving prophylaxis) [4], and NVP prophylaxis to breastfeeding infants.

In an oral presentation Dr Lee from Stanford University reported findings from a small study conducted in Zimbabwe, comparing the relative concentrations of NVP resistant virus in 33 women enrolled in HPTN 023 who received single dose NVP at the onset of labour [5]. Plasma and breast milk samples were obtained at two, eight, 16 and 20 weeks post partum. At eight weeks 23/33 (70%) women had detectable HIV RNA in plasma. Sequences were available for 33 of the plasma and 20/33 of the breast milk samples. Detection of NVP mutations was significantly higher in the breast milk 3/20 (65%) than the plasma 8/33 24.2%).

K103N (the mutation most commonly associated with NVP resistance) was the most frequently observed mutation in both breast milk (12/20) and plasma (5/33). Only 4/20 pairs of plasma and breast milk demonstrated the same mutations and all samples were found to be subtype C. The investigators also observed: "The 20 breast milk and plasma samples from each woman were more closely related to one another than to sequences from other women."

And they concluded: "Significantly higher frequency of resistance mutations in breast milk compared to plasma provides evidence for differential selection and expression of NVP resistance in the BM compartment after single dose nevirapine."

Questions raised following the presentation concerning the limitations of the assays and the possibility that the investigators may be missing minor variants, implications for transmission of resistant virus and the limits these findings may have on the use of NVP prophylaxis for a breastfeeding infant were largely unanswered.

Rapid test

Finally, a poster from Susan Eshleman's group reported results from an evaluation of NVP resistance in women in HIVNET 012 using the rapid assay Amp-RT (this assay measures reverse transcriptase (RT) enzymic activity and NVP resistance directly in plasma) compared to genotyping using the Applied Biosystems ViroSeq HIV-1 Genotyping System.

Twenty-nine plasma samples from 17 women, including pre- and post-NVP samples were tested. They found that 17 samples had no detectable NVP mutations (wild type) and 12 samples had minor variants with NVP resistance mutations.

Results were obtained for 26 (90%) of the 29 samples, including 16 wild type (WT) samples and 10 samples with minor NVP variants. The other three samples had undetectable RT activity. The Amp-RT assay detected NVPR in six (60%) of the 10 samples with minor NVPR variants. Thirteen (13; 81%) of the 16 wild type samples were susceptible to NVP in the Amp-RT assay, and three had reduced susceptibility. Two of the samples with reduced susceptibility were pre- and post-NVP samples from the same woman who was antiretroviral drug naïve prior to NVP administration. The pre-NVP sample had a lower level of NVP resistance than the post-NVP sample.

The authors reported that "in this study, results from the Amp-RT assay were concordant with results from genotyping in the majority of cases" (including detection of minority variants). They speculate that the finding of reduced susceptibility to NVP in the three wild type samples may indicate that mutations other than those defined in subtype B analysis may cause NVP resistance in other subtypes. Using this rapid assay does not require time isolation and culture and therefore can provide results in one or two days in contrast to conventional phenotype. They also suggest that further studies be undertaken to characterise the full genetic correlates in non-subtype B HIV and to assess the utility of biochemical testing in resource poor settings.

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C O M M E N T

Amongst the discussion points the from the HIVNET study the investigators explained that 'Selection of NVP resistance in this setting is not unexpected… Because women in HIVNET012 had relatively advanced HIV-1 disease, they may be more likely to develop NVP resistance than women in other cohorts. Data from HIVNET 012 indicates that NVP resistance *fades in women over time.* Clinical studies are needed to determine whether the emergence of nevirapine resistance after single dose NVP prophylaxis will affect the efficacy of NVP prophylaxis in subsequent pregnancies. It is not clear whether the selection of NVP resistance will limit the use of NVP or other NNRTIs for subsequent treatment of HIV-1 infection.' They continue ' If antiretroviral drugs become more widely available in those countries women who received NVP *could be offered treatment with other drugs…' (our italics).*

We would urge for more caution with this approach. By our understanding these findings clearly do warrant a change in policy. Resistance does not fade. Other treatments will not be readily available.

As for the rapid test, given the ease at which NVP resistance appears to develop in both mothers and infants receiving prophylaxis and the not inconsiderable numbers of programmes using this intervention such an assay may prove to be invaluable.

TREATMENT ACCESS

Global Fund gives $210 million for treatment in Thailand

Graham McKerrow, HIV i-Base

The Global Fund to Fight AIDS, TB and Malaria has given US$209.7 million to Thailand to treat the rising number of cases of all three illnesses caused by an influx of migrant workers.

It is the largest donation given to an Asian country by the fund and will enable the government to distribute antiretrovirals and drugs to treat secondary infections such as TB.

Public Health Minister Sudarat Keyuraphan said: "We expect that all HIV-positive people that have shown symptoms will have access to the medicines within five years. This will in turn help to reduce the number of TB cases greatly."

A recent growth in the number of migrants from neighbouring countries, together with drug-resistant strains of malaria and TB have led to soaring infection rates.

Anti-HIV combination drug for Indonesia

Thailand's Government Pharmaceutical Organisation has signed an agreement to supply antiviral drugs to its Indonesian counterpart for three years. They also announced plans to export ARVs to other countries including China and South Africa.

The drug supply worth 84 million baht (£1.2 million) was in accordance with the public health cooperation pact agreed by the 10 Asian nations. The first delivery of the drugs - GPO-VIR, Lanavir, Anti-vir and Fluzoral - was expected at the end of this month. They will be used to treat between 80,000 and 120,000 people.

Public Health Minister Sudarat Keyuraphan and her Indonesian counterpart Dr Achmad Sujudi presided over the signing of the agreement.

Source: Bangkok Post
http://ww2.aegis.org/news/bp/2003/BP030204.html

Links:

Reuters coverage:
http://ww2.aegis.org/news/re/2003/RE030219.html

Indian generic drug maker Ranbaxy Laboratories to launch own-brand abacavir

Ranbaxy Laboratories, India's largest drug maker in terms of sales, has launched a new antiretroviral drug, which is a generic formulation of a patented medication made by GlaxoSmithKline, Dow Jones International News reports. The Ranbaxy drug, which is equivalent to GSK's abacavir (Ziagen), will be sold under the brand name Virol in 300 milligram tablets. According to a Ranbaxy spokesperson, the drug, which is taken twice a day, will cost about $136 a month, with an Indian market size of approximately $6.3 million. "The company will be able to carve out a sizable share of the market as most other drugs in currency are older molecules," Sri Hari, a pharmaceutical analyst with Mumbai-based brokerage Khandwala Securities, said. The antiretroviral drug market in India is about $31.4 million a year, with Indian drug makers Aurobindo Pharma and Cipla playing large roles (Dow Jones International News).

Source: Kaiser Daily Report
http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=15876

Bush blocks deal allowing cheap drugs

American President George W Bush's close links with the drugs industry have been blamed for the failure of talks in Geneva aimed at securing access to cheap medicines for developing countries.

Delegates at the World Trade Organisation expressed frustration after the USA again rejected a deal that would have loosened global patent rules to enable more poor countries to import generic versions of ARVs.

"We believe that governments should maintain their distance and should not be directed by pressure groups," one EU trade official said.

Negotiators said a solution to the deadlock lay in America's hands. "The pharmaceuticals lobby is running the show in Washington," one development activist said.

The WTO's 144 members agreed more than a year ago that countries could override patent rules in the interests of public health and license local producers to copy essential drugs. But they failed to spell out how countries with no manufacturing capacity would gain access to life-saving medicines.

A draft accord on imports was rejected by the USA last December after lobbying from drugs firms, which fear that relaxing the rules to allow poor countries to import copycat drugs will help generics manufacturers in India and Brazil to steal their markets.

America's counter proposal, limiting imports to drugs for a shortlist of diseases including HIV/Aids, malaria and tuberculosis, was rejected by developing countries as too restrictive.

Eduardo Perez Motta, the Mexican ambassador to the WTO, who chairs the drugs talks, admitted the organisation's reputation had been damaged by the deadlock.

A Brazilian proposal, to let the World Health Organisation decide which countries were allowed to import copycat drugs, was not even discussed.

A South African plan that would have required countries to declare a national emergency also failed to win over the US drug industry.

Source: Mail&Guardian online, SA
http://www.mg.co.za/Content/l3.asp?a=13&o=16101

Roche to sell nelfinavir, saquinavir at cost to least-developed nations

Swiss drug maker Roche has announced that it will begin selling its antiretroviral drug nelfinavir (Viracept) at cost to least-developed nations beginning in March, "bowing" to criticism that the drug maker has not "done enough" to make the drug affordable, the Wall Street Journal reports. In least-developed nations an annual regimen of nelfinavir, would cost approximately $900 per person under the new plan, compared to $3,300 previously. In low-income nations that are "slightly more developed," such as Albania and Egypt, the price of the drug will be reduced to approximately $2,970 per person annually; the current retail cost of nelfinavir is more than $6,000 per person per year. According to the Journal, the price adjustment will bring the cost of nelfinavir "in line" with the cost of four other significant antiretroviral drugs whose prices were reduced in May 2000 after an "intense" international lobbying effort (Fuhrmans/Zimmerman, Wall Street Journal, 2/13).

Under a plan negotiated with the United Nations, Roche, Bristol-Myers Squibb, GlaxoSmithKline, Merck and Boehringer Ingelheim agreed to reduce their AIDS drug prices, trying to "significantly increase health care services in sub-Saharan Africa and other areas where the AIDS epidemic is reaching crisis levels" (Kaiser Daily HIV/AIDS Report, 5/15/00).

However, international humanitarian groups said that Roche failed to reduce the cost of its drug as much as its competitors and claimed that health care workers often could not receive nelfinavir from local distributors at the reduced price Roche had pledged. According to the Journal, governments and humanitarian groups will receive the new discount by buying nelfinavir directly from Roche's headquarters instead of through local suppliers. The drug maker also announced that it would sell the antiretroviral drug saquinavir hard gel (Invirase), at cost; the drug maker currently sells the drug at "near-cost" prices, according to the Journal. Roche will add additional fees for shipping, taxes and distribution to the price of both drugs, a move that could increase the drug's cost by 20%, according to Daniel Berman, a spokesperson for Doctors Without Borders, an international humanitarian organisation. Berman added that competitors such as Merck and Bristol-Myers Squibb did not charge the additional fees. David Reddy, head of Roche's HIV products and disease strategy, said that the company was not including the additional costs onto the drug's listed price because the cost of shipping and taxes varies greatly among countries (Fuhrmans/Zimmerman, Wall Street Journal, 2/13).

Source: Kaiser Daily Report
http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=16035

South Africa appoints another dissident

Graham McKerrow, HIV i-Base

The South African government has revived controversy about its AIDS policy by appointing an AIDS dissident, Roberto Giraldo, to a team of experts advising the government on how to combat HIV. The move follows strenuous efforts by South Africa to distance itself from the dissidents – who question the link between HIV and AIDS – in the wake of President Thabo Mbeki's repeatedly voiced sympathies for dissident views. The appointment also follows the appointment two years ago of other AIDS dissidents to a presidential advisory board on AIDS.

Mbeki and AIDS dissidents who influence him believe AIDS is caused by poverty and a combination of other infections, and that antiretroviral drugs also cause AIDS.

The South African opposition Democratic Alliance has reacted to the appointment of Dr Giraldo by calling for the resignation of the health minister, Manto Tshabalala-Msimang who has long had the full support of the president. The minister said Dr Giraldo would only be offering advice on how to use diet to boost people's immune systems.

Again Ms Tshabalala-Msimang tried to distance herself from controversy surrounding the president's dissident views on the link between HIV and AIDS, telling newspapers: "I think we are past that stage. Our own strategic plan is based on the premise that HIV causes AIDS. I am only looking [to Dr Giraldo] for expertise on nutrition."

Meanwhile few positive South Africans can access ARVs and 200,000 are expected to die this year. The Treatment Action Campaign is launching a campaign of civil disobedience to back up its demand that treatment is made more widely available by the government.

IMMUNOLOGY

US implementation of large-scale smallpox vaccination plan has special implications for people with HIV

Gareth Hardy, HIV i-Base

The increased threat of biological warfare has led to a renewed smallpox vaccination plan in the USA, which could be echoed by other countries including Britain. In December, the US President, George W Bush, announced plans to vaccinate 500,000 key workers against the disease and an intention that by mid-2003 10 million US citizens would be vaccinated. However, on Tuesday 3 December the UK Department of Health (DoH) announced that it had no plans to introduce a mass vaccination programme against the disease and that only 700 key health and military staff would be vaccinated who would form new 'Regional Smallpox Response Groups' in the event of an attack.

Nevertheless the DoH report Guidelines for Smallpox Response and Management in the Post-Eradication Era did state that this policy could change if public demand for protection from smallpox increased. Thus the UK government is on course to stockpile 60 million doses of the vaccine.

Smallpox is caused by the *variola virus,* which belongs to the poxviridae family. This virus is highly contagious, airborn and persistent and has mortality rates ranging up to 40%. Between 1966 and 1973 the World Health Organisation (WHO) carried out a vigorous global programme of smallpox vaccination, which has culminated in eradication of *variola virus* from the human population. There is no known animal reservoir of *variola*, thus complete global eradication is now assumed. The last naturally occurring outbre ak of smallpox was in Somalia in October, 1977. Since then two reference stocks of *variola* have been stored at the Centres for Disease Control and Prevention, (CDC) in Atlanta, Georgia, USA and at the Research Institute for Viral Preparations in Moscow, Russia.

Persons aged younger than 30 are not likely to have been vaccinated or to have any protective immunity to the virus. Protective immunity to *variola* in those older than 30, who will have received childhood vaccination, is likely to have waned over the elapsed three decades since vaccination. The lack of vaccination for smallpox over the last 30 years leaves a world population with gradually returning susceptibility to the virus and a consequent liability for massive epidemics of the disease. Modern day rapid transport coupled with physicians' unfamiliarity with the disease may both facilitate reintroduction of smallpox into the global human population if a new source of the virus emerged. The use of smallpox in biological weapons cannot be ruled out and would have the potential for devastating effects.

On 23 September 2002, the CDC presented its plan for renewed smallpox vaccination of the US population. In *Clinical Infectious Diseases* John G Bartlett of Johns Hopkins University, Baltimore, reviews the important aspects of smallpox vaccination strategies that affect those living with HIV and their health care providers. These considerations are a serious concern as vaccination for smallpox and its subsequent eradication occurred before HIV became apparent.

The main concern raised is the high risk of disease occurring in immunocompromised individuals as a direct result of vaccination for smallpox. The smallpox vaccine is a live attenuated virus of the poxviridae family known as *vaccinia virus*, which is closely related to the *variola virus*. The *vaccinia virus* is derived from *cowpox*, or possibly *horsepox*. Due to successive propagation in many laboratories the vaccinating strain has become considerably attenuated and while it is very similar to *variola virus*, *vaccinia* itself rarely causes serious complications in healthy individuals.

There are several contra-indications for inoculation with *vaccinia virus* that apply to potential vaccinees and laboratory or healthcare workers whose work may involve handling the virus. These contra-indications include eczema and immunosuppression. Cell mediated immune responses play a major role in protection from *vaccinia* dissemination and disease in healthy individuals. In persons infected with HIV the impairment of this component of the immune response removes protection from disease such that generalised or progressive vaccinia (vaccinia necrosum) may occur. This reaction to smallpox vaccination may affect anyone with compromised immune responses, including people with HIV, organ transplant recipients, patients undergoing cancer chemotherapy, patients receiving long-term cortico-steroid therapy, patients with

haematologic malignancies, and patients with congenital immunodeficiencies. Vaccinia necrosum has also rarely been seen in patients with agammaglobulinaemia. Dissemination of cutaneous lesions from the primary site of inoculation occurs, with viraemic spread, involving minimal lymphocytic infiltration. This reaction may result from primary vaccination or from revaccination and is usually fatal.

Very limited experience of smallpox vaccination in persons with HIV enables some case studies and observational reports, which Bartlett discusses. These studies were made before the HAART era and the patients in them had AIDS. Smallpox vaccination is thus considered clearly unsafe in persons with CD4 counts <200 cells/ml blood. However an assumption of safety in HIV infected persons with CD4 counts >200 cells/ml blood is problematic. Additionally the impact of HAART on susceptibility to vaccinia necrosum is unknown. The CDC recommendations state that HIV infection is a contra-indication for smallpox vaccination, regardless of CD4 count.

Since smallpox vaccination in people with HIV is unsafe, the risk to people with HIV from an outbreak of smallpox is enormous. While the smallpox mortality rate in unvaccinated immunocompetent subjects is up to 30 or 40%, the expected mortality rate in HIV infected individuals is speculated to be much higher and to inversely correlate with CD4 count. In persons with AIDS the smallpox mortality rate would be expected to be very high.

For HIV infected individuals older than 30 years, who received childhood vaccination for smallpox, remaining immunity is likely to be negligible. Even in HIV uninfected persons antibodies to *vaccinia* are now largely undetectable and cell mediated responses are likely to be low. The smallpox vaccine is considered to confer protection for only three to seven years, although recent evidence suggests protection may last longer. The impact of HIV induced immunosuppression on this is unlikely to leave any protective immunity to smallpox.

Thus the CDC states that smallpox vaccination will be voluntary. In the event of an outbreak of infection, anyone who has been potentially exposed will be advised to receive smallpox vaccine, regardless of their medical condition. In immunocompetent individuals protective immunity develops seven to 10 days after vaccination, which can prevent disease developing if vaccination is administered quickly after exposure, given that the incubation period of smallpox is about 12 days. Hence smallpox is one of the few examples of the utility of post-exposure, therapeutic vaccination, as also is the case for rabies and tetanus. The CDC also recommends that before vaccination a medical screen should be performed, including HIV testing, with informed consent. The CDC states that in the presence of HIV infection, smallpox vaccination should not be recommended, unless there is a smallpox attack.

The problems posed to HIV infected individuals from smallpox vaccination go beyond those of direct, voluntary vaccination. Other non-immunocompromised persons, vaccinated for smallpox, also present a significant risk for persons with HIV. Inoculation with *vaccinia* results in localised ulceration, which sheds virus for approximately 10-14 days subsequently. Shedding even occurs through sealed bandages. Thus there is a risk of secondary spread of *vaccinia*. The frequency of such cases is low at two to six cases per 100,000 primary vaccinations and requires close contact. The frequency of progressive vaccinia developing as a result of such secondary spread was very rare during the smallpox eradication programme. However there is concern that because of the increased number of immunodeficiencies now, such as HIV, the frequency of progressive vaccinia from secondary contact may be higher. Thus it is recommended that vulnerable patients, including those with HIV infection, be removed from direct contact with vaccine recipients until virus shedding has resolved. If a potential vaccinee has a household contact with HIV infection, vaccination is contra-indicated. The CDC recommends that the alternative is living apart, until public health officials state that there is no longer a risk, which is likely to be 10 -20 days following vaccination. Healthcare workers who provide for HIV infected persons should be reassigned to furlough duties until the inoculation scab dislodges.

Finally, in the event that progressive vaccinia does develop, investigational treatment is available (in the USA) with informed consent. Treatment with *vaccinia* immunoglobulin (VIG) is recommended, although it has never been studied in a controlled trial. Availability of VIG in the US is controlled by the CDC. The dosage is 0.6ml/kg body weight administered I/M, or approximately 40 ml usually given over 24 - 36hrs. Cidofovir has shown *in-vitro* activity against *vaccinia*, and *in-vivo* activity in a rodent model. However in a study in which immunodeficient mice were challenged with *cowpox*, cidofovir failed to prevent death. There is no clinical experience of cidofovir treatment of *vaccinia*. The CDC recommends both VIG and cidofovir as treatments for severe reaction to smallpox vaccination.

While this article details the US plans for mass smallpox vaccination and its implications for people with HIV, the UK stance remains unclear. On 3 March 2003, the BBC carried a news story detailing concerns of a “senior government advisor” over government lethargy about a smallpox terror attack. It was claimed that inactivity was being shrouded as secrecy. Within hours Home Secretary David Blunkett explained that London’s ability to respond to a catastrophic terror attack would be tested in the next few weeks, in an exercise involving all the emergency services, which would cover mass evacuations and the ability to decontaminate affected areas. In the meantime concerns on this issue for HIV infected individuals in the UK remain to be addressed.

The author wishes to thank his colleague Dr Nesrina Imami for useful comments and source information.

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Smallpox Vaccination and HIV Infection - Hopkins report Jan 2003

By John G. Bartlett, M.D.
http://www.hopkins-aids.edu/publications/report/report_toc_03.html

OTHER NEWS

UK HIV new cases at record high

The UK Public Health Laboratory Service released new figures on the number of new HIV infections diagnosed during 2002. The report showed that the trend for more new cases of HIV to be diagnosed in heterosexual people than gay men has been maintained. This has been the case since 1999.

Since recording began in 1982, the cumulative total of HIV infections to the end of 2002 now stands at 54,261. Thirty-five percent (19,166) of the total have been diagnosed with an AIDS-defining condition, of which 12,544 (65%) have died.

2001- the highest new HIV diagnoses ever

The total number of HIV cases diagnosed during 2001 has now reached 4,909; the highest number ever recorded. Fifty-six percent (2,749) of the diagnoses were made in heterosexual men and women. This too is the highest proportion of reports infected via this route ever recorded. The total of new heterosexual infections reported in 2000 is now 1,974 (40% lower than reports now received for 2001).

In 2001 sex between men accounted for 34% (1,662) of reports of new diagnoses.

2002- first figures released today

So far for 2002, the total number of new cases of HIV diagnosed in the UK is 4,202 but this figure is expected to rise significantly once delayed reports have been received. To put this figure in perspective, the total figure for 2001 at this point last year stood at 3,342. Heterosexual sex accounts for 52% of new HIV infections diagnosed so far in 2002, whilst diagnoses attributed to sex between men account for 28% (1,195 reports).

The proportion of those infected through injection drug use has declined year-on-year since 1995. In 2001 there were 123 (2.5%) reports of HIV infection through injection drug use. Sixty-four new diagnoses were reported among injection drug users in 2002; this represents 1.5% of the total infections reported.

Mother-to-infant transmission accounted for less than 2% (57) of reports of new diagnoses in 2002.

London and the South East remain the epicenter of the UK's HIV epidemic, with 69% of all new diagnoses occurring in these regions. Overall the proportion of all new HIV diagnoses that are made in London has declined from 61% in 1992 to 53% in 2002, whilst in the same time period the proportion of all new HIV diagnoses made in the South East has risen from 8% to 12% and in the Eastern region the proportion has increased from 3% to 9%.

The North West region has the third largest number of HIV diagnoses in the UK, accounting for 6% of all new diagnoses in 2002.

The number of reports in England has risen by 54% from 2,544 in 1992 to 3,937 in 2002. Similarly, there has been a 53% rise in Scotland (from 132 diagnoses in 1992 to 202 in 2002).

Reference: CDR Weekly.

AIDS and HIV infection in the United Kingdom: a monthly report. 6 January 2003.

Link: PHLS CDR Weekly
http://www.phls.co.uk/publications/cdr/pages/hiv.html

Trizivir-only arm closed in PI-sparing, naïve therapy trial

Simon Collins, HIV i-Base

Important interim results from a Phase III, randomised, double-blind comparison of three protease-inhibitor-sparing regimens for the initial treatment of HIV infection (AACTG Protocol A5095)

A large randomised US trial (ACTG 5095) comparing triple nucleoside therapy AZT/3TC/abacavir (Trizivir) to two efavirenz containing regimens in almost 1,150 treatment naïve patients has closed the triple-nucleoside arm on the recommendation of the studies data and safety monitoring board (DSMB) due to almost double the incidence of virological failures.

The triple-nucleoside AZT/3TC/abacavir (Trizivir) arm was inferior to efavirenz/AZT/3TC and to the four-drug combination of efavirenz/AZT/3TC/abacavir with patients experiencing virologic failure earlier and more frequently. The data met pre-specified guidelines for stopping this one arm of the study based on virologic failure which was defined as plasma HIV RNA level above 200 copies/ml at least four months after starting study treatment.

At baseline, the median CD4+T cell count was 238/mm 3 ,and the median viral load was 78,825 c/mL, with 57% of subjects having HIV-1 RNA<100,000 c/mL and 43% >100,000 c/mL. After an average of 32 weeks on study, a total of 167 study volunteers experienced virologic failure: 21% in the group receiving ABC/3TC/ZDV versus 10% in the other two groups combined. Virologic failure occurred sooner and more often in those receiving ABC/3TC/ZDV alone, regardless of their initial viral load (whether above or below 100,000 copies/mL, p<0.001for both groups). Although data on CD4+ T cell counts were not available at the time of the interim analysis, the DSMB felt that they would not reverse the outcome.

In a post-review analysis the estimated risk of virologic failure (confirmed HIV RNA >200 c/mL) in those receiving ABC/3TC/ZDV with HIV RNA <200 c/mL was about 7% over three months, compared to 3.5% for subjects on the combined EFV-containing arms.

The NIAID letter to healthcare providers states: “Although we are confident of these findings, they have not been presented at a scientific meeting, peer reviewed, or published. These results will be submitted to the upcoming International AIDS Society meeting in Paris (July 2003), and further analyses (eg, CD4+ T cell count and adherence data) will be forthcoming... It is important to consider this interim study finding in the context of published results, particularly those from prior studies that investigated either triple nucleoside regimens or EFV-based regimens. The risk of virologic failure is clearly an important factor in selecting an initial antiretroviral regimen. Other factors such as safety, toxicity, adherence, preservation of future treatment options, access, cost, and other issues also remain important in selecting the optimal first regimen for an individual patient.”

Additional information about the study design and interim analysis are available on the National Library of Medicine Web site at

http://www.nlm.nih.gov/databases/alerts/clinical_alerts.html

and on NIAID’s Division of AIDS Web site at

http://www.niaid.nih.gov/daids/default.htm

Source: National Institute of Allergy and Infectious Diseases (NIAID).

C O M M E N T

These finding are of concern due to the fact that higher incidence of failure was reported across a wide range of baseline viral load levels, and not just at the higher levels above 50-100,000 copies/ml for which triple-nucleoside regimens are currently not recommended?

If awareness of the importance of adherence is now more widely appreciated among patients, these findings could more accurately reflect the differences in potency that were often obscured in earlier studies of Trizivir, when triple nucleoside therapy was compared to more complicated protease-based regimens. Also, in order to assure double-blinding of all study drugs, each patient took two pills each morning and five pills each evening, effectively negating the inherent benefits of a low pill burden with Trizivir?

As supported by other GSK studies, Trizivir may still be more cautiously and appropriately used to provide solid, tolerable, potent, pharmacologically forgiving and four-drug combinations with a low pill burden, as in the third arm of this study?

Reduced testosterone levels in HIV-positive women

Polly Clayden, HIV i-Base

A paper from Massachusetts General and Harvard Medical School published in Clinical Infectious Diseases investigates the relationship between reduced androgen levels and antiretroviral regimen amongst HIV-positive women with low weight or weight loss.

Research into sex-specific and hormonal factors in women either with or without HIV is scarce. There are data from the pre-HAART era to suggest that women with HIV have reduced androgen levels and more recently that reduced levels in this

population may be caused by altered androgen metabolism. In contrast to androgen deficiency in men, androgen deficiency in women and in turn the contribution this may make to their general health and well being, particularly with respect to weight loss, fatigue and decreased functional status has not been well characterised.

This study investigates hormone levels in 69 HIV-positive women participants with AIDS wasting syndrome screened for a testosterone intervention study with 25 age, ethnicity and BMI-matched uninfected women as control subjects. Women were excluded from screening if they had used growth hormone, systemic corticosteroids, megastrol acetate, estrogens, androgens or any hormonal products that could affect androgen levels up to three months before entering the study or if they had switched their antiretroviral regimen up to six weeks before.

Participants were asked their pre-illness maximum weight and were stratified according to their current menstrual status and their height and weight measured. Antiretroviral history was also obtained from HIV-positive women.

Serum samples were obtained during visits scheduled independently to the menstrual cycle and time of day and free testosterone levels determined. All samples obtained from the same subject were tested in duplicate.

The normal range for total testosterone concentration in adult women is 10-55ng/dL (0.4-1.9n*M*). The normal ranges for total testosterone (n=215) and free testosterone (n=141) were determined for healthy subjects tested during the course of the day and also with regard to menstrual cycle. Testosterone levels were compared among HIV-positive women by menstrual status – eumenorrheic (normal menstrual function) or not and by weight loss of >10% from pre-illness maximum and antiretroviral regimen.

HIV-positive women had low weights, with a BMI of 21.0+- 3.0kg/m2. Subjects had lost a mean of –17.6%+-9.7% from their pre-illness maximum and more HIV-positive women had a BMI of <205kg/m2. Seventy five percent of HIV-positive subjects were using antiretroviral therapy and 49% were using HAART (triple therapy including two nucleosides and either a PI or NNRTI).

Total and free testosterone levels were reduced in the HIV women compared to the controls. Free testosterone levels were less than the normal range in 49% of HIV-positive subjects but only in 8% of control subjects, but only 26% of HIV-positive women had total testosterone levels that were less than the normal range.

Free testosterone levels were compared by disease and menstrual status and by various weight and antiretroviral regimen variables in the HIV-positive women and significant differences in free testosterone levels were seen in the comparison arm by percentage of weight loss.

Fifty-eight percent of the patients with weight loss of >10% versus 24% of subjects with weight loss of <10% of body weight had a free testosterone level that was less than the normal range. Free testosterone levels were significantly higher in eumenorrheic subjects. But no differences in free testosterone levels were seen in comparisons by antiretroviral use or by HIV disease status.

The investigators also found that among HIV-positive women free testosterone levels correlated with age, length of HIV infection and percentage of change in weight but not weight itself. They also reported that among the eumenorrheic group (n=39) greater numbers of women had low free testosterone levels in the follicular phase (the first seven days of cycle n=14, 71.4% had levels below the normal range) than in other phases of the cycle.

The investigators report: “Our data demonstrate severely reduced testosterone levels in HIV-infected women with weight loss of >10% of pre-illness maximum weight. In contrast, other weight parameters, including historical low weight and percentage of ideal body weight, as well as use of antiretroviral medication, did not contribute significantly to testosterone levels in this population. Menstrual status did appear to correlate with serum free testosterone levels but did not remain a significant predictor in multivariate modeling.”

They also noted: “In this study, we demonstrated the relationship between weight loss and androgen levels in HIV-infected women. A large percentage of HIV-infected women with significant weight loss have reduced androgen levels, even in the era of HAART. Determination of the functional consequences of androgen deficiency and the role of physiological androgen replacement will be important in this population.”

Ref: Huang JS, Wilkie SJ, Dolan S et al Reduced testosterone levels in Human Immunodeficiency Virus-infected women with weight loss and low weight. Clinical infectious diseases 2003;36:499-506.

Fosamprenavir expanded access programme available in UK

Simon Collins, HIV i-Base

A named patient programme (NPP) for fosamprenavir (GW908, Telzir), a pro-drug version of amprenavir, has been announced by GlaxoSmithKline for patients in the UK.

Access criteria are for all patients for whom a regimen containing a protease inhibitor with a low pill count offers the best therapeutic option, in the judgment of the prescribing physician. This may include patients who have previously experienced

failure on a PI, are currently taking amprenavir, as well as those for whom adherence is a major problem. There are no CD4 or viral load count criteria.

The usual adult daily dose for fosamprenavir is either 2 x 700mg tablets plus 2 x 100mg capsules of ritonavir taken once daily or split to 1 x 700mg plus 100mg ritonavir twice daily.

The charge for a pack of 70 x 700mg tablets of fosamprenavir is £319.73. Ritonavir is not supplied with this programme.

Further details, information packs containing current clinical trial results and application forms for the NPP can be obtained by contacting Louise Walton, clinical study manager on 020 8990 3363 or Jan Williams, HIV named patient administrator on 020 8990 2317. Completed applications then need to be faxed to 020 8990 2078.

In order to facilitate patient management, therapeutic drug monitoring is available to patients in this programme through the TDM laboratories at Liverpool University. Further details of this service are available by contacting Sara Gibbons on 0151 794 5553, by email at hivgroup@liv.ac.uk or visiting the Liverpool website at http://hiv-druginterractions.org

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C O M M E N T

Results from the Phase III studies for fosamprenavir were presented at the Retrovirus conference and are reported earlier in this issue of HTB.

It is very encouraging to note that GSK has included a sponsored therapeutic drug monitoring programme through the Liverpool TDM service. As drug levels remain a concern with protease inhibitors, even in some patients using ritonavir-boosted regimens. Also, fosamprenavir is likely to be included in regimens for which there is limited drug interaction data but where interactions are likely, such as dual and triple-PI containing combinations.

European approval of adefovir for hepatitis B

Simon Collins, HIV i-Base

The European Commission granted marketing authorisation for adefovir dipivoxil 10 mg (Hepsera™) in all 15 member states of the European Union on 11 March 2003. Adefovir is indicated in Europe for the treatment of chronic hepatitis B in adults with compensated liver disease with evidence of active viral replication, persistently elevated serum alanine aminotranseferase (ALT) levels and histological evidence of active liver inflammation and fibrosis; or decompensated liver disease.

Adefovir is administered as a once-daily 10mg tablet and works by blocking HBV DNA polymerase, an enzyme involved in the replication of the virus in the body. The US Food and Drug Administration (FDA) cleared adefovir for marketing in the United States in September 2002.

The early access programme in France, Italy, Greece, Spain, Portugal, Germany, the United Kingdom, Canada and Australia, which Gilead says has provided adefovir to over 1,600 patients since June 2002, will continue until the drug is commercially available to patients in these countries. For more information regarding the Early Access Programme for adefovir in Europe, call +33 1 44 90 34 75.

Source: Gilead PR

Links:
http://www.gilead.com/

Full prescribing information (pdf download):
http://www.hepsera.com/pdf/hepsera_pi.pdf

European activists highlight importance of gender based research: women experience HIV differently

Differences between men and women need to be pertinently highlighted in the process of making new HIV medicines available to the public. This is the demand of the European Community Advisory Board (ECAB), which held a three-day meeting in Brussels in February exclusively dedicated to women and regulatory issues in the development and approval of HIV-treatments.

Founded in 1997, the ECAB is a Working Group of the European AIDS Treatment Group (EATG), a pan-European non-profit organisation comprising more than 100 members from virtually every country of the new and the old Europe. The ECAB is involved in treatment activism, community-based research and treatment training programmes at national and international levels.

Within the ECAB, 40 members are working together with pharmaceutical companies, researchers, investigators and the European HIV-positive communities to improve the research and development of new agents to combat HIV, the

understanding of their complications and the access to therapy for people living with HIV/AIDS all over Europe.

More than 30 Pan-European treatment activists worked together with research experts and representatives of pharmaceutical companies and the European Agency for the Evaluation of Medicinal Products (EMEA). The focus of the meeting was to identify current gaps concerning sex and gender in the clinical evaluation of drugs and to provide suggestions for the 'Note for Guidance on the Clinical Development of HIV-Medicinal Products' issued by the EMEA.

"Even though globally more than 50% of HIV-positive people are women, HIV medicine is tested mainly in men's bodies," explained Heidemarie Kremer, EATG and ECAB member. "The numbers of women enrolled in clinical trials should be statistically relevant to the patient populations in which the drugs will be used in order to draw meaningful conclusions about their efficacy and safety in different groups," she added.

Although HIV-therapy has dramatically reduced the number of deaths due to AIDS in industrialised countries, lack of knowledge about sex and gender differences in response to therapy has led to severe life-threatening side effects and death. In Europe, women account on average for only 12% of the participants in clinical trials. "HIV trials are not enrolling enough women to answer gender-specific questions. In order to avoid therapies failing women, we need more gender based research to optimise treatment for everybody", said Kremer.

Source: EATG PR Contacts: HeidemarieKremer@yahoo.de

Links:
http://www.eatg.org

Roche prices enfuvirtide (T-20) at €18,980 a year – making it the most expensive HIV drug yet

Graham McKerrow HIV i-Base

Roche has priced its new HIV drug enfuvirtide (T-20, Fuzeon) at ¤52 a day, or ¤18,980 (£12,951) a year, which makes it the most expense anti-HIV drug to date. The price has fuelled controversy about the cost of HIV treatments, although the company says it has impressive cost effectiveness data that it will publish soon.

Roche blamed the high price on the complexity of the manufacturing process which involves more than 100 production steps, compared to eight to ten steps for most drugs. Making enfuvirtide involves threading 36 amino acids one by one onto three separate molecular fragments, which are then assembled to create a fragile chain. It requires 45kg of raw materials to make 1kg of the drug.

The price of the twice daily injections was greeted with criticism from American activist groups. The AIDS Treatment Activists Coalition said enfuvirtide would be "at least four to five times higher" than other HIV drugs which could prove prohibitive for people on Medicaid and AIDS Drug Assistance Programmes. The price is not expected to be an issue in the UK, where the National Health Service is thought willing to meet the costs.

Enfuvirtide is already available to some patients through an Early Access Programme and the new price is for a special pre-licence sales programme. The European Medicines Evaluation Agency is expected to licence the drug later this year. Marketing authorisations are also being sought in Australia, Canada, and Switzerland. A licence was granted in the USA in March. Roche will then announce its price in different markets, although the company said those prices would be close to ¤52 a day.

Enfuvirtide is particularly useful for people who have multi-drug resistant HIV or who are intolerant of other drugs. It can act against resistant virus because it is the first of a new class of drugs, fusion inhibitors, that tackles HIV in a different way. Other drugs work inside the cell to stop replication, but enfuvirtide is designed to block HIV from entering healthy T-cells.

David Reddy, head of Roche's HIV business, said the cost of bringing enfuvirtide to market was $600 million, not including marketing expenses. He added: "It's something new and something that can bring hope to some patients. And if you consider this in the balance, I think pricing will not be a big issue."

While some observers are critical of the high costs, others say the company has to recoup a considerable investment and pay for a complicated production process and it has to do so from a small patient population, because enfuvirtide is only suitable for a minority of people with HIV, and it has to recoup its costs before competitor drugs are launched in perhaps two years. Enfuvirtide is an inconvenient drug, which can cause discomfort when administered.

Links:

Roche Press Release: European price announced for AIDS drug Fuzeon
http://www.roche.com/med-corp-detail-2003?id=939&media-language=e

AIDS Treatment Activist Network: Papers and community discussions about US pricing
http://www.atac-usa.org/Roche.html

FDA Approves First Drug in New Class of HIV Treatments
http://www.fda.gov/bbs/topics/NEWS/2003/NEW00879.html

New England Journal of Medicine
http://content.nejm.org/cgi/content/abstract/NEJMoa035026v1

Project Inform Press Release:
http://www.projectinform.org/news/03_03fuzeonpr.html

ACT UP Creates "Fuzeon Graveyard" at Roche HQ
http://www.ultinet.net/~kfo/roche.html

C O M M E N T

The emmergency access programme (EAP) for T-20 is due to finish at the end of March 2003. A few unfilled places may remain available for a short time until T-20 is licensed.

Any HIV centre in England, Wales and Northern Ireland can apply for EAP access for any patient meeting the criteria (vL >10,000 and CD4 count <100, currently on treatment). Having a viable background i.e. 1-2 active drugs to combine with T-20 is very important.Contact Dr Leroy Benons, Medical Advisor HIV, Roche. Tel: +44 (0) 1707 367515. Mobile: + 44 (0) 7769 935741. Email: leroy.benons@roche.com

As HTB went to press, FDA approval was granted in the USA and the EMEA expressed a positive opinion indicated European approva within the next 1-3 months.

European positive opinion for tenofovir for first line therapy

The Committee for Proprietary Medicinal Products (CPMP), the scientific committee of European Medicines Evaluation Agency (EMEA), adopted a positive opinion to extend the indication of tenofovir disoproxil fumarate (Viread) to include the product's use in antiretroviral-naive HIV-infected patients. The label extension is based on 48-week results from Gilead's Study 903 in 600 treatment-naive patients infected with HIV. The European Commission will consider granting of the label extension on the basis of the CPMP's recommendation. Gilead anticipates a decision by the European Commission in the next few months.

The indication recommended by the CPMP is for tenofovir to be taken in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults over 18 years of age. This indication is based on the demonstration of benefit of tenofovir from results of one study in treatment-naive patients, including patients with a high viral load (>100,000 copies/mL), and studies in which tenofovir was added to stable background therapy (mainly tritherapy) in antiretroviral pre-treated patients experiencing early virological failure (<10,000 copies/mL, with the majority of patients having <5,000 copies/mL).

Tenofovir was first authorised for sale in the European Union in February 2002. On the basis of the safety and efficacy data submitted for tenofovir in the original submission, which only included data from studies of the drug in treatment-experienced HIV infected patients, the committee recommended authorisation under exceptional circumstances. The indication recommended by the CPMP was for tenofovir taken in combination with other antiretroviral agents in HIV infected patients over 18 years of age experiencing early virological failure. Full approval for the indication in treatment-naïve patients is expected within four months.

Source: Gilead PR
http://www.gilead.com/wt/pr/recent_news

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

Vaxgen announces disappointing results from first large international vaccine trial

Bad news and good news on AIDSVAX Phase III trials results

Vaxgen Inc has announced the initial results from its three-year Phase III trials of AIDSVAX, a recombinant gp120 HIV vaccine. The reduction of HIV infection within the vaccinated population as a whole was not statistically significant. However, there was a statistically significant reduction of HIV infection in vaccinated non-white, non-Hispanic volunteers. More importantly, protection in this subgroup appeared to correlate with a higher level of neutralising antibodies.

Phillip Berman, VaxGen's senior vice president of Research and Development and inventor of the vaccine remarked that this is the first time they had specific numbers that suggested that a vaccine had prevented HIV infection in humans. He added that they were

not sure why some subgroups of volunteers had a better immune response, but that the preliminary data indicated that a vaccine constructed with the virus' surface protein could elicit neutralizing antibodies that correlated with protection of infection.

AIDSVAX B/B Trial Statistics

No. of volunteers to complete 3 immunizations:	5,009
Placebo recipients:	1,679
AIDSVAX B/B recipients:	3,330
White volunteers:	4,185
Hispanic volunteers:	326
Non-white volunteers (Black, Asian, Other):	498
Black volunteers:	314
Annual study infection rate	2.7%

Approximate Efficacy (after at least 3 primary doses)

All volunteers:
3.8% (p-value = 0.76; confidence interval: -23% to 24%)
Non-white volunteers:
67% (p-value < 0.01; confidence interval: 30% to 84%)
Black volunteers:
78% (p-value < 0.02; confidence interval: 29% to 93%)

Source:
http://www.aaas.org/

GMHC criticises Vaxgen for obfuscation of trial results of its AIDS vaccine

Gay Men's Health Crisis (GMHC), the USA's oldest AIDS service organisation, has criticised VaxGen, the maker of the AIDS vaccine candidate, AIDSVAX, for obfuscation of its trial results. Despite showing no effect overall in protecting against infection with HIV, the company highlighted a subset of results that seemed to show efficacy in African-Americans and Asians.

GMHC said it looks forward to the day when HIV will be a preventable disease and is a strong supporter of AIDS vaccine research, including VaxGen's research efforts. However, the conduct of vaccine research must be held to the highest standards of ethics and accuracy, as millions of lives depend on the results of these scientific studies, the organization said in a statement.

"Subset analyses are problematic in the best of cases. With small numbers of African-Americans and Asians in the trial and wide confidence intervals associated with the results, making any statements about efficacy in this subpopulation is grossly premature," said Gregg Gonsalves, Director of Treatment and Prevention Advocacy at GMHC. VaxGen's assertions of its vaccine's efficacy among blacks are based on 13 infections in this population in a trial of more than 5,000 participants. The assertions about efficacy among Asians are based on only four HIV infections in the study.

GMHC is particularly worried that the 'spin' of these results will sow confusion in communities particularly at risk in the United States, specifically African-Americans. "VaxGen has not proven that this vaccine is effective among African-Americans or Asians, yet preliminary press reports are claiming that this may be the case," said Ana Oliveira, GMHC's Executive Director. GMHC is asking the company to clarify its statements on the subset analysis of African-Americans and Asians, particularly its claims of efficacy for this population, and is calling on the media to look more closely at the data before drawing any conclusions.

GMHC also has concerns that VaxGen's interpretation of its results will also provide false hopes in Africa and Asia, where the rates of HIV infection are the highest in the world, and which will be the major market for AIDS vaccines. The organization said it is important to note that the vaccine in this study did not use strains of HIV prevalent in Africa and Asia. GMHC fears that claims of partial protection for African-Americans and Asians, by extension, could imply that Africans and Asians living outside the United States could see some protection from this vaccine. GMHC is urging the company not to overstate the promise of its product based on scant and inconclusive data.

Source: GMHC press release

Links:

VaxGen held a briefing to announce findings from clinical trials of the vaccine AIDSVAX regarding its ability to prevent people from becoming infected with HIV. AIDSVAX is the first AIDS vaccine to enter large-scale human clinical trials. The archived audiocast and accompanying slide presentation

are available by clicking here. (NOTE: Access to audiocast requires free registration.) Also an Interview with Chris Collins, executive director, AIDS Vaccine Advocacy Coalition (video):
http://www.kaisernetwork.org/health_cast/hcast_index.cfm?display=detail&hc=789

VaxGen Press Release:
http://www.vaxgen.com/pressroom/index.html

C O M M E N T

These are obviously disappointing results, and in the attempt by Vaxgen to salvage something from this study it is unfortunate that this controversy over the presentation of racial differences has somewhat soured the significant logistic difficulties of running a large scale international vaccine study. Results from the Thailand study are expected in the next few months but this candidate has fallen far short of the reduced efficacy that the company hinted at over the last year, and the increases in stock value following each of those announcements has now fallen.

Antibiotic-resistant skin infections spreading among gay men, also in prisons

John S. James, AIDS Treatment News

In the last few months doctors have seen a large increase in aggressive, antibiotic-resistant 'staph' (Staphylococcus aureus) skin infections in gay men in some areas — and a separate epidemic in certain prisons. Symptoms include boils or blisters; treatment can be difficult, and sometimes requires hospitalisation. One HIV doctor in Los Angeles who used to see about one case a year is now seeing two a week. In the past this infection occurred mainly in hospitals.

Physicians should note a 1 February 2003 review in the British Medical Journal ("Old Drugs for New Bugs," BMJ 2003; volume 326, pages 235-236) on evidence for the value of older antimicrobials for resistant bacteria, including staph. It suggests using co-trimoxazole (Bactrim or other brand names) as an alternative to vancomycin for resistant S aureus (also called MRSA). In one case co-trimoxazole was used successfully after a patient had failed the new and very expensive antibiotic linezolid (Zyvox). The article is at:

http://bmj.com:80/cgi/content/full/326/7383/235?maxtoshow=?eaf

A fact sheet by the US CDC, revised February 7, 2003, is at:

http://www.cdc.gov/ncidod/hip/aresist/mrsafaq.htm

Source: AIDS Treatment News

ON THE WEB

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

Conference reports and links:

Report from Sixth ICDTHI – Glasgow, November 2002. IAPAC January 2003

Mark Mascolini

Heavy lifting in Glasgow (wherein HIV researchers uncrate some Clydeside surprises)

Report from Sixth International Congress on Drug Therapy in HIV Infection, 17-21 November 2002, Glasgow, in IAPAC Monthly.

http://ww2.aegis.org/pubs/iapac/2003/IA030101.html

10th Conference on Retroviruses and Opportunistic Infections (CROI)

Links to further online coverage:

HIVandHepatitis.com

http://www.hivandhepatitis.com/2003icr/10thretro/main.html

including:

- Challenges in Evaluating HIV Vaccine Candidates: A Symposium
- Nevirapine Versus Efavirenz: The 2NN Study
- Resistance Testing Plays an Increasingly Important Role in HIV Therapy Decisions
- Drug-Resistant HIV Persists after Treatment Interruption, but Suppression Possible
- Protease Inhibitors Linked to Increased Stroke Risk
- Genital Tract HIV Viral Load Fluctuates During the Menstrual Cycle
- HIV/HCV Co-infected Patients Are at Increased Risk of Hepatic Decompensation
- Immune Reconstitution Is Not Associated with Liver Disease Progression

Medscape

Over 20 individual news reports and expert commentaries. Longer overview articles to be published online shortly.

http://www.medscape.com/viewprogram/2221

NATAP

Full Retrovirus coverage, 45 reports so far (lipodystrophy, STIs/interruptions, Hep C & B, acute HIV, reservoirs etc. More coming.

http://www.natap.org/2003/Retro/ndxRetro.htm

Including:

- Entry Inhibitors, the how and why of new agents at Retrovirus: an update
- “908”: New formulation of amprenavir
- Tipranavir report: phase II dose study
- New HIV antiretroviral drugs: atazanavir resistance, T-1249 for T-20 resistance, plus more
- New HIV drugs at retrovirus 2003

HIV InSite

Site providing many useful summaries

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

AIDS Treatment News no. 399

Conference coverage and links including first of a 2-part interview with Dr Cal Cohen.

http://www.aids.org/immunet/atn.nsf/page

Clinical Care Options for HIV

New site in association with Northwestern University Medical School offering coverage that includes bullet text, tables, and figures from the studies covered.

The Clinical Care Options for HIV Conference Coverage program is free but require one-time registration.

http://clinicaloptions.com/hiv/croi2003>http://clinicaloptions.com/hiv/croi2003

Link to Clinton speech at opening ceremony

http://www.clintonpresidentialcenter.com/retroviral_2003.html

Medcape Online Articles:

Journal articles in full

From AIDS:

Recent Observations on HIV Type-1 Infection in the Genital Tract of Men and Women

http://www.medscape.com/viewarticle/449876

Effects of Interleukin-2 Therapy Combined With Highly Active Antiretroviral Therapy on Immune Restoration in HIV-1 Infection: A Randomised Controlled Trial

http://www.medscape.com/viewarticle/449481

Candidate HIV/AIDS Vaccines: Lessons Learned From the World's First Phase III Efficacy Trials

http://www.medscape.com/viewarticle/448600

HIV RNA in Plasma Rebounds Within Days During Structured Treatment Interruptions

http://www.medscape.com/viewarticle/448601

From The AIDS Reader:

Update on Antiretroviral Drug Resistance Testing: Combining Laboratory Technology With Patient Care - John W. Wilson, MD

AIDS Read 13(1):25-38, 2003

http://www.medscape.com/viewarticle/448717

A Solitary Brain Lesion in a Patient With AIDS - Susan C. Ball, MD, MPH

http://www.medscape.com/viewarticle/448708

Recurrent Clinical Hepatitis in an HIV-Positive Patient With Hepatitis B Virus Pre-Core Mutant Infection

AIDS Clinical Care

http://www.medscape.com/viewarticle/449286?mpid=10225

From Journal AIDS:

http://www.medscape.com/viewpublication/878_toc?vol=32&iss=2

The Efficacy of Lopinavir in Individuals Experiencing Protease Inhibitor Failure

Once-Daily Saquinavir-sgc Plus Low-Dose Ritonavir (1200/100 mg) in Combination With Efavirenz: Pharmacokinetics and Efficacy in HIV-Infected Patients With Prior Antiretroviral Therapy

Results of a Phase 2 Clinical Trial at 48 Weeks (AI424-007): A Dose-Ranging, Safety, and Efficacy Comparative Trial of Atazanavir at Three Doses in Combination with Didanosine and Stavudine in Antiretroviral-Naive Subjects

Newsletters and Reports:

BETA - Winter 2003

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

Salvage Therapy - *Simon Collins*

http://www.thebody.com/sfaf/winter03/salvage.html

HIV and Hepatitis Coinfection – *Liz Highleyman*

http://www.thebody.com/sfaf/winter03/coinfection.html

The many faces of Human Growth Hormone – *Bob Roehr*

http://www.thebody.com/sfaf/winter03/hgh.html

amfAR Global link directory

Two excellent articles by Anne-christine d'Adesky on growing access to ARV treatment in Cuba and Morocco.

Cuba Fights AIDS Its Own Way

http://www.amfar.org/cgi-bin/iowa/td/feature/record.html?record=80

Morocco's Bold Experiment: Treatment as Prevention

http://www.amfar.org/cgi-bin/iowa/td/feature/record.html?record=76

amfAR Treatment Insider - March 2003

Retrovirus coverage from amFAR

http://199.105.91.6/treatment/HIV+/EN0603.pdf

Back issues available online in English, French and Spanish

http://199.105.91.6/treatment/HIV+/insidermenu.html

The price of resistance: virus hunters chase a moving target

Dave Gilden

http://www.amfar.org/cgi-bin/iowa/td/conf/record.html?record=85

Treatment Interruptions Still Have Their Admirers

Gretchen Schmelz Armstrong

http://www.amfar.org/cgi-bin/iowa/td/conf/record.html?record=84

Vaccine Research at a Crossroads

Kristen Kresge

http://www.amfar.org/cgi-bin/iowa/td/newsan/record.html?record=83

PRN Notebook: March 2003

Pre-press articles

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

View From the Pipeline: The 2003 Review of Experimental Antiretrovirals - *Scott Hammer, MD*

Metabolic & Morphologic Complications in HIV Disease: What's New? - *Donald P. Kotler, MD*

Youth and HIV:The Epidemic Continues - *Donna Futterman, MD*

GMHC Treatment Issues – January/February 2003

http://www.gmhc.org/living/treatment/ti1702/ti1702.html

ur Biology is Social: science, power and surprise

In Their Own Words: The Current State of Women and HIV

Salvage Strategies and STI at the 10th Annual Retrovirus Conference

Global Treatment Update: TAC on the march and more

Boulder Blues: Lei Chou seeks the Rocky Mtn. source of T-20

Notes on HIV Drugs in Development

News from Retrovirus and elsewhere

Other links:

New HIVinSite Knowledge Base chapters

Molecular Insights Into HIV Biology

Warner C. Greene, MD, PhD, and B. Matija Peterlin, MD

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

Surgery in Patients with HIV

William P. Schecter, MD, and Peter Stock, MD

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

HIV Transmission and Prevention in Prisons

Elizabeth Kantor, MD

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

Epidemiology of HIV/AIDS in the United States

Dennis H. Osmond, PhD, published 3/03.

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

Coinfection with Hepatitis Viruses and HIV

Mandana Khalili, MD, updated 3/03.

http://hivinsite.ucsf.edu/InSite.jsp?page=kb-05-03-04

New website for information on herbs and supplements

Information on herbs and supplements referenced to scientific literature is now available on the website for the Integrative Medicine Service at Memorial Sloan-Kettering Cancer Center, New York.

Summarised information on clinical summary; scientific, brand and AKA names; purported uses; constituents; mechanism of action; contraindications; adverse reactions; drug interactions; literature summary; critique and references is provided for around 300 herbs and supplements.

http://www.mskcc.org/aboutherbs

HHS Clinical Guide on Palliative Care of HIV/AIDS Patients

http://hab.hrsa.gov/tools/palliative/

A guide for clinicians offering 'experience-based' advice and guidelines regarding the provision of palliative services for people with HIV/AIDS.

The guide is organized into five parts, each focusing on different aspects of palliative care, including how to deal with the management of advanced HIV; psychosocial, cultural and ethical issues surrounding the disease; and end-of-life care.

PUBLICATIONS AND SERVICES FROM i-BASE

New i-Base web address

Our web address has changed slightly and is now http://www.i-Base.info

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

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

Portuguese translation of 'Introduction to Combination Therapy'

Introdução à Terapêutica de Combinação

This essential non-technical patient guide to combination therapy has now been translated into Portuguese. It is available to download as a pdf file and reprint free from the i-Base website:

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

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

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

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

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

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

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

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

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

For additional free copies, including bulk orders see below

UK-Community Advisory Board reports and presentations

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

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

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

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

Genetics, resistance and HIV – by Professor Clive Loveday

Approaches to Salvage Therapy – by Dr Mike Youle

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

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

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

Guide to Avoiding and Managing Side Effects

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

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

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

Positive Treatment News (PTN)

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

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

HIV Treatment Bulletin (HTB)

This is the journal you are reading now; a review of the latest research and other news in the field. HTB is published 10 times a year on our website (http://www.i-base.info) and in a printed version. The printed version is available at most HIV clinics in the UK and is available free by post: see below for details.

Treatment information request service

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

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

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

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