d4T+ ddI for Individuals with Prior Treatment-Experience

The Pollard study of d4T+ddI (preliminary results reported on our web site) explored different dosing regimens of these two drugs for only treatment-naive individuals. The following results of two small pilot studies using the combination of d4T+ddI were reported at the conference for individuals with prior reverse transcriptase inhibitor experience (RTI).

A Pilot Study of the Combination of d4T and ddI in Patients with < 350 CD4 and Who are not Eligible For Treatment with AZT
authors: J Durant, V Rahelinirina, B Delma, F Dupre, MF Carmagnolle, P Halfon, P Ngo Van,, P Dellamonica--Hopital de l'Archet, Nice, France; Bristol-Myers Squibb, France; Alphabio, Nice, France

Twenty-five individuals were treated with the standard doses of both drugs. Eighteen participants were experienced with AZT, 3 with ddI, 2 with ddC, 1 with AZT/ddC and one had no prior treatment-experience.

Mean baseline values: CD4--116, range 15-315; viral load--5.3 log (199,790 copies/ml), range 2.7-5.9 log (500-794,400 copies/ml).

Preliminary Mean changes in HIV RNA and CD4:

	mean viral load down	< detectable (500 copies)	mean CD4 up
4 weeks	-1.0	7 (33%)	+57
12 weeks	-0.9	7 (33%)	+45
24 weeks	-0.7	4 (33%)	+38
	n=13	n=17	n=17

No AIDS defining events were noted

4 patients discontinued:

- 2 due to grade 2 peripheral neuropathy- complete recovery one month after d4T stopped
- 1 due to grade 3 neuropathy- complete recovery three months after d4T stopped
- 1 patient with asymptomatic grade 3 amylase- complete recovery I month after therapy

The authors concluded that the therapy was well-tolerated in this advanced pretreated group, with a substantial and sustained benefit out to 24 weeks.

Antiviral Effect and Safety of ddI/d4T Combination Therapy in HIV-Infected Subjects: Interim Results of a Pilot Trial
authors: F Raffi, S Auger, E Billaud, JM Besnier, JM Chennebault, C Michelet, P Berre, and others--France

Sixty individuals who had < 3 months prior RTI-experience with the exclusion of ddI and d4T received open label d4T (40 mg bid) and ddI (200 mg bid).

Prior treatment experience:

- AZT- median 25 months
- ddC- median 11 months

Mean baseline CD4 and HIV RNA: 217 cells, and 5.0 log (100,000 copies/ml)

Preliminary Mean Changes in CD4 and Viral Load (undetectable is <500 copies)

	mean HIV RNA down	> 1 log down	> 2 log down	< 500 copies	mean CD4 up
4 weeks	-1.0 log	18 (53%)	7 (21%)	5 (15%)	+71
	n=34	n=34	n=34	n=34	n=53
12 weeks	-1.0 log	18 (51%)	7 (20%)	3 (9%)	+41
	n=35	n=35	n=35	n=35	n=44
24 weeks	-1.0 log	14 (42%)	4 (12%)	5 (15%)	+37
	n=33	n=33	n=33	n=33	n=33

Adverse events: total 22/60 (37%)

- grade 2 peripheral neuropathy - 3 at weeks 12, 18, and 19
- 2 discontinued therapy before week 24
- all 3 improved off drug

Paresthesia with subnormal neurological exam: 4 at weeks 3, 9, 11, and 12

- reduction in d4T dose in one (80 to 60 mg daily), regression in parasthesia
- 3 others continued therapy

GI (abdominal pain, flatulence, diarrhea): 10

- possible relationship to therapy in 3/10
- no modification of therapy required

LFT elevations (> 5x uln): 3

- week 12: d4T+ddI interruption
- week 24: d4T+ddI interruption
- week 18: continue drug; improvement at week 24

Withdrawal before week 24: 6/60 (10%)

- side effects: 4
- compliance : 2

CSF Penetration:

Bristol-Myers says--
"After a single d4T 40 mg dose in 12 healthy subjects, CSF and simultaneous plasma concentrations were determined. Mean CSF concentration was 40% of mean simultaneous plasma concentrations. Mean CSF concentration 4 to 5 hours post dose was 63.1 ng/ml (0.28 um). These results demonstrate that d4T does penetrate into the CSF and produces CSF concentration which exceed the ED50 of HIV clinical isolates."

At the 4th Retrovirus Conference, a research group from Amsterdam presented a small set of data concluding that d4T/3TC should be comparable to AZT/3TC in reducing CSF RNA (see NATAP Newsletter)