d4T + ddI-- for treatment-naive and experienced

Treatment Naive. In April 1997 at the 10th International Conference on Antiviral Research (ICAR) in Atlanta, Dr. Richard Pollard reported an early final analysis of a small open-label study of the double nucleoside combination of d4T+ddI in relatively healthy treatment-naive individuals. Several aspects of this study are interesting: five different dosing combinations of the two drugs were explored including one arm with full dose of both drugs; the viral load reductions were well sustained for the full term of the study, which is 52 weeks; the range of CD4 increases were relatively impressive; and, the combination appeared to be relatively well-tolerated; the incidence of peripheral neuropathy was low but that was defined by Pollard's narrow definition of peripheral neuropathy. An earlier report of study data is available on the NATAP web site.

An appealing aspect for combining these two nucleosides is that both have favorable resistance profiles. Resistance to both d4T and ddI have been relatively slow to develop. The development of specific mutations responsible for d4T resistance have been difficult to identify, but it has not been clearly identified what may be other reasons for d4T failure. (see article on nucleoside resistance in this issue of NATAP Reports).

If choosing a nucleoside therapy you will want to consider your prior treatment-experience, if any; the potential side effects or toxicities of the drugs in question; the potential cross-resistance implications for future treatment options; and, you ought to select what would be your next combination to switch to if the first regimen fails.

The study. Ninety four participants were randomized, 86 received therapy and for purposes of study analysis 66 had baseline viral loads 1,000. All participants were treatment-naive with median baseline CD4 counts of about 330 cells and HIV-RNA of about 25,000 to 31,600 copies/ml (4.4-4.5 log). Participants were randomized to following dose regimens (doses adjusted for weight):

group A- ddI 100 mg/bid + d4T 10 mg/bid;

group B- ddI 100 mg/bid + d4T 20 mg/bid;

group C- ddI 100 mg/bid + d4T 40 mg/bid;

group D- ddI 200 mg/bid + d4T 20 mg/bid;

group E- ddI 200 mg/bid + d4T 40 mg/bid.

The full dose of ddI is normally 200 mg bid and the full dose of d4T is normally 40 mg bid.

Mean changes from baseline in CD4 counts and HIV-RNA (viral load-VL)

	CD4 increase 24 wks	CD4 increase 51 wks	VL decrease 24 wks	VL decrease 51 wks
groups A & B	+85	+60	-1.2 log	-1 log
groups C, D, & E	+85	+160	-1.2 log	-1.3 log

changes viral load are for those with at least 1,000 copies/ml at baseline; while, changes in CD4 are for all participants. At week 51, CD4 data for a total of about 44 participants were available; while at week 51, viral load data were available for about 30 individuals. Both CD4 and viral load values in table were taken by visual observation of line graphs, so are approximations.

The author stated that the viral load and CD4 differences between the two groups in the table are statistically significant. Groups C, D and E included at least one drug at full recommended dose, while group E received both drugs at full dose. Dr. Pollard is recommending full dose of both drugs for use in treatment based on the CD4 and viral load changes and the low incidence of peripheral neuropathy in this group of less advanced and treatment-naive individuals. Persons with more advanced HIV and more treatment-experience tend to develop peripheral neuropathy more easily.

AZT+3TC. It is usually accepted that it is difficult to compare results between studies. But, the NUCA 3001 study sponsored by Glaxo Wellcome examined treatment-naive individuals (< 4 weeks previous AZT use). Those receiving AZT (200 mg 3X/day) + 3TC (150 mg 2X/day) had median baseline CD4 of 364 cells, and median baseline viral load of 4.4 log (about 25,000 copies/ml). Within the first 4 weeks of the study, peak reductions from baseline in viral load were achieved: -1.19 log by the 3TC monotherapy arm (300 mg 2X/day), which returned to a -0.5 log reduction from baseline at week 24; about -1.6 log for those receiving AZT/3TC (150 mg 3TC 2x/day). After 52 weeks for those taking AZT/3TC (150 mg bid), CD4 increases were about 69 cells, and viral load reductions from baseline were about -0.8 log. In a subgroup of 224 study participants with baseline viral load 20,000 copies/ml, the mean maximum reduction was -2.11 log; and, in this group, the percentage of participants with at least one viral load measure, while receiving study treatment, that showed a 2 log or greater reduction was 61%.

Serious Adverse Events. Peripheral neuropathy: 2 cases; one in group A and one in group C. The one in group C developed a grade 3 neuropathy, drug was stopped and restarted 4 weeks later reduced doses (50 mg/bid ddI-20 mg/bid d4T). Diarrhea: 3 cases- one each in groups B, C and D. Abdominal pain: 3 cases- 2 in group D, I in group E. Lipase elevations: 2 each in groups A and D, 3 in group B. Liver enzyme elevations: 3 each in groups A and B, 2 each in groups D and E. Neutropenia: 1 each in groups A, B, and E.

There were no discontinuations from study drugs. Dr. Pollard defined peripheral neuropathy as the development of pain. Less severe symptoms such as tingling or numbness were not defined as neuropathy. As such, Pollard concluded that the

combination is generally well-tolerated. Bristol Myers reports that the combination of d4T+ddI is being evaluated in several other studies exploring a variety of treatment strategies for both treatment-naive and experienced in combinations utilizing protease inhibitors and NNRTIs. On the NATAP web site preliminary data is available from a pilot study of nelfinavir+d4T/ddI.

Treatment-experienced. At the 4th Retroviral Conference in January 1997, the preliminary results of two small open-label studies of d4T+ddI in treatment-experienced individuals was presented. In the first study 25 individuals were treated with the standard doses of both drugs, 18 of whom were experienced with AZT, 3 with ddI, 2 with ddC, 1 with AZT/ddC and one had no prior treatment-experience. Mean baseline CD4 counts were 116 and viral load was 5.3 log (199,790 copies/ml).

Preliminary Mean changes in HIV RNA and CD4:

	mean viral load decrease	**< detectable (500 copies)**	**mean CD4 increase**
4 weeks	-1.0	7 (33%)	+57
	n=21	n=21	n=24
12 weeks	-0.9	7 (33%)	+45
	n=21	n=21	n=21
24 weeks	-0.7	4 (33%)	+38
	n=13	n=17	n=17

Safety. No AIDS defining events were reported and 4 persons discontinued from the study: 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 person developed asymptomatic grade 3 amylase - complete recovery I month after therapy; , although its incidence of occurrence is low, a potential toxicity associated with use of ddI is pancreatitis. Elevations in amylase and lipase (standard blood lab tests) signals concern for this potential.

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

In the second study, 60 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).

Their prior treatment experience consisted of an average of 25 months AZT-experience and 11 months ddC-experience. Their mean baseline CD4 counts 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 decrease	**>1 log decrease**	**>2 log decrease**	**<500 copies**	**mean CD4 increase**
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

Safety: 22/60 (37%) individuals experienced adverse events. Grade 2 peripheral neuropathy- 3 persons at weeks 12, 18, and 19;-2 discontinued therapy before week 24; all 3 improved off drug. Paresthesia (tingling and/or numbness) with subnormal neurological exam: 4 persons at weeks 3, 9, 11, and 12; 1 person reduced their d4T dose (80 to 60 mg daily) but did worse; 3 others continued therapy. Gastrointestinal (abdominal pain, flatulence, diarrhea): 10 persons but only 3 were related to study drugs and there was no modification of therapy required. Liver enzyme elevations (>5x upper limit of normal): 3 persons; 1 at week 12- d4T+ddI interruption; 1 person at week 24- d4T+ddI interruption; 1 person at week 18 continued drugs and improved at week 24. There were 6 persons (10%) who withdrew from the study by week 24: 4 due to side effects and 2 due to non-compliance with taking study drugs.

CNS Penetration. At the Conference in January, a research group from the Netherlands reported data from a small study suggesting that d4T/3TC penetrated the central nervous system or CSF (Cerebral Spinal Fluid) as well as AZT/3TC. The details were reported in NATAP Reports February issue; the issue is available on our web site. It is generally conceded that d4T penetrates the CSF, but there is not enough data confirming this. Bristol-Myers needs to conduct more studies to collect additional data.