National AIDS Treatment Advocacy Project

Stavudine (d4T) and Didanosine (ddI) Combination Therapy in HIV-Infected Subjects: Antiviral Effect and Safety in an On-going Pilot Randomized Double-Blinded Trial

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In January 1996 at the Human Retrovirus Conference, Dr. Richard Pollard presented data from a pilot randomized double-blinded study of antiretroviral naive individuals, which evaluates combination therapy of d4T and ddI for safety and antiviral effect.

Data was presented in Vancouver for additional study participants. Following is a discussion of this study.

Study Design:

- antiretoviral treatment-naive
- 200-500 CD4 cells/mm3
- 52-weeks in duration
- individuals randomized to one of 5 different combinations of dosing regimens
- to measure safety and changes in CD4 and viral load

Pollard said,

- in vitro, ddI and d4T in combination shows synergy for HIV inhibition and
- antagonism for cytotoxicity
- pilot pharmacokinetic study revealed no significant influence on the profile of each drug when administered together
- ddI resistance develops slowly, d4T resistance has been difficult to demonstrate
- peripheral neuropathy is dose-related for each drug and is reported more frequently for those with lower CD4 cell counts and prior nucleoside neuropathy; we need to study this combination in additional patient populations, because there is potential for patients who've had a lot of other nucleosides or HIV related neuropathy to have more symptoms.

Eighty-five individuals started therapy with one of the following treatment regimens; 65 of the 85 study subjects had baseline RNA copies/ml of 1,000 or more:

	ddI (mg/bid)*		d4T (mg/bid)*	
Study Arm (60 kg=132 lbs)	under 60 kg	above 60 kg	under 60 kg	above 60 kg
A	75	100	7.5	10
B	75	100	15	20
C	75	100	30	40
D	125	200	15	20
E	125	200	30	40

Baseline Characteristics:

	started therapy	1000 or more RNA copies/ml
CD4 cell count/mm3	(n=82)	(n=65)
median	330	325
mean	343	337
Viral load (RNA log10)	(n=73)	(n=65)
median	31,600 RNA copies/m (4.5 log10)	31,600 RNA copies/ml (4.5 log10)
mean	15,800 RNA copies/ml (4.2 log10)	25,100 RNA copies/ml (4.4 log10)

Mean Change in Viral Load:
subjects with at least 1000 RNA copies/ml at baseline; combined data from all 5 dosing regimen groups; it is important to bear in mind that the number of subjects is small for each of the different dosing regimens, upon which this collective data is based, therefore results can vary when larger numbers of subjects are factored in--

baseline	(n=65)	
4 weeks	(n=57)	1.20 log reduction from baseline
8 weeks	(n=50)	1.20
16 weeks	(n=46)	1.00
28 weeks	(n=36)	1.30
52 weeks	(n=18)	1.30

Comments--The sustained RNA reduction after 52 weeks may be at least partially due to the slow development of resistance to both drugs.

Mean Change in CD4:
for all subjects including those with RNA levels above and below 1000 RNA copies/ml at baseline, combined data from all 5 dosing regimen groups--

baseline	(n=82)	
4 weeks	(n=72)	61 CD4 cell increase from baseline
8 weeks	(n=76)	83 CD4
16 weeks	(n=69)	81 CD4

28 weeks (n=66) 80 CD4
36 weeks (n=58) 88 CD4
52 weeks (n=35) 75 CD4

Antiviral Response (combined data of all 5 dosing groups)
baseline RNA levels 1000 or more RNA copies/ml--

Weeks	# of subjects	1 log fall	2 log fall
		n (%)	n (%)
0	65	--	--
4	57	37 (65)	10 (18)
8	50	28 (56)	9 (18)
16	46	18 (39)	9 (20)
28	36	23 (64)	11 (31)
52	18	10 (56)	6 (33)

Adverse Events Based on the set of data discussed above, Pollard reported the following information:

- no dose related adverse events
- one case of grade 2 peripheral neuropathy, which was resolved by discontinuing medications, but therapy was tolerated at a reduced dose
- 8 subjects had liver enzyme elevations, some were related to hepatitis A

Prior to Vancouver, a set of data was available based on a fewer number of study participants, but the data was broken down by dosing regimen; again, it is important to remember the number of subjects for each dosing regimen group is small, and results can be less consistent with a smaller number of subjects. Therefore, these results may vary when larger numbers of study subjects are considered.

Mean Reduction in Viral Load:
for subjects with at least 1000 RNA copies/ml at baseline; in parenthesis is the n or number of study subjects in a particular study arm at the given time--

	Group A	B	C	D	E
baseline	(n=11)	(n=12)	(n=11)	(n=9)	(n=11)
4 weeks	-0.90 log (10)	-1.20 log (10)	-0.80 log (8)	-1.70 log (8)	-1.40 log (10)
8	-1.10 log (8)	-1.20 log (10)	-0.90 log (7)	-1.20 log (6)	-1.40 log (10)

16	-1.10 log (9)	-0.50 log	-0.80 log (8)	-1.20 log	-1.60 log (10)	(6) (8)
28	-1.10 log (6)	-1.40 log	-1.30 log (7)	-1.30 log	-1.40 log (7)	(4) (8)
52	-1.50 log (3)	-1.10 log	-1.80 log (4)	-1.80 log	-1.40 log (3)	(2) (2)

Mean increases in CD4 cell count:
for all subjects, including those with and below 1,000 RNA copies at baseline--

	Group A		B	C	D	E	
baseline	(n=13)		(n=16)	(n=15)	(n=13)	(n=14)	
4 weeks (n=9-15/arm)		70		68	62	44	47
8 weeks (n=11-16/arm)		65		74	93	93	85
16 weeks (n=10-13/arm)	57		86	89	52	90	
28 weeks (n=8-12/arm)	54		76	42	66	112	
52 weeks (n=4-6/arm)	-22		64	72	85	141	

Adverse Events:
these events are based on the 2nd set of data for the smaller number of subjects (n=76), again, these results can also vary when larger numbers of subjects are factored in --

	Number of Events					
	A	B	C	D	E	
	n=15	n=18	n=15	n=14	n=14	
peripheral neuropathy	-	-	1	-	-	
diarrhea	-	1	1	1	-	
abdominal pain	-	-	-	1	1	
lipase elevation (grade 3 or 4 events)	1	2	-	1	-	
liver enzyme rise						
-SGOT		2	1	-	2	1
-SGPT		3	2	-	2	1
-bilirubin	-	1	-	-	-	
neutropenia	-	-	-	-	1	

The data has not been fully analyzed yet, but it appears as though there have been 2 discontinuations due to lipase elevations.

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."