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D4T nucleoside combinations for HIV

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There are several nucleoside analogues which have proven to have clinical activity in HIV-infected individuals; these include the first three developed, zidovudine, didanosine and zalcitabine. A more recently developed nucleoside analogue, stavudine (d4T), has been shown to have activity in HIV and has been explored in Phase I/II studies and the results have been reported previously [1–3]. In addition, a relatively large clinical end point trial has recently been completed and the clinical benefit in patients receiving stavudine was superior when compared to patients receiving zidovudine. The major side effects in preliminary trials occurred at higher dosages of d4T and included peripheral neuropathy as the major dose-related side event [4]. It has been reported that decreasing the dosage in patients who develop early signs of neuropathy will allow reinstitution of the compound with decreased frequency of peripheral neuropathy in the majority of patients.

The are several reasons for conducting this trial combining ddI and d4T (Table 1).

Both didanosine and stavudine have been shown to be well absorbed and both have a relatively long intracellular half life [5]. In previous studies, both drugs have been shown to have significant clinical activity.

The objectives of the current study include evaluating the safety of the combination of d4T and ddI as a major objective (Table 2). Also, the study is designed to measure the antiviral effect of various dose combinations and then to utilize the information in the design of larger control trials depending on the results.

This study combined d4T and ddI and ~75

Table 1
Background

- Pilot pharmacokinetic study revealed no significant influence on the profile of each drug when administered together.
- Development of resistance to didanosine appears slower than to zidovudine. Stavudine resistance has been difficult to demonstrate.
- Potential for combined neurotoxicity. Dose related for each drug and appears more frequent in patients with lower CD4 cells and prior nucleoside neuropathy.
- Didanosine and Stavudine both well adsorbed and have prolonged intracellular half life.
- Didanosine shown to be superior to continuing AZT in ACTG 116B/117 and superior in patients taking zidovudine for > 8 week in ACTG 116A.
- Stavudine studied in Phase I and II trials, approved on surrogate marker data in 1994 and clinical endpoint trial showing superiority over continuing zidovudine recently completed.
- In vitro didanosine and stavudine appear synergistic and no additive cytotoxicty.

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Table 2
ACTG 290 — Objectives

Primary
To compare short-term and long-term changes from baseline in magitude of CD4+ cell counts over time between the treatments
To compare short-term and long-term changes from baseline in magnitude of HIV RNA over time
To compare changes in RNA with treatment according to magnitude of baseline viral load.
To evaluate the safety of the ddI/d4T combination.

Table 3
Dosing regimens

Schematic				
	mg/BID			
	$n = 75$		15/arm	
	ddI		d4T	
Study arm	<60 kg	≥60 kg	<60 kg	≥60 kg
1	75	100	7.5	10
2	75	100	15	20
3	75	100	30	40
4	125	200	15	20
5	125	200	30	40

Simultaneous BID dosing of both agents

patients will be evaluated. The patients will be continued on therapy for 52 weeks after the last subject has entered and patients who participate for less then 1 month for other then toxicity reasons can be replaced. The study is randomized by dosage level so all dosage cohorts are accruing from the very beginning of the protocol.

The inclusion criteria for the study include a CD_4 count of 200–500 and is being conducted in patients who are antiviral niave. They also cannot have prior evidence of AIDS-defining conditions and no history of prior episodes of pancreatitis or peripheral neuropathy. This study is relatively intensive with frequent clinical monitoring and, also, with materials collected at frequent intervals for HIV viral load monitoring. The dosage regimens utilized involve 15 patients per arm nad include 5 different arms. These include combinations of lower to the currently approved dosages of both drugs. Study arm (1): 100mg of ddI and 10 mg of d4T (BID); study arm (2): 100 mg of ddI and 20 mg of d4T (BID); study arm (3): 100 mg of ddI and 40 mg of d4T (BID); study arm (4): 200 mg of ddI and 20 mg of d4T (BID); and study arm (5): receives full dosage of both drugs, 200 mg of ddI and 40 mg of d4T (BID) (Table 3)

As mentioned previously, this study is ongoing and continuing to enrol patients. The baseline characteristics of the patients enrolled include a medium age of 31, with a medium CD_4 count of 326. To date, there have been ~70 patients randomized, five withdrew before starting therapy. Five patients can be replaced and between 10–15 patients are needed to complete accrual. There are 21 patients off study for various reasons. Only one patient developed significant peripheral neuropathy. He required dose adjustment and is currently receiving study therapy at half dose levels.

The conclusions from this ongoing study are as follows (Table 4):

The pre-clinical and earlier efficacy data suggests that the combination of didanosine and stavudine might provide significantly better antiviral effect then with each drug alone. This clinical trial should be enrolled by the end of August of 1995 and will provide significant information about this combination. To date no significant toxicity has been observed. Only one patient has developed peripheral neuropathy.

In addition to this ongoing clinical trial, there are two other studies which have been undertaken by the ACTG to examine combination therapy using d4T (Table 5 and Table 6). The first is ACTG 290 and is the protocol for patients who have had greater then six months AZT and have between 300 and 600 CD_4 cells. This study will include 100 patients per arm and will examine whether it is better to switch or add nucleoside regimens.

The second trial is a study in AZT antiviral niave patients with between 300 and 600 CD_4 cells. Patients in this smaller study of 35 per arm will be randomized to begin d4T, begin AZT, or begin the combination. This study has as its pri-

Table 4
Conclusions

1.	Preclinical and prior efficacy data suggests that the combination of didanosine and stavudine may provide greater antiviral effect than each drug alone.
2.	A randomized trial designed to determine the toxicity and antiviral efficacy of this combination is underway with some patients completing up to 60 weeks of combination therapy to date.
3.	No significant incidence of any unique or predictable toxicity (i.e neuropathy) has been observed on combination therapy to date even though some patients have received combination therapy at the recommend dosages of each.
4.	The study emains blinded as to dosages and will continued to enroll to thescheduled total of 75 patients. It is being periodically reviewed by a DSMB.

Table 5
ACTG 290

- Phase II study, 300-60 CD4.
- Greater than 24 weeks ZDV.
- Duration — 48 weeks after last subject enrolled.
- Sample size — 100/arm, based on CD4 change D4T

Regimen		
ddI	ZDV + ddI	ZDV + D4T.

Table 6
ACTG 298

Phase II Study, 300–600 CD4
Anti-Retroviral naive.
Duration — 48 weeks after last subject enrolled.
Sample size — 35/arm, based on viral load.

Regimen		
D4T	D4T and ZDV	ZDV

mary endpoint changes in viral load measurements which will be examined frequently in this study. All patients will be continued for 48 weeks after the last patient enters.

These two clinical trials should further our understanding of the role of d4T in early therapy and provide information about its relative antiviral effectiveness as compared to other approved nucleosides. The utilization of nucleosides in combination, if proven to be safe, can proceed in patient populations who may benefit with additional antiviral efficacy which could improve the outcome of their HIV infection.

References

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