A Randomized Study of the Safety and Antiretroviral Activity of Hydroxyurea Combined with Didanosine in Persons Infected with Human Immunodeficiency Virus Type 1

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This randomized open-label trial of human immunodeficiency virus type 1–infected persons compared safety and efficacy for 38 patients receiving hydroxyurea/didanosine combination therapy with findings in 42 persons given didanosine monotherapy for 12 weeks, followed by 12 weeks of hydroxyurea/didanosine combination therapy for all patients. Week 12 on-treatment group comparisons showed a mean decrease in virus load between hydroxyurea/didanosine versus didanosine groups of −0.93 versus −0.74 $\log_{10}$ copies/mL ($P = .20$); a higher percentage of the hydroxyurea/didanosine group below the assay's detection limit (500 copies/mL), 29% versus 7% ($P = .017$); and median change in CD4 cells for the hydroxyurea/didanosine versus didanosine group of 0 versus 43 cells/mm^3 ($P = .045$), although median change in CD4 percentage was similar (0.9% vs. 1.2%, $P = .64$). Week 24 virus load reductions and CD4 cell changes were similar in both groups. Intent-to-treat and on-treatment analyses showed similar results. The hydroxyurea/didanosine combination was well tolerated.

In vitro and early clinical studies indicate that hydroxyurea, an agent without intrinsic activity against human immunodeficiency virus (HIV), enhances the anti-HIV activity of didanosine and other purine and pyrimidine dideoxynucleoside and nucleotide reverse-transcriptase inhibitors [1–4]. Although the principal mechanism of hydroxyurea in vivo is unknown, it is presumed from in vitro studies that low-dose hydroxyurea synergizes with didanosine by hydroxyurea inhibition of the cellular enzyme ribonucleotide reductase, decreasing the pool of intracellular dNTPs essential to DNA synthesis. Hydroxyurea preferentially blocks the synthesis of dATP, which competes with the active metabolite of didanosine for incorporation into viral DNA and results in chain termination. Hydroxyurea predictably increases phenotypic sensitivity to didanosine of both clinical isolates resistant to didanosine and to laboratory constructs generated with typical didanosine resistance mutations [5].

Pilot studies and small clinical trials of hydroxyurea in combination with didanosine have been conducted in HIV-infected persons [6–16]. Results suggest that hydroxyurea/didanosine and hydroxyurea/didanosine/2′,3′-didehydro-2′,3′-dideoxythymidine (d4T) combinations exhibit antiretroviral activity and drug tolerance at a hydroxyurea dose of 500 mg twice daily or 250 mg 4 times daily [1, 9, 17]. The empirical choice of twice daily hydroxyurea dosing for HIV may avert the higher blood levels and toxicity of once daily dosing, yet may also allow the lower concentrations of intracellular hydroxyurea to synergize with didanosine in laboratory models [2–4]. Dose-ranging studies to optimize didanosine/hydroxyurea combinations are in progress.

This open-label trial randomized patients to either didanosine with hydroxyurea for 24 weeks or didanosine alone for the first 12 weeks with hydroxyurea added for the last 12 weeks. It was designed to enable comparisons with respect to safety and antiretroviral activity. The primary analysis compared combination therapy of didanosine and hydroxyurea with didanosine monotherapy at 12 weeks. A secondary analysis com-

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Written informed consent was obtained from patients in accordance with the guidelines of the participating centers where the study was conducted and the US Department of Health and Human Services. Local institutional review boards approved the study design implemented.

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pared immediate dosing of hydroxyurea and didanosine at 24 weeks with delayed dosing of hydroxyurea after didanosine monotherapy.

Methods

Study protocol. The study was conducted from March 1996 through July 1997 at 6 US clinical centers. Patients were eligible to be randomized into the study if they were aged ⩾13 years; had documented HIV infection; had not previously taken didanosine, dideoxycytidine, or lamivudine at any dose for >7 days total; had >10,000 HIV copies/mL; had an entry CD4 cell count of 50–600 cells/mm^3; had no evidence of significant bone marrow suppression or renal insufficiency that may have limited their tolerance to hydroxyurea; and had no contraindication to didanosine or hydroxyurea. Prior zidovudine or d4T therapy was allowed but was discontinued on the day of study drug assignment. Patients were excluded if they had <10.0 g of hemoglobin/dL; <1500 absolute neutrophils/mm^3; <100,000 platelets/mm^3; aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, or total bilirubin >2.5× the upper limit of normal (ULN); serum creatinine >1.5× ULN; or laboratory data suggesting pancreatitis as assessed by serum amylase, pancreatic amylase isoenzyme, or serum lipase. Women were excluded if they were pregnant or breast-feeding, as were persons who had a known sensitivity or intolerance to hydroxyurea or didanosine; had an active acute infection requiring treatment; used cytokines including granulocyte or granulocyte macrophage colony-stimulating factors, erythropoietin, or interleukin-2 within 30 days before enrollment; had evidence of moderate or severe peripheral neuropathy; received any vaccine within 45 days before the screening visit; or were receiving ganciclovir or foscarnet.

Patients who met the entry criteria were randomly assigned to 1 of 2 open-label treatment regimens: (1) initiation of hydroxyurea and didanosine simultaneously and continuation of treatment for 24 weeks (immediate hydroxyurea group) or (2) initiation of didanosine alone for the first 12 weeks with hydroxyurea added to didanosine for the last 12 weeks (delayed hydroxyurea group). The hydroxyurea dose was 1 500-mg capsule twice daily. The didanosine dose was 2 100-mg tablets twice daily for patients weighing ⩾60 kg and 1 100-mg and 1 25-mg tablet twice daily for patients weighing <60 kg. Patients in whom didanosine therapy was withdrawn or interrupted were simultaneously withdrawn from hydroxyurea. Hydroxyurea (Hydrea) and didanosine (Videx) were provided by Bristol Myers-Squibb (Princeton, NJ).

Laboratory samples from all centers were processed at a central laboratory (SmithKline-Beecham Clinical Laboratories, Van Nuys, CA). Plasma virus load was measured by the second generation branched DNA assay (Quantiplex HIV1 RNA branched DNA assay; Chiron Diagnostics, Emeryville, CA), with a lower limit of detection of 500 copies/mL. Plasma virus load was assessed at baseline and weeks 2, 4, 12, and 24 in both the hydroxyurea immediate and delayed groups, with additional measurements taken at weeks 14 and 16 in the hydroxyurea delayed group. CD4 cells were counted at baseline and weeks 4, 12, and 24 in both the hydroxyurea immediate and delayed groups; an additional measurement was done at week 16 in the hydroxyurea delayed group. All laboratory and virus load measurements were made available to patients to assist clinical management.

Adverse events were graded according to severity (mild, moderate, severe, and life threatening). A data safety and monitoring board periodically reviewed the study data.

Laboratory tests, including serum chemistry, hematology, and urinalysis, were performed by use of samples taken at baseline and weeks 1, 2, 4, 8, 12, 16, 20, and 24 in both the hydroxyurea immediate and delayed groups. The hydroxyurea delayed group had additional evaluations at weeks 13 and 14. Measurements were graded by use of the AIDS Clinical Trials Group toxicity severity grading scale. Neutropenia was graded as mild (absolute neutrophil count, 1000–1499/mm^3), moderate (750–999/mm^3), or severe (500–749/mm^3); and thrombocytopenia was graded mild (75,000–99,000/mm^3), moderate (50,000–74,900/mm^3), or severe (platelet count, 20,000–49,900/mm^3).

At baseline, a complete physical examination was conducted and medical history collected. At weeks 1, 2, 4, 8, 12, 16, 20, and 24, symptom-directed physical examinations were conducted, and interim medical histories were collected. The hydroxyurea delayed group had additional examinations at weeks 13 and 14 if there were abnormal findings.

Statistical analysis. Virus load at week 12 was compared between groups by the use of the following: an analysis of covariance (ANCOVA), with the week 12 $\log_{10}$ virus load as the outcome and the baseline $\log_{10}$ virus load as the covariate; a 2-sample *t* test with the change in $\log_{10}$ virus load from baseline to week 12 as the outcome; and Fisher's exact tests that compared the proportions of patients who reached the assay's lower limit of detection at week 12, who had ⩾1 $\log_{10}$ decrease in virus load at week 12, and who had ⩾0.5 $\log_{10}$ decrease in virus load at week 12. For patients with a week 12 measurement, we compared the change from weeks 12 to 24 by using Wilcoxon signed rank tests and the last available measurement.

Intent-to-treat (ITT) analyses included all patients and used the last available measurement for patients missing their week 12 measurement. On-treatment analyses that used the last available measurement taken while on assigned treatment were also performed. Measurements taken after starting nonstudy antiretroviral therapies, including protease inhibitors, were omitted from on-treatment analyses, because they occurred after discontinuation of assigned treatment in all cases. The baseline value was used as the last available measurement for patients who were missing all follow-up virus load measurements; this resulted in a zero change from baseline. Virus load measurements below the detection limit (<500 copies/mL) were set equal to 500 copies/mL in analyses. An additional analysis, however, was performed with the Kaplan-Meier method that censored rather than imputed values below the detection limit. Although this method is usually applied to time-to-event data in clinical studies, it was applied here to change from baseline virus load and not from time-to-event, as described by Marschner et al. [18]. By this method, the median week 12 change from baseline in $\log_{10}$ virus load was estimated for the groups, and a log-rank test was performed. Assumptions were evaluated [18]. Similar analyses were conducted at week 24. In analyses, the week

12 visit window extended through 14 weeks, and the week 24 visit window extended through 28 weeks.

Wilcoxon signed rank tests were used to compare changes in CD4 cell count and CD4 percentage at weeks 12 and 24. Fisher's exact test determined the statistical significance of group differences in treatment-emergent adverse events and laboratory or physical examination abnormalities. All statistical tests were two-sided and used a 5% significance level.

Results

From March 1996 through January 1997, 80 patients were randomized in the study, 38 in the hydroxyurea immediate group and 42 in the hydroxyurea delayed group. The treatment groups were balanced on demographic characteristics and on selected laboratory measures (table 1). Table 2 shows the patient disposition. In all, 76% of patients in the hydroxyurea immediate group and 86% in the hydroxyurea delayed group completed the 12-week regimen; 61% and 67% in the respective groups completed the 24-week regimen. Table 1 also shows the distribution of the week of the last value used in weeks 12 and 24 on-treatment efficacy analyses.

The ITT and on-treatment efficacy analyses of virus load produced similar results for all statistical tests performed. The on-treatment analysis gave slightly smaller average group decreases from baseline because it excluded measurements taken after the start of protease-inhibitor therapy that lowered virus load. To simplify the presentation, we focused on on-treatment results; ITT results are presented parenthetically for the main efficacy end points to show the similarity between analyses.

Figure 1 shows plots of the on-treatment change in $\log_{10}$ virus load against $\log_{10}$ virus load at baseline, with the maximal response line superimposed. Although the week 12 mean $\log_{10}$

Table 1. Baseline characteristics of study patients.

	Hydroxyurea therapy	
	Immediate (n = 38)	Delayed (n = 42)
Demographics		
Age, mean (SE), in years	35 (1.1)	36 (1.3)
Gender		
Male	36 (95)	33 (79)
Female	2 (5)	9 (21)
Race		
White	24 (63)	23 (55)
Black	5 (13)	10 (24)
Latino/Hispanic	9 (24)	7 (17)
American Indian/Alaska Native	0	1 (2)
Other	0	1 (2)
HIV history		
Year of HIV diagnosis		
1985–1989	5 (13)	6 (14)
1990–1994	14 (37)	15 (36)
>1995	18 (47)	21 (50)
Unknown	1 (3)	0
HIV risk factors		
Man-to-man contact	26 (68)	27 (64)
Heterosexual	9 (24)	10 (24)
Injection drug use	4 (11)	5 (12)
Receipt of blood transfusion	0	1 (2)
Other	0	1 (2)
Unknown	0	1 (2)
HIV drug history		
Zidovudine	7 (18)	8 (19)
d4T	3 (8)	1 (2)
Lamivudine	1 (3)	1 (2)
Other	1 (3)	2 (5)
Any antiretroviral therapy	9 (24)	9 (21)
Initial didanosine dosing (twice daily)		
125 mg	4 (11)	5 (12)
200 mg	34 (89)	37 (88)
Selected laboratory measures		
Virus load by bDNA ($\log_{10}$ copies/mL)		
Mean (SE)	4.68 (0.08)	4.76 (0.07)
Median (25th, 75th percentiles)	4.78 (4.23, 5.04)	4.75 (4.43, 5.16)
CD4 cells/mm^3, median (25th, 75th percentiles)	293.5 (238, 385)	308 (181, 424)
Absolute neutrophils/mm^3, median (minimum, maximum)	2460 (1160, 6260)	2230 (1060, 5780)

NOTE. Data are no. (%) of patients unless stated otherwise. HIV, human immunodeficiency virus; d4T, 2′,3′-didehydro-2′,3′-dideoxythymidine.

Table 2. Patient disposition.

	Hydroxyurea therapy	
	Immediate	Delayed
Randomized	38	42
Stopped regimen before week 12	9	6
Lost to follow-up	2	3
Wanted protease inhibitor or started antiretroviral therapy	4	1
Not compliant with protocol	0	1
Adverse event		
Hematuria	1	0
Headache	1	0
Nausea/cramping	1	0
Decreased sensation in lower extremity	0	1
Completed 12 weeks on regimen (%)	29 (76)	36 (86)
Week of last value used in week 12 on-treatment efficacy analysis[a]		
Week 12	28	32
Week 8	0	1[b]
Week 4	7	7
Week 0	3	2
Stopped regimen after week 12 but before week 24	6	8
Lost to follow-up	0	3
Began protease inhibitor or poor therapeutic response	4	3
Adverse event: nausea/diarrhea	0	1
Not compliant with protocol	2	1
Completed 24 weeks on regimen (%)	23 (61)	28 (67)
Week of last value used in week 24 on-treatment efficacy analysis[a]		
Week 24	17	22
Week 16	2[b]	8
Week 12	10	2
Week 4	6	5
Week 0	3	2

NOTE. Data are no. of patients.

[a] Data from week 12 or week 24 visit that occurred beyond visit window were excluded from efficacy analyses.

[b] Unscheduled end of treatment measure.

virus load was lower in the hydroxyurea immediate group than in the hydroxyurea delayed group (on-treatment, 3.7 ± 0.15 vs. 4.0 ± 0.11; ITT, 3.7 ± 0.15 vs. 4.0 ± 0.12) and the mean change in $\log_{10}$ virus load was larger in the immediate group (on-treatment, −0.93 ± 0.14 vs. −0.74 ± 0.08; ITT, −0.98 ± 0.14 vs. −0.77 ± 0.08), the group difference was not statistically significant by ANCOVA and 2-sample *t* test (on-treatment, P = .19 and .20, respectively; ITT, P = .18 and .18, respectively). Analyses that removed patients with only baseline virus load measurements gave comparable nonsignificant results. The 2 on-treatment curves in figure 2 show a higher percentage in the immediate group with large virus load reductions (P = .03, log rank). Significantly more patients in the immediate group had virus load decreasing below the limit of detection of 500 copies/mL (on-treatment, 29% vs. 7%, P = .017; ITT, 32% vs. 10%, P = .023). No significant group differences were found for the percentage with virus load decreases ⩾0.5 $\log_{10}$ copies/mL or at least 1.0 $\log_{10}$ copies/mL. For those with high baseline virus load (>100,000 copies/mL), 4 of 10 immediate group patients and 0 of 12 hydroxyurea delayed group patients decreased below the detection limit in a week 12 on-treatment subset analysis (P = .029).

At week 24, the mean decrease from baseline virus load was similar for the immediate and delayed groups (−1.01 and −0.95 $\log_{10}$ copies/mL, respectively), based on last on-treatment values. From weeks 12 to 24, the mean change was −0.26 (P < .001, Wilcoxon signed rank test) for the delayed group and −0.009 (P = .98, Wilcoxon signed rank test) for the immediate group, based on the last on-treatment value for patients with a week 12 measurement. With regard to the durability of the dual therapy benefit, 7 of 10 patients in the hydroxyurea immediate group, who had complete on-treatment follow-up and had a >1 $\log_{10}$ decrease in virus load at week 12, maintained at least a 0.5 $\log_{10}$ decrease at week 24.

To address the issue of whether hydroxyurea can add to the benefit already provided by didanosine alone in patients with low baseline virus load, 12 of 14 patients in the hydroxyurea delayed group who had complete on-treatment follow-up and a virus load <10,000 copies/mL at week 12 showed further declines at week 24 (including 5 patients whose virus load decreased below the detection limit).

Analysis of CD4 cell changes revealed progressive differences through week 12 that diminished once both groups were taking hydroxyurea with didanosine. At week 4, there was modest evidence of CD4 blunting associated with the combination therapy. The median CD4 cell change from baseline was 6.5 cells/mm^3 in the immediate group, compared with 24.5 cells/mm^3 in the delayed group; CD4 percentage changes in the 2 groups

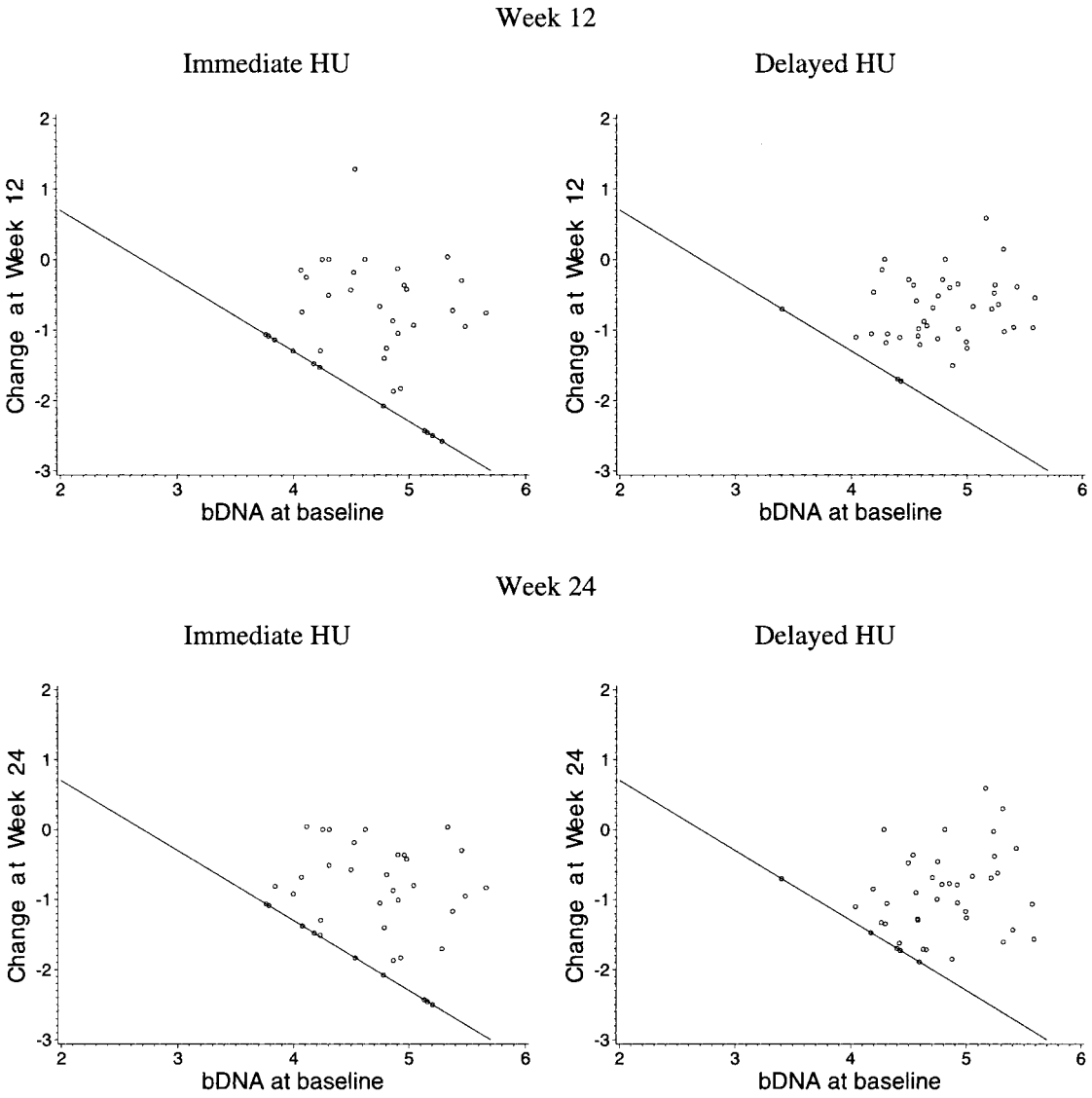

Figure 1. Changes in human immunodeficiency virus load vs. baseline virus load (log_{10} copies/mL) by use of last available value from on-treatment analysis (see table 2 for distributions of week this value occurred). Line superimposed on plots is maximal reduction possible for each bDNA value at baseline given assay's lower limit of detection (500 copies/mL). HU, hydroxyurea.

were 0.9% and 0.8%, respectively. By week 12, this evidence persisted. The median change in CD4 cell count from baseline was lower in the hydroxyurea immediate group than in the hydroxyurea delayed group (0 vs. 43 cells/mm^3, $P = .045$); the median change in CD4 percentage was similar in the 2 groups at week 12 (0.9% vs. 1.2%, $P = .64$). At week 16, the delayed group, 4 weeks after initiation of hydroxyurea, had a median change from baseline of 22.5 CD4 cells/mm^3 and a 1.3% change in CD4 percentage. The change at week 24 was not significantly different between the immediate and delayed groups (−2.5 vs. 17.5 CD4 cells/mm^3, $P = .08$; CD4%, 1.2% vs. 1.4%, $P = .57$).

Grade 3 and 4 adverse events (amylase increase, herpes zoster, hyperglycemia, hyperlipemia, neutropenia, abdominal pain, AST increase, ALT increase, surgery, and weight decrease) occurred infrequently (maximum of 0–4 patients for each event), and group differences were not statistically significant. One patient in the immediate group developed a moderate case of peripheral neuropathy during the last 12 weeks, and 3 patients in the delayed group developed mild cases of peripheral neuropathy during the first 12 weeks. Of note, through the first 12 weeks, 4 patients in the hydroxyurea immediate group experienced nail discoloration; none in the hydroxyurea delayed group experienced this side effect. No deaths occurred during the study.

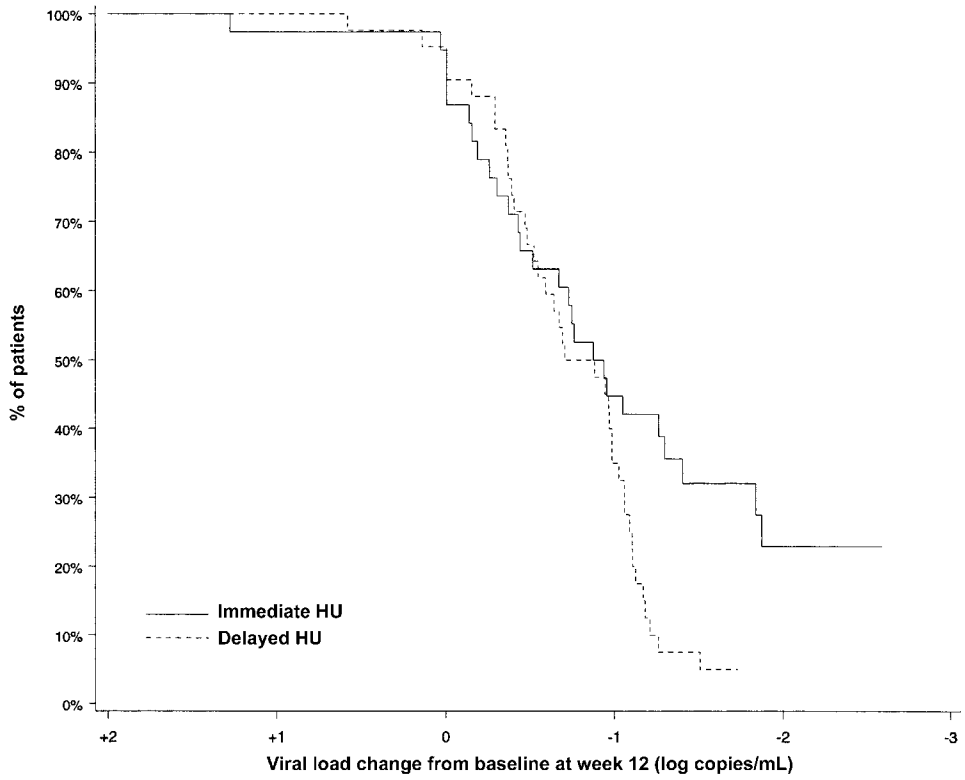

Figure 2. Cumulative % of patients as function of week 12 change from baseline $\log_{10}$ human immunodeficiency virus load. At each point on curve, *y*-axis value is % of patients who have change in virus load equal to or greater than reduction shown on *x*-axis. Last available on-treatment data used (see table 2); those below detection limit were censored. HU, hydroxyurea.

With respect to hematologic adverse events, no statistically significant group differences were found for neutropenia, thrombocytopenia, or anemia. Ten patients in the immediate group developed neutropenia through week 12, and 1 patient first developed it after week 12. Fourteen patients in the delayed group developed neutropenia during the first 12 weeks before starting hydroxyurea therapy, as did another 6 patients during the second 12 weeks. All cases were mild to moderate except for 2 patients with severe neutropenia in the delayed group (1 before and 1 after starting hydroxyurea therapy). Other agents could possibly cause toxicity; 5 of the 14 patients with neutropenia in the delayed group during the first 12 weeks were taking trimethoprim-sulfamethoxazole during their episodes of neutropenia, compared with only 2 of 10 patients in the immediate group. One severe case of thrombocytopenia occurred in the immediate group, and 5 patients in the delayed group had mild to moderate thrombocytopenia, 3 during the first 12 weeks. Four patients in the delayed group developed mild anemia (1 in the first 12 weeks and 3 in the last 12 weeks); none in the immediate group developed anemia. Overall, 10 patients in the immediate group developed some hematologic adverse event (neutropenia, thrombocytopenia, or anemia) within the first 12 weeks, compared with 15 patients in the delayed group (P = .47). During the entire 24 weeks, 11 patients in the immediate group developed some hematologic event, compared with 21 patients in the delayed group (P = .069).

Management of adverse events, including study drug–related toxicity, was left to the discretion of each investigator. Overall, 16 patients (20%) had study medications temporarily discontinued or had the dose reduced (11 in the immediate group and 5 in the delayed group, P = .092). Of these 16 patients, 4 had the hydroxyurea dose adjusted because of a hematologic event. One patient in the delayed group started hydroxyurea at a reduced dose (500 mg/day) because of pre-existing moderate neutropenia, 2 patients had the hydroxyurea dose reduced to 500 mg/day (1 had moderate leukopenia and the other severe thrombocytopenia), and 1 patient had hydroxyurea temporarily discontinued (1 had mild pancytopenia). All 3 patients who had hydroxyurea doses reduced were permanently discontinued from the drug 13–26 days after dose reduction. The patient whose hydroxyurea was temporarily discontinued for 37 days in response to pancytopenia was rechallenged at a reduced dose and was maintained on a reduced dose for the remainder of the study without further hematologic effects.

Discussion

The primary results of this study are short-term: a significantly greater proportion of persons starting didanosine with hydroxyurea experienced virus load decreases to <500 copies/mL at the 12 week time point than did patients who started didanosine monotherapy (29% vs. 7%). Subgroup analysis that showed greater proportions of patients with undetectable HIV at 12 weeks for the didanosine/hydroxyurea combination among patients with >100,000 copies/mL at baseline provide further indication of hydroxyurea's role to potentiate didanosine antiviral activity. These results should be explored in extended long-term studies that combine didanosine/hydroxyurea with additional nucleosides and other medication classes, to achieve enhanced HIV control.

The group difference in the week 12 mean decrease from baseline in $\log_{10}$ copies/mL was slightly less pronounced than seen in a Swiss placebo-controlled 12 week comparison of didanosine/d4T/hydroxyurea with the 2 nucleosides [17]. The fact that we did not find a statistically significant group difference could be due in part to the higher detection limit in this study compared with that in other studies, such as the Swiss study, which used HIV quantitation methods with lower limits (20–200 copies/mL). The possibility that the hydroxyurea response occurred in a subset of patients in the immediate group might also explain the lack of a significant overall group difference (figure 2). At week 24, the mean decrease in virus load in the delayed hydroxyurea group reached a level that was similar to that in the immediate hydroxyurea group.

This study, initiated in March 1996, just before the widespread use of protease-inhibitor therapy in the United States, offered prompt access to surrogate marker results and allowed patients to discontinue study participation in order to adjust antiviral therapy. Overall, 19% of study patients discontinued use of the assigned study drug before the week 12 study visit, and 36% discontinued use of the drug before week 24. Excluding patients lost to follow-up, most who dropped out of the study did so because of insufficient therapeutic response or side effects and had elected to start highly active therapy containing HIV protease inhibitors.

The median change in CD4 cells in the immediate group was lower than that in the delayed group at 12 weeks, 0 versus 43 cells/mm^3, respectively ($P = .045$). At 24 weeks, however, after 12 weeks of combination therapy in the delayed group, the median change decreased to 17.5 CD4 cells/mm^3. Several investigators have reported blunted CD4 cell benefit when hydroxyurea and didanosine are given alone or with d4T, although impressive CD4 cell gains are reported with protease-inhibitor combinations [7, 17, 19, 20]. Studies showing blunted benefit in absolute CD4 cell counts also document comparable gains in CD4 percentage in hydroxyurea-containing study groups as noted in this study. This discrepancy is most likely because of hydroxyurea dose–dependent marrow suppression resulting in mild leukopenia and other immunologic perturbations that require further study. Lisziewicz et al. [20] described 12 patients with chronic HIV infection who were taking didanosine/hydroxyurea. These patients experienced CD4 cell count benefit with partial virus suppression at 6 months and enhanced suppression at 2 years, suggesting enhanced HIV immune control. Five patients had high levels of HIV-specific helper cell activity—an immune response that is uniformly lost with untreated primary HIV infection and that may have a central role in control of HIV infection. Future studies should clarify the critical issues of whether hydroxyurea, an agent used for its antiproliferative and potentially immunosuppressive properties, will influence immune control of HIV and HIV-related infections.

Results of this study support those of previous studies showing safety and enhanced antiviral activity of didanosine with hydroxyurea, but do not allow firm conclusions as to the optimal benefit and timing of when or whether to introduce hydroxyurea to intensity suboptimally suppressive regimens. Applied to clinical practice, this strategy may allow clinicians to evaluate the tolerability and success with didanosine or didanosine combination therapy, delaying the addition of hydroxyurea for the 8–12 weeks required for didanosine combination therapy to boost CD4 cells. As suggested in the Swiss study, delay of addition of hydroxyurea for 12 weeks to persons not maximally suppressed on didanosine/d4T therapy may boost antiviral activity and sustain CD4 cell benefit [17]. Although data trends from our study suggest that the addition of hydroxyurea may boost the antiviral activity of a partially suppressive regimen containing didanosine, the small numbers and short follow-up period hamper interpretation of this result. Larger studies should be designed to evaluate this strategy when used with highly active combinations.

This study provides evidence that hydroxyurea can be given safely and that it potentiates the HIV antiviral activity of didanosine monotherapy but that it also blunts the CD4 cell count benefit. The optimal timing and integration of hydroxyurea in combination therapy for HIV infection requires further study.

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