# Long-term hydroxyurea in combination with didanosine and stavudine for the treatment of HIV-1 infection

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**Objective and methods:** In 1998 we reported on a randomized comparison between stavudine plus didanosine plus placebo versus stavudine plus didanosine plus hydroxyurea (HU), in patients with a CD4 count of 200–500 $\times$ $10^6$cells/l. After 3 months, the HU group had a higher proportion of patients with viral load $< 200 \times 10^6$cells/l. At the end of the 3 months blinded period, patients in the placebo group had the option to add HU if their viral load remained $> 200 \times 10^6$cells/l. We report results after 24 months.

**Results:** Seventy-two patients were randomized to the HU arm, and a further 30 elected to add HU after 12 weeks. Twenty-four months after the start of the trial, only 25% of the 72 patients originally randomized to HU, and 20% of the 30 who added HU after week 12, were still taking it. The reasons for stopping HU were: lack of efficacy (45%), adverse events (37%) and patient or physician preference (18%). Side effects were more frequent in the didanosine/stavudine/HU group than in the didanosine/stavudine group: neuropathy (35 versus 15%, $P < 0.02$), fatigue (22 versus 7%, $P < 0.01$), and nausea or vomiting (26 versus 9%, $P < 0.01$). Of those who had discontinued HU, 73% were taking three drugs including a protease inhibitor. Patients who had started HU were compared with similar patients who had started protease inhibitors in the Swiss cohort. The probability of stopping HU was higher than the probability of stopping nelfinavir or indinavir, and similar to the probability of stopping ritonavir.

**Conclusion:** HU increased the antiviral effect of stavudine plus didanosine. However, side effects were more frequent, and after 24 months the majority of patients had switched to protease inhibitor regimens. 

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**Keywords: Hydroxyurea, didanosine, stavudine, highly active antiretroviral therapy.**

## Introduction

The cost of highly active antiretroviral treatment (HAART), lack of efficacy in some patients, the emergence of resistant viruses, adverse events and the impossibility to eradicate HIV have led to a persistent interest in alternative antiretroviral combinations [1]. Hydroxyurea (HU), a ribonucleotide reductase inhibi-

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tor which decreases intracellular levels of deoxynucleotide derivatives, has synergistic activity with didanosine, and increases the short-term antiviral activity of the combination of didanosine and stavudine [2,3]. The long-term tolerance and efficacy of HU in combination with didanosine or with didanosine and stavudine has only been examined in small case series of highly selected patients [4,5].

The aim of this follow-up study was to analyse the long-term safety, tolerance and efficacy of HU in patients previously included in a randomized, controlled trial comparing the combination of didanosine and stavudine with or without HU (the ddH trial) [3].

## Patients and methods

HIV-1-infected patients participating in the Swiss HIV Cohort Study (SHCS) [6] were eligible for a randomized comparison of the combination of didanosine and stavudine, with or without HU [3], if they had two consecutive CD4 cell counts between 200 and $500 \times 10^6$ cells/l and two HIV-1 RNA plasma levels above 1000 copies/ml, and no prior use of stavudine and HU. Didanosine treatment of less than 6 months' duration was allowed.

The primary endpoint was the proportion of patients who reached a level of less than 200 HIV RNA copies/ml at week 12. Secondary endpoints were long-term changes in HIV-1 RNA levels and in CD4 and CD8 cell counts, and clinical tolerance. Patients who were treated with didanosine, stavudine and placebo, and whose viral load remained above $200 \times 10^6$ cells/l at week 12 were offered the option to replace placebo with open-label HU. Patients continuing on didanosine plus stavudine, or on didanosine plus stavudine plus HU were prospectively followed as long as they received one of these treatments. The reasons for stopping or changing treatment, and post-withdrawal therapeutic regimens were recorded.

Clinical and laboratory assessments were obtained at baseline, after 4, 12 and 24 weeks and every 3 months thereafter. Virological and immunological tests included CD4 and CD8 cell counts, and measure of HIV-1 viraemia with the Amplicor Monitor assay (Roche, Basel, Switzerland). Safety measures included complete blood counts, AST and ALT, and lipase. Adverse events were prospectively collected and graded according to AIDS Clinical Trials Group criteria. HIV-related clinical events were recorded and defined according to the Centers for Disease Control and Prevention 1993 classification 2.

Statistical methods for group comparisons included $\chi^2$ tests for proportion and *t*-tests for the continuous variables. Due to the study design, with open treatment after week 12, on-treatment analyses were performed for the comparison of patients receiving or not receiving HU. Intent-to-treat analyses for the first 12 weeks of the study were previously reported [3].

In order to put the rate of withdrawal of HU in context, we selected patients in the SHCS who would have fulfilled the entry criteria for the ddH study, but who started a protease inhibitor during the period of the ddH trial (May 1996 to December 1997). The probability of stopping the protease inhibitor was calculated using the life-table method, and compared with the probability of stopping HU in the ddH study.

## Results

A total of 144 patients were randomized in the trial. 75% were antiretroviral naive; 23% had been previously treated by zidovudine, 10% by didanosine, 8% by zalcitabine, 1% by lamivudine, and 3% by saquinavir. Baseline HIV RNA was 4.53 log copies/ml and mean CD4 count was $367 \times 10^6$ cells/l. Seventy-two were randomized to receive didanosine, stavudine and placebo, and 72 received didanosine, stavudine and HU. After week 12, patients receiving placebo had the option of adding open-label HU to their regimen. Thirty patients chose to do so; therefore, 102 patients (72 initially randomized + 30 after week 12) received HU, stavudine and didanosine at some point.

Two years after the beginning of the trial, only 24 patients were still on didanosine plus stavudine plus HU, and 15 patients on didanosine plus stavudine. Seventy-eight of 102 (76%) had stopped the combination of didanosine, stavudine and HU, 42% because of an insufficient decrease in viraemia and/or increase in CD4 cell counts, 37% because of the occurrence of an adverse event, 18% at the discretion of the patients, and 3% because of an AIDS-defining event. Among the 72 patients initially randomized to didanosine and stavudine, thirty had added HU to their treatment, and 27 additional patients stopped their didanosine/stavudine combination. Reasons for interruption were an insufficient virological or immunological response (37%), adverse events (48%), and patient choice (15%). Patients naive of antiretroviral treatment at inclusion had a slightly higher chance of continuing treatment than pre-treated patients (30% of continuation at 2 years versus 19%, $P = 23$).

The most common clinical adverse events were gastrointestinal symptoms, fatigue, peripheral neuropathy, and headaches (Table 1), which were all statistically more frequent in patients receiving HU when com-

**Table 1.** Clinical adverse events observed in more than 10% of the patients according to treatment received.

| | Number of patients with the adverse event/number of patients receiving the treatment at the time of the adverse event (%) | | |
|---|---|---|---|
| | ddI + d4T + HU | ddI + d4T | *P*-value[a] |
| Diarrhoea | 23/73 (32%) | 15/71 (21%) | 0.2 |
| Nausea, vomiting | 20/76 (26%) | 6/68 (9%) | 0.006 |
| Abdominal pain | 11/74 (15%) | 9/70 (13%) | 0.7 |
| Fatigue | 16/72 (22%) | 5/72 (7%) | 0.009 |
| Neuropathy (all grades) | 28/79 (35%) | 10/65 (15%) | 0.02 |
| Grade 1 | 13 | 5 | 0.1 |
| Grade 2 | 14 | 5 | 0.08 |
| Grade 3 | 1 | 0 | 0.4 |
| Headache | 9/75 (12%) | 8/69 (12%) | 0.9 |

ddI, didanosine; d4T, stavudine; HU, hydroxyurea.
[a] $\chi$ comparing ddI + d4T + HU versus DdI + d4T, on treatment analysis.

pared with patients receiving didanosine and stavudine alone, on an on-treatment analysis.

Among gastrointestinal symptoms, nausea and vomiting were the most common, usually occurred during the first weeks of treatment, and resolved without discontinuation of the treatment. Only one case of clinical pancreatitis was observed in a patient receiving didanosine and stavudine without HU. All but one case of peripheral neuropathy were mild to moderate (grade one or two), and resolved after stopping treatment. Among adverse events observed in less than 10% of the patients (Table 2), oral ulcerations were significantly associated with the use of HU.

The virological and immunological responses for the first 24 weeks were previously reported [3]. Long-term follow-up results are summarized in Figure 1. After 2 years 58% of patients who still took one of the study regimens had levels of HIV-1 RNA below 200 copies/ml (54% of the patients receiving HU, didanosine and stavudine; 67% of the patients on didanosine and stavudine only, $P = 0.4$). The mean $\pm$ SE increase in CD4 cell counts after two years was $88 \pm 40 \times 10^6$ cells/l for patients still receiving HU, and $145 \pm 32 \times 10^6$ cells/l for patients treated with didanosine and stavudine ($P = 0.3$).

Virological, immunological, and clinical data were obtainable for 94 of 105 (90%) patients who stopped their treatment with didanosine, stavudine $\pm$ HU. Of these patients, 14% were not treated at all, 73% received a combination of two or more antiretrovirals including one or more protease inhibitors (considered as HAART), and 13% were treated with combinations of reverse transcriptase inhibitors without a protease

**Table 2.** Adverse event observed in less than 10% of the patients according to treatment received.

| | Number of patients with the adverse event | | |
|---|---|---|---|
| | ddI + d4T + HU | ddI + d4T | *P*-value[a] |
| Muco-cutaneous | | | |
| Rash | 8 | 5 | 0.4 |
| Oral ulcerations | 5 | 0 | 0.02 |
| Xerostomia | 1 | 3 | 0.3 |
| Alopecia | 1 | 1 | <0.001 |
| Hypertrichosis | 1 | 1 | <0.001 |
| Erythema nodosum | 1 | 0 | 0.3 |
| Nail dystrophy | 2 | 0 | 0.1 |
| Neuro-muscular | | | |
| Muscle pain | 5 | 3 | 0.4 |
| Depression | 1 | 5 | 0.1 |
| Decrease in libido | 1 | 0 | 0.3 |
| Dizziness | 2 | 0 | 0.1 |
| Blurred vision | 2 | 1 | 0.5 |
| Insomnia | 1 | 2 | 0.6 |
| Gastrointestinal | | | |
| Anorexia | 4 | 1 | 0.2 |
| Pancreatitis | 0 | 1 | 0.3 |

ddI, didanosine; d4T, stavudine; HU, hydroxyurea.
[a] $\chi^2$ comparing ddI + d4T + HU versus DdI + d4T, on treatment analysis.

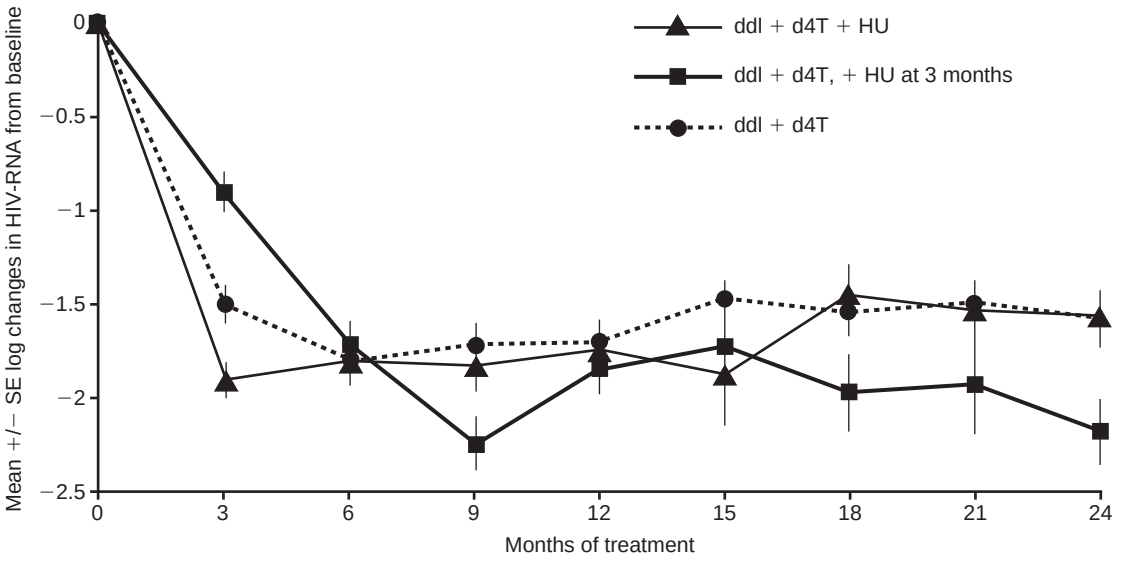


**Fig. 1.** Mean ± SE changes in HIV-RNA from baseline, and number of patients with viraemia <200 copies/ml, according to received treatment. ddI, didanosine; d4T, stavudine; HU, hydroxyurea.

inhibitor. Seventy-five percent of patients receiving a PI-containing regimen had viraemia below 200 copies/ml compared with 17% of the patients treated with IRT alone ($P < 0.001$).

Mean ± SE increase in CD4 cell counts were $221 \pm 29 \times 10^6$ cells/l, and $146 \pm 52 \times 10^6$ cells/l for patients with or without HAART respectively ($P = 0.2$).

Thirty-three CDC-B events (18 in patients receiving HU, didanosine and stavudine and 15 in patients receiving didanosine and stavudine only, $P = 0.9$), and five Kaposi's sarcomas (four in the HU/didanosine/stavudine group, and one in the didanosine/stavudine group, $P = 0.2$) occurred during the follow-up.

Figure 2 shows the probability of remaining on HU, and the probability of remaining on indinavir, nelfinavir or ritonavir, in comparable patients of the Swiss HIV cohort study. The results suggest that the probability of stopping HU is higher than the probability of stopping nelfinavir and indinavir, and similar to the probability of stopping ritonavir.

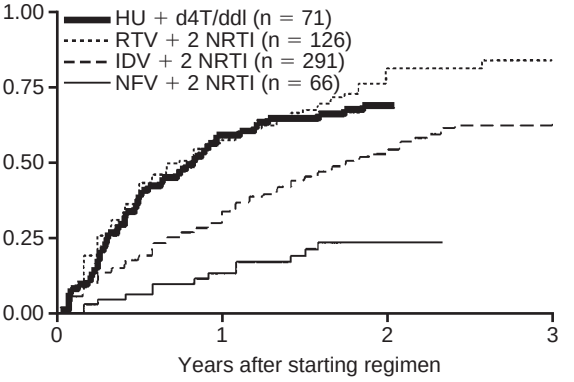


**Fig. 2.** Probability of stopping treatment with the protease inhibitors ritonavir (RTV), indinavir (IDV), and nelfinavir (NFV) compared to the probability of stopping hydroxyurea (HU). ddI, didanosine; d4T, stavudine; NRTI, nucleoside reverse transcriptase inhibitor. IDV + 2NRTI versus HU, $P = 0.0005$; NFV + 2NRTI versus HU, $P < 0.0001$; RTV + 2NRTI versus HU, $P = 0.43$.

## Discussion

Most of the available data on the use of HU come from highly selected patients with a relatively short follow-up, and have shown an increase in antiviral activity in patients treated with HU, with little associated toxicity [2–5]. In our study, patients and their physicians were free to change the treatment according to viraemia, clinical tolerance and their own desire after the first 12 weeks of treatment. This resembles use of HU in a real life situation, outside of clinical trials.

We observed a high withdrawal rate with only 24% of the patients still receiving the study treatments after 2 years of follow-up, which contrasts with some previous studies [5,6,8], but is in accordance with Pollard *et al.* who report a withdrawal rate of 58% after 52 weeks of didanosine and stavudine [7]. Virological failure and adverse events were the most frequent reasons for withdrawal. In addition, some of the patients expressing a wish to stop treatment objected not to HU, but to the discomfort associated with the long-term ingestion

of twice daily didanosine. Once-daily administration has since been proven to be as effective as the twice-daily schedule, and might conceivably increase compliance[9,10].

The high rate of adverse events is also of concern. Symptoms of peripheral neuropathy were more frequent in HU recipients (35% of the patients receiving HU in addition to didanosine and stavudine versus 15% of the patients receiving didanosine and stavudine only). The rate of peripheral neuropathy observed in the didanosine plus stavudine group is similar to previous reports [10–12].

Treating physicians were instructed to discontinue treatment rapidly when they were facing symptoms of peripheral neuropathy, which may explain the rarity of severe neuropathies and the resolution of symptoms after the interruption of treatment. The increase in neural toxicity observed in HU recipients should be kept in mind when this treatment is considered, especially in patients treated with other potentially neurotoxic agents or in advanced HIV infection with pre-existing neuropathy.

Fatigue was three times more frequent in HU-treated patients and sometimes associated with severe limitations of daily activity. Fatigue was not correlated with decrease in haemoglobin, as no significant hydroxyurea-induced anaemia occurred during the follow-up. Dramatic improvement of fatigue was observed after the stopping of HU in two patients, in spite of the continuation of didanosine and stavudine, and this improvement was not explained by an increase in haemoglobin levels.

Gastrointestinal troubles were frequent at the initiation of the treatment, but resolved during the first few weeks of treatment or were relieved by symptomatic treatment. Only one case of acute pancreatitis was observed in a patient treated with didanosine and stavudine, in contrast to a recent study where HU was combined with didanosine/stavudine and indinavir [11].

Haematological toxicity of high doses of HU is well known from the oncological literature, although it is usually reversible [13,14]. In this study, mild to moderate neutropenia and thrombopenia were observed (Table 3); they were associated with the use of HU, and rapidly resolved when HU was stopped. Thrombopenia might be of concern in HIV-infected patients known to be more susceptible to platelet abnormalities and thrombopenia [15,16]. In addition, there is some evidence that long-term use of HU might be leukemogenic, especially in patients with myelodysplastic syndromes [17]. The use of novel ribonucleotide reductase inhibitors with reduced hematopoietic toxicity and potential anti-HIV-1 activity could be an alternative to HU in the future [18].

HU decreases lymphocyte counts [3]. Increases in CD4 cell counts were persistently less in HU-treated patients than in those who received only didanosine and stavudine. This might be of particular concern in patients with advanced HIV infection and low baseline CD4 cell counts. In contrast, in patients with a good baseline immunity, the immune modulation induced by HU might be beneficial. In addition to causing lymphopenia, HU has also been shown to reduce apoptosis and immune activation [19]. Lymphopenia

**Table 3.** Laboratory abnormalities observed during long-term follow-up.

| | Number of patients with the abnormality/number of patients receiving the treatment at the time of the abnormality | | |
|---|---|---|---|
| | ddI + d4T + HU | ddI + d4T | P-value[a] |
| Neutropenia | 18/77 | 8/67 | 0.08 |
| grade 1 | 14 | 8 | 0.3 |
| grade 2 | 1 | 3 | 0.3 |
| grade 3 | 3 | 0 | 0.1 |
| Thrombopenia | 29/74 | 8/70 | <0.001 |
| grade 1 | 24 | 5 | <0.001 |
| grade 2 | 3 | 3 | 0.9 |
| grade 3 | 2 | 0 | 0.2 |
| AST/ALT elevation | 46/80 | 32/64 | 0.4 |
| grade 1 | 33 | 20 | 0.2 |
| grade 2 | 11 | 9 | 0.9 |
| grade 3 | 2 | 3 | 0.2 |
| Lipase elevation | 6/71 | 10/73 | 0.3 |
| grade 1 | 5 | 9 | 0.3 |
| grade 2 | 1 | 1 | 1.0 |

ddI, didanosine; d4T, stavudine; HU, hydroxyurea; AST, ALT
[a] $\chi^2$ comparing ddI + d4T + HU versus DdI + d4T, on treatment analysis.

**Table 4.** The following is part of Fig. 1

| | Number (%) of patients with HIV-RNA <200 copies/ml / total patients on treatment | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Months of treatment | 3 | 6 | 9 | 12 | 15 | 18 | 21 | 24 |
| ddI + d4T + HU | 39/65 (60%) | 27/34 (79%) | 23/33 (70%) | 20/30 (67%) | 11/20 (55%) | 11/20 (55%) | 8/18 (44%) | 9/18 (67%) |
| ddI + d4T + HU at 3 months | 20/69 (29%) | 8/24 (33%) | 7/16 (44%) | 5/14 (36%) | 3/10 (30%) | 5/10 (50%) | 3/8 (38%) | 4/6 (67%) |
| ddI + d4T | 20/69 (29%) | 15/19 (79%) | 11/19 (58%) | 10/19 (53%) | 11/19 (58%) | 10/15 (67%) | 7/15 (47%) | 10/15 (67%) |

and reduced immune activation might decrease the number of cells which can sustain HIV multiplication, thus preventing the outgrowth of drug-resistant escape mutants [20,21].

Due to the high withdrawal rate, results on CD4 cell counts and viraemia must be interpreted cautiously. Nevertheless, 24 months after the start of the trial, only 14% of the patients who had been on HU at any one time, were still on the drug and had HIV RNA levels below the level of detection, which is lower than values that are reported from trials using HAART with a protease inhibitor or efavirenz [1,22–25].

High rates of withdrawal are expected after long-term follow-up, especially in trials involving HIV [26]. In an attempt to put the HU experience in context, we identified patients from the SHCS who had similar CD4 counts as the ddH participants and who had started treatment with a PI. We then compared the probability of stopping the PI with the probability of stopping HU as shown in Figure 2. Nelfinavir and indinavir regimen fared better than HU, and the differences were highly significant.

The place of HU for the treatment of HIV infection remains to be determined. The high rate of adverse events and virological failures, and the modest effect on CD4 cell counts, does not encourage its use in combination with didanosine and stavudine. In addition, the appearance of zidovudine and multidrug-resistant mutations in the HIV reverse transcriptase gene during treatment with didanosine and stavudine might jeopardize future treatments in patients with virologic escape [26]. Nevertheless, the low cost of HU , its action on macrophages and resting lymphocytes, and the absence of recognized resistance make it a candidate for further investigations, for instance in combinations of didanosine and HU with PIs or non-nucleoside reverse transcriptase inhibitors.

In conclusion, the combination of didanosine, stavudine and HU fared rather poorly in competition with conventional HAART. Only 39% of patients continued the combination after 1 year and only 24% after 2 years, which is lower than the results observed in a cohort of patients treated with conventional HAART [23,24]. Low efficacy and side effects both contributed to the high drop-out rate [27]. The place of HU in the treatment of HIV infection remains to be determined and should be studied in controlled trials.

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