Published in final edited form as:
Psoriasis Forum. 2011 ; 17(3): 180–187.

Hydroxyurea for the Treatment of Psoriasis including in HIV-infected Individuals: A Review

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Abstract

Hydroxyurea is a drug that has been long forgotten for the treatment of psoriasis. In addition to its anti-psoriatic effects, it has also been shown to have antiviral effects. This dual effect makes it a drug that dermatologists may want to consider when treating psoriasis in HIV-infected individuals. There are currently no studies that discuss the safety and efficacy of hydroxyurea in the treatment of psoriasis in this immunocompromised group; however, there are multiple reports that discuss the safety and efficacy of hydroxyurea in psoriasis and HIV separately. This review suggests that hydroxyurea is generally safe and effective. The main risk involves the hematologic adverse events (anemia, leukopenia, thrombocytopenia, and macrocytosis) which appear to be dose-dependent. Because of the common hematologic adverse events, hydroxyurea may be considered as a viable therapeutic option for patients with generalized psoriasis inadequately responsive to other safer options, whether the patient is HIV-positive or not.

INTRODUCTION

Psoriasis is a skin condition that affects 1–3% of the general population. In patients with human immunodeficiency syndrome (HIV), one study reports the prevalence of psoriasis as 6.4 percent[1] while others report it to be in the same range as the general population.[2,3] The National Psoriasis Foundation published guidelines for the treatment of psoriasis in HIV-infected individuals.[4] In the guidelines, the use of hydroxyurea as a possible treatment for severe resistant psoriasis in HIV-infected individuals was brought up. This is an interesting concept because hydroxyurea is a long-forgotten medication that has been used since 1970 for the treatment of psoriasis, which was before the use of cyclosporine, acitretin, and biologics.[5] Only methotrexate preceded hydroxyurea for systemic treatment for psoriasis. Hydroxyurea fell out of favor in part because it has always been used “off-label”; but mainly

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because new medications were developed that had better efficacy and were FDA-approved for treatment of psoriasis. Coincidentally, hydroxyurea is also a medication efficacious for the treatment of HIV itself. Hence, this review revisits the use of this “unsung” medication, and aims to reevaluate hydroxyurea especially for the treatment of psoriasis in HIV-infected individuals.

Hydroxyurea was first developed in the late 1800’s as an antineoplastic drug. It has inhibitory effects in DNA synthesis, so it was speculated to have efficacy on the treatment of psoriasis by inhibiting the rapidly dividing skin cells. Hydroxyurea has also been shown to have some antiviral properties and hence, was shown to be a useful adjunct for the treatment of HIV as well. Available data on hydroxyurea use for psoriasis and HIV infection will be systematically reviewed and the possibility of using this treatment modality will be discussed.

METHODS

A search of Pubmed’s Medline database was conducted of articles published from August 1970 to February 2010. Articles containing the keywords “HIV”, “psoriasis”, and “hydroxyurea” were reviewed. Additionally, the different disease states (i.e., psoriasis or HIV) were all combined with the keyword “hydroxyurea”. The search was limited to articles in English only or with English abstracts. Reference lists were reviewed in order to identify any missing articles. The search resulted in 23 relevant articles.

RESULTS

Hydroxyurea use in Psoriasis

In 1970 Leavell and Yarbro[5] conducted a crossover double-blinded study where 10 patients with recalcitrant psoriasis were treated with either placebo or hydroxyurea (500mg BID) for the first 4 weeks and then switched to the other arm for the following 4 weeks. Hydroxyurea was then continued in the patients where hydroxyurea was beneficial. Patients’ evaluation, dermatologist’s evaluation, biopsy response, WBC counts, hemoglobin level, and platelet counts were monitored throughout the study. During the hydroxyurea treatment period, 9 of the 10 patients stated that their psoriasis had improved and biopsies confirmed this. The dermatologist’s evaluation showed that 7 of 10 patients “improved”. In the placebo period, 9 of the 10 patients showed no change or progression of disease (per patient and dermatologist), which was also in accordance to biopsy results. After the 8 weeks, patients who improved on hydroxyurea were kept on the same treatment and all showed further improvement with maximal clearance on average of after approximately 6 weeks. There were no statistically significant changes in WBC counts, hemoglobin level, and platelet counts between the hydroxyurea and placebo treatment periods.

Rosten[6] performed a short-term open-label study of 12 patients with refractory psoriasis who were treated with 1.5–2.0g/day of hydroxyurea for 8 weeks. Patients were evaluated and labs (WBC, Hb, and platelets) were taken weekly. Of the 12 patients, six patients had “considerable improvement”. In the remaining six, four discontinued treatment due to side effects (lack of energy, vertigo, mouth ulceration, slight nose bleeds) and two discontinued

after 8 weeks because they had no improvement. In the six patients who improved, there was no rebound of psoriasis after discontinuing hydroxyurea. On average, psoriatic lesions gradually started to recur 4 weeks after discontinuing hydroxyurea. Leukopenia (WBC below 2700 per mm^3) occurred in two of the patients. Recovery time after discontinuation of medication was not mentioned in the report.

Hunter *et al*[7] performed an open-label study of 24 patients with psoriasis treated with hydroxyurea (1g/day) ranging from between 4–40 weeks of treatment. Sixteen of the patients (67%) showed "very substantial improvement". In 10 of the 24 (42%) patients there was a decrease in WBC counts. Four patients (17%) had to discontinue the treatment because their WBC counts dropped below 4,000/mm^3, but all recovered after being off hydroxyurea for one week. Macrocytosis was seen in the majority of the patients, however, returned to normal after discontinuation of hydroxyurea.

Dahl and Comaish[8] conducted an open-label study of 16 patients with psoriasis treated with hydroxyurea (initial dose: 0.5–1g/day, dose after 1–3 weeks: 1g/day, dose if inadequate response: 1.5g/day) ranging from 6–28 weeks. Seven patients (44%) had "excellent" response, seven patients (44%)had "good" response, and two patients (13%) had "fair" response. Improvement was seen within 2–3 weeks, while maximum response occurred between 4–8 weeks in most patients. Mean hemoglobin levels before treatment and after 7–9 weeks of treatment showed a decrease from 14.1 g/100ml to 12.5 g/100ml. Mean WBC counts before treatment and after 7–9 weeks of treatment showed a decrease from 8010/mm^3 to 5480/mm^3. There was no evidence of renal or hepatic toxicity during this study.

Layton *et al*[9] performed a large open-label study of 85 patients with psoriasis who were treated with hydroxyurea (0.5–1.5g/day). The study included all the patients who were on hydroxyurea over an 8 year period (range was 3–96 months). 68 (80%) of the patients had a good or moderate response. Among these, 51 (60%) had complete or almost complete clearance of lesions and 17 (20%) had partial clearance. 17 patients (20%) discontinued treatment because of inadequate response. Adverse events occurred in 37 (43%) patients. The main adverse effects were anemia (11.7%), pancytopenia (11.7%), and leukopenia (7%). Hematologic adverse events resolved when the dosage of hydroxyurea was decreased or when hydroxyurea was discontinued. 16 (18.8%) patients had adverse events that necessitated discontinuation of treatment. Macrocytosis was seen in all patients who received hydroxyurea, but was reversible with discontinuation of the medication.

Moschella *et al*[10] conducted a larger, long-term open-label study of 60 patients with psoriasis treated with hydroxyurea (500mg BID) for periods of 4–12 weeks (depending on patient's response) over a course of 18 months. In the initial 6 weeks of treatment, 23 patients (38%) had excellent response (80%+ of lesions cleared), 15 patients (25%)had good response (60%–79% of lesions cleared), 6 patients (10%) had fair response (30–59% of lesions cleared), and 10 patients (17%) had poor response (<30% lesions cleared). Hence, 63% of the 60 patients had good to excellent response in the first 6 weeks of treatment. During the remainder of the 18 months, 19 patients (32%) had excellent response, 11 (18%) patients had good response, 5 patients (8%) had fair response, and 4 patients (7%) had poor response. Hence, 50% of the 60 patients had good to excellent response in the remainder 18

months of the study. Hematologic adverse events (anemia, leukopenia, thrombocytopenia, drug eruption) occurred in 25% of the patients, in which 9 patients (15% of total) had to discontinue the drug due to this. Eight patients (13%) were dropped from the study because they did not respond to hydroxyurea.

More recently in 2001, Kumar *et al*[11] conducted a prospective non-randomized case series of 31 patients with chronic plaque psoriasis treated with hydroxyurea (1–1.5g/day). At 12 weeks of treatment, 6 of the 14 (43%) patients who remained on hydroxyurea treatment achieved PASI 75. The mean PASI was 17.2 at baseline and 4.1 at week 12. At the end of the observation period ranging from 6–136 weeks, eight patients (26%) had complete clearance (>PASI 90) and 17 patients (55%) had excellent improvement (PASI 70–90). Hence, 25 patients (81%) achieved PASI 70 at the end of the study. Mean hematologic parameters (hemoglobin, total leukocyte count, and platelets) showed decreasing values from the mean pretreatment baseline. Hematologic parameters were dose-dependent, hence, the dose was decreased in 3 patients with leukopenia and they all recovered. Macrocytosis was seen in all patients at week 2, but returned to normal after 4–6 weeks after discontinuation of hydroxyurea. Renal and liver function tests showed no abnormalities.

Most recently, in 2007 Ranjan *et al*[12] conducted a comparative study between hydroxyurea and methotrexate. 34 patients were alternately assigned to either oral methotrexate (15mg/week) or a very low dose of only 2g per week of hydroxyurea for 12 weeks. Dosage was increased if there was less than 25% reduction of their psoriasis after the first 4 weeks. Six patients from methotrexate group and eight patients from hydroxyurea group had a dosage increase. At the end of 12 weeks, 10 patients (66.6%) patients from the methotrexate group achieved PASI 75 while only 2 (13.3%) of patients from the hydroxyurea group achieved PASI 75. Side effects in both groups were mild and did not require discontinuation of the treatment. Additionally, there were no hematologic toxicities or hepatotoxicity.

Table 1 summarizes the preceding results for Hydroxyurea safety and efficacy in patients with psoriasis.

Hydroxyurea use in HIV

There are multiple large, randomized controlled studies that have shown that the combination of hydroxyurea with didanosine, a nucleoside analog reverse transcriptase inhibitor (NRTI), can suppress HIV infection even though hydroxyurea as monotherapy has not shown to be beneficial in HIV-infected individuals.[13,14] The majority of the studies show that there is some efficacy of hydroxyurea in the treatment of HIV infection when combined with didanosine.[15,16,17,18,19,20,21] Hematologic adverse events were also more common with increasing hydroxyurea doses.[19] No study used hydroxyurea at a dose greater than 1500mg daily. These studies are summarized in the table below.

Table 2 summarizes the preceding results for Hydroxyurea safety and efficacy in patients with HIV.

Hydroxyurea for psoriasis in HIV-infected individuals

There have been no studies to date that discuss its use of treating psoriasis in HIV-infected individuals, however, as previously presented, there have been studies showing its efficacy for chronic plaque psoriasis alone and HIV alone.

DISCUSSION

Hydroxyurea gained popularity in the treatment of psoriasis in the 1970's when Leavell and Yarbro reported its safety and efficacy in the treatment of psoriasis. Further studies were conducted which validated the use of hydroxyurea as a treatment for psoriasis. Because each study used a different method of evaluating improvement of psoriasis, we defined "excellent" improvement as the group of patients in the best efficacy group. The percent of patients achieving "excellent" improvement for each study is displayed in table 1. In the aforementioned studies, 43% to 90% of the patients achieved what is considered "excellent" improvement of their psoriasis with hydroxyurea. The study conducted by Ranjan *et al* showing only 13.3% of patients achieving PASI 75 was excluded because patients were not treated with a typical therapeutic dose of hydroxyurea. In the study, hydroxyurea was given only on two consecutive days per week rather than every day. As a result, only 2 grams per week of hydroxyurea was used for treatment of psoriasis in the study. In the other studies, the dosage of hydroxyurea ranged from 500mg–1.5g daily.

The duration of treatment in the studies ranged from 6 weeks to 8 years of treatment. Though dosage and duration of treatment were not consistent between the studies, it appears that there was an increased incidence of hematologic toxicity with increasing dose and longer duration of treatment. Hematologic toxicity was the main reason for discontinuation of treatment in these studies. Hence, it is important that a dermatologist monitor a patient's blood counts routinely. We recommend weekly monitoring which can then be extended to every 4 weeks when hematologic values are stable.

Hydroxyurea is also believed to be effective in the treatment of HIV infection because it targets the cellular enzyme rather than a viral enzyme (the mechanism by which antiretroviral agents work). Hence, it impedes the disease process at multiple steps of HIV replication. The majority of the aforementioned studies showed that there was a decrease HIV-1 RNA levels when hydroxyurea was added to a HIV regimen that contains didanosine. The majority of the studies also showed that there was higher rate of side effects in patients treated with a regimen containing hydroxyurea because of the hematologic adverse events (anemia, leukopenia, thrombocytopenia, and macrocytosis) which are known side effects of the medication. As discussed earlier, hematologic adverse events are dose-related. The most common dosage used in HIV was 500mg BID (or 1g daily).

Because hydroxyurea is known to cause a decrease in blood counts, the primary concern in a HIV-infected individual is the drop in the CD4 T lymphocytes which can lead to an increase in opportunistic infections. In four of the seven studies discussed, there was a decrease in CD4 counts in the patients treated with combination antiretroviral agents and hydroxyurea. In the other 3 studies, there was actually an increase in CD4 counts in the patients treated with combination antiretroviral agents and hydroxyurea. Because the results are

inconsistent, blood counts (CBC and CD4 counts) should be monitored very closely if hydroxyurea were added to combination antiretroviral agents to be used for the treatment of psoriasis in HIV-infected individuals. Additionally, the study by Malhotra *et al*[20] mentioned that even though there was a decrease in CD4 count, it does not necessarily indicate that there was a decrease in CD4 T lymphocyte function.

This literature review failed to identify any studies or even reported cases discussing the use of hydroxyurea in the treatment of psoriasis in HIV-infected individuals. However, from the review above, hydroxyurea appears to be helpful in not only psoriasis but also HIV infection. Hence, this drug that is nearly forgotten in the treatment of generalized psoriasis in the general population can be considered for treatment of psoriasis in HIV-infected individuals due to this dual effect. In all the studies, the major concern for the use of hydroxyurea was its hematologic adverse events, which usually occurs at higher doses and with longer duration of treatment. More importantly, the hematologic adverse events are reversible after the discontinuation of hydroxyurea. There was a study that showed that a dose of 600mg daily was better tolerated and most effective in improving HIV status.[22] Dosing for psoriasis in the general population usually was 1.0–1.5g/day. However, if hydroxyurea therapy is initiated, our recommendation is a low dose of hydroxyurea 500mg daily, which can be slowly titrated up to minimize hematologic adverse events in a HIV-infected individual.

Hydroxyurea seems to be an effective treatment for psoriasis; however, hematologic adverse events were quite common in the aforementioned reports. Hence, hydroxyurea should only be an option for patients who have failed the more accepted therapies (methotrexate, cyclosporine, biologic agents, and phototherapy) and willing to accept the risk-benefit ratio. Many of these well accepted therapies have undergone years of experience and large, double-blinded, placebo-controlled, randomized clinical trials, while hydroxyurea has not. Other indications for use of hydroxyurea include melanoma, resistant chronic myelocytic leukemia, ovarian carcinoma, primary squamous cell carcinomas of the head and neck, and pain crisis in patients with sickle cell anemia. Therefore, hydroxyurea should be strongly considered in patient populations with these disease states. Hydroxyurea is contraindicated in individuals who have marked bone marrow suppression (i.e. leukopenia <2500 WBC or thrombocytopenia <100,000), are pregnant (Pregnancy category D), or are nursing (excreted in human milk).

Aside from the safety and efficacy of hydroxyurea, cost is another aspect to consider in this age of expensive medications. The average total monthly expense on for methotrexate, acitretin, cyclosporine, and biologic therapies were $78.60, $400.50, and $735.00, and $1,300 per month, respectively.[23] The cost of hydroxyurea is approximately $27/month (calculated from Drugstore.com) at 500mg daily, $54/month at 1000mg daily, and $81/month at 1500mg daily. Hence, even a high dose of hydroxyurea is more cost-friendly than acitretin, cyclosporine, and biologic therapies.

CONCLUSION

The majority of the studies for the use of hydroxyurea for psoriasis or HIV infection (along with didanosine) show efficacy in both disease processes. Hence, we revisited a drug that has been forgotten in the treatment of psoriasis. Dermatologists should consider hydroxyurea as a valid treatment option for psoriasis, especially in HIV-infected individuals where it may also have anti-HIV effects. Our recommendations on starting dose is to begin low at 500mg/day, slowly titrate up to 500mg twice daily and finally increase to 500mg three times daily in order to decrease hematologic adverse events at higher doses. We recommend initial laboratory monitoring every week which can be extended to every 4 weeks as hematologic values stabilize. Lastly, in this age of extremely expensive and frequently unaffordable medications, the fact that hydroxyurea is more affordable than acitretin, cyclosporine, and biologic agents, may prove helpful for many clinicians and patients alike even though it's use is off-label.

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Table 1

Summary of Hydroxyurea safety and efficacy in patients with psoriasis.

Study	Type of Study	Patients	Dosage	Effectiveness	% of Patients achieving "excellent"*improvement	Adverse Events
Leavell and Yarbro 1970	Double- blinded placebo-controlled crossover study	10	500mg BID vs. placebo Treatment period was 8 weeks.	Hydroxyurea treatment period: 9/10 improved per patient and biopsy Placebo treatment period: 9/10 showed NO improvement per patient, dermatologist, and biopsy	90%	No statistically difference in CD4 count, hemoglobin level, platelet count
Rosten 1971	Open-label	12	1–1.5g daily Treatment period was 8 weeks	6/12 had "considerable improvement" 2/12 had no improvement	50%	4/12 side effects (lack of energy, vertigo, mouth ulceration, slight nose bleed)
Hunter *et al* 1972	Open-label	24	1g daily Treatment period was between 4–40 weeks	16/24 had "very substantial improvement"	67%	Leukocyte decreases in most cases 4 had to d/c treatment because WBC dropped below 4,000
Dahl and Comaish 1972	Open-label	16	Initial: 500mg – 1g daily After 1 – 3 weeks: 1g daily Inadequate response: 1.5 g daily Treatment period was 6–28weeks	7/16 had "excellent response" 7/16 had "good response" 2/16 had "fair response"	44%	Decrease in hemoglobin and WBC levels
Moschella *et al* 1973	Open-label	60	500mg BID Treatment periods were 4–12 weeks for 18 months.	Initial 6 weeks: 23/60 had >80% of lesions cleared, 15/60 had 60–80% clearance, 6/60 had 30–59% clearance, and 10 patients hat <30 clearance. At 18 months: 50% had >60%	63% had >60% improvement at week 6. 50% have >60% at 18 months	9/60 discontinued treatment because anemia, leukopenia, thrombocytopenia, and drug eruption. 8/60 dropped because of refractoriness to drug
Layton *et al* 1989	Open-label	85	500mg – 1.5g/day Treatment period was between 3–96 months over 8 year period	60% had complete or almost complete clearance 20% had partial clearance 20% stopped because of inadequate response	60%	11.7% had anemia 11.7% had pancytopenia 7% had leucopenia 18.8% had adverse events that required discontinuation of medication
Kumar *et al* 2011	Prospective non- randomized case series	31	1–1.5 g daily Treatment period was between 6–136 weeks	At week 12: 43% achieved PASI 75, mean PASI decreased from 17.2 to 4.1 Overall: 26% had PASI90, 55% had PASI 70–90	43% achieved PASI 75 at week 12 Overall 71% achieved PASI 70	Decreased hemoglobin, total leukocyte count, platelets NO nephrotoxity or hepatotoxicity
Ranjan *et al* 2007	Open-label comparative study	34	Hydroxyurea (2g weekly) ** vs. methotrexate (15mg weekly)	Methotrexate group: 66.6% achieved PASI 75 Hydroxyurea group: 13.3% achieved PASI 75	13% achieved PASI 75	No hematologic toxicities or hepatotoxicity

Study	Type of Study	Patients	Dosage	Effectiveness	% of Patients achieving "excellent"*improvement	Adverse Events
			Dosage was increased if there was <25% reduction of psoriasis Treatment period was 12 weeks			

*"excellent" is defined as the group of patients in the best efficacy group

**This is a very low dose of hydroxyurea given over 2 consecutive days in one week.

Table 2

Summary of Hydroxyurea safety and efficacy in patients with HIV.

Study	Patients	Treatment	Effectiveness on HIV status	Adverse Effects
Lori *et al*[15]	57 HIV-infected CD4 count 250–500	Didanosine + hydroxyurea (500mg) Didanosine Treated for 24 weeks	Decrease in viral load greater in hydroxyurea treated group. No difference in the increase in CD4 count.	No major toxic event Minor bone marrow toxicity (did not warrant discontinuation of treatment)
Rutschmann *et al*[16]	144 HIV-infected CD4 count 200–500 HIV-1 RNA levels >1000	**Hydroxyurea treated**: Didanosine + stavudine +hydroxyurea (500mg BID) **Placebo**: didanosine + stavudine Treated for 24 weeks	First 12 weeks: hydroxyurea group had greater decrease in HIV-1 RNA levels.	Fatigue, neuropathies, neutropenia, thrombocytopenia. All resolved with discontinuation of treatment CD4 count had lesser increase in hydroxyurea treated group. CD8 count had lesser increase in hydroxyurea treated group
Havlir *et al*[17]	202 HIV-infected CD4 count >200 HIV RNA levels <200	Original group: indinavir + zidovudine + lamivudine New treatment (2 groups): Indinavir + didanosine + stavudine +/− hydroxyurea Treatment for median follow-up time of 40 weeks	Hydroxyurea treated group: 32% failed treatment (mostly due to drug toxicity) Placebo: 17.6% failed treatment Original group: 7.6% failed treatment	Pancreatitis (4 in hydroxyurea treated group, 3 in group without hydroxyurea). CD4 count drop in first 4 weeks of treatment with hydroxyurea.
Lafeuillade *et al*[18]	69 HIV-infected	Placebo: stavudine + didanosine + efavirenz + abacavir. Hydroxyurea (500mg BID) + placebo Hydroxyurea (500mg BID) + IL-2 + placebo Treated for 48 weeks.	Placebo: 25%, 20.8% reached HIV-1 RNA levels <200, <20 Hydroxyurea group: 59.1%, 54.5% reached HIV-1 RNA levels <200, <20 Hydroxyurea + IL-2 group: 56.5%, 47.8% reached HIV-1 RNA levels <200, <20	CD4 decreased in hydroxyurea treated group Lactic acidosis, peripheral neuropathy, LFT elevation. 2 patients from hydroxyurea treated group and 3 from hydroxyurea +IL-2 treated group required dose decrease due to cytopenia. No AIDS defining illnesses.
Frank *et al*[19]	134 HIV-infected CD4 count 200–700	Combination arm: Didanosine + hydroxyurea (1g or 1.5g/day) group Hydroxyurea (1 or 1.5g/day) group (didanosine added at week 4) Didanosine group (hydroxyurea added at week 12)	Didanosine group: 0.9 (week 8) and 1.1 (week 24) log10 decrease in HIV-1 RNA levels Combination arm: 1.9 (week 8) and 1.6 (week 24) log10 decrease in HIV-1 RNA levels Hydroxyurea group: 1.2 log10 decrease at week 24 CD4 counts increased slightly with combination arm while decreased in hydroxyurea group and didanosine group	Hydroxyurea 1.5g/day had more hematologic adverse events than hydroxyurea 1g/day and didanosine alone Longer exposure = increased hematologic AE
Malhotra el al[20]	39 HIV-infected CD4 count >200 HIV-1 RNA <200 Treated for 24 weeks	Original group: indinavir + lamivudine + zidovudine New therapy: indinavir +didanosine + stavudine + placebo or hydroxyurea (600mg BID)	Placebo: 7% failure rate Hydroxyurea group: 27% failure rate Original group: 0% failure rate Markers of HIV activation between groups showed no difference.	Drug toxicity (unspecified) of 2/11 patients in hydroxyurea treated group. Hydroxyurea group: CD4 count had greater decline than other groups
Stebbing *et al*[21]	21 HIV-infected Failed HAART (zidovudine, stavudine, didanosine, lamivudine) HIV-1 RNA >5,000	Stavudine + didanosine Stavudine + didanosine + hydroxyurea (500mg BID) Treated for 12 weeks	Both groups had significant decrease in HIV-1 RNA levels, but hydroxyurea did not have added benefit.	Decrease in CD4 count in hydroxyurea treated group.