IVD. OTHER ANTIRETROVIRAL MECHANISMS

i. Hydroxyurea / Hydrea® / Droxia™ (Bristol-Myers Squibb)

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Background

Hydroxyurea (HU) is an oral drug approved for the treatment of some types of leukemia and other cancers. (In Europe the drug is known as hydroxycarbamide.) It has been widely used for these indications for over 30 years. More recently, it was also found to be effective in decreasing painful crises in patients with sickle cell anemia. HU directly inhibits DNA synthesis as a result of its effect on a cellular enzyme, ribonucleotide reductase. This enzyme is essential for creating the special nucleotide units needed to form DNA. The most significant side effect of this drug is dose-related bone marrow suppression.

Interest in HU as a potential anti-HIV medication started with the observation, first publicized by Robert Gallo's group from the US National Cancer Institute (NCI) at the IX International Conference on AIDS in Berlin in 1993, that drugs that block this key cellular enzyme were likely to inhibit HIV's creation of DNA from its own RNA template, resulting in an antiviral effect. In addition to this, since HU's effect on the cellular enzyme ribonucleotide reductase results in fewer natural nucleotides available to create DNA, HIV's reverse transcriptase enzyme would presumably be more likely to incorporate nucleoside analogue compounds such as ddI, 3TC or d4T into the new DNA chain. These nucleoside analogues are defective versions of the natural nucleotides, and they force the viral DNA chain under construction to terminate prematurely. Thus, it was thought that combining HU with AZT, ddI, and other nucleoside analogues might achieve a synergistic antiretroviral effect.

Another advantage of HU is that its target is a cellular protein, contrary to most of the other anti-HIV medications that target viral proteins. Cellular enzymes normally remain unchanged in cells that are exposed to drugs that inhibit these enzymes. On the contrary, genes encoding for viral proteins mutate under selective pressure, so HIV strains resistant to antiviral drugs eventually develop and, in most cases, render these drugs ineffective. HAART, by inhibiting replication to a minimum level, slows down the development of viral resistance to currently approved antiviral drugs when used properly in combination.

A third potential advantage of HU is that it affects the activation status of cells. It affects activated cells and restores them to a resting state, or at least dampens activation. Cellular activation is a vital part of the retroviral life cycle. Thus, an HIV particle may enter a cell and uncoat, and become ready for reverse transcription, but cellular activation will increase the availability of nucleotides (the building blocks of RNA and DNA) and of relevant cellular proteins, such as HU's target, ribonucleotide reductase, thus making the cell more permissive for infection (activation is also required for import of the newly synthesized DNA provirus into the nucleus for integration into the host cell genome).

Hence, the introduction of HU into a cell which is beginning the activation cycle may dampen activation by interfering with ribonucleotide reductase, and thus reducing the pool of nucleotides available to the retroviral RT enzyme for transcription (Gao 1993a-c). Thus, for example, it may potentiate the activity of ddI by changing the ratio of various 'prodrugs' of the active form, which is ddA-triphosphate (ddA-TP).

Some nucleoside analogues are selectively active in activated cells, such as AZT and d4T, which use thymidine kinase. Others, however, work in both activated and resting cells (it is important to remember that HIV can still undergo reverse transcription, but not integration, in a resting cell).

It is thus at least theoretically possible that HU, if given along with antiretrovirals early in the course of infection, may help prevent the build-up of latently infected CD4 cells which shelter latent virus.

About the Manufacturer

Bristol-Myers Squibb (BMS) markets hydroxyurea (Hydrea®) in 500 mg capsules. It is FDA approved for use, concomitant with radiation, against a variety of cancers. In addition, BMS has recently received marketing clearance from the FDA to sell the drug in 200, 300 or 400 mg capsules as DROXIA™ (hydroxyurea) for the treatment of sickle cell anemia. The drug's patent has expired, and Roxane makes a generic version of 500 mg hydroxyurea capsules as well.

Nevertheless, BMS, which also makes ddI and d4T, has provided and is providing financial support to at least 25 independent investigators studying HU in combinations with other anti-HIV therapies. Michael R. Stevens, Pharm. D., who as Director of Immunology Clinical Trials and Medical Development, Oncology/Immunology, Bristol-Myers Squibb, oversees most of this work, has stated that the company is committed to continue supporting these studies.

Initial HIV-Related Laboratory Studies

A series of crucial papers published in 1994 presented the results of the first three laboratory studies that evaluated the potential of HU as an anti-HIV therapy. Two of the studies were performed at the National Cancer Institute (USA), one of them by Wen-Yi Gao and colleagues, the other by Franco Lori and colleagues. The third study was conducted in France by Serge Malley and colleagues, of the Compagnie de Developpement Aguettant, SA, which produces similar hydroxamate compounds. The three studies concurred in the observation that the combination of HU and didanosine (ddI) has a particularly dramatic effect in blocking HIV replication. These results were achieved at relatively low and nontoxic doses of HU. The effects of combining HU with either AZT or ddC were ambiguous, but nowhere as impressive as the ddI combination. The two NCI studies found some added suppression with the combination with AZT and ddC (Gao's study), while the French study found no synergistic effect whatsoever with combinations with AZT or ddC.

The synergistic effect of HU with ddI in particular was not totally unexpected. It was already noted in a previous study by Gao and colleagues that the inhibition of the cell's ribonucleotide reductase enzyme was particularly effective in reducing the pool of natural dATP nucleotides, of which the active metabolite in ddI, ddATP, is a competitor for the integration into the DNA chain. In other words, since the dATP pool is most rapidly depleted by HU treatment, a higher uptake of ddI would be anticipated.

CLINICAL STUDIES

ddI + Hydroxyurea

French study. One of the first (1994) clinical studies of the HU/ddI combination took place in the French cities of Saint-Etienne and Lyon, France. The Compagnie de Developpement Aguettant sponsored the study. The Principal Investigator was Dr. Jorge Vila, who co-authored the paper by Serge D. Malley describing the initial laboratory studies. This uncontrolled study involved twelve asymptomatic HIV-infected participants with CD4 counts greater than 250 (263-582). None of the twelve had had previous anti-HIV therapy. They all received one gram HU (500 mg twice a day) and 400 mg ddI (200 mg twice a day) for 90 days.

Plasma viral load, as measured by RNA PCR, was detectable in all twelve participants at the start of the study (values ranged from 3,500 to 129,000 copies/ml). At the end of the treatment, viral load was below the limits of detection in the six trial participants who had the lowest HIV levels at baseline. HIV levels decreased by a median of 1.71 log, or 98%, in the remaining 6 patients. The average CD4 count for the group as a whole went from 392 to 556. The combination was well tolerated with no side effects requiring interruption of treatment. Of the six patients who did best (median rise of CD4 was 240, virus undetectable at first post-baseline PCR), four showed no detectable virus even after repeated cycles of PCR amplification.

Researchers went ahead with a second study, also uncontrolled, to evaluate the effects of this combination for a longer period (180 days). Twenty asymptomatic HIV-infected participants with CD4 counts greater than 189 were recruited. Results for all patients after 180 days of treatment were presented at the Vancouver AIDS conference. No patients interrupted treatment due to side effects. At day 180, eleven participants had non-detectable plasma viremia (average PCR count 13872 copies/ml at baseline) with an average CD4 increase of 188 cells (from 508 to 696). The remaining nine participants showed an average reduction of 1.5 log (from 43,766 to 2,064 copies/ml) with an average CD4 increase of 31 cells (from 397 to 428). Overall, CD4 counts rose from a baseline mean of 525 to 610 cells (day 180) and were sustained at 601 cells after one year of treatment. Viral load remained undetectable in half of the twenty patients who completed one year of therapy.

The small number of patients and the lack of a control arm are significant limitations of these studies. Nevertheless, Dr. Vila continues to follow-up most of these and other patients taking the ddI/HU combination. In August, 1997, he reported two cases of individuals who had been on the combination for one year, then stopped all treatment and have shown no signs of viral replication after many months off therapy (other cases have been reported – see the RIGHT study below). These patients had very low initial viral loads: 676 and 1,120 copies/ml. At the time they stopped all treatments, HIV RNA levels were too low to quantify in both blood and lymph tissue. However, very low levels of proviral DNA remain in the lymph nodes. Over two years later (November 1997), HIV RNA levels remained below the level of quantification. Both patients still have trace amount of proviral DNA in their lymph nodes. Dr. Vila asserts that this provirus is defective and cannot replicate properly and that no infectious virus could be grown from it in his lab.

RIGHT study. Some of the most significant studies of HU in combinations with ddI and other antivirals have been conducted at the Research Institute for Genetic and Human Therapy (RIGHT). The Institute, which is based in Pavia, Italy, and Georgetown, Washington DC, is co-directed by Franco Lori and Julianna Lisziewicz. Both researchers were previously at the National Cancer Institute (NCI), where they were part of the original team that did the initial laboratory studies of HU's activity against HIV.

In the longest controlled study yet of ddI versus ddI/HU, 57 HIV-positive patients with CD4 counts greater than 250 were randomized to either ddI alone (19 patients), or ddI plus HU (38 patients). The doses used were 200 mg of ddI twice a day and 500 mg of HU, also twice a day. The objectives of the study were to assess drug toxicity, as well as its effect on plasma viral load and CD4 counts.

Both treatment groups registered a similar initial drop in the plasma viral load of approximately 1 log (90%) during the first two weeks of treatment. Starting at week 4, the ddI monotherapy group experienced a rebound in viral load, whereas in the combination group viral load continued to decrease at a slow rate. At week 24, HIV viral load was 0.78 log (83%) below baseline in the ddI monotherapy arm and 1.32 log (95.2%) below baseline in the combination arm. The ddI monotherapy arm was then dropped, and 34 patients were evaluated at week 40. Mean plasma viral load drop from baseline remained essentially the same during these 16 weeks.

An analysis of the HIV genotype at week 24 showed that two out of eight participants in the ddI monotherapy group had mutations associated with ddI resistance (positions 65 or 74 of the reverse transcriptase gene). But ddI resistance mutations (position 74 and in one case, 184) also appeared in 6 of the 11 participants on ddI/HU who were analyzed. Additional test-tube experiments with laboratory-created ddI resistant virus showed marked inhibition of viral replication in the presence of ddI/HU at concentrations similar to the ones used in the clinical studies. These data suggest that the ddI/HU combination can suppress the virus even after it mutates into ddI-resistant strains.

There was no significant CD4 cell increase to accompany the reduction in viral load observed in the study. This is probably due to the "cytostatic" nature of HU. The compound inhibits cellular DNA synthesis and suppresses the growth and multiplication of cells. It was also noted that those with lower CD4 cells also exhibited the lowest CD4 improvement with the ddI/HU regimen (in some cases CD4 cells actually decreased). Initially, RIGHT investigators put a positive spin on these results, arguing that active cell proliferation would result in more HIV being created. The combination, it seemed, would benefit essentially people with CD4 counts greater than 250. However, at least one recent study adding a protease inhibitor to this combination showed a significant increase in CD4 counts along with the viral load decreases (see below).

AmFAR study. A more recent 80-person study conducted in the US by the American Foundation for AIDS Research (AmFAR), compared a ddI monotherapy arm to a ddI/HU arm for 12 weeks. All participants in the study were ddI naive. Those in the ddI monotherapy arm who were able to tolerate ddI and had an anti-viral response then added HU for 12 additional weeks. Results indicated that those patients in the arm that added HU after week 12 experienced additional suppression, almost, but did not quite "catch up" with the group that started on the combination. A previous pilot study conducted in Canada by Julio Montaner had found that ddI-experienced volunteers who added HU to their regimen responded in ways comparable to persons who start ddI and HU together.

AmFAR study: ddI + HU versus ddI alone (12 weeks) : ddI alone arm added HU after week 12				
Stratified by baseline CD4 (0-300, 301-600)	*ddI + HU combination*		*ddI monotherapy; HU added after week 12*	
	Week 12	*Week 24*	*Week 12*	*Week 24*
Viral load (logs)	-1.26	N/A	-.97	N/A
> 300				
< 300	-1.05	N/A	-.68	N/A
Both	**-1.13**	**-1.0**	**-.82**	**-1.2**
VL undetectable	5/12	7/12	6/17	8/15
> 300				
< 300	5/18	6/18	1/18	2/18
Both	**10/30 (33%)**	**13/30 (43%)**	**7/35 (14%)**	**10/33 (30%)**
CD4 changes	+40	N/A	+57	N/A
> 300				
< 300	-7	N/A	+42	N/A
Both	**+11**	**-6**	**+48**	**+27**

Aviano study. A small controlled study in Italy (21 patients, 14 evaluated) found no added benefit in the ddI/HU combination over ddI-alone in AZT-experienced patients. One patient in the ddI group developed severe allergic dermatitis; one patient in the ddI/HU group had a milder skin rash; one patient in the ddI group and 4 in the ddI/HU group were lost to follow up. There were 2 cases of grade 2 leukopenia (reduction in the number of white blood cells), and 2 of alopecia (hair loss) in the ddI/HU group. The high incidence of side effects may be due in part to the dose of HU used in this study: 1,500 mg divided into three daily doses. This daily total is greater than the dosages used in most other studies, which range from 1,000 to 1,200 mg.

ACTG study. The AIDS Clinical Trials Group study ACTG 307, which completed patient enrollment early in 1998, is comparing is comparing ddI/HU for six months to ddI alone for three months with HU added the second three months in 132 ddI-naive individuals. Preliminary results may be presented in Geneva.

Combination ddI, d4T + Hydroxyurea

Swiss Cohort Study. The first randomized study compared the impact of either ddI/d4T alone or ddI/d4T/HU in 144 patients, 75% of them antiretroviral-naive, at the University Hospital in Geneva, Switzerland. The rest had no more than six months of ddI and no previous exposure to d4T or HU (given at 500 mg bid). At inclusion, mean HIV RNA was 4.5 log, and mean CD4 count was 370. At week 12, poor responders (those with viral load continuing above 200 copies/ml) in the HU group were withdrawn, while those in the ddI/d4T/placebo group added HU to their regimen. There is, of course, empirical reason in the real world to discontinue therapy simply because one's viral load is over 200 copies/ml, especially on a novel regimen such as ddI/d4T/HU.

ddI+d4T+HU vs. ddI+d4T+Placebo (Week 12)			
	ddI/d4T/HU	*ddI/d4T/Placebo*	*p-value*
Viral load < 200 copies/ml	39/72 (54%)	20/72 (28%)	<0.001
Mean decline in HIV RNA†	–1.9 log	-1.5 log	?
Viral load < 20 copies/ml	14/72 (19%)	6/72 (8%)	0.05
Mean VL decline, lower cutoff‡	-2.3 log	-1.7 log	0.001
Mean CD4 cell increase	28	107	0.001

† Lower limit of quantification = < 200 copies/ml *(Rutschmann 1998)*

‡ Lower limit of quantification = < 20 copies/ml.

* VL = viral load; BLQ = below limit of quantification (<200 copies/ml)

CD4 counts did not rise in the HU arm, and total lymphocytes fell considerably. Similar results were seen in the RIGHT study (above), this is probably due to the inhibitory effect of HU on cell division. Notably, 15 out of 72 (20.8%) volunteers on HU withdrew by week twelve, compared to 5/72 9 (6.9%) on placebo.

88 patients were followed out to week 24. Of those patients that continued on the HU regimen, 84% had persistent viremia below 200 copies (this implies that 6/34 in this arm at week 24 had become detectable between weeks 12 and 24, since all those with VL > 200 on HU at week 12 were discontinued at that time).

Adding HU to the 52 poor responders in the placebo group resulted in reduction of viremia below 200 copies/ml in 55% (28?) of those patients (Rutschmann 1998).

Shared Medical Research Foundation study. This on-going 52-week study in California recruited 42 patients with CD4 cells 9-994/ml and stratified them by whether they were on to HU alone, ddI/HU or d4T/ddI/HU. Jeffrey Galpin presented 28 week results at the 1998 Retrovirus Conference. All participants showed improvements in viral load and CD4 counts. The authors asserted, though the poster did not demonstrate, that those on the triple combination therapy showed a greater statistical response/trend than those on HU or ddI/HU ($p<0.002$). Investigators also found significant increases in several types of naïve cells on those taking the combination. Two patients required HU dose reduction for neutropenia (Galpin 1998). Further results from this study will be presented in Geneva.

Combination ddI + HU + Protease Inhibitor

RIGHT Pilot study. The RIGHT group is carrying a pilot study to see what the effect would be of adding a protease inhibitor (indinavir, or nelfinavir in cases of intolerance) to the ddI/HU combination. Eight recently infected individuals took ddI, HU (300 or 400 mg tid), and indinavir for a median of five +months. A comparison group did not receive the protease inhibitor. Adding a protease inhibitor (in this case indinavir) appeared to increase the potency of the combination significantly, further suppressing the virus and thus allowing the CD4 cells to bounce back. A significant degree of immune restoration was also seen, including higher CD3-ζ expression ($p=0.0043$ in CD4 and $p=0.0021$ in CD8 cells), more new naive CD4 cells ($p=0.02$) and fewer activated CD8+CD38+ cells ($p=0.004$).

easuring standard immunological functions such as responses to flu antigen and HIV envelope protein, but also when analyzing a new marker known as CD3-ζ expression. Expression of CD3-ζ, part of the T cell receptor signalling complex, is crucial for signaling and activating the CD8 cells responsible for killing HIV-infected cells (Lori 1998a).

RIGHT Pilot Study: HU + ddI + Protease Inhibitor	
N	17
Treated before seroconversion (WB negative)	5
Treated within 1 year of seroconversion	5
Treated 1 year after seroconversion	7
Average baseline PVL	493,665
Average baseline CD4	448
Average length of treatment	8 months (1-12)
PVL went undetectable	17/17
Semen viremia went undetectable	6/6
HIV RNA undetectable in lymph nodes	7/8
HIV DNA undetectable in lymph nodes	2/6
Average CD4 increase	159
Toxicity	Some, mainly PI-related

WB = western blot; PVL = plasma viral load *(Lori 1998a)*

One of the patients in this pilot study is the third case reported of an individual that has stopped all treatment and has shown no signs of viral replication for over a year and 4 months. This individual continues to be monitored by his physician in Berlin, Germany, Heiko Jessen, who is also a principal investigator in the study. The patient was recently infected and had a viral load of 85,000 copies/ml at baseline. After being treated with the combination, his viral load quickly became undetectable. Because he developed a severe case of hepatitis A, he had to be taken off the HIV drugs 144 days after he started treatment. After being off drugs for three weeks and remaining undetectable, he went back on treatment for two months. In December 1996, he decided to refuse further treatment. His plasma viral load has remained undetectable for over 17 months, and only small levels of HIV are found in his lymph nodes (Lori 1998b).

Adverse Events & Toxicity

The toxicity profile of HU therapy is well documented in the medical literature. he most serious problem is dose-related myelosuppression, the inhibition of bone marrow activity, which results in decreased production of blood cells and platelets. This toxicity is directly related to the inhibition of DNA synthesis in hematologic precursors. This is one of the reasons why researchers had been cautious of testing HU in combination with AZT, which also induces myelosuppression.

However, the initial laboratory studies both in the US and France found that, based on the amounts required to block HIV replication in the test tube, the doses that would be required to achieve the same results in humans might be enough to avoid clinically significant myelosuppression.

Data from clinical trials as well as anecdotal experience from individuals who have been using HU indicate that side effects have occurred, in some cases requiring interruption of treatment. A limited number of patients have experienced some degree of alopecia (hair loss) and leukopenia (reduction in

the number of white blood cells). One patient in a Spanish study conducted in Barcelona by Bonaventura Clotet developed pancreatitis, and in at least one uncontrolled study in the US, patients had to stop treatment due to major drops in CD4 and total lymphocyte count. Evidence suggests that doses of 500 mg three times a day are problematic, especially in patients with low CD4 counts. Franco Lori has suggested that 1,200 mg daily is probably the upper limit to avoid toxicity, while his associate Heiko Jessen is using weight-adjusted doses. The new BMS formulation for sickle-cell anemia, DROXIA™, comes in 200, 300 and 400 mg capsules, allowing more dosing flexibility, though no one knows the optimal dose (or timing) of HU in combination with antiretroviral drugs.

A recent "Brief Communication" piece published last January in the *Annals of Internal Medicine* reported the development of leg ulcers that are usually difficult to treat and require cessation of HU therapy in 14 cancer patients. This was a retrospective study of medical records, and on the average these 14 patients had been taking HU for 2-3 years. These patients were generally older, and in most cases (12/14) were taking doses higher that the ones used as an experimental HIV therapy. The two patients taking 1,000 mg daily developed these ulcers after 13 and 15 years on therapy. There are no reports of this happening in any of the HIV-related studies.

In general, HU treatment in doses up to 1,200 mg has been well tolerated in these trials. It is noteworthy that in some studies with ddI, like the AmFAR study described above, it was intolerance to ddI that forced some patients to drop out after the first weeks. Those taking HU outside formal clinical studies must be careful to have their physicians monitor their blood counts (white blood cells and platelets) frequently to detect any toxicity.

Other Current & Planned Studies

Bristol-Myers Squibb is currently supporting several protocols for different populations (early and primary infection, treatment naïve, and salvage). Studies of novel combinations of HU with other antivirals, including one or more protease inhibitors, are planned or starting in several countries. [This summary does not include all the clinical trials completed or planned. For further information on these studies you can look at the references included, and also at the clinical trials guides available from AMFAR and other organizations.]

Current Status & Recommendations

An evaluation of the data from the studies already completed strongly suggests that a combination that includes HU and ddI can decrease and stabilize viral loads, although in many cases at levels above the limits of quantification. These improvements appear to be sustained. Side effects have been limited, and the treatment has been for the most part well tolerated.

1. Dose-ranging studies are urgently needed.

Considering HU's toxicity profile, it is clear that we need to know what is the **lowest dose** that is needed to reap the benefits of a combination that includes this drug, while avoiding its potential short and long-term toxicity. To address this issue, this summer Franco Lori and colleagues will begin a dose ranging

study of 600 mg (given every day, twice taily, and thrice daily), 800 and 900 mg (qd, bid and tid) or 1,200 mg (qd, bid or tid) HU along with ddI and d4T in 225 patients (Stevens 1998).

2. The new ddI formulation should be expedited.

Many people have either stopped or avoided taking ddI as part of their regimen because of the gastrointestinal problems associated with the buffer. The buffer is required to prevent the destruction of the active substance in ddI by the acid environment in the stomach.

It seems, however, that their emphasis on developing d4T as the market leader of the nucleoside analogues drugs (dethroning AZT) has resulted in less energies and resources being focused on the improvement of ddI. Nevertheless, **if a combination regimen including HU and ddI is to become a real option for treating HIV patients, this problem must be resolved.** This is especially true when considering the potential use of a cheaper ddI/HU regimen in poorer countries, where ddI-induced diarrhea among populations with little access to anti-diarrheal drugs would make it totally impractical.

To improve the drug's tolerability, Bristol-Myers Squibb is currently studying three approaches:

1. A 200 mg chewable ddI tablet;
2. Once-a-day dosing with the current formulation in a 700 patients registrational trial;
3. A new formulation which can pack in more medication with less buffer, in a pill form in ddI is encapsulated in "beads".

Bristol says it is in discussions with the FDA to begin registrational trials for this new formulation later in 1998. In addition, BMS is working on registrational trials of once daily ddI (Stevens 1998).

3. The impact of HU on HIV "reservoirs" should be studied.

HIV "reservoirs", such as latently infected T cells and macrophages, and sanctuary sites such as the brain, the testes, the eyes, the thymus and the spinal cord, are challenging researchers pursuing strategies to totally eradicate HIV from the body. It is known that these reservoirs are created very early, as they are already found in acutely infected patients. Due to its apparent effect on inactivated T cells, HU has at least the potential to prevent the setting of some of the viral reservoirs, if given early in the infection. The data presented by the RIGHT investigators suggests that possibility. **HU therapy must be included in the development and testing of these strategies.**

4. Larger studies, some in combination with protease inhibitors, should be undertaken.

Considering the implications of developing a cheaper alternative to the current antiretroviral cocktails, in particular for countries with limited financial resources, stronger efforts must be made to conclusively demonstrate the benefits of combinations that include ddI and HU. In particular, **we need larger studies of these combinations, and we need to conduct these studies both in developed and developing countries.** We must also study new combinations, **including one or more protease inhibitors.** RIGHT researchers are moving in this direction, but their current study is really a compilation

of the experience of Heiko Jessen patients in Germany. (RIGHT is developing a protocol for a 225-patient study in the US, with several sites across the country.)

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