# III.     NEW TREATMENT STRATEGIES: AN INTRODUCTION

## *by Spencer Cox*

For the last two years, TAG has tracked the development of all recently-approved antiretrovirals and experimental agents entering phase II/III trials, with a view towards exploring what sorts of information people with HIV and their physicians would want about new antiretrovirals. We wrote to and called the sponsors of the new antiretrovirals and, again, found a spectrum of responses. Some companies, such as Agouron, DuPont Merck (now Dupont Pharma), Gilead, and Vertex, were forthcoming about their development plans, while others were downright obstructive, refusing to provide us with the information we needed to develop policy. Hoffmann-LaRoche was eager to supply information about its new soft gelatin capsule formulation of saquinavir (Fortovase™), due to the poor market share of the already approved, but not substantially bioavailable, hard gelatin capsule formulation (Invirase™). We hope that the future larger pharmaceutical sponsors will enter into good-faith negotiations about their development plans in this exciting and confusing era.

We have focused on several examples from the three major classes of antiretroviral agents, and one example of a drug which apparently targets cellular enzymes involved in HIV replication:

1.      The nucleoside and nucleotide analogues, with Glaxo's Ziagen brand abacavir (1592) and Gilead's Preveon brand adefovir dipivoxil (bis POM-PMEA);

2.      The non-nucleoside reverse transcriptase inhibitors, with Pharmacia & Upjohn's Rescriptor brand delavirdine mesylate, Roxane Laboratories' Viramune brand nevirapine, and DuPont Pharma's Sustiva brand efavirenz (formerly known as DMP-266);

3.      The protease inhibitors, with Agouron's VIRACEPT brand nelfinavir, Hoffmann-LaRoche's new Fortovase brand saquinavir soft gel cap, and Glaxo Wellcome/Vertex's amprenavir (GW141/VX);

4.      The ribonucleotide reductase inhibitor hydroxyurea, manufactured as Hydrea and Droxea by Bristol-Myers Squibb

Things are moving too rapidly in the field for this to be a comprehensive overview, and we have not developed enough information about many interesting new approaches, such as ABT-538, CCR5 receptor blockers, F-ddA, integrase inhibitors, lobucavir, PMPA, or zinc finger inhibitors, to include them substantially in our analysis here. We hope that the coming months will see an evolving consensus about how best to study new antiretroviral agents in the era of polytherapy and viral load-driven HIV treatment.

One of the most important changes in HIV clinical research over the past few years has been a major shift from studies that concentrated almost exclusively on particular drugs, to studies that look at a wider range of treatment strategies, including new combinations of drugs, induction/maintenance regimens, and alternative dosing regimens. These changes, which do not necessarily lead to "breakthroughs" of the magnitude seen at the XI International Conference on AIDS in Vancouver, are nonetheless important in that they help us to understand the pathogenesis of HIV disease, and to rationally look for strategies to optimize therapy.

| ACTG 306 RESULTS | | | | | | |
|---|---|---|---|---|---|---|
| Group | Week 20/24[1] | | | Week 44/48[2] | | |
| | N | Mean Log | % BLQ[3] | N | Mean Log | % BLQ[3] |
| ddI limb | 50 | -0.80 | 42% | 43 | -0.88 | 51% |
| AZT/3TC | 51 | -0.82 | 47% | 44 | -0.94 | 48% |
| ddI/delayed 3TC[4] | 36 | -0.68 | 44% | 33 | -1.10 | 55% |
| d4T limb | 41 | -0.81 | 45% | 50 | -1.01 | 58% |
| AZT/3TC | 53 | -1.03 | 57% | 52 | -1.08 | 50% |
| ddI/delayed 3TC[4] | 34 | -0.49 | 35% | 30 | -0.76 | 47% |
| [1] Average of week 20 and 24 measurements | | | | | | |
| [2] Average of week 44 and 48 measurements | | | | | | |
| [3] BLQ = below limit of quantification, 500 copies by bDNA assay (~ 1500 by RT-PCR) | | | | | | |
| [4] 3TC added at 24 weeks | | | | | | |

*(Kuritzkes 1998)*

In the d4T limb, participants receiving d4T/3TC and AZT/3TC had no significant difference in (1) reduction in viral load (mean decrease of 1.08 logs or 92% and 1.01 logs or 90% respectively); (2) increase in CD4 cell count (mean increase of 118 cells and 87 cells respectively); or (3) percent of patients below the limit of quantification (50% and 58% respectively). d4T monotherapy was significantly less effective than the combinations with regard to reduction in viral load (a decrease of 0.76 log or 82.6%).

Results in the ddI limb indicate that there was no additional benefit in adding 3TC to ddI. At week 24, there were no statistical differences in CD4 or virologic response in those starting with ddI/3TC as compared to those starting with ddI monotherapy. What is surprising is that there were also no significant differences over 48 weeks between the ddI monotherapy arm (which started receiving 3TC plus ddI after 24 weeks) and the AZT/3TC arm: an average mean CD4 rise of 105 and 77 cells respectively; and a mean viral load decrease of 1.10 logs or 92% and 0.88 logs or 86.8% respectively. According to the protocol chair, Daniel Kuritzkes of the University of Colorado, "ddI certainly performed better than expected in this arm and that accounts for a failure to see a difference between AZT/3TC and ddI. It isn't that AZT/3TC did worse than expected but that ddI did really quite well." Of course, ddI monotherapy also performed unexpectedly well in ACTG 175, conferring a clinical benefit equal to AZT/ddI and AZT/ddC.

ACTG 306 suggests that 3TC combined with either d4T or AZT achieves equivalent antiretroviral effect. It also observed that d4T monotherapy is quite weak and adding 3TC to d4T significantly improves antiviral activity. Also, ddI monotherapy is surprisingly robust so there is little basis for adding 3TC to ddI. In addition, the side effects experienced by participants in the ddI limb were fewer than expected.

Unfortunately, because of the insensitivity of the bDNA viral load assay and the fact that participants had low baseline viral loads, it is very difficult to draw definitive conclusions about which is the preferred combination therapy or the role of ddI monotherapy. Dr. Kuritzkes explained that since all participants had viral loads in the 10,000 to 12,000 range by bDNA and that about half went below the limit of quantification (500 copies of plasma), differences in treatment arms may have been difficult to discern. (Then, too, 500 copies by bDNA is roughly equivalent to 1500 copies by the PCR assay for viral load, so that the limit of quantification left a relatively large lower range of viral loads unmeasured.)

The blood samples were reanalyzed using the ultrasensitive PCR assay in a presentation at the Fifth Conference on Retroviruses and Opportunistic Infections held in Chicago in February 1998 (Kuritzkes 1998) As would be expected, there were far fewer study subjects below the limit of quantification using the more sensitive assay, whose limit of quantification is about 30 times lower than the bDNA assay, or 50 copies. Only 4% to 12% of participants in each of the trial's combination arms (AZT/3TC, d4T/3TC and ddI/3TC) had fewer than 50 copies of HIV RNA by week 44 and 48 (in the reanalysis, participants had to be undetectable at both time points to be included). This difference between arms again was not statistically significant.

## d4T/3TC

The up-front use of d4T/3TC is an increasingly popular option as part of highly active antiretroviral therapy (HAART). Although Glaxo has made dosing easier in its own first choice for the foundation of HAART by bringing AZT and 3TC together in one twice-a-day tablet known as Combivir, d4T/3TC is also quite attractive, requiring only two pills taken twice a day. Several preliminary studies have supported the efficacy of this combination.

The ALTIS 1 and 2 studies were open-label protocols in which everyone received d4T/3TC. ALTIS 1 found that treatment-naïve patients experienced a 1.66 log (97.9%) viral load drop after 24 weeks of d4T/3TC. (Katlama 1997) ALTIS 2 enrolled participants with prior use of AZT/ddI or AZT/ddC (but no previous history with d4T or 3TC). This group attained only a 0.66 log (78.2%) viral load drop by week 24. It should be noted that the participants in ALTIS 2 had a higher viral load and a lower CD4 cell count at baseline (Katlama 1997). In addition, 30% more of the ALTIS 2 participants experienced HIV-related symptoms than those in ALTIS 1.

A retrospective AmFAR trial evaluated 330 participants who received treatment with d4T/3TC. Calvin Cohen, M.D., of the Community Research Initiative of New England, was the principal investigator. Over 90% of the study subjects were nucleoside analogue experienced. The study found that the d4T/3TC combination retained antiviral activity in those who were treatment naïve or had received prior therapy with d4T alone, AZT alone, AZT/d4T, or AZT/ddI/d4T, but the efficacy diminished if patients had previously taken AZT/3TC. This suggests that those who start on AZT/3TC will not experience additional benefit by switching to d4T/3TC. The question remains as to what will happen if a patient first starts on a d4T-containing regimen and then needs to change therapy due to treatment failure (Cohen 1997).

## The START Trials

The aptly named START trials are randomized open-label equivalency studies in treatment-naïve subjects. They are funded by Bristol-Myers, makers of ddI and d4T. Kathleen Squires of the University of Alabama at Birmingham, presented interim results of START I at the Chicago Retrovirus conference (Squires 1998). This

trial is comparing d4T/: 3TC/indinavir and AZT/3TC/indinavir in 100 participants with an average CD4 cell count of about 400 and an average viral load of about 36,000 (using bDNA). After 24 weeks of treatment, a total of 79 participants in both treatment arms (40 in the d4T/3TC arm and 39 in the AZT/3TC arm) experienced a greater than 1.5 log (97%) reduction in viral load and 80% had viral loads below the limit of quantification (500 copies). Both therapies were well tolerated, although there were more minor gastrointestinal side effects in the AZT-containing arm.

Joseph Eron of the University of North Carolina, presented interim START II findings. This trial is comparing d4T/ddI/indinavir and AZT/3TC/indinavir in 100 subjects with a median CD4 count of about 450 and a median viral load of about 32,000 at baseline. After 24 weeks of treatment, 64 participants across both study arms (34 in the d4T/ddI arm and 30 in the AZT/3TC arm) experienced a median 1.5 (97%) log reduction in viral load and about 70% were below the limit of detection. Both regimens were well tolerated (Eron 1998).

Although both START I and II involve relatively small numbers of participants in the 24-week interim analyses, the data do seem to indicate that d4T and AZT are equally effective as first-line therapy, at least over six months. Similarly, the data suggest that d4T/3TC or d4T/ddI are as effective as AZT/3TC. Questions may arise about whether the highly active protease inhibitor indinavir, used in all the study subjects, masks any differences in the efficacy of the nucleoside analogues across the treatment arms.

**Concerns about 3TC**

3TC is a potent antiviral but it is plagued by the rapid emergence of resistance caused by just one mutation at position (codon) 184 of the HIV reverse transcriptase gene. Since resistance narrows future treatment options, several clinicians have suggested holding 3TC in reserve for second-line therapy. Richard D'Aquila of Massachusetts General Hospital, notes that theoretically ddI may be better used before, rather than after, 3TC. This could be because the activity of ddI is reduced *in vitro* in the presence of the 184 mutation. If a patient uses 3TC first and develops this mutation, the subsequent potency of ddI may be somewhat diminished. Dr. D'Aquila stated that "the change in ddI susceptibility is small, about five-fold. So it may be that the drug is still having some antiviral effect, maybe not as much as it would if the virus didn't have the [184] mutation, but maybe enough." On the other hand, if a patient uses ddI first, resistance will occur most commonly with a mutation at codon 74, which does not appear to decrease the efficacy of 3TC. While the 184 mutation can also occur with ddI use, it is much less common (D'Aquila 1997).

Dr. D'Aquila stresses the lack of *in vivo* data and the need for additional research, as clinical practice does not always corroborate the laboratory findings. In addition, he notes that some patients prefer not to take ddI because of its taste, inconvenience and side effects (the advent of once-a-day ddI at some point in the near future may make it more attractive). Dr. Eron agrees that the theoretical cross-resistance between 3TC and ddI has not been documented in the human body, stating, "I think this is equivocal information at best." He continues to include 3TC in first-line therapy regimens. While agreeing that there is little hard data, Dr. Cohen stated, "The soft data pushed me a little bit more to use ddI first." (Eron 1997, Cohen 1997)

Certainly, if a patient does choose to include 3TC in first-line combination therapy, or, for that matter, at any time during the course of treatment, it is important that the regimen be maximally suppressive or the 184 mutation will emerge very quickly. A study from the Netherlands randomized 47 antiretroviral-naïve patients to receive either AZT/3TC or d4T/3TC with the option to add indinavir after 12 weeks if viral load still exceeds

500 copies. Baseline CD4 counts were greater than 200 and viral loads were above 10,000 copies. After 24 weeks, 19 of 20 in the AZT/3TC arm had added indinavir and 15 of 20 had viral loads below the limit of quantification. In the d4T/3TC arm, 16 of 19 had added indinavir at week 24 and 13 of 19 had viral loads below the limit of quantification. Before starting indinavir, 3TC resistance was found in seven of eight in the AZT/3TC arm and seven of seven in the d4T/3TC arm. While d4T/3TC and AZT/3TC demonstrated similar antiviral effect, the virologic response of the double combinations was of short duration and both led to the emergence of 3TC resistance. Despite the development of the 184 mutation and not switching to two new nucleoside analogues, the majority of participants across both study arms achieved undetectable viral loads when indinavir was added to their existing treatment. The authors concluded that to prevent 3TC resistance it is mandatory to start triple-combination therapy simultaneously (Foudraine 1998).

A group from Spain examined 96 patients with CD4 counts less than 350 and at least six months of AZT pretreatment who were randomized to receive d4T/indinavir plus either 3TC or ddI. Twenty percent of the participants in the 3TC arm did not achieve durable suppression of HIV RNA levels below the limit of quantification (by the bDNA assay). In two-thirds of these participants, the 184 mutation was seen after the third month of therapy. The authors of the study concluded that the emergence of the 184 mutation might be used as a surrogate marker for lack of full HIV suppression in any regimen containing 3TC (Villalba 1998).

## ddI/d4T

Fairly good results have been reported with a d4T/ddI regimen. Richard Pollard of the University of Texas, and colleagues conducted a randomized double-blind study of combination therapy with varying doses of d4T/ddI in 79 treatment-naïve patients. One-year follow-up data were presented at the Eleventh International Conference on AIDS in Vancouver in 1996. Study subjects, who had a median baseline CD4 count of 330 and a median viral load of 4.4 logs (25,000), experienced sustained mean decreases in viral load of 1.2 to 1.3 logs (93.7% to 95%) and mean increases in CD4 count of 60 to 160. Those on full dose of at least one drug did significantly better with regard to viral load and CD4 count than those on the lower doses (Pollard 1996).

Other trials have also looked at the efficacy of the d4T/ddI combination in various patient populations. Several French studies have been presented recently. Two at the 1997 Retrovirus Conference (Duran 1997 and Raffi 1997) found that the combination reduced viral loads by 0.7 to 1 log (80% to 90%) at 24 weeks, accompanied by a CD4 count rise of about 40. Participants in both studies had advanced disease, with average baseline CD4 counts of 116 and 227 and viral loads on average of 200,000 and 100,000, and were heavily pretreated (although no one had prior exposure to d4T and only three had previous ddI). Another French study was presented at the 37th ICAAC in September 1997 (Reynes 97). It looked at once-a-day ddI in combination with the standard twice-a-day d4T dose in 52 antiretroviral-naïve patients with an average of 330 CD4 cells and a viral load of 32,359 (by bDNA). Participants experienced a 1.48 log (96.7%) decrease in viral load and 62% went below the limit of detection (500 copies) at week 24. Another study, conducted by Russell Petrak of Hinsdale, Illinois, and colleagues, was presented at the 1997 Annual Meeting of the Infectious Disease Society of America Conference last September 1997. This protocol combined d4T/ddI with indinavir. (Because ddI/indinavir is a particularly difficult combination due to food restrictions and the need to avoid any interaction between the two drugs, once-a-day ddI was used.) Study subjects, who were nucleoside experienced and protease naïve, had a median viral load of 25,090 and 95 CD4 cells at baseline. At a six-month interim analysis, 27 participants achieved a 1.70 log (98%) decrease in viral load and 94% went below detection (500 copies), accompanied by an increase of 164 CD4 cells (Petrak 1997).

Dr. Cohen is looking at d4T/ddI as the foundation for a potent triple-combination regimen. At a pre-ICAAC presentation entitled "Sequencing Antiretroviral Agents for Long-Term HIV Suppression" (Cohen 1997) Dr. Cohen noted that there is little evidence of resistance with d4T/ddI even after prolonged therapy. He cited a study that examined isolates from patients treated with ddI/d4T and found very little change in phenotypic sensitivity over the course of one year (Coakley 1997). Dr. Cohen stated, "The fact that we don't see phenotypic changes in the virus doesn't mean d4T works forever, it means we don't have a test yet that explains d4T resistance. ddI resistance similarly isn't as straightforward as 3TC resistance. The fact that phenotypically there's no change in the sensitivity of the virus to these drugs over time might allow more durability, but I don't think we know." Dr. Cohen stressed that efficacy must also be considered when choosing a regimen. He noted that the antiviral activity of ddI/d4T is equal to that of AZT/3TC, based on the as yet unpublished START II trial data mentioned above. To sum up, he stated "3TC can easily follow ddI-resistant virus so it makes sense to save 3TC for second, as it also makes sense to use d4T before AZT because AZT makes d4T less effective." Dr. D'Aquila concurs, "Everything else being equal, I think I would prefer to start someone on d4T/ddI."

Keith Henry of Regions Hospital in Minnesota, shares his colleagues' concerns regarding the lack of unequivocal data to provide a preferred order of drugs. Nonetheless, he acknowledges that in the real world a high percentage of patients on treatment fail the first regimen they try and then, by definition, are sequenced to a second-line regimen. He stated, "From my reading of the tea-leaves, I've been using d4T/ddI heavily recently because it seems to me, based on too little data, that going from that to AZT or 3TC is more likely to work than going the other direction. Right now, even in people who are apparently doing well on a 3TC regimen, I've been putting them on a d4T/ddI regimen, partly because I'm trying to save 3TC and abacavir (Glaxo's new nucleoside analogue, abacavir). The question remains: Is the cost of failure on d4T/ddI for future options less than the cost of failure on the AZT/3TC regimen? The data are pretty thin on that so the pharmaceutical companies assemble along the lines you would expect as far as their spin." A major concern is that there is no clinical trial data on what happens to subsequent d4T failures. This is because the majority of those currently being treated with d4T in studies are people who were either treatment naïve or first used, and may have failed, AZT. What is needed is a trial that compares the initial use of AZT versus the initial use of d4T, as this affects subsequent sequencing options. An ACTG protocol is being designed to address this issue, although the primary goal of the study will be to determine the optimal sequencing of protease inhibitors and NNRTIs. Protocol 384 will examine participants who begin with d4T or AZT and then switch to the other drug. Four arms will include a protease inhibitor or an NNRTI plus either ddI/d4T or AZT/3TC and later switch to the other nucleoside pair. Martin Hirsch, of Harvard Medical School, is one of the protocol chairs. He emphasized that the trial is still in development and has many obstacles to overcome before it becomes a reality, including lack of interest by the manufacturers of the protease inhibitors.

**Other Factors**

Ultimately, the choice of drugs for any regimen must also consider convenience and tolerability. Whatever two nucleoside analogues are decided upon, they will usually be combined with a protease inhibitor or an NNRTI. Food restrictions, drug interactions, dosing requirements and side effects may then make the use of a particular drug more complicated and therefore less desirable. Until there are more data, the combinations of AZT/3TC, d4T/3TC and ddI/d4T all appear to be equivalent with regard to initial antiretroviral effect, but may not all equally allow for viable backup regimens should initial therapy lose its effect. *[Reprinted with thanks from GMHC's Treatment Issues, Vol. 12, No. 2, February 1998]*

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