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Forum for Collaborative HIV Research

Simplifying Antiretroviral Treatment Regimens - a Summary of Current Research

*A Monograph by Dave Gilden, prepared for the Forum for Collaborative
HIV Research*

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Simplifying Antiretroviral Treatment Regimens: *a Summary of Current Research*

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HIV anti-retroviral therapy is prolonging survival and AIDS-free time for people with HIV disease¹. However, in order to remain effective, treatment regimens must be strictly followed. Adherence to therapy is complex and difficult for many, if not most patients. Simpler treatment regimens – including fewer drugs, fewer pills per day and/or fewer doses per day - should make it easier for patients to adhere to treatment. This monograph reports on recent advances to simplify treatment regimens.

With the FDA approval of both efavirenz (Sustiva™) and abacavir (Ziagen™) approval in November, options for simplifying therapy seem to be widening. Efavirenz dosing consists of taking three pills (soon to be reduced to one larger pill) once a day. Its side effects are mainly transitory, although the mental confusion many are reporting when they start the drug has disconcerted many experts. As a highly potent nonnucleoside reverse transcriptase inhibitor (NNRTI), efavirenz may also replace one of the more difficult-to-take protease inhibitors in highly active antiviral treatment (HAART) regimens.

Abacavir is taken as one pill twice a day. It is the most active nucleoside analog yet developed. Its sponsor, Glaxo Wellcome, has tested it in a very convenient protease-sparing regimen that includes AZT/3TC combined as Combivir™, another one tablet twice a day therapy. Abacavir also is noted for its low toxicity – except in the up to 3% of patients who may experience a serious hypersensitivity reaction that can turn into anaphylaxis on rechallenge.

These two agents are just examples of many ways now existing to simplify HIV

therapies. The increasing experience with the more established antiviral drugs has led to suggested alterations in dosing schedules and treatment strategies that make for less onerous therapies. Approaches to simplification follow two main lines right now: reduction of thrice daily (tid) schedules to twice daily (bid) and of twice daily to once daily (qd), and the use of therapeutic combinations with a limited number of mechanisms and, one hopes, side effects – the “protease sparing” regimens.

These changes come none too soon: A national survey published last spring found that the duration of “drug holidays” increased from an average of 6.2 days for those on therapy 2 to 12 months to an average of 14.4 days in those on therapy for more than two years. Overall 43% admitted to not adhering to their regimen during the past week. (See Joel Gallant et al., *Journal of the International Association of Physicians in AIDS Care*, May 1998, pages 32-5.) Patients and doctors listed fewer, simpler doses per day, removal of any restrictions on taking medication with or without food, fewer pills per dose or day and fewer side effects as the main ways to improve adherence. Experience in other diseases bears out the impression that simpler regimens lead to better adherence,² but actual adherence studies in people with HIV have been few and their results tentative. In two reports,^{3,4} presented this fall, number of pills and the number of times were *not* found to be associated with nonadherence – although length of time on therapy, depression, and lack of belief in a therapy’s effectiveness were associated with missed and irregularly scheduled doses. These studies did not stratify participants by disease stage, though, and this factor may have confounded the results.

Many such simplification strategies were presented at the 12th World AIDS Conference, which took place in Geneva last July, the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) last September in San Diego, and the 4th International Congress on Drug Therapy in HIV Infection this November in Glasgow. These will be summarized below.

There once was hope that the number of anti-HIV drugs taken could be reduced after

a short initial induction period. Trials to test these maintenance therapies (the Dutch ADAM study,⁵ ACTG 343⁶ and the Trilège study⁷ in France) have had disappointing results, with greatly elevated rates of HIV breakthrough. However, they have only waited three or six months before switching to maintenance therapy, and perhaps waiting longer might produce better results.

Abacavir with or without Combivir™

Glaxo Wellcome has successfully tested in this country the reduction of AZT's schedule from 200mg TID to 300 mg every 12 hours.⁸ This was a practice that had already become common in Europe. At the same time, Glaxo Wellcome introduced a 300 mg AZT tablet as an alternative to the former 100 mg capsules. The company then went a step further by combining AZT with its other twice daily nucleoside analog, 3TC. The result was an AZT/3TC combination tablet that is taken once every 12 hours and is known as Combivir™, which was approved by the FDA in 1997 on the basis of data showing its bioequivalence with AZT and 3TC taken separately.

At the same time, Glaxo's new guanosine-based nucleoside analog abacavir is highly potent and could conceivably be substituted for two nucleosides in some regimens. The original phase I dose ranging trial found that abacavir monotherapy caused nearly a two log (99%) drop in viral load over four weeks, above the range expected from previously studied 2 NRTI regimens. In addition, resistance to abacavir is slow to develop and requires step-wise mutations. Although the same single mutation at the reverse transcriptase gene's codon 184 that is responsible for 3TC resistance does appear in HIV cultured with abacavir, persons whose HIV has only this mutation seem to respond well to abacavir. Abacavir more generally fails in persons with multiple reverse transcriptase mutations, in particular, those that give joint resistance to AZT and 3TC.⁹

Preliminary, incomplete results from a trial of abacavir combined with only amprenavir, Glaxo Wellcome's experimental protease inhibitor, indicate that the first 9

study participants out to 48 weeks had viral loads below 500 copies/mL of plasma (by bDNA assay, which gives lower readings than the more common Roche Amplicor assay). Eight of these nine had Amplicor-measured viral loads below 50 copies/mL.¹⁰ All volunteers were treatment-naïve at the initiation of therapy.

In Glaxo Wellcome's CNA 3003 protocol, a 16-week trial of AZT/3TC/abacavir versus AZT/3TC, 86% of the 72 subjects completing 16 weeks of the triple combination had viral loads less than 400 copies/mL (standard Amplicor assay limit of detection). 67% also were below 50 copies/mL.¹¹ In the AZT/3TC-only arm of protocol CNA 3003, just 43% were below 400 copies/mL at week 16, and 19% were below 50. Again, all subjects were without prior treatment.

Glaxo Wellcome is conducting a blinded comparison of AZT/3TC/abacavir versus AZT/3TC/indinavir (CrixivanTM). While the study remains blinded, the two arms have demonstrated equivalent virologic response and equivalent CD4 increases at 24 weeks. The potential of the abacavir/indinavir combination is not being studied at this time.

From Three Times a Day to Two

The advent of twice-a-day AZT and CombivirTM triggered a trend towards eliminating tid dosing from antiviral therapy. In developing amprenavir, Glaxo Wellcome decided upon a twice daily schedule, although the pill burden of this regimen is high – eight large capsules twice a day. Adherence research shows that both pill burden and number of doses per day will affect patient adherence. It is difficult to know which factor will have a more significant effect on adherence and patient quality of life.

Many of the scheduling innovations involve using the Abbott Laboratories' protease inhibitor ritonavir (NorvirTM) to inhibit the metabolism of other protease inhibitors by liver enzymes. This approach was first used to good effect in the combination of ritonavir plus InviraseTM, the old hard capsule form of saquinavir. InviraseTM suffered from slow absorption and rapid liver breakdown. Ritonavir bid at 400 mg (four capsules) raised the

saquinavir blood levels obtained from Invirase™ 20 times, in the process converting an almost impotent three times-a-day drug into a highly active twice-a-day one. At the same time, the required dose of Invirase™ was reduced from 600 mg (three capsules) three times a day to 400 mg (two capsules) twice a day. The required ritonavir dose was reduced from 600 mg bid to 400 mg bid, with a concomitant reduction in pill burden and, especially, in ritonavir's side effects. Abbott's main trial of the ritonavir/Invirase™ combination, M96-462, has now followed its initially protease inhibitor naïve volunteers for more than 72 weeks.¹² At that time point, 90% of study participants treated for 72 weeks had viral loads below 200 copies/mL. Especially noteworthy is the fact that most of the volunteers received only the two protease inhibitors without concurrent reverse transcriptase inhibitors at least through the first year.

Abbott and Merck are now hoping to repeat this success with indinavir. At the World AIDS Conference, the companies' scientists repeated earlier observations that ritonavir/indinavir, both dosed at 400 mg bid, resulted in a total exposure to indinavir that was nearly the same as with the standard indinavir dosing schedule, 800 mg three times a day.¹³ Peak indinavir levels were reduced, while trough levels between doses were increased substantially so that possible windows of opportunity for HIV replication were eliminated. Further, taking the drugs with meals made no difference in indinavir levels whereas indinavir without ritonavir should be taken with at most a light snack to achieve effective blood levels. Merck is currently evaluating indinavir at 800 mg with ritonavir to determine the optimal dose of this combination.

A pilot, uncontrolled study of indinavir/ritonavir, both 400 mg bid, plus two nucleoside analogs was presented at the 4th International Congress on Drug Therapy in HIV Infection by a group of German doctors.¹⁴ The study recruited 71 subjects with no prior treatment and a median baseline viral load of 210,000. Of the 45 subjects who had reached week 12, 90% had viral loads below 500 copies/mL, and 75% were below 80 copies/mL. At the 12th World AIDS Conference, four Australian doctors also reported

similar dramatic viral load drops with 8 treatment nonresponders and 18 treatment-naïve patients on d4T/3TC/ritonavir/indinavir.¹⁵

A French study of ritonavir/saquinavir presented at the 12th World AIDS Conference reduced the ritonavir dose to 100 mg or 200 mg while increasing the saquinavir dose to 600 mg or 1,000 mg (at each ritonavir dose) and found that saquinavir blood levels again were dramatically increased.¹⁶ At the 4th International Congress on Drug Therapy in HIV Infection, two groups described the use of 100 mg of ritonavir administered twice daily with 800 mg of indinavir.^{17,18} Median peak indinavir levels were similar to those achieved with indinavir alone at 800 mg every eight hours while the between-dose minimum levels were four times higher when the 100 mg of ritonavir was included.

Abbott is following a parallel reduced-ritonavir strategy with its new protease inhibitor, ABT-378. Adding 50 to 200 mg ritonavir to ABT-378 extends its brief half-life in the body to as much as 24 hours. A phase 2 trial, presented as a late-breaker in Geneva¹⁹ and in a satellite symposium in Glasgow, tested the ABT-378/ritonavir combination at a bid dose of either 200/100 mg or 400/100 mg. After three weeks of dual ABT-378/ritonavir alone, the trial regimen was expanded to include d4T/3TC. The 32 treatment-naïve volunteers who started the trial experienced an average 2 log (99%) drop in their viral loads over the first two weeks. Sixteen of 17 volunteers (94%) followed through 20 weeks of therapy had viral loads below 400 copies/mL. (In the reports, the two dosing arms were still blinded, so combined results were given for the entire trial cohort.)

For the past year, Merck, in contrast, has been researching twice-daily indinavir without any ritonavir. Merck's favored bid dose for its protease inhibitor was 1,200 mg, compared to the standard 800 mg three times a day. But on September 18, Merck publicly warned against administering indinavir on this twice daily dosing schedule. Starting a year ago, Merck recruited 635 volunteers without prior treatment to compare AZT/3TC plus either twice daily or thrice daily indinavir. Using an intent-to-treat

analysis, of the 87 participants who reached 24 weeks, 91% on the standard regimen had viral loads under 400, but only 64% on the twice-daily regimen. Twice-a-day indinavir had been controversial because it was feared that the minimum blood levels of drug after 12 hours would be too low to adequately suppress HIV. Those fears seem to have been justified.

Roche is also looking at the efficacy of twice-daily saquinavir. The old Invirase™ formulation of saquinavir has now been largely supplanted by the saquinavir soft gel capsules known as Fortovase™. Fortovase™ contains special lipids that speed saquinavir absorption so that liver enzymes have less chance to break down the drug. But Fortovase™ capsules are very large, and six are supposed to be taken three times a day.

Roche recently has begun releasing the results of its “TIDBID” trial to test the feasibility of administering Fortovase™ twice a day. The TIDBID trial is seeking 825 recruits with no prior treatment history or one limited to nucleoside analogs. They will receive one of three treatments Fortovase™ 1600 mg twice daily or Fortovase™ 1200 mg thrice daily, each in combination with two new nucleoside analogs of choice, or Fortovase™ at 1200 mg twice daily plus nelfinavir at 1250 mg twice daily plus one new nucleoside analog of choice. At Glasgow, researchers reported the preliminary results from the 165 study participants with 32-week data.²⁰ Using an on-treatment analysis, they found that 72% of those taking the twice daily Fortovase™ regimen through 32 weeks had viral loads below 400 copies/mL. The equivalent figures were 75% in the thrice daily Fortovase™ group and 74% in the dual protease inhibitor group.

Twice daily Fortovase™ may be more convenient than three times a day, but the total daily pill burden (16 capsules) is only two capsules less than the total thrice daily burden. Though also given on a twice a day schedule, the Fortovase™/nelfinavir (Viracept™) pill burden, a total of 22 tablets and capsules per day, is largest of all and causes considerably more diarrhea than Fortovase™ alone.

Agouron Pharmaceuticals has long considered a twice daily schedule for its protease

inhibitor nelfinavir because of its 3.5 to 5 hour half-life in the body. The company's Study 542 recruited 279 subjects for a one-year trial of d4T/3TC plus either 750 mg of nelfinavir three times a day (the standard dose) or 1250 mg of nelfinavir twice a day. After 48 weeks, 80% of those still on either of the study regimens had viral loads below 400 copies/mL while about 70% were below 50 copies/mL.²¹ This is using an on-treatment analysis. Peak and trough levels as well as total body exposure were virtually identical on the bid and tid regimens.

The non-nucleoside reverse transcriptase inhibitor delavirdine (Rescriptor™) affects inhibits liver enzymes in the same way as nelfinavir, but this antiviral agent is prescribed on a thrice daily schedule consisting of four 100 mg tablets at each dose. A previous study²² by delavirdine's manufacturer, Pharmacia & Upjohn, found that when nelfinavir and delavirdine are taken concurrently, nelfinavir levels and half-life are doubled – at the expense of decreasing the total delavirdine exposure by half.

These and other data convinced Pharmacia & Upjohn to conduct a study of a twice-a-day regimen of nelfinavir (1250 bid)/delavirdine (600 mg bid) plus d4T (Zerit™) and/or ddI (Videx™) at their standard twice daily doses. Very preliminary data on this 63-person study, covering only 18 participants on the bid regimens at 12 weeks, were released last November.²³ Responses are being compared to 19 persons receiving d4T/ddI plus thrice daily nelfinavir (750 mg) and thrice daily delavirdine (400 mg or 600 mg). Participants' prior treatment was limited to less than one month of ddI. Given the small numbers of people treated so far to 12 weeks, the results are equivalent statistically for all the regimens, with viral load drops ranging from 2.25 to 3.5 logs (99.4% to 99.9%). Only one transient case of neutropenia has been observed so far in the twice-daily treatment cohorts.

Delavirdine also raises indinavir blood levels such that Pharmacia & Upjohn advises reducing the standard 800 mg tid indinavir dose to 400 or 600 mg. The company is now recruiting for a new trial to test twice a day dosing with a combination of indinavir (800

mg), delavirdine (600 mg) and AZT (300 mg).

And From Two Times a Day to One

While delavirdine is moving toward a twice daily schedule, the other NNRTIs are achieving once-a-day (qd) status. Efavirenz was approved by the FDA in September in a once-a-day regimen. DuPont Pharma's most notable trial of this NNRTI was its DMP-006 protocol, which compared 300 bid AZT/150 bid 3TC/800 mg tid indinavir to 600 mg qd efavirenz/1,000 mg tid indinavir to 300 mg bid AZT/150 mg bid 3TC/600 mg bid efavirenz. The last of these regimens is very attractive from a simplification point of view. When using Combivir™, it consists of one tablet in the morning and three capsules and one tablet in the evening. (The evening dose will go down to one capsule and one tablet when the 600 mg efavirenz capsule is introduced next year.) Using an intent-to-treat analysis that counts dropouts as treatment failures, the AZT/3TC/efavirenz arm, in fact, did somewhat better than the others (70% below 400 copies versus about 50% for each of the other two regimens).^{24,25}

But restricting analysis to the people who stayed on treatment yields results that are very close together. This differences between the intent-to-treat and the “on-treatment” analyses occurred because the 006 trial was marked by very high dropout rates, especially for those on indinavir: In the AZT/3TC/efavirenz arm, 25% had left the trial by week 36, compared to 30% for the efavirenz/indinavir arm and 41% for AZT/3TC/indinavir. No records were kept as to how well the remaining volunteers adhered to indinavir's dosing schedule. The differences seen between these regimens could be due to better adherence from a twice-a-day dosing schedule compared to a four-times-a-day one (when you add together the indinavir doses taken every eight hours and the two doses of AZT and 3TC, which are 12 hours apart).

There are concerns about the durability of the AZT/3TC/efavirenz combination. Although the viral suppression seems to hold through 36 weeks, all the drugs in this

combination target the highly malleable reverse transcriptase enzyme. One or two HIV mutations would render efavirenz and all other NNRTI's ineffective, while 3TC requires just one resistance mutation. Viral breakthrough on this regimen might affect the efficacy of other reverse transcriptase inhibitors, too, because of the possible development of cross-resistance. A twice-a-day protease inhibitor would collapse the five daily medicine-taking sessions to two, as with AZT/3TC/efavirenz. A more user-friendly protease inhibitor regimen may have greater success than the efavirenz triple combination, in terms of durable viral suppression, or in the number of salvage therapy options it allows should HIV rebound.

ddI has also been investigated in a once-daily schedule since the early stages of its development because of the long intracellular half-life of its active metabolite (greater than 24 hours for ddA triphosphate). Bristol-Myers has stepped up tests of once daily ddI with the expectation that a 400 mg qd schedule will become the FDA-approved standard. Two relevant 50-person studies were presented in Geneva, one combining ddI with d4T for 48 weeks²⁶ and the other using ddI with and without hydroxyurea for 16 weeks.²⁷ Both found no difference between once daily and twice daily ddI. At Glasgow, investigators reported the results of two Bristol Myers studies (AI454-143²⁸ and -146²⁹) that combined bid or qd ddI with bid d4T in a total of 176 volunteers with little or no prior treatment. Both found no difference between the two ddI schedules, either in terms of CD4 count boost, viral load drop or side effects in the course of 16 to 24 weeks follow-up time. (At week 12, 30% of participants in one trial had viral loads below 500, and 40% in the other had viral loads below 400 regardless of ddI dosing schedule.)

French doctors at ICAAC described treating 60 antiviral-naïve patients with once daily ddI plus twice daily d4T and nevirapine.³⁰ By week 16, 84% of these patients had viral loads below 500 copies/mL. But here's a true once a day regimen: German doctors at Glasgow reported on ddI/3TC/nevirapine, all given once a day.³¹ They prescribed this regimen to 24 patients who had achieved viral loads below 500 on two nucleoside

analogs plus a protease inhibitor but were having toxicity problems. Eighteen of the 24 still had viral loads below 500 after 17 to 52 weeks on treatment. Of the six persons whose HIV rebound, five had had prior treatment with an NNRTI. Further support for the once-a-day administration of the NNRTI nevirapine came from a Dutch study that followed nevirapine blood levels in six persons receiving either 400 mg qd or 200 mg bid nevirapine.³² Trough levels were slightly lower with once daily dosing, but overall, little difference was seen in these blood levels over a 24-hour period. (The possibility of using 3TC once daily has long been noted, given its 10.5 to 15.5 hour intracellular half-life.³³)

Nucleotide analogs, which are singly phosphorylated versions of nucleoside analogs, generally have very long intracellular half-lives. Adefovir, an adenosine analog under development by Gilead Sciences, has been tested from the beginning on a once daily schedule. But the 120 mg dose used since phase I testing turns out to have long-term renal toxicities. Viral load reductions also are modest (about 0.5 log, or 68%).³⁴ Studies of a 60 mg once daily dose are now in progress. The oral prodrug version of PMPA, Gilead's other nucleotide analog based on adenosine, is further behind in development, but it seems more potent and may be a more successful once-a-day drug.³⁵ PMPA's toxicities remain to be fully defined. Other promising once-daily drugs include the two fluoridated nucleoside analogs FTC,³⁶ F-ddA^{37,38} and Bristol-Myers' new protease inhibitor BMS-232632.³⁹

Conclusion

While waiting for the new compounds, there is still much that can be done to simplify the regimens of existing antiviral agents. One attempt along these lines is embodied by trial protocol ICC 604. This newly commenced, 24-week study is coordinated by the Inter-Company Collaboration. It will test a once-daily quadruple combination consisting of adefovir, efavirenz, 3TC and ddI. To be eligible for this protease-sparing combination, potential volunteers must have no prior treatment with either nucleoside analogs or

NNRTTs.

One of the problems with the once daily regimens with the older antiviral drugs has been the inclusion of ddI, which must be taken with a strong antacid on an empty stomach. Last fall, Bristol-Myers Squibb displayed samples of its long-promised capsules containing 400 mg of “enteric-coated” ddI beads. Such a formulation would protect the compound from stomach acid, eliminating the need both to package ddI with a buffer and to take the tablets on an empty stomach separate from other drugs. ddI could then be a true one pill a day, easy-to-take agent and achieve its full potential as one of the most potent nucleoside analogs.

These moves to simplify therapies come none to soon. Although studies may be lacking to support idea that easier anti-HIV regimens will lead to better adherence, the concept seems intuitive. People who are not taking antiviral therapy may not appreciate how hard it is to follow the onerous combination regimens prescribed at present. Anecdotal evidence indicates that “treatment fatigue” is a widespread and growing phenomenon. This fatigue is not a personal character flaw and needs to be confronted compassionately and responsibly. If not, it will lead to still more treatment failure as nonadherence and even treatment cessation increases with time.

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