Daily Dosing of Highly Active Antiretroviral Therapy

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Complex treatment schedules for human immunodeficiency virus (HIV) disease, which can have a high pill burden and can include multiple daily doses, in addition to the adverse effects that the medications can cause, may reduce patient adherence to therapy. Reduced adherence prevents achievement of the desired goal of full suppression of HIV replication, and it also promotes the development of drug-resistant strains of HIV. Thus, the focus of treatment has shifted toward the use of simpler regimens. A major strategy is the development of medications and regimens for management of HIV infection that can be taken once per day. The goal of such a strategy is to improve convenience and optimize adherence, which is critical to maximizing the likelihood of sustained virologic response. Several studies involving regimens with once-daily dosing, which have involved both available agents and agents in development, have yielded promising results. In comparison with standard regimens, which involve dosing 2 or 3 times daily, the regimens with once-daily dosing improved tolerability while maintaining efficacy and safety. The results are expected to increase adherence rates among patients, reduce the incidence of antiretroviral-resistant variants of HIV, and improve the clinical outcomes during a prolonged treatment course.

During the past 2 decades, there has been a steady increase in both the number of antiretroviral medications and the number of possible regimens available to manage HIV and AIDS. Concerns about pill burden, complex treatment schedules, dietary restrictions associated with some regimens, toxicity, adverse effects, and consequent difficulties with patient adherence present substantial barriers to achievement and sustentation of virologic control of HIV replication [1]. The development of drug-resistant strains of HIV is often the result.

To address these issues, researchers have shifted the focus of treatment toward development of simpler regimens that would still maintain efficacy, tolerability, and safety. One strategy involves combining different agents into 1 tablet, as exemplified by the development of Combivir (Glaxo Wellcome; zidovudine and lamivudine), Trizivir (Glaxo Wellcome; zidovudine, lamivudine, and abacavir), and Kaletra (Abbott Laboratories; lopinavir and ritonavir). Other strategies involve the development of drugs with longer half-lives and the development of safer drugs with lower levels of toxicity, which would permit the administration of higher doses of the drug with less frequency. Another approach is to exploit drug-drug interactions to enhance therapeutic drug levels, such as those associated with dual-protease inhibitor (PI) regimens. The pharmacokinetic result of this approach is improved drug exposure, which is defined by plasma-drug concentrations (especially trough levels \(C_{\text{min}}\)), area-under-the-curve (AUC) values, and the time above the concentration needed to inhibit 50% (IC\(_{50}\)) or 90% (IC\(_{90}\)) of viral replication. On the basis of these strategies, medications and regimens with once-daily dosing are becoming increasingly available for management of HIV infection. These medications and regimens offer improvements...
in convenience and optimization of adherence to therapy, both of which are critical to maximize the likelihood of sustained virologic response.

REVERSE-TRANSCRIPTASE INHIBITORS (RTIs) TAKEN ONCE DAILY

RTIs are an integral part of antiretroviral therapy; they include the nucleoside reverse-transcriptase inhibitors (NRTIs) and the nonnucleoside reverse-transcriptase inhibitors (NNRTIs). Medications currently approved for once-daily dosing are the NRTI didanosine (400 mg) [2] and the NNRTI efavirenz (600 mg) [3, 4]. To improve tolerability, didanosine is now available in an enteric-coated form. Trials are in progress to evaluate once-daily dosing of some established RTIs that have been approved for twice-daily dosing (nevirapine, lamivudine, and stavudine). Other trials are in progress to evaluate the new agents of tenofovir and emtricitabine for once-daily dosing.

NNRTIs

Nevirapine is an NNRTI licensed for dosages of 200 mg twice per day. In 3 separate studies, 400 mg of nevirapine given once daily was found to be as safe and effective as the standard dosage (200 mg b.i.d.) when it was given to antiretroviral-naive patients in combination with stavudine (40 mg b.i.d.) and didanosine (400 mg q.d.) [5, 6, 7]. Capravirine is a new, “second-generation” NNRTI that is effective against both wild-type and NNRTI-resistant variants of HIV type 1 (HIV-1), including strains with the K103N mutation. Phase II trials (AG 1549-508 and 1549-509, sponsored by Agouron Pharmaceuticals) are comparing the safety and potency of twice-daily administration of capravirine with the safety and potency of placebo, given in combination with nelfinavir and 2 NRTIs; they are being given to PI-naive, HIV-infected patients (all of whom experienced treatment failure with an initial regimen that contained an NNRTI) for 48 weeks. A pharmacokinetic study that involved healthy volunteers supports the possibility that once-daily administration of capravirine will be safe and effective [8]. Recently, capravirine development was suspended because vasculitis occurred in dogs that underwent long-term dosing. The implications for human patients must be explored.

NRTIs

Stavudine is licensed for dosages of 40 mg twice per day. A phase III trial (AI455-099) is comparing standard dosages of stavudine with an extended-release stavudine formulation, which is given as a single 100-mg capsule once per day, for 56 weeks. Emtricitabine, a new NRTI, is a fluorinated cytosine analog that is administered in a daily dose of 200 mg [9]. Emtricitabine is similar to lamivudine in structure, has activity against HIV and hepatitis B virus (HBV), and is associated with the M184V mutation in drug-resistant variants of HIV-1. The safety and efficacy of emtricitabine given once daily are discussed below.

Tenofovir, a new nucleotide RTI, is administered as one 300-mg tablet taken daily. Initial studies have demonstrated that tenofovir is effective for up to 48 weeks when it is added to existing regimens of antiretroviral therapy in patients with NRTI-resistant variants of HIV-1. Tenofovir, when given in daily doses of 75 mg, 150 mg, and 300 mg, yielded 0.4-log, 0.6-log, and 0.7-log reductions in virus loads, respectively [10, 11]. A phase III trial (GS-99-903) is comparing tenofovir with stavudine in regimens that also contain lamivudine and efavirenz; these regimens are being given to HIV-1–infected, antiretroviral-naive patients for 48 weeks.

PI THERAPY GIVEN ONCE DAILY

Dual-PI regimens have been used in salvage therapy for HIV-1–infected patients with PI-resistant variants of HIV. Ritonavir is a potent inhibitor of the cytochrome P-450 CYP3A4 isozyme; therefore, it can enhance the plasma concentrations of indinavir, saquinavir, amprenavir, lopinavir, and nelfinavir. Regimens that contain dual PIs have proven efficacy when the medications are given twice daily, and the efficacy of once-daily dosing of these regimens is now under investigation. Several pharmacokinetic studies support the daily administration of dual-PI regimens, with the 24-h Cmin being more than the IC50 of drug-susceptible HIV isolates [12–14]. An example of the curves that compare the pharmacokinetic concentration of a standard split dose versus that of a dose given once-daily is shown in figure 1 (Saah, personal communication).

Indinavir (1200 mg) and ritonavir (100 mg) taken daily in a regimen that also contains 2 NRTIs were found to be safe and effective in a study by Maggiolo et al. [15]. In this small study, 9 patients received the standard dose of indinavir every 8 h; they also received 2 NRTIs in standard split doses, twice per day. All patients had suppressed virus loads (<500 copies/mL), and 8 of the 9 subjects had ultrasuppressed virus loads (<50 copies/mL). Indinavir therapy was then switched to indinavir-ritonavir therapy given daily. The virus loads of all patients remained suppressed after 4 weeks. Higher doses of ritonavir may be needed to achieve an optimum increase in the 24-h Cmin levels of indinavir.

A study demonstrated that the combination of a saquinavir soft-gel capsule (1200 mg or 1600 mg) plus ritonavir (100 mg) is effective when given once daily as part of a salvage regimen for patients who have difficulty adhering to treatment regimens [16]. Virus loads were suppressed to less than the levels of detection in most patients who were studied. A follow-up trial
A small study of saquinavir was performed, which was similar to the aforementioned study of saquinavir given daily; in this study [17], HIV-1 infected patients received therapy with saquinavir (1600 mg q.d.) plus ritonavir (100 mg q.d.) in combination with 2 NRTIs. Prior to the switch of saquinavir given twice per day to saquinavir-ritonavir given once per day, combination with 2 NRTIs. Prior to the switch of saquinavir given twice per day to saquinavir-ritonavir given once per day, 6 of the 15 subjects who received saquinavir twice daily had suppressed virus loads (<500 copies/mL), and 4 of these 6 subjects had ultrasuppressed virus loads (<50 copies/mL). Thirty weeks after therapy was switched, 12 (80%) of the 15 subjects had suppressed virus loads, and 8 of these 12 subjects had ultrasuppressed virus loads. The CD4 cell count increased by a mean of 164 cells/μL in 13 (87%) of 15 patients. The rate of adverse effects among patients who received dual-PI therapy once daily decreased 80%–90%, and the adherence rates for these patients increased from 33% to 93% when compared with their prior regimen.

Combination therapy with nelfinavir and ritonavir has also been evaluated in studies of a regimen of dual PIs given once daily. The only available reports provide pharmacokinetic data for healthy HIV-negative volunteers, and the results of these reports support once-daily administration of nelfinavir-ritonavir at 1875 mg/200 mg, 2500 mg/100 mg, or 2500 mg/200 mg [14]. This regimen had AUC, maximum concentration (Cmax), and Cmin values comparable to those achieved with nelfinavir (1250 mg b.i.d.), and it would simplify the dosing schedule but increase the pill burden. However, a new 625-mg formulation of nelfinavir, which is in the advanced stages of development, would reduce the pill burden.

One of the newly approved PIs, amprenavir, has limited cross-resistance with nelfinavir, ritonavir, indinavir, and saquinavir. Thus, like nelfinavir, amprenavir may be of benefit in PI sequencing. Amprenavir may also have a role in salvage regimens. Amprenavir has been approved for doses of 1200 mg twice per day, and studies examining salvage therapy with amprenavir (600 mg b.i.d.) plus ritonavir (100 mg b.i.d.) are underway [18]. In one study (APV 20001), a 24-week course of amprenavir (600 mg b.i.d.) plus ritonavir (100 mg b.i.d.) is being compared with a 24-week course of amprenavir (1200 mg q.d.) plus ritonavir (200 mg q.d.); these 2 regimens also include the standard dosages of abacavir (300 mg b.i.d.) and lamivudine (150 mg b.i.d.). At 12 weeks of treatment, 9 of 12 patients who received the drugs twice daily had virus loads of <400 copies/mL, and 7 of these 12 patients had virus loads of <50 copies/mL. The mean CD4 count increased from 348 cells/μL to 579 cells/μL. Of the 10 patients who received amprenavir-ritonavir once daily, 10 had virus loads of <50 copies/mL, and the mean CD4 count increased from 185 cells/μL to 334 cells/μL [19]. A second study, in which amprenavir administered once daily in being evaluated in a regimen that uses dual PIs, is discussed below.

Lopinavir-ritonavir (Kaletra; Abbott Laboratories) is a newly licensed dual PI coformulated in a single tablet for twice-daily dosing [20]. Unpublished pharmacokinetic data on once-daily dosing have been discussed in several forums, including a small study in which lopinavir-ritonavir (400 mg b.i.d./100 mg b.i.d.), in combination with stavudine and lamivudine, was compared with lopinavir-ritonavir (800 mg q.d./200 mg q.d.), in combination with stavudine and lamivudine (M. Robinson, Abbott Laboratories; personal communication).

Atazanavir (BMS 232632; Bristol-Myers Squibb) is a promising new PI that does not require the boosting effect of ritonavir for once-daily dosing. Phase I and II studies indicate that atazanavir, when given at dosages of 200 mg, 400 mg, or 500 mg per day, was as effective as nelfinavir. Both drugs were tested as monotherapy for 14 days and then were tested in combination with stavudine plus didanosine for 12 weeks. Although atazanavir was associated with fewer episodes of diarrhea than was nelfinavir (percentage of patients who had diarrhea, 22% vs. 65%), it was associated with a 51% incidence of dose-dependent isolated hyperbilirubinemia [21]. The unconjugated hyperbilirubinemia was not associated with elevated liver enzyme levels. Atazanavir was not associated with hyperlipidemia, unlike nelfinavir. Phase II data for 265 patients treated with the 400-mg dose were analyzed at week 12 of treatment; 70% of the patients were found to have a virus load of <400 copies/mL, and 31% of the patients had a virus load of <50 copies/mL [22]. HIV variants that were resistant to other PIs remained susceptible to atazanavir. Phase III studies

![Figure 1. Indinavir and ritonavir. The curves represent the pharmacokinetic concentrations of standard split dosing of indinavir (800 mg q8h) over time compared with the once-daily dosing of indinavir-ritonavir (1200 mg/100 mg q.d.) from the Merck 021 study. ▲, indinavir-ritonavir (1200 mg/100 mg q.d.); ●, indinavir (800 mg 8h). (Provided by A. Saah, Merck Pharmaceuticals, studies 021 and 089.)](image-url)
<table>
<thead>
<tr>
<th>Study parameter</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs (dose)</strong></td>
<td>ddI (300 mg), 3TC (300 mg), and EFV (600 mg)</td>
<td>ddl (400 mg), FTC (200 mg), and EFV (600 mg)</td>
<td>ddl (300 mg), EFV (600 mg), Idv (1200 mg), and Rtv (400 mg)</td>
<td>3TC (300 mg), ABC (600 mg), APV (1200 mg), and Rtv (300 mg)</td>
<td>ddl (400 mg), NVP (400 mg), and EFV (600 mg)</td>
</tr>
<tr>
<td><strong>Pill count</strong></td>
<td>8</td>
<td>7</td>
<td>g</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td><strong>Study population (therapy)</strong>^b</td>
<td>Treatment-naive subjects</td>
<td>Treatment-naive subjects with a virus load &gt;5000 copies/mL and a CD4 count &gt;100 cells/μL</td>
<td>Treatment-naive subjects (dual PI)</td>
<td>Treatment-naive subjects (dual PI)</td>
<td>Treatment-naive and PI-experienced subjects (dual NRTI)</td>
</tr>
<tr>
<td><strong>Number of subjects</strong></td>
<td>57</td>
<td>40</td>
<td>10</td>
<td>25</td>
<td>15 PI-naive and 11 PI-experienced subjects</td>
</tr>
<tr>
<td><strong>Duration of study</strong></td>
<td>32 weeks and 48 weeks^c</td>
<td>24 weeks and 48 weeks^c</td>
<td>12 weeks</td>
<td>48 weeks</td>
<td>9 months</td>
</tr>
<tr>
<td><strong>End points</strong></td>
<td>Mean CD4 count, cells/μL</td>
<td>Increase of 300 ± 228 to 558 ± 298 at week 32; no change from weeks 32 to 42</td>
<td>Increase of 159 at week 24</td>
<td>Increase of 165</td>
<td>Pending</td>
</tr>
<tr>
<td><strong>Virus load, copies/mL</strong></td>
<td>At week 32, &lt;500 for 94% of subjects and &lt;50 for 76%; at week 42, &lt;50 for 60%</td>
<td>At week 24, &lt;400 for 98% of subjects and &lt;50 for 93%; at week 48, &lt;500 for 95%</td>
<td>&lt;400 for 8 of 10 subjects</td>
<td>Pending</td>
<td>&lt;400 for 12 of 12 PI-naive and 9 of 9 PI-experienced subjects</td>
</tr>
<tr>
<td><strong>Adverse drug reactions</strong></td>
<td>6 patients discontinued therapy: 1 quit, 2 had rash, 1 had nausea, and 1 had heart failure and died</td>
<td>1 patient quit the study; 73% of the subjects had mild CNS effects, 33% had diarrhea, and 10% had rash</td>
<td>1 subject quit the study because of vomiting, and 1 subject was noncompliant</td>
<td>Pending</td>
<td>3 of 15 PI-naive and 2 of 11 PI-experienced patients discontinued therapy because of rash or CNS toxicity</td>
</tr>
<tr>
<td><strong>Published in peer-reviewed journal [reference]</strong></td>
<td>No [21, 22]</td>
<td>Yes [9]</td>
<td>Yes [26]</td>
<td>No^f</td>
<td>No [23]</td>
</tr>
</tbody>
</table>

**NOTE.**  
ABC: abacavir; APV, amprinavir; ddl, didanosine; EFV, efavirenz; FTC, emtricitabine; Idv, indinavir; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; Rtv, ritonavir; 3TC, lamivudine.

^a In addition to 5 cc of Rtv.
^b All studies were open label and prospective.
^c The duration of the initial studies was 32 weeks for A and 24 weeks for B. The follow-up studies extended the duration of both A and B to 48 weeks.
^d Data are mean values ± SDs.
^e Dizziness, headache, and/or insomnia.
^f This study was sponsored by the National Institute for Allergy and Infectious Diseases (AIDSTRIALS Listing of Clinical Trials trial number 00 I-0053).
of atazanavir given at a dosage of 400 mg per day are being conducted.

FINDINGS FROM STUDIES OF REGIMENS WITH ONCE-DAILY DOSING SCHEDULES

The optimum schedule for highly active antiretroviral therapy (HAART) may be a regimen in which all medications are taken once daily. Although studies have suggested that the adherence breakpoint is between 2 and 3 doses per day [1], a regimen in which medications are taken once daily may be physically and psychologically easier for many patients who are undergoing lifelong treatment. There is real potential for use of therapy with a once-daily dosing schedule as directly observed therapy (DOT) in selected settings, such as in correctional facilities or methadone clinics. Practical considerations may suggest a need for 30–32-h Cmin levels that are greater than the protein-adjusted IC50, if one considers the following scenarios: (1) the medications are usually taken in the morning, but the patient forgets to take the medications until after work; and (2) the medications are usually taken in the evening, but the patient falls asleep and takes the medications in the morning. These situations suggest that an extra 6–8-h margin of levels of suppression may be needed to maintain the durability of virus suppression. Regimens with once-daily dosing schedules do appear to be safe and effective in studies (table 1), as illustrated below.

A regimen that contained didanosine (300 mg q.d.), lamivudine (300 mg q.d.), and efavirenz (600 mg q.d.) was evaluated in 57 antiretroviral-naive, HIV-infected patients (see regimen A in table 1) [23]. Before the subjects received treatment, the baseline virus loads ranged from 6520 copies/mL to 750,000 copies/mL, and the mean CD4 cell count (±SD) was 300 ± 228 cells/μL. At week 32 of treatment, 94% of the subjects had a virus load of <500 copies/mL, 76% had a virus load of <50 copies/mL, and the mean CD4 cell count (±SD) had increased to 558 ± 298 cells/μL [23]. Sixty-eight patients were followed up, and it was demonstrated that 60% of the patients who took the medications once daily maintained an ultrasuppressed virus load at 48 weeks of treatment and at 1 year of follow-up [24].

Another study examined a regimen of didanosine (400 mg q.d.), emtricitabine (200 mg q.d.), and efavirenz (600 mg q.d.), which was used to treat 40 antiretroviral-naive, HIV-infected patients (see regimen B in table 1) [9]. At week 24 of treatment, 98% of the patients had suppressed virus loads (<400 copies/mL), and 93% of patients had ultrasuppressed virus loads (<40 copies/mL). The CD4 count had increased by a mean of 159 cells/μL [9]. At week 48 of treatment, 95% of the patients maintained an undetectable virus load (<400 copies/mL).

It is not standard practice for persons to receive treatment that combines 2 NNRTIs. The scientific basis for this is unclear; perhaps it is not done because each agent alone has a half-life that is long enough to justify once-daily administration. Once-daily administration of dual-NNRTI therapy was studied in an investigator-initiated trial [25]. In this trial, 15 antiretroviral-naive, HIV-infected patients and 11 antiretroviral-experienced, HIV-infected patients received a regimen of didanosine (400 mg q.d.), efavirenz (600 mg q.d.), and nevirapine (400 mg q.d.; see regimen E in table 1). A total of 5 patients discontinued therapy because they experienced rash or CNS-related adverse events. After 9 months of treatment, 12 of the 12 antiretroviral-naive patients who remained in the study had suppressed virus loads (<400 copies/mL), and the mean increase in CD4 cell

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Table 2. Potential options for highly active antiretroviral therapy with once-daily dosing.

<table>
<thead>
<tr>
<th>Drug (dose)</th>
<th>Column A</th>
<th>Column B</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER stavudine and EC didanosine</td>
<td>Atazanavir&lt;sup&gt;a&lt;/sup&gt; (400 mg)</td>
<td>Ritonavir-enhanced dual PI</td>
</tr>
<tr>
<td>ER stavudine and lamivudine</td>
<td>Indinavir-ritonavir (1200 mg/200 mg or 1200 mg/400 mg)</td>
<td></td>
</tr>
<tr>
<td>ER stavudine and emtricitabine</td>
<td>Amprinavir-ritonavir (1200 mg/200 mg or 1200 mg/300 mg)</td>
<td></td>
</tr>
<tr>
<td>EC didanosine and lamivudine</td>
<td>Saquinavir-ritonavir (1600 mg/100 mg)</td>
<td></td>
</tr>
<tr>
<td>EC didanosine and emtricitabine</td>
<td>Nelfinavir-ritonavir (2500 mg/100 mg or 2500 mg/200 mg)</td>
<td></td>
</tr>
<tr>
<td>EC didanosine and tenofovir</td>
<td>Dual NNRTI&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Tenofovir and lamivudine</td>
<td>Ritonavir-enhanced dual PI</td>
<td></td>
</tr>
<tr>
<td>Tenofovir and emtricitabine</td>
<td>Nevirapine (400 mg)</td>
<td></td>
</tr>
<tr>
<td>Possibly abacavir with any single or combined NRTI listed above</td>
<td>Possibly capravirine</td>
<td></td>
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</tbody>
</table>

NOTE. Choose a nucleoside reverse-transcriptase inhibitor (NRTI) combination from column A and a protease inhibitor (PI) or nonnucleoside reverse-transcriptase inhibitor (NNRTI) option from column B. EC, enteric-coated; ER, extended release.

<sup>a</sup> Study drug BMS 232632 (Bristol-Myers Squibb).

<sup>b</sup> Efavirenz (600 mg) plus nevirapine (400 mg).
count was 351 cells/µL. Nine of the 9 antiretroviral-experienced patients who remained in the study had suppressed virus loads (<400 copies/mL), and the mean increase in the CD4 cell count was 203 cells/µL [25].

Two studies evaluated dual-PI regimens given once daily [26]. In the first study, 10 antiretroviral-naive, HIV-infected patients received indinavir (1200 mg q.d.), ritonavir (400 mg q.d.), efavirenz (600 mg q.d.), and didanosine (300 mg q.d.; see regimen C in table 1). After 12 weeks, 8 of the 10 subjects had suppressed virus loads (<400 copies/mL), and the average increase in their CD4 cell counts was 165 cells/µL [26]. The second study (00 I-0053; sponsored by the National Institute for Allergy and Infectious Diseases) is in progress. It is evaluating the safety, tolerability, and efficacy of a regimen of amprenavir (1200 mg q.d.), ritonavir (300 mg q.d.), abacavir (600 mg q.d.), and lamivudine (300 mg q.d.) being given to antiretroviral-naive, HIV-infected patients for 48 weeks (see regimen D in table 1).

DISCUSSION

Several antiretroviral agents and combination drug regimens with once-daily dosing schedules are becoming available as part of HAART. Efavirenz has been approved by the US Food and Drug Administration for once-daily administration; didanosine, given as the new, single, enteric-coated 400-mg capsule, has also been approved. Pharmacokinetic data support the potential use of lamivudine, nevirapine, several dual-PI combinations, and, possibly, nevirapine plus efavirenz as therapy with once-daily dosing. New agents are being developed for once-daily administration, including extended-release stavudine, emtricitabine, tenofovir, atazanavir, and, possibly, capravirine. The regimens with once-daily dosing schedules that have been studied include (1) didanosine (300 mg), lamivudine (300 mg), and efavirenz (600 mg); (2) didanosine (400 mg), emtricitabine (200 mg), and efavirenz (600 mg); (3) didanosine (400 mg), nevirapine (400 mg), and efavirenz (600 mg); (4) didanosine (300 mg), indinavir (1200 mg), ritonavir (400 mg), and efavirenz (600 mg); and (5) saquinavir (1600 mg) and ritonavir (100 mg), in combination with 2 NRTIs.

A study evaluating the regimen of amprenavir (1200 mg q.d.), ritonavir (300 mg q.d.), abacavir (600 mg q.d.), and lamivudine (300 mg q.d.) is presently in progress. Future studies may examine various combinations of medications, including tenofovir, extended-release stavudine, capravirine, lamivudine, and atazanavir, in regimens with once-daily administration. If one considers the agents that are available and in development, there are numerous attractive regimens that can be crafted (table 2).

Most reports regarding regimens with once-daily administration are from the abstracts of reports presented at national and international conferences. Very few reports are from peer-reviewed journals. Although the data from the initial studies are promising, these regimens have not been proven to be as effective as the accepted regimens in large, carefully controlled trials. Therefore, regimens with once-daily administration must be considered experimental.

The new agents that are being developed for once-daily administration are promising, as are the results of studies of newer ways to administer older agents once daily. The hopes are that the pill burden may be reduced and the dosing schedule simplified while effective and safe treatment is maintained and that the regimens be made more tolerable, which would yield improved rates of adherence among HIV-infected patients. This would result, one hopes, in reductions in the incidence of antiretroviral-resistant variants of HIV and improvements in the clinical outcomes over prolonged courses of treatment.

References


