Pharmacological Basis for Concentration-Controlled Therapy with Zidovudine, Lamivudine, and Indinavir

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Conventional antiretroviral therapy involves administration of standard fixed doses to adults and adolescents. This approach ignores interindividual variability in pharmacokinetics and results in substantial differences in systemic concentrations among patients. Thus, variability in systemic concentrations contributes to variability in response to therapy. This study was designed to evaluate the feasibility and safety of a regimen of zidovudine, lamivudine, and indinavir designed to achieve select target concentrations versus standard dose therapy. Twenty-four antiretroviral-naïve subjects completed the 24-week study; 13 received standard therapy, and 11 received concentration-controlled therapy. There were no differences in baseline characteristics. Oral clearance for all three drugs was not different between weeks 2 and 28; average ratios of week 2 oral clearance to week 28 oral clearance were 0.95, 1.09, and 1.06 for zidovudine, lamivudine, and indinavir, respectively, with 95% confidence intervals including 1. The selected target concentrations were average steady-state concentrations of 0.19 mg/liter for zidovudine and 0.44 mg/liter for lamivudine and a trough concentration of 0.15 mg/liter for indinavir; mean concentrations achieved at week 28 in the concentration-controlled arm were 0.20, 0.54, and 0.19 mg/liter, respectively. Concentration-controlled therapy significantly reduced interpatient variability in zidovudine concentrations and significantly increased indinavir concentrations. There was no difference in adverse drug effects or adherence. This investigation has provided a pharmacologic basis for concentration-controlled therapy by demonstrating that it is feasible and has a safety profile no different from that of standard therapy. Additional studies to evaluate the virologic effect of the concentration-controlled approach to antiretroviral therapy are warranted.

Combination therapy with three or more highly active antiretroviral agents is advocated for the treatment of human immunodeficiency virus (HIV) infection (b; Panel on Clinical Practices for Treatment of HIV Infection [http://www.hivatis.org/trtgdnls.html]. Recommended first-line regimens include the use of two nucleoside reverse transcriptase inhibitors with either one or two protease inhibitors, or with a nonnucleoside reverse transcriptase inhibitor. Among these combination regimens, zidovudine, lamivudine, and indinavir have demonstrated the most effective and most durable response to date (15–17, 20). Unfortunately, not all patients adequately respond to highly active antiretroviral therapy. This heterogeneity has been attributed to pharmacologic, virologic, immunologic, and behavioral differences among patients. Conventional antiretroviral therapy involves the administration of standard fixed doses to adults and adolescents. This approach ignores interindividual variability in pharmacokinetic processes and results in substantial differences in systemic concentrations among patients. It is becoming increasingly evident that pharmacodynamic relationships exist between antiretroviral drug concentrations and response for all classes of antiretrovirals (1, 4, 5, 11, 14, 18, 19, 22, 23, 31, 33; E. P. Acosta et al., 7th Conf. Retrovir. Opportun. Infect., abstr. 455, 2000; A. S. Joshi et al., 39th Int. Conf. Antimicrob. Agents Chemother., abstr. I-1201, 1999; D. Slain et al., 38th Int. Conf. Antimicrob. Agents Chemother., abstr. A-74, 1998). Therefore, heterogeneity in the response to antiretroviral therapy may arise from variability in systemic antiretroviral concentrations. Employing doses regimens to achieve a target systemic concentration may improve clinical outcome by reducing variability in the pharmacologic contribution to therapeutic success. The specific aims of this study were, first, to determine whether a novel dose adjustment strategy we developed to achieve and maintain selected concentrations of zidovudine, lamivudine, and indinavir in plasma was feasible and, second, to evaluate the safety of the concentration-controlled approach versus the standard dose regimen.

MATERIALS AND METHODS

Human subjects and study design. This investigation was approved by the Human Subjects Committee of the University of Minnesota and was conducted at the Outpatient Clinic of the General Clinical Research Center at the University of Minnesota. Subjects were informed about the study and gave written consent prior to participation. Antiretroviral-naïve, HIV-infected persons (age, 18 to 60 years) with plasma HIV RNA levels of ≥5,000 copies/ml and CD4 T-lymphocyte counts of ≥100 cells/μl were eligible for participation. Exclusion criteria included active opportunistic infection that would require interruption of antiretroviral therapy and known history of nonadherence with medications or scheduled physician and clinic visits. After enrollment, individuals missing scheduled clinic visits and not rescheduling within 1 week or in <85% adherence with their assigned regimen as assessed by medication counts or interview were discontinued from the study.

This study was a randomized, open-label study of standard dose therapy compared with concentration-controlled therapy. The initial phase of the study

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was 6 months; long-term follow-up will be presented separately. All participants were initially treated with lamivudine (150 mg twice daily) and indinavir (800 mg every 8 h) for the first 2 weeks. Zidovudine was started at a dose of 100 mg twice daily for the first week and then increased to 200 mg twice daily for the second week to minimize gastrointestinal side effects. By week 2, patients were randomized to either standard therapy—consisting of zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and indinavir (800 mg every 8 h)—or concentration-controlled therapy. Randomization was performed using a permuted block approach with assignments contained in sealed, opaque envelopes sequentially numbered. Patients randomized to standard therapy received separate zidovudine and lamivudine tablets for the 6-month study period. Study participants to receive concentration-controlled therapy received an individualized regimen developed to maintain targeted antiretroviral drug concentrations in plasma. An average steady-state concentration in plasma (C\text{ss}) of 0.19 mg/liter was selected for zidovudine. This concentration was based on our previous experience with concentration-controlled zidovudine monotherapy (12). The target C\text{ss} selected for lamivudine was 0.44 mg/liter. This target was selected because it is the C\text{ss} that persons receiving 150 mg of lamivudine would have if they were perfectly adherent and had average values for lamivudine bioavailability and total body clearance (30). This was the same conceptual approach originally used to define the target concentration for zidovudine. The C\text{ss} was chosen for both drugs based upon in vitro data showing that the amount of intracellular triphosphate formed is related to the extracellular concentration of the parent drug (21). A trough concentration (C\text{tr}) of 0.15 mg/liter was selected for indinavir based on two considerations. First, the concentration of indinavir necessary to inhibit 95% of HIV replication in vitro ranges from 0.015 to 0.061 mg/liter for wild-type HIV isolates. Plasma protein binding of indinavir is approximately 56%; therefore, a concentration in plasma above 0.110 mg/liter in vivo would theoretically be necessary to achieve unbound concentrations sufficient to inhibit 95% of wild-type virus. Second, an exploratory study of indinavir concentrations and effect in a cohort of 23 persons receiving nucleoside therapy originally used to define the target concentration for zidovudine. The C\text{ss} was selected for lamivudine was 0.44 mg/liter. This target was selected compared with those that had HIV RNA detectable in plasma (1). For both of

For lamivudine, the median indinavir concentrations and effect in a cohort of 23 persons receiving nucleoside therapy was 6 months; long-term follow-up will be presented separately. All participants were initially treated with lamivudine (150 mg twice daily) and indinavir (800 mg every 8 h) for the first 2 weeks. Zidovudine was started at a dose of 100 mg twice daily for the first week and then increased to 200 mg twice daily for the second week to minimize gastrointestinal side effects. By week 2, patients were randomized to either standard therapy—consisting of zidovudine (300 mg twice daily), lamivudine (150 mg twice daily), and indinavir (800 mg every 8 h)—or concentration-controlled therapy. Randomization was performed using a permuted block approach with assignments contained in sealed, opaque envelopes sequentially numbered. Patients randomized to standard therapy received separate zidovudine and lamivudine tablets for the 6-month study period. Study participants to receive concentration-controlled therapy received an individualized regimen developed to maintain targeted antiretroviral drug concentrations in plasma. An average steady-state concentration in plasma (C\text{ss}) of 0.19 mg/liter was selected for zidovudine. This concentration was based on our previous experience with concentration-controlled zidovudine monotherapy (12). The target C\text{ss} selected for lamivudine was 0.44 mg/liter. This target was selected because it is the C\text{ss} that persons receiving 150 mg of lamivudine would have if they were perfectly adherent and had average values for lamivudine bioavailability and total body clearance (30). This was the same conceptual approach originally used to define the target concentration for zidovudine. The C\text{ss} was chosen for both drugs based upon in vitro data showing that the amount of intracellular triphosphate formed is related to the extracellular concentration of the parent drug (21). A trough concentration (C\text{tr}) of 0.15 mg/liter was selected for indinavir based on two considerations. First, the concentration of indinavir necessary to inhibit 95% of HIV replication in vitro ranges from 0.015 to 0.061 mg/liter for wild-type HIV isolates. Plasma protein binding of indinavir is approximately 56%; therefore, a concentration in plasma above 0.110 mg/liter in vivo would theoretically be necessary to achieve unbound concentrations sufficient to inhibit 95% of wild-type virus. Second, an exploratory study of indinavir concentrations and effect in a cohort of 23 persons receiving nucleoside therapy originally used to define the target concentration for zidovudine. The C\text{ss} was selected for lamivudine was 0.44 mg/liter. This target was selected compared with those that had HIV RNA detectable in plasma (1). For both of

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Dose adjustment for indinavir was based on the following rearrangement of an equation for steady-state C\text{ss}:
subsequently enrolled in the study. No potential participant
terminated to be eligible based upon laboratory criteria and were
with HIV consented to participate in this study; all were de-
used for statistical analyses. For all statistical analyses, a

tain the patient database. Statview 5.0.1 (SAS Institute, Inc., Cary, N.C.) was
by ANOVA. Excel 98 (Microsoft Inc., Redmond, Wash.) was used to main-

HIV RNA (log10 copies/ml) (mean ± SD) 4.56 ± 0.47 4.71 ± 0.65

these considerations, a sample size of 24 patients was sufficient at an α of 0.05
and 80% power.

Baseline patient characteristics were evaluated with the Mann-Whitney U
test. Comparisons of pharmacokinetic parameters between treatment groups
and between weeks 2 and 28 were analyzed with repeated-measures ANOVA.
Variances were compared by using the F test. Assessment of adherence data was done
by ANOVA. Excel 98 (Microsoft Inc., Redmond, Wash.) was used to main-
tain the patient database. Statview 5.0.1 (SAS Institute, Inc., Cary, N.C.) was used for statistical analyses. For all statistical analyses, a P value of <0.05 was
considered significant.

RESULTS

Human subjects. Thirty-two antiretroviral-naïve persons with HIV consented to participate in this study; all were
determined to be eligible based upon laboratory criteria and were
subsequently enrolled in the study. No potential participant
was excluded from participation for a known history of non-
adherence with medications or scheduled physician and clinic
visits. Eight patients did not complete the 28-week study
period. One subject moved out of state. Two participants at study
weeks 4 and 8, respectively, were lost to follow-up. One
participant randomized to concentration-controlled therapy with-
drew from the study at week 8 because of an unwillingness to
meet protocol requirements. Four individuals withdrew prior
to week 28 for medical reasons or because of drug toxicity; two
people (one each randomized to concentration-controlled and
standard therapy) withdrew for gastrointestinal intolerance,
one person (standard therapy) withdrew after the development
of peripheral neuropathy at study week 4, and one person
(standard therapy) was discontinued after the development of
a brain lesion and anemia at week 12. Of the remaining 24
subjects, 13 were randomized to standard therapy and 11 were
randomized to concentration-controlled therapy. There were
no differences in baseline characteristics between the two

treatment groups (Table 1).

Pharmacokinetic evaluations. The week 2 and 28 pharma-
cokinetic parameters for zidovudine, lamivudine, and indinavir,
for both arms of the study are presented in Table 2. There was
no difference in CL/F for zidovudine, lamivudine, and indinavir
between week 2 and week 28 or between standard and concen-
tration-controlled therapy recipients. Figure 1 presents CL/F values for all 24 patients at week 2 and week 28. The average ratios of week 2 to week 28 CL/F (and 95% confidence
interval) for the following medications were as indicated:

zidovudine, 0.95 (0.78 to 1.12); lamivudine, 1.09 (0.96 to 1.22);
and indinavir, 1.06 (0.9 to 1.22).

Dose adjustments for zidovudine, lamivudine, or indinavir
were necessary for 10 out of 11 concentration-controlled pa-

| TABLE 2. Pharmacokinetic parameters of zidovudine, lamivudine, and indinavir at weeks 2 and 28 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug and parameter             | Wk 2a           | Wk 28a          | Mean ± SD for indicated subjects at: |
|                                | Std (n = 13)    | CC* (n = 11)    | All (n = 24)    | Std (n = 13)    | CC (n = 11)     | All (n = 24)     |
| Zidovudine                      |                 |                 |                 |                 |                 |                 |
| CL/F (liters/h/kg)             | 2.52 ± 1.52     | 1.78 ± 0.52     | 2.18 ± 1.21     | 2.07 ± 0.41     | 2.15 ± 0.37     | 2.11 ± 0.38     |
| V/F (liters/kg)                | 2.31 ± 0.96     | 2.04 ± 0.55     | 2.21 ± 0.83     | 2.79 ± 0.42     | 2.41 ± 0.87     | 2.61 ± 0.68     |
| t1/2 (h)                       | 0.72 ± 0.29     | 0.71 ± 0.17     | 0.71 ± 0.24     | 0.96 ± 0.16     | 0.74 ± 0.20     | 0.86 ± 0.21d    |
| Cmin (mg/liter)                | 0.19 ± 0.08     | 0.20 ± 0.06     | 0.20 ± 0.07     | 0.20 ± 0.06     | 0.20 ± 0.03e    | 0.19 ± 0.05     |
| Lamivudine                      |                 |                 |                 |                 |                 |                 |
| CL/F (liters/h/kg)             | 0.38 ± 0.09     | 0.37 ± 0.06     | 0.38 ± 0.08     | 0.38 ± 0.10     | 0.37 ± 0.09     | 0.38 ± 0.09     |
| V/F (liters/kg)                | 1.47 ± 0.54     | 1.36 ± 0.35     | 1.42 ± 0.46     | 1.33 ± 0.33     | 1.38 ± 0.33     | 1.35 ± 0.32     |
| t1/2 (h)                       | 2.65 ± 0.61     | 2.53 ± 0.29     | 2.59 ± 0.49     | 2.46 ± 0.50     | 2.60 ± 0.40     | 2.53 ± 0.45     |
| Cmin (mg/liter)                | 0.51 ± 0.11     | 0.51 ± 0.11     | 0.50 ± 0.09     | 0.52 ± 0.13     | 0.53 ± 0.12     | 0.53 ± 0.12     |
| Indinavir                       |                 |                 |                 |                 |                 |                 |
| CL/F (liters/h/kg)             | 0.89 ± 0.26     | 0.64 ± 0.24     | 0.78 ± 0.28     | 0.85 ± 0.33     | 0.67 ± 0.24     | 0.77 ± 0.27     |
| V/F (liters/kg)                | 1.23 ± 0.44d    | 0.93 ± 0.35     | 1.09 ± 0.42     | 1.29 ± 0.45     | 1.02 ± 0.22     | 1.16 ± 0.38     |
| t1/2 (h)                       | 0.97 ± 0.23     | 1.05 ± 0.26     | 1.01 ± 0.24     | 1.09 ± 0.16     | 1.08 ± 0.13     | 1.08 ± 0.14     |
| Cmin (mg/liter)                | 0.09 ± 0.05     | 0.14 ± 0.13     | 0.11 ± 0.10     | 0.10 ± 0.07d    | 0.19 ± 0.10     | 0.14 ± 0.09     |

a Week 2 results are pharmacokinetic parameters obtained with all subjects receiving the same dose and prior to any dose adjustments in those randomized to concentration-controlled therapy.

b Week 28 results are pharmacokinetic parameters obtained with standard therapy subjects receiving the standard doses of zidovudine, lamivudine, and indinavir and the concentration-controlled subjects receiving the regimen designed to achieve the target concentrations which was implemented at week 4.

c P < 0.05, standard therapy versus concentration-controlled therapy (repeated-measures ANOVA)

d P < 0.05, week 2 versus week 28 (repeated-measures ANOVA).

P < 0.05, variance of standard therapy versus concentration-controlled therapy (F test).

STD, standard dose therapy.

CC, concentration-controlled therapy.
patients. All initial dose adjustments were based on the pharmacokinetic study conducted at week 2 and were implemented at week 4. Nine subjects required a change in their dose of indinavir. These adjustments were a change from the standard dose of 800 mg every 8 h to 800 mg every 6 h (n = 5), 800 mg every 6 h (n = 4), or 1,000 mg every 8 h (n = 3). During the course of the 28-week study only one subject required a subsequent change in indinavir dose based upon pharmacokinetic data, and this was from 1,000 mg every 8 h to 800 mg every 6 h. Zidovudine doses were changed in five patients: one patient’s dose was increased to 900 mg/day, one patient’s dose was increased to 700 mg/day, and three patients’ doses were changed to 800 mg/day. Only one patient had a subsequent change in zidovudine dose, which was a reduction from 800 to 600 mg/day due to nausea and vomiting. Only two patients required a change in their dose of lamivudine, both of which were an increase from 150 mg twice daily to 150 mg thrice daily.

Figure 2 shows the measured C ss for zidovudine at week 28 in the standard and concentration-controlled recipients. There was no difference in C ss values between the treatment arms; however, variability in C ss was significantly less in the concentration-controlled recipients (P = 0.001). All concentration-controlled recipients achieved the target zidovudine C ss at week 28, whereas 8 of 13 (62%) of standard therapy recipients achieved the target (P = 0.04). There was no difference in lamivudine C ss at week 28 between the two groups. Three patients in the standard arm had C ss values below the desired target, compared with none in the concentration-controlled group.

Figure 2 also presents indinavir trough concentrations measured at week 28 in the standard therapy and concentration-controlled recipients. The mean C min with standard therapy was 0.10 mg/liter, which was significantly less than the mean C min of 0.19 mg/liter achieved in concentration-controlled recipients (P = 0.02). At week 28, 9 of 11 (82%) concentration-controlled recipients had mean C min values at or above the target, compared with 3 of 13 (23%) standard dose recipients (P = 0.01).

Adherence evaluations. Among the 24 study participants, 18 (75%) were eligible for adherence evaluation. These 18 subjects returned study medication for 87.5% (126 of 144) of the clinic visits. The overall mean adherence values were 96% for zidovudine, 97% for lamivudine, and 96% for indinavir. Standard therapy recipients (n = 10) had mean adherence values of 96, 95, and 94% for zidovudine, lamivudine, and indinavir, respectively. The mean adherence values for concentration-controlled patients were 96% for zidovudine and 98% for both lamivudine and indinavir. There was no difference in adherence between the two groups. No particular time period during the 28-week study was associated with more or less adherence. No subject was discontinued from the study for poor adherence.

Safety. Overall, there was no significant difference in the number of adverse events between the standard and concentration-controlled treatment arms. Asymptomatic hyperbilirubinemia was the most frequent objective side effect noted. Grade I or II elevations in total bilirubin occurred in nine standard therapy recipients and seven concentration-controlled recipients. Two patients who received concentration-controlled therapy developed grade III hyperbilirubinemia; one patient was on 800 mg of indinavir every 8 h at the time, and the other was on 800 mg every 6 h. Three concentration-controlled recipients had grade I or II elevations in liver enzymes; a fourth patient had grade IV elevations but also had hepatitis C coinfection at the time.

Crystalluria was present in two patients, one from each group, during the study. The crystals were not specifically identified for origin but were believed to be indinavir related.

FIG. 1. Estimated CL/F at weeks 2 and 28 for zidovudine (top), lamivudine (middle), and indinavir (bottom). Solid lines represent standard therapy patients (n = 13); dashed lines represent concentration-controlled patients (n = 11).
Neither patient reported flank pain, dysuria, or any other symptoms related to nephrolithiasis. Flank pain was reported at weeks 12 and 16 in two patients randomized to standard therapy; one patient also had dysuria. One patient randomized to concentration-controlled therapy developed nephrolithiasis at week 28, requiring hospital admission. This patient was receiving an indinavir dose of 800 mg every 8 h.

Hematologic toxicities were mostly mild to moderate, with the exception of the one previously described case. Four patients receiving concentration-controlled therapy and three patients receiving standard therapy experienced a grade I decrease in absolute neutrophil count; one standard patient each developed a grade II and a grade IV drop. None of the 24 patients that completed 24 weeks of therapy required discontinuation or modification of therapy or supportive medications (i.e., transfusion or erythropoietin) for hematologic toxicities. Six patients (three in each arm) had nausea and fatigue during the initial part of therapy despite the zidovudine titration scheme. The majority of patients reported feeling better after 4 weeks of therapy. Nausea was not associated with the use of higher zidovudine doses.

Other side effects that were possibly related to study medications included partial hair loss ($n = 3$), hypercholesterolemia ($n = 2$), hyperglycemia ($n = 1$), and hypertension ($n = 1$). None of the patients developed fat redistribution syndrome or excessive weight gain or loss.

**DISCUSSION**

We have shown that the administration of zidovudine, lamivudine, and indinavir in a regimen designed to achieve a specific target concentration was feasible and had a safety and tolerance profile not different from the standard dose regimen. The concentration targets selected were average $C_{ss}$ of 0.19 and 0.44 mg/liter for zidovudine and lamivudine, respectively, and a $C_{min}$ of 0.15 mg/liter for indinavir. The actual mean values at week 28 in the concentration-controlled recipients were 0.20 mg/liter for zidovudine, 0.54 mg/liter for lamivudine, and 0.19 mg/liter for indinavir. A significantly higher proportion of subjects receiving concentration-controlled compared with standard dose therapy achieved these targets for zidovudine and indinavir.

The 24 subjects who participated in this study and were randomized to receive either standard dose or concentration-controlled therapy were well balanced with respect to baseline characteristics, including $CL/F$ (determined at week 2) for zidovudine, lamivudine, and indinavir. Thus, differences in concentrations accomplished with the use of a concentration-controlled regimen did not arise because of baseline differences in pharmacokinetic behavior. A necessary element for the successful application of a concentration-controlled strategy is for intrapatient pharmacokinetic variability to be less than interpatient variability. Figure 1 shows individual patient $CL/F$ values at weeks 2 and 28 and illustrates a general consistency within patients over the 28-week study duration. There was no difference in $CL/F$ for zidovudine, lamivudine, and indinavir between weeks 2 and 28. The mean week 2- to 28-week ratios of $CL/F$ for all three drugs were between 0.95 and 1.09, with 95% confidence intervals encompassing 1. These data provide clear evidence that intrapatient variability over a 6-month period was low and did not result in statistically significant differences in $CL/F$.

The target concentrations selected for zidovudine and lamivudine were the average $C_{ss}$ expected in a patient perfectly
adherent with the standard dose regimen of 600 mg/day for zidovudine and 300 mg/day for lamivudine and who had the population average values for bioavailability and total body clearance. Thus, the concentration-controlled strategies for zidovudine and lamivudine were designed not to produce average $C_s$ values that were different from those with the standard dose but rather to reduce interpatient variability in $C_{ss}$ as we have previously shown in a study of zidovudine mono-
therapy (11). Use of the concentration-controlled regimen for lamivudine did not result in a significant reduction in interpa-
tient variability in $C_{ss}$. This is not surprising, as only two per-
sons in the concentration-controlled arm required a lamivu-
dine dose adjustment to achieve the desired concentration. For zidovudine, however, interpatient variability in $C_{ss}$ was signif-
ically reduced by 50% with the concentration-controlled regi-
men. This magnitude of reduction is consistent with that found in an earlier concentration-controlled study with zidovu-
dine monotherapy. The range of zidovudine doses used in the present study, 600 to 900 mg/day (average, 690 mg/day), to achieve a target $C_{ss}$ of 0.19 mg/liter is less than the range needed in a previous study (with doses up to 1,200 mg/day) to reach the same target (11). The discrepancy between these studies may in part be due to a drug interaction between zidovudine and indinavir. Indinavir has been shown to increase zidovudine area under the curve by 17 to 36% (25).

The target concentration strategy for indinavir was designed to achieve a $C_{min}$ of $\geq 0.15$ mg/liter. The average $C_{min}$ with the concentration-controlled approach was 0.19 mg/liter, which was significantly greater than the 0.10 mg/liter produced with the standard dose. Indinavir doses necessary for concentration-
controlled regimens ranged from 2,400 to 3,200 mg/day; dosing intervals of every 8 h and every 6 h were employed. Even with these efforts, 2 of the 11 concentration-controlled recipients could not be dosed to attain the desired target concentration, as we chose to not exceed an indinavir dose of 3,200 mg/day for safety considerations. Such patients may represent rapid me-
tabolizers of indinavir, and perhaps other drugs that are sub-
strates for similar metabolic pathways, and may explain why some antiretroviral-naive patients fail highly active antiretro-
viral therapy at standard doses despite good adherence. At-
ttempts to prospectively identify these patients may prove use-
ful. The erythromycin breath test has been suggested as a tool for this purpose, but a prospective study failed to demonstrate any utility (Slain et al., 38th ICAAC).

As assessed by counts of returned medications, overall ad-
herence in this study was high for all three drugs. Furthermore, adherence was equally good between the concentration-con-
rolled and standard therapy recipients. We were concerned that the more frequent dosing and greater capsule or tablet burden necessary to implement the concentration-controlled regimens would affect adherence adversely. However, we found no evidence to support this concern. This observation is consistent with a study of adherence that found no difference in patient adherence to a regimen of protease inhibitors given twice daily compared with thrice daily (29). These data indicate that factors distinct from the complexity of the regimen play an important role in adherence to a medication regimen; a pa-
tient’s understanding of disease and drug therapy, motivation, and relationship with his or her health care provider are likely possibilities. The participants in this study may have been bi-
ased towards a more adherent population, as an exclusion criterion was a known history of nonadherence with medica-
tions or scheduled physician and clinic visits. While no poten-
tial participant was excluded based upon this criterion, we do not know if some individuals were not referred by their physi-
cian for potential participation in this study because of this criterion. Thus, the overall high degree of medication adher-
ence achieved in both the concentration-controlled and stan-
dard therapy recipients may not extrapolate to a larger popu-
lation of HIV-infected persons receiving antiretroviral therapy.

Overall, zidovudine, lamivudine, and indinavir were safe and well tolerated by the participants during this 28-week study. The adverse reactions of primary concern with this regimen were anemia, neutropenia, and nephrolithiasis. Grade III or IV adverse events occurred in 4 of the 24 patients (17%); there was no difference in events between the concentration-con-
trolled and standard therapy recipients. This is consistent with the findings in our previous study of concentration-controlled zidovudine therapy where, despite an overall higher dose, sys-
temic concentrations, and intracellular zidovudine triphos-
phate concentrations, there were no differences in the rates of anemia and neutropenia between standard dose and concen-
tration-controlled therapy (11). This 17% rate is consistent also with the 26% incidence of grade III or IV adverse reac-
tions in the AIDS Clinical Trials Group study (1320) of zidovudine, lamivudine, and indinavir (17). We found no dif-
ference in the incidence of urologic complaints in standard dose recipients compared with concentration-controlled recip-
ants. Frank nephrolithiasis developed in one patient during the course of treatment, and two others reported flank pain. All three patients had no prior history of renal disease. The concentration-controlled patient who developed the kidney stone had been receiving indinavir (800 mg every 8 h) through-
out the course of study. It has been suggested that higher plasma concentrations of indinavir are associated with a higher incidence of urologic complaints, including nephrolithiasis (9). However, the basis for a higher dose in a patient receiving concentration-controlled therapy is to adjust for a higher-than-
average clearance of the drug. Therefore, these patients may not have the same risk of dose- or concentration-related neph-
rolithiasis as would a person with average clearance receiving an increased dose. Nevertheless, antiretroviral therapy is a long-term undertaking, and a more prolonged comparative assessment of the safety and tolerance of concentration-con-
trolled versus standard dose therapy would be important.

Irrefutable progress in the pharmacotherapy of HIV infec-
tion has been made (28). Improving the use of currently available antiretroviral agents is as important as the rational devel-
opment of promising new compounds in order to advance the- rapeutics further. This investigation has provided a phar-
macologic basis for concentration-controlled combination an-
tiretroviral therapy by demonstrating that it is feasible and that it has a short-term safety profile comparable with the standard dose regimen. Studies to learn whether concentration-con-
trolled therapy provides a virologic advantage over the con-
ventional approach of administering the same dose of antire-
roviral agents to all adults now appear warranted.

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