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A Retrospective, Cohort-Based Survey of Patients Using Twice-Daily Indinavir + Ritonavir Combinations: Pharmacokinetics, Safety, and Efficacy

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Objective: To describe the pharmacokinetics, safety, and efficacy of twice-daily indinavir + ritonavir regimens

Design: A cohort-based survey of HIV-infected patients who either used indinavir 800 mg + ritonavir 100 mg twice daily or indinavir 400 mg + ritonavir 400 mg twice daily.

Methods: Data were extracted from a database of samples sent to our laboratory for measurement of indinavir + ritonavir plasma concentrations. Patient characteristics, safety, and efficacy measurements were collected by retrospective chart review.

Results: 100 Patients using 800-mg indinavir + 100-mg ritonavir twice daily and 32 patients using 400-mg indinavir + 400-mg ritonavir twice daily were eligible. Median peak and trough concentrations of indinavir were 6.8 and 0.77 mg/L in the 800/100 group and 2.6 and 0.45 mg/L in the 400/400 group. The most frequently found side effects were nausea and vomiting, which occurred in 22.1% and 34.9% of the patients in the 800/100 and the 400/400 groups, respectively. Viral load data were analyzed for patients who switched from 800-mg indinavir three times daily to one of the indinavir + ritonavir twice daily regimens. At the time of switch 63% (800/100 group) and 60% (400/400 group) had an undetectable viral load and this increased to 77% and 70%, respectively, during follow-up. Patients who switched to the 400/400 group discontinued treatment more frequently than patients who switched to the 800/100 group (70% vs. 26%, $p = .008$).

Conclusions: Indinavir + ritonavir regimens show improved pharmacokinetic properties, allowing twice-daily dosing with food. Clinical data suggest that safety and efficacy is at least as good as with indinavir three-times-daily regimens without ritonavir. Prospective, comparative trials are needed to properly assess the role in HIV therapy of these twice-daily indinavir + ritonavir regimens.

Key Words: Indinavir—Ritonavir—Pharmacokinetics—Efficacy—Safety.

Indinavir is one of the most widely used protease inhibitors. The popularity of this drug can be explained by its well-documented clinical efficacy, which has been reported to last at least 3 years (1), its relatively benign toxicity profile (2,3), and its mild (relative to that of ritonavir) drug-drug interaction profile (4).

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In contrast to these favorable characteristics, however, use of indinavir has also some disadvantages. The drug should be taken with a low-fat, low-calorie meal or on an empty stomach, which means 1 hour before or 2 hours after a meal. Because indinavir is dosed three times daily, patients must deal with arranging meals and drug intake during a large part of the day. From a pharmacokinetic perspective, indinavir has also some unfavorable characteristics. Due to good absorption, especially when indinavir is ingested on an empty stomach, the plasma concentration increases rapidly, leading to high concentrations that may be related to nephrologic and urologic complications (5,6). Furthermore, due to extensive cytochrome P450-mediated metabolism, indinavir plasma concentrations decrease rapidly, resulting in trough concentrations that are only 2 to 4 times higher than the 95% (IC_{95}) inhibitory concentration. Interpatient and intrapatient variability may result in trough concentrations that are even closer to the IC_{95}, which has been associated with suboptimal viral suppression (7–9). The small difference between indinavir trough concentration and the IC_{95} necessitates strict adherence to the every-8-hours regimen. Intervals of >8 hours between two doses and/or neglecting food requirements will result in exposure to suboptimal drug concentrations [i.e., <0.10 mg/L (7,8)], which may be associated with the emergence of drug resistance and, eventually, loss of antiviral effect.

If it were possible to improve the pharmacokinetic profile of indinavir while maintaining its antiviral potency and tolerability, this would be a welcome extension of today's antiretroviral therapeutic options. Combining indinavir with ritonavir is one way to improve the pharmacokinetic profile of indinavir (10). Ritonavir inhibits cytochrome P450-mediated metabolism of indinavir (and other protease inhibitors), which makes it possible to administer indinavir twice daily with or without food (11,12). Healthy volunteer studies have shown that there are two different dosing strategies to combine indinavir with ritonavir: 800-mg indinavir + low-dose (e.g., 100–200 mg) ritonavir (12) or 400 mg (11) of both protease inhibitors. Although these regimens are becoming increasingly popular in clinical practice, no systematic review of the pharmacokinetics, safety, and efficacy in HIV-infected patients has been available so far. In this study, we have investigated the pharmacokinetics, safety, and efficacy of both twice-daily indinavir + ritonavir combinations.

METHODS

Patient Selection

All physicians in the Netherlands who treat HIV-infected patients were offered the possibility of sending samples for drug concentration monitoring. Physicians were instructed to record the following information on the sample application form: reason for requesting drug concentration measurement (suspicion of drug interaction, suboptimal therapy, toxicity or noncompliance, routine control), date, dosage of antiretroviral drugs, time of blood sampling, time of last drug ingestion, and use of concomitant medications.

Information on the sample application forms was entered in a Microsoft Access 2.0 database (Microsoft, Redmond, WA, U.S.A.) between spring 1997 and July 1999. At the time of analysis, July 1999, the database contained data on >1,000 patients who were using indinavir as part of their antiretroviral regimen. For the purpose of this study, data were extracted from the database for patients who had been prescribed both indinavir and ritonavir as part of their antiretroviral regimen.

Drug Concentration Measurement and Pharmacokinetic Analysis

Indinavir plasma concentrations were measured according to the methods described elsewhere (13,14). Ritonavir plasma concentrations were measured by the method of Hugen et al. (14). Individual drug concentrations at each specific sampling time postingestion were entered into a pharmacokinetic curve-fitting program (Kinfit, Mediware, J.H. Proost, Groningen, The Netherlands) (15). The appropriate pharmacokinetic model was selected by using Akaike's information criterion and the average population pharmacokinetic curve was drawn.

Safety and Efficacy Measurements

A brief questionnaire was sent to various hospitals to collect information on previous use of antiretroviral drugs and the reason to switch to an indinavir + ritonavir combination. Data on viral load, the occurrence of side effects, and lipid concentration measurements before and after switching to an indinavir + ritonavir combination were also requested. Physicians who had submitted samples for measuring indinavir concentrations were asked to complete these questionnaires.

RESULTS

Pharmacokinetic Data

In all, 132 patients were identified, 100 of whom used indinavir 800 mg + low-dose ritonavir (100 mg) twice daily (800/100 group) and 32 who used both drugs in a dose of 400 mg twice daily (400/400 group). A total 225 samples were analyzed: 177 from the 800/100 group; 48 from the 400/400 group. Samples were taken at random times postingestion with no specific cluster of timepoints, except a relatively high number of trough samples. After entering the individual plasma concentrations of indinavir and ritonavir into the Kinfit program, pharmacokinetic parameters were calculated (Table 1). In all cases, a two-compartment model with a lag-time best fit the data. The fitted average pharmacokinetic curves of indinavir and ritonavir in both dosing regimens are shown in Figures 1 and 2. Analysis of the trough concentrations of indinavir and ritonavir in patients using

TABLE 1. *Pharmacokinetic paramaters of indinavir and ritonavir as calculated by the Kinfit program*

Regimen	800/100		400/400	
Drug	Indinavir	Ritonavir	Indinavir	Ritonavir
C_{max} (mg/L)	8.9	2.2	3.3	9.1
T_{max} (hr)	1.4	3.0	3.4	3.3
$AUC_{0-12\ hr}$ (mg/L × hr)	46.6	17.4	21.0	57.2
C_{min} (mg/L)	1.3	0.53	0.31	1.5
CL/F (L/hr)	16.3	5.3	17.9	6.6
Vd/F (L)	80.7	24.4	44.3	16.1

C_{max}, maximum concentration; T_{max}, time of maximum concentration; CL/F; clearance; Vd/F, volume of distribution.

800/100 combination revealed a remarkably strong correlation between these two parameters. The fitted correlation has the following equation: [indinavir trough concentration in mg/L] = 2.01 × [ritonavir trough concentration in mg/L] + 0.07; r = 0.89; $p < .01$. The number of trough samples in the 400/400 group was too small to repeat this analysis in this group of patients.

Several patients who suffered from toxicity while using the 800/100 regimen had a dose modification to 600-mg or 400-mg indinavir twice daily + 100-mg ritonavir twice daily. The peak and trough drug concentrations that were measured while these patients followed the modified regimen are listed in Table 2. In this subgroup of selected patients, the modified drug combination regimen resulted in drug concentrations that were comparable with those observed on average in the 800/100 group.

Safety and Efficacy Data

In all, 132 questionnaires were sent to participating physicians. The response rate to the questionnaire was 72% in the 400/400 group and 77% in the 800/100 group. Data for the 800/100 group and the 400/400 group are presented separately.

800/100 Group

More than half of the patients (56%) had used 800-mg indinavir three times daily before starting 800/100 twice daily. Other regimens included combinations without indinavir (17%), 1200-mg indinavir twice daily (12%), no therapy (10%), or the 400/400 indinavir + ritonavir combination (3%). The reasons to start 800/100 twice daily were: a less complex regimen (26%), a low indinavir plasma level (26%), a high viral load (12%), side effects (10%), drug interactions (4%) or not specified (22%).

Side effects that were reported in more than 4% are listed in Table 3. Nausea and vomiting were the most frequently reported side effects, followed by nephrotoxicity (renal stones, hematuria, crystalluria), lipodystrophy syndrome, skin reactions, and hyperbilirubinemia. Analysis of plasma cholesterol concentrations measured before and after starting 800/100 showed that the median cholesterol concentration increased from 5.2 (interquartile ratio [IQR], 4.5–6.2) mmol/L to 5.7 (IQR, 4.9–7.4) mmol/L. Median triglyceride concentrations increased from 2.5 (IQR, 1.4–4.0) mmol/L to 3.1 (IQR, 1.9–4.4) mmol/L. Most physicians noted on the questionnaire that they did not know whether the patient was fasting, so these data must be considered as nonfasting results.

Because most patients had been using 800-mg indinavir three times daily before switching to 800/100, and the other patients represent a rather heterogenous group (treatment-naive and nonnaive; indinavir-experienced and nonexperienced, and the like), it was decided to perform the viral load analysis only in those 43 patients who switched from 800-mg indinavir three times daily to the 800/100 regimen. The median follow-up of these patients on 800/100 was 5 months (range, 1–13 months). Of the 43 patients, 11 (26%) had stopped taking the indinavir + ritonavir combination at the time of analysis; in 10 of these 11 patients, side effects were the cause, while in 1 case no cause was specified.

Viral load data at baseline (i.e., before switching regimens) and at the end of follow-up were available for 41 patients (the other 2 patients had HIV-2 infection). Median viral load in these patients before the switch was <400 copies/ml, with 26 of these 41 patients (63%) having a viral load below the limit of detection (which varied from 5 to 400 copies/ml, depending on the assay used in each given hospital). During follow-up, the proportion of patients with an undetectable viral load increased from 63% to 78% (intention-to-treat analysis) or 77% (on-treatment analysis). Of the 26 patients with an undetectable viral load before switch, 24 (92%) also had an undetectable viral load during follow-up, whereas of the 15 patients with a detectable viral load before switching, 8 (53%) became undetectable after the switch.

400/400 Group

The largest group of patients (44%) had taken 800-mg indinavir three times daily before starting the 400/400 regimen. Other regimens included combinations without indinavir (30%), no therapy (17%) or the 800/100 indinavir + ritonavir combination (9%). The reasons to start 400/400 were: a less complex regimen (43%), a high viral load (26%), side effects (17%), a low indinavir plasma level (4%), or not specified (9%).

Side effects that were reported in more than 4% are

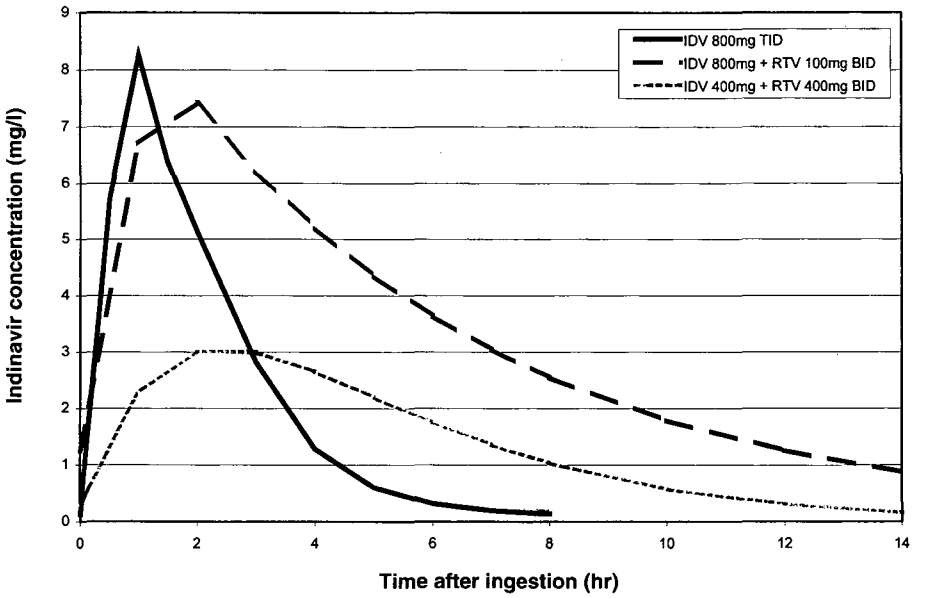

FIG. 1. Fitted pharmacokinetic curves of indinavir when administered with ritonavir.

listed in Table 3. As with the group receiving 800/100, nausea and vomiting were the most frequently reported side effects, followed by nephrotoxicity (renal stones, hematuria, crystalluria), diarrhea, and lipodystrophy. Analysis of plasma cholesterol concentrations measured before and after starting the 400/400 regimen showed that the median cholesterol concentration increased from 5.2 (IQR, 4.2–5.8) mmol/L to 5.7 (IQR, 5.4–6.6) mmol/L. Median triglyceride concentrations increased from 2.6 (IQR, 1.3–3.7) mmol/L to 3.1 (IQR, 1.8–4.5) mmol/L. Again, most physicians noted on the questionnaire that they did not know whether the patient was fasting.

Because the largest part of the patients had been taking 800-mg indinavir three times daily before switching to 400/400, and to make a comparison with the 800/100 group, viral load analysis was only performed in the 10 patients who switched from 800-mg indinavir three times daily to 400/400 twice daily. The median follow-up of

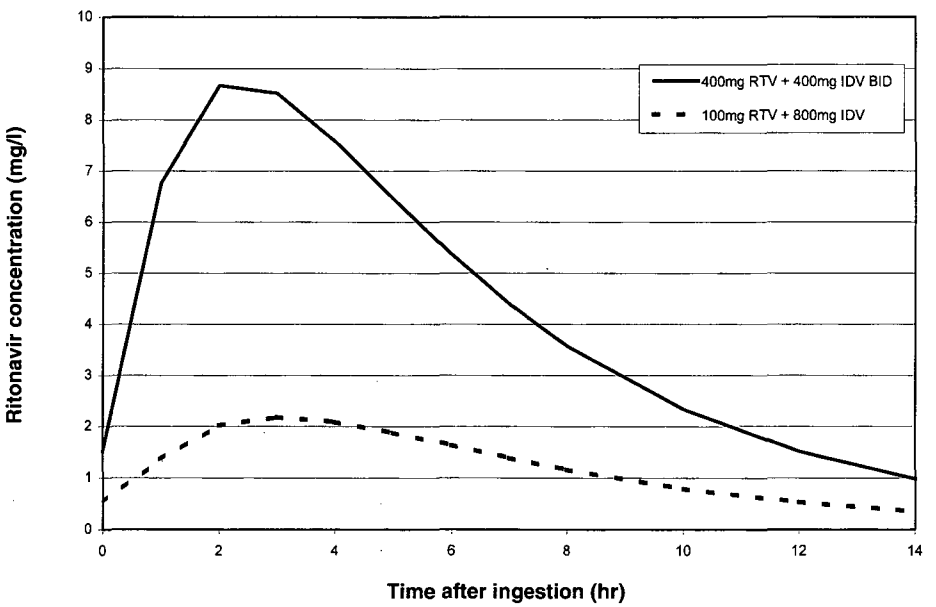

FIG. 2. Fitted pharmacokinetic curves of ritonavir when administered with indinavir.

TABLE 2. *Dosage modifications (800/100 group only)*

	Dose	*N*	Indinavir concentration (mg/L)	Ritonavir concentration (mg/L)
Peak concentration	400/100 twice daily	2	4.9 ± 1.7	2.3 ± 1.1
	600/100 twice daily	2	5.8 ± 0.8	2.2 ± 0.2
	800/100 twice daily	86	7.6 ± 3.9	2.2 ± 1.7
Trough concentration	400/100 twice daily	5	1.2 ± 0.5	0.74 ± 0.36
	600/100 twice daily	7	1.4 ± 0.5	0.64 ± 0.18
	800/100 twice daily	63	1.2 ± 1.1	0.55 ± 0.48

these patients was 7 months (range, 1–14 months). Seven patients (70%) had stopped taking the indinavir + ritonavir combination at the time of data analysis. Side effects were the reason given in 4 patients, 2 others stopped because of noncompliance or myocardial infarction, and no reason for discontinuation was specified for 1 patient.

The median viral load before switch was <400 copies/ml, with 6 patients (60%) having a viral load below the limit of detection. During follow-up, the proportion of patients with an undetectable viral load increased from 60% to 70% (intention-to-treat analysis) or 100% (on-treatment analysis). All patients with an undetectable viral load before switching continued to have undetectable viral loads.

DISCUSSION

The first clinical data on combining ritonavir + indinavir were reported in 1997 at the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) in Toronto and published 1 year later (11). However, since then, only limited data have become available, despite widespread use of the combination in clinical practice. Until now, the pharmacokinetics of indinavir + ritonavir when both are given in a 400-mg dose twice daily have only been described in healthy volunteers (11,12). Furthermore, toxicity and efficacy data of indinavir + ritonavir regimens in HIV-infected patients have only been presented in abstract form (16–19), and these studies usually involved only small numbers of patients.

In the healthy volunteer studies conducted by both Merck (12) and Abbott (11), it was demonstrated that indinavir can be given twice daily with food when combined with 100- to 400-mg ritonavir. The indinavir + ritonavir combination is more convenient for patients than the registered regimen that requires the intake of indinavir (without ritonavir) on an empty stomach or with a light meal every 8 hours. The healthy volunteer studies also showed that total exposure to indinavir does not differ when both drugs are given on an empty stomach or with food, so this indicates that indinavir + ritonavir represents the first dual PI combination that can be administered without food restrictions. It may be advisable, however, to take indinavir + ritonavir with food because this results in blunting of the peak indinavir concentration (see following discussion) (11,12). Although it is clear from Figure 1 that both twice daily regimens of indinavir + ritonavir result in improved pharmacokinetics of indinavir compared with the 800-mg three-times-daily regimen of indinavir without ritonavir, the two twice-daily regimens are not interchangeable (11,12). The 800/100 regimen leads to similar peak concentrations of indinavir as is the situation with the 800-mg three-times-daily regimen of indinavir without ritonavir, although trough concentrations are approximately tenfold higher. These data are in agreement with those from the healthy volunteer study (12) and the 6 patients reported by Van Heeswijk et al. (20). The indinavir peak concentrations in the 400/400 regimen are substantially lower than with either of the two other regimens, whereas trough concentrations fall somewhere between those obtained with the 800-mg three times daily and the 800/100 twice daily regimens. These data are in accordance with the healthy volunteer data (11). The implications of these differences have been the subject of much debate at recent international conferences. Most attention has focused on the differences in peak indinavir concentrations between the two twice-daily regimens because the development of nephrotoxicity, caused by precipitation of indinavir base in the kidneys, may be related to the height of the indinavir concentration in plasma (5). Given the values of peak indinavir concentration in this study, it can be expected that the incidence of nephrotoxicity in the 800/100 twice-daily regimen will equal the incidence in patients using indinavir 800 mg three times daily without ritonavir, whereas incidence in the 400/400 regimen will probably be lower. This is in agreement with the reported incidences of nephrotoxicity shown in Table 3. Less attention has been paid to possible differences in indinavir trough concentrations between the various regimens. Our data show that indinavir trough concentrations in the 800/100 twice daily regimen are substantially higher than observed in either of the

TABLE 3. *Side effects*

Regimen	800/100	400/400
N	77	23
Nausea, vomiting	22.1%	34.9%
Renal stones, hematuria, crystalluria	14.3%	8.7%
Lipodystrophy	13.0%	4.3%
Hyperbilirubinemia	11.7%	—
Diarrhea	5.2%	4.3%
Skin reaction	13.0%	—

other regimens (Table 1, Fig. 2). This may allow the 800/100 twice-daily regimen to suppress HIV with moderately decreased susceptibility to indinavir (i.e., a 4-fold to 10-fold increase in IC_{95}) because of the 10-fold higher indinavir trough concentrations. Trough concentrations of indinavir after intake of the 400/400 regimen may not be sufficiently high enough to overcome such an increase in IC_{95}. Because of the almost 100% cross-resistance between indinavir and ritonavir (21), it seems unlikely that ritonavir in the 400/400 combination will have much virologic effect on virus with decreased susceptibility to either drug.

The interpretation of the reported side effects is complicated. First, this study was not randomized and patients may not have been similar while starting one of the twice-daily regimens. Second, the data collection may be unreliable because physicians may remember the most recent or the most impressive side effects most clearly. Third, some side effects may result from incorrect use of the drugs. For example, the first patients who started on the 800/100 regimen did so by taking the drugs on an empty stomach because no information on influence of food on this regimen was known at that time. This may have led to higher peak concentrations of indinavir than after eating because food blunts the peak concentration as a result of delayed absorption (11,12). Another problem in the evaluation of side effects in this study may be that such side effects were already present with the previous regimen (e.g., lipodystrophy syndrome) and are not likely to be specifically related to the indinavir + ritonavir regimen. Therefore, no definitive conclusions can be drawn concerning any differences in toxicities between the two twice-daily regimens.

Given the uncertainty of reporting side effects in this study, the following observations ought be noted. Nausea is a well known side effect of both indinavir and ritonavir, so it is not surprising that this side effect was reported most frequently in the questionnaires. The higher incidence of nephrotoxicity (defined as kidney stones, hematuria, or crystalluria) in the 800/100 regimen when compared with the 400/400 regimen is in agreement with the already discussed differences in indinavir peak concentrations. It must also be noted, however, that the incidence of nephrotoxicity in the 400/400 regimen is not zero in this study, in contrast to the data reported by Workman et al. (22). Padberg et al. (23) recently reported a 12% incidence of elevated serum creatinine levels in patients using 400-mg indinavir + 400-mg ritonavir twice daily. A 32% incidence in nephrotoxicity was reported by O'Brien et al. (16), but they were using a combination of 800-mg indinavir + 200-mg ritonavir, which leads to higher peak concentrations of indinavir than with 800/100 (12). Furthermore, their patients were suffering from an extremely hot summer in Texas at the time the data were being collected (W. O'Brien, oral communication, April 1999).

Recent data from Youle et al. (24) suggest that, when combined with indinavir, higher ritonavir doses lead to a more pronounced risk of lipid abnormalities than with lower ritonavir doses. Given the uncertain long-term effects of increased lipid concentrations, minimal changes in lipid concentrations are desirable, which suggests a preference for the 800/100 regimen over the 400/400 regimen. Our data do not confirm these observations of Youle et al. Nonstandardized (i.e., nonfasting) measurements of lipids in our study and small numbers in the various regimens in Youle's study (there were only 2 patients in their 800/100 group) may explain the difference in the findings.

This study is the first to report on the virologic efficacy of the 800/100 regimen. In the subset of patients who switched from 800-mg indinavir three times daily to the 800/100 regimen, almost all patients who had an undetectable viral load remained undetectable, whereas a significant proportion of patients with a detectable viral load became undetectable. This indicates that the antiviral activity of the 800/100 combination is at least similar to regimens containing 800-mg indinavir three times daily. Although not specified in the questionnaire, most physicians reported that nucleosides were not changed when adding low-dose ritonavir. Approximately 25% of the patients in the 800/100 group discontinued this regimen, showing that tolerability issues may compromise the antiviral activity. Most physicians were not aware that dose modification to 600/100 or even 400/100 is possible. All patients who had a dose modification because of toxicity from the 800/100 regimen had adequate trough indinavir concentrations (Table 2) and demonstrated sustained virologic response. Patients suffering from toxicity while using the 800/100 regimen are likely to represent a subpopulation of patients with greater than average increased exposure to indinavir, and they can benefit from dosage modifications. Because there were only 10 patients who switched from an 800-mg indinavir three times daily regimen to the 400/400 twice-daily regimen, it is difficult to compare the virologic potency and tolerability of this combination with the 800/100 twice-daily regimen. Patients who switched to the 400/400 group discontinued treatment more frequently than patients who switched to the 800/100 group (70% vs. 26%, $p = .008$; using the two-sample proportion test). We have no experience in modifying the dose in the 400/400 regimen. The observed intolerance may be partly due to the use of the liquid formulation of ritona-

vir, because capsules were not available during most of the time during which this survey was conducted. The same phenomenon was observed in the study of Rockstroh et al. (19). Whether the discontinuation rate will be lower using ritonavir capsules instead of a liquid formulation remains to be established. All patients who were able to tolerate the 400/400 regimen had a good virologic response (3 of 3 patients with an undetectable viral load in the on-treatment analysis), which is in agreement with the data from Rockstroh et al. (19) and Workman et al. (25).

In conclusion, both the 800/100 and the 400/400 twice-daily regimens showed improved pharmacokinetic properties when compared with regimens supplying 800-mg indinavir three times daily without ritonavir. The virologic efficacy of both regimens appears to be at least similar to what is observed with 800-mg indinavir three times daily. The 800/100 regimen had a lower discontinuation rate than the 400/400 regimen. Prospective, comparative trials are needed to properly assess the role in HIV therapy of these twice-daily indinavir + ritonavir regimens.

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