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Comparison of Indinavir+Ritonavir 600+100 mg vs. 400+100 mg BID Combinations in HIV1-infected Patients Guided by Therapeutic Drug Monitoring

J.-C. Wasmuth, E. Rodermann, E. Voigt, M. Vogel, E. Lauenroth-Mai, A. Jessen, D. Burger, J. K. Rockstroh

Department of Internal Medicine I, University of Bonn, Bonn, Germany

Abstract

Objective: To compare two reduced dose indinavir (IDV) + ritonavir (RTV) combinations guided by therapeutic drug monitoring (TDM) in treatment-naive HIV1-infected patients.

Methods: HIV1-infected treatment naive patients were prospectively randomized to treatment with IDV 600 mg or 400 mg BID each in combination with RTV 100 mg BID. Boosted IDV was combined with 2 NRTI, and patients were followed for 48 weeks. IDV-trough levels and initially also peak levels (C2h) were performed to allow dose modification of IDV following a specified protocol.

Results: 14 patients were randomized (age 38 ± 10.4 years; mean ± SD; 3 female, 11 male). 8 were treated with 600 mg (group 1), 6 with 400 mg IDV BID (group 2). Efficacy of treatment was good: CD4-cell count increased from 198/µl (14-523; median, range) to 371/µl (214-927) after 48 weeks ($p<0.01$). All but one patient with adherence problems achieved a viral load below the limit of detection. At the beginning two patients had plasma levels below 0.1 mg/l, most likely due to adherence problems. However, in the course of the observation period all patients had adequate plasma levels. 3 patients in group 1 could further reduce their IDV dose to 400 mg BID due to high plasma (peak and trough) levels. Rate of discontinuation was high (1: 4 pat., 2: 2 pat.), but only one discontinuation was possibly associated with IDV (alopecia; group 2). There were no significant changes in laboratory parameters (bilirubin, triglycerides, cholesterol) or suspicious urine results. Incidence and severity of adverse events was lower than in previous studies.

Conclusion: Despite the low number of patients it seems reasonable to state, that boosted IDV may be used in significantly reduced dose. Efficacy seemed not to be altered, whereas tolerability was improved.

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Key words: HIV – HAART – Indinavir – Ritonavir – reduced dose

Introduction

The protease inhibitor indinavir (IDV) is a substance with good antiretroviral efficacy. In combination with ritonavir (RTV), which is meant as a pharmacokinetic enhancer or "booster", it is widely used in clinical practice. The two most common regimens have been IDV/RTV 400 mg/400 mg and 800 mg/100 mg, respectively [1, 2]. The latter combination has the advantage of fewer pills and less RTV toxicity, which might be beneficial in the long term. However, the obstacle of this combination is a higher rate of nephrotoxicity due to the development of kidney stones as compared to the unboosted IDV regimen (800 mg TID) or the 400 mg/400 mg combination. It is assumed that the development of IDV-related toxicity depends on the height of the plasma level, whereas efficacy depends on the time of IDV maintained above a threshold of 0.1 mg/l. In particular nephrotoxicity, which is caused by precipitation of IDV-containing crystals in the urinary tract, seems to be dependent on the height of the plasma level [3]. Furthermore, there is anecdotal evidence that other IDV-related side effects (e.g., nausea, vomiting, hyperbilirubinemia) are associated with higher peak plasma levels of IDV [4]. Therefore, a dose reduction of IDV might mitigate the rate and severity of side effects, on top of that reducing the costs of antiretroviral treatment. Clinical data with combinations of IDV/RTV of 600 mg/100 mg and 400 mg/100 mg suggest that such a dose reduction will not affect the antiviral potency of the combination [5-7]. However, pharmacokinetic data on these particular IDV/RTV combinations did not exist in detail so far. In addition, we could show that dose reduction of IDV to 400 mg BID resulted in suboptimal plasma levels in 3 out of 15 healthy volunteers [8]. Therapeutic drug monitoring appeared to be necessary to guarantee appropriate drug levels and simultaneously minimize toxicity, if reducing IDV drug dosage. Therefore, we outlined this protocol to compare the efficacy and safety of two reduced dose IDV/RTV

BID combinations guided by therapeutic drug monitoring (TDM) in HIV-infected patients (IDV/RTV 600/100 mg BID vs. IDV/RTV 400/100 mg BID).

Methods

Subjects and Treatment

The study was conducted on an outpatient basis at the Medizinische Klinik I, University of Bonn, Germany and two other German centers from March 2003 until November 2004. HIV1-positive, treatment naive patients were randomized by a central computer based fax procedure to two treatment arms: patients in group 1 received 600 mg IDV and 100 mg RTV BID, patients in group 2 received 400 mg IDV and 100 mg RTV BID. Randomization was implemented to avoid inadvertent selection bias that could influence pharmacokinetic parameters (e.g. weight). In both groups one of three combinations of two nucleosides was given as backbone therapy, chosen by the treating physician according to individual needs (tenofovir / lamivudine, lamivudine / stavudine, or zidovudine / lamivudine). Main exclusion criteria were severe laboratory abnormalities (hemoglobin < 7.5 mM, leucocytes < 3 * 10^9/L, ASAT or ALAT > 2 times upper limit, serum creatinine > 1.5 upper limit, bilirubin > 2 times upper limit, platelets < 100 * 10^9 / L), concomitant medication known to interact with IDV or RTV (e.g. carbamazepine or rifampicin), or severe impairment of liver function. All patients gave written informed consent. All study procedures were done in accordance with the current revision of the Helsinki declaration of 1975 and Good Clinical Practice. The study was approved by the Ethics committee of the University of Bonn, Faculty of Medicine, Bonn, Germany.

Dose Adjustment and Therapeutic Drug Monitoring

At day 28 a pharmacokinetic assessment of IDV trough and levels taken two hours after drug intake (C2h), that approximate peak levels, was performed in both groups. A dose reduction of IDV to 400 mg BID was allowed in group 1, if IDV C2h levels were above 10 mg/L and / or trough levels were above 0.25 mg/L. This level of 0.25 mg/L was chosen to maintain the anticipated trough levels above 0.1 mg/L after dose reduction. At day 56 measurements of IDV trough and C2h levels were performed to document the effect of dose modification and regular monitoring of IDV trough levels was performed thereafter in 12-week intervals to ensure appropriate trough levels of IDV. In case of insufficient IDV trough levels at any time, an increase of IDV dose was foreseen. Pharmacokinetic assessment of IDV plasma levels that were analyzed with a validated high performance liquid chromatography followed standardized procedures as described elsewhere [8, 9].

Assessment of Efficacy and Tolerability

Safety and tolerability were assessed on every study visit by physical examination and a standardized, previously validated questionnaire presenting 17 possible adverse events that may occur during treatment with IDV or RTV [8, 10]. Participants were asked to grade every complaint as mild (symptoms do not interfere with daily activities), moderate (symptoms may interfere with daily activities) or severe (symptoms interrupt daily activities). In addition, an extensive blood chemistry and hematology screen, and urine analysis were performed. HI-viral load and CD4 counts were determined at day 28, week 12, and every third month thereafter.

Data Analysis

All statistical evaluations were performed with SPSS for Windows, version 10 (SPSS Inc, Chicago, Ill., USA). Changes in HIV-RNA levels were tested with the McNemar test for dichotomized paired samples. Changes of other laboratory parameters were tested with the two-sided Student t test for paired samples after testing for normal distribution. A p-value < 0.05 was considered to be significant in all analyses. Unless otherwise stated, data are given as median and range.

The incidence of adverse events was calculated for the whole study period. It was expressed as the percentage of participants that reported a particular adverse event at least one time during the six consecutive reporting times. Consequently, every reported mild, moderate or severe adverse event was ascribed a severity score of 1, 2 or 3 points, respectively. All scores were added up for every participant and were divided by the number of reporting times. In this way the mean toxicity scores were obtained for all individual participants. No formal comparison between both dose groups was performed with regard to either parameter as the number of patients was too small to allow such testing.

Results

Study Subjects and Antiretroviral Treatment

Fourteen HIV-infected patients were included into this study. Baseline characteristics are summarized in Table 1, the study flow is depicted in Figure 1. 8 patients were randomized to group 1, 6 to group 2 without a difference with regard to CD4-counts, viral load, age and other parameters between groups. 6 patients discontinued treatment; 4 in group 1 and 2 in group 2 due to the reasons given in Figure 1. Only alopecia was regarded to be possibly related to IDV. In three patients a dose reduction of IDV from 600 mg to 400 mg BID was performed.

CD4-counts increased significantly in all patients from 198/µl (14-523) at baseline to 371/µl (214-927; $p<0.01$) at week 48. HIV-RNA fell below the limit of detection in all, but one patient (7/8 = 88 % as observed; 7/14 = 50 % missing equals failure). This particular patient had adherence problems at the beginning with insufficient IDV plasma levels. Resistance mutations (NRTI: K219K; PI: L10F/L, K20R/T, D30D/N, M36I, L63P, V77I, N88D/N) associated with resistance against IDV and nelfinavir were found

Table 1. Baseline characteristics of patients.

	All n = 14	IDV 600 mg BID n = 8	IDV 400 mg BID n = 6	
Age, years	35.5 (27-63)	36.5 (27-63)	34.5 (28-52)	
Sex, m/f	11/3	6/2	5/1	
Duration HIV, months	27 (8-94)	27 (15-94)	23 (8-48)	
Ethnicity				
Caucasian/African	12/2	7/1	5/1	
Height, cm	175 (163-186)	176 (168-183)	170 (163-186)	
Weight, kg	72 (52-95)	74 (52-95)	62 (56-72)	
NRTI, n				
D4T/3TC	4	4	-	
TDF/3TC	6	3	3	
AZT/3TC	4	1	3	
Transmission, n				
MSM	5	3	2	
IVDA	3	2	1	
Endemic	2	2	-	
Hetero	3	1	2	
unknown	1	-	1	
CDC-stage, n				
AIDS	1	1	-	
B	7	4	3	
A	6	3	3	
Concomitant Diseases				
Hepatitis C	3	2	1	
HIV-RNA, log copies/ml	4.97 (3.25-5.78)	4.90 (3.78-5.58)	5.07 (3.25-5.78)	0.85
CD4-count, no./μl	198 (14-523)	190 (95-400)	251 (14-523)	0.76

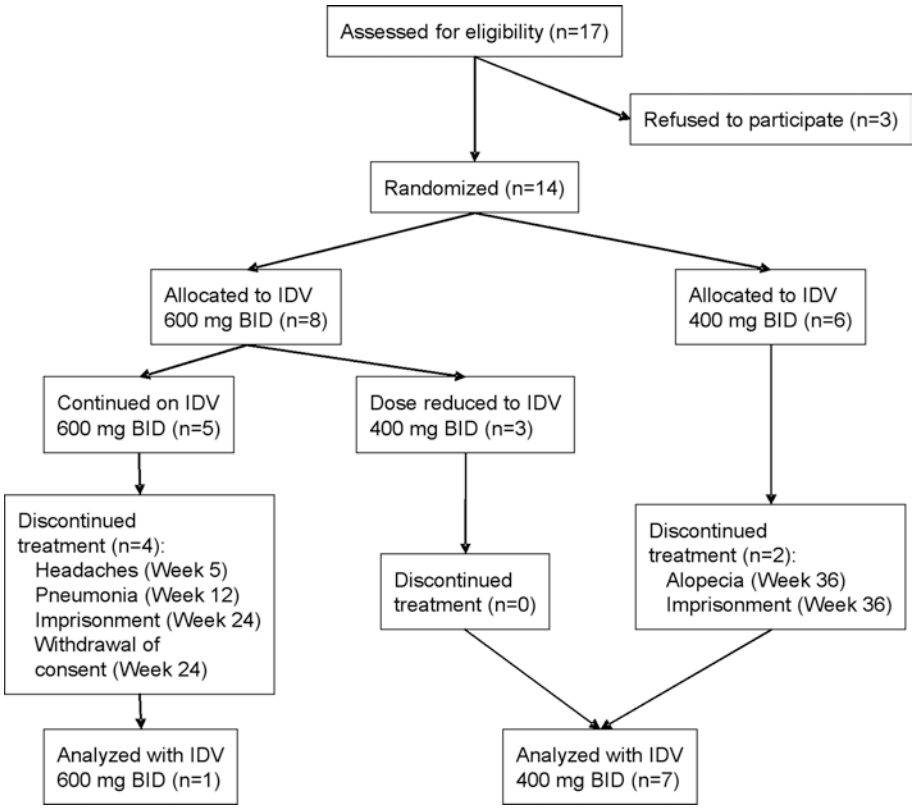

Fig. 1. Flow diagram of the progress of patients through the study period.

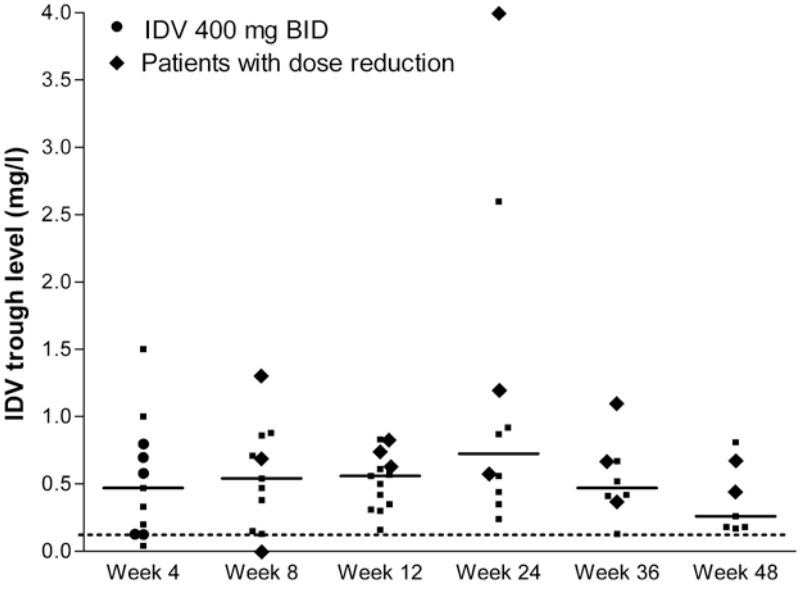

Fig. 2. IDV trough levels of all patients throughout 48 weeks.
At week 4 trough levels of patients who started on IDV 400 mg BID can be identified by circles as compared to patients who started on IDV 600 mg BID. There was no significant difference between the trough levels of both dose groups. After week 4 when dose reduction was performed, trough levels of patients whose dose was reduced from IDV 600 mg to 400 mg are given in diamonds. Trough levels were maintained above the threshold of 0.1 mg/l (dashed line) despite dose reduction. This level is regarded as necessary to maintain complete viral suppression.
The solid lines indicate the median IDV trough level at the respective date.

in the follow-up.

IDV Plasma Levels

With the exception of two IDV plasma levels below the threshold of 0.1 mg/l, all trough levels were above this threshold throughout the whole observation period (Fig. 2). Of note, in all patients, who reduced IDV dose, sufficient trough levels were found at any time. Both patients with insufficient trough levels (one at week 4 and one at week 8) obviously had adherence problems. After counseling on importance of adherence these two particular patients had sufficient trough levels in the further follow-up. At week 24 there were two patients with unexpected high IDV trough levels with no obvious explanation for this finding.

Peak levels decreased after dose reduction, although the median peak level did not change significantly (4.7 mg/L, 0.23-10.8 at week 4 to 3.7 mg/L, 0.38-5.3 at week 8; p = 0.84; see Fig. 3).

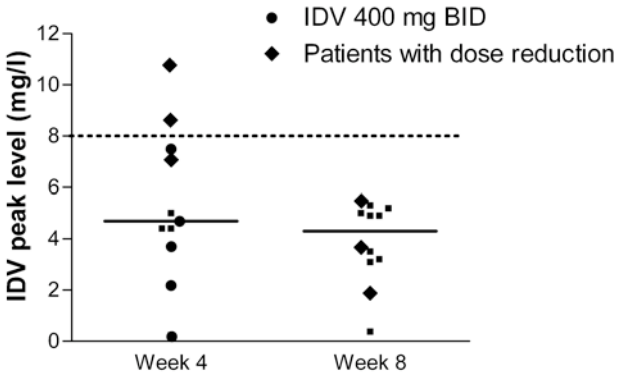

Fig. 3. IDV peak levels of all patients at weeks 4 and 8.
At week 4 peak levels of patients who started on IDV 400 mg BID can be identified by circles as compared to patients who started on IDV 600 mg BID. In contrast to trough levels, peak levels were lower in patients with the lower IDV dose. Peak levels of patients whose dose was reduced from IDV 600 mg to 400 mg after week 4 are given in diamonds. Peak levels in these patients decreased after dose reduction, whereas trough levels did not change significantly (see Fig. 2).
The solid lines indicate the median IDV peak level at the respective date. The dashed line indicates the threshold of 8 mg/l, which is regarded as critical for IDV related toxicity.

Safety and Tolerability

Despite the high discontinuation rate tolerability of the reduced dosages was good. At baseline all laboratory parameters were in the normal range, and there was no significant change in ALT, AST, GGT, bilirubin, cholesterol, triglycerides, creatinine, or glucose. Two patients experienced a transient elevation of ALT and AST. Both had chronic hepatitis C, and elevation of liver enzymes was interpreted as flare of hepatitis following immune reconstitution. Accordingly, antiretroviral treatment was continued in both patients, and transaminases normalized thereafter.

The incidence of adverse events experienced by patients throughout the study period is summarized in Table 2. In addition, severity of adverse events was graded and toxicity scores were calculated. The overall median toxicity score was 0.08 (0.01-0.46), indicating that on average each patient perceived far less than one AE per visit of grade 1. These were mostly of unspecific nature. Typical IDV-associated AE as flank-pain and dysuria were seldom (14 %) and of negligible intensity (toxicity score 0.02). There were no cases of crystalluria. Mild leucocyturia was observed in 5 patients (<70/µl each), erythrocyturia in 3 patients (<10/µl in 2 patients; ca. 200/µl in 1 patient at one time). Incidence of gastrointestinal AE was slightly higher (27 %), whereas severity was mild as well (toxicity score 0.13).

Discussion

In this study we compared two reduced doses of RTV-boosted IDV (600 mg and 400 mg BID). We were able to show that significant dose reductions of IDV are

Table 2. Incidence of adverse events in %.

Adverse Event	Incidence
Abdominal Pain	23
Diarrhea	31
Meteorism	46
Nausea	38
Vomiting	8
Total GI	**27**
Crystalluria	0
Dysuria	0
Flank pain	31
Total kidney-related	**14**
Fever	0
Headache	54
Joint Pain	31
Muscle Pain	31
Oral discomfort	23
Paresthesia	15
Skin abnormalities	38
Taste disturbance	31
Tiredness	54
Weakness	77

possible maintaining antiviral efficacy while enhancing tolerability. Importantly, with the exception of two patients with adherence problems IDV trough levels were sufficient in all patients – regardless of the dose taken. This is in contrast to own findings in healthy volunteers, where three out of 15 patients had IDV trough levels below a threshold of 0.1 mg/l [8]. Insufficient plasma levels might have been found, if more patients could have been studied. Therefore, it can not be concluded from this study that regular drug monitoring is not necessary. Other groups have found some insufficient drug levels in larger proportions of patients, although measurement of plasma levels was retrospective in one of these studies [5, 7].

Efficacy of the treatment was good. An increase of CD4-cells was achieved in all patients, and the viral load was suppressed in all, but one patient. This particular patient had adherence problems as illustrated by insufficient IDV trough level and subsequent genotypic resistance associated with IDV and nelfinavir. It only can be speculated, whether this resistance had been transmitted prior to inclusion into this study or was acquired during treatment. Another possibility is antiretroviral pre-treatment that was not reported by the patient to study personnel. The good efficacy observed is in line with other observations with reduced doses of boosted IDV [5-7].

Tolerability of the combination regimen was better than in own historical control data [2, 11]. No clinical significant nephrotoxicity was observed throughout the observation period in line with findings of a pharmacokinetic study in Thai patients, where no cases of nephrotoxicity were observed [12]. In our study 5 patients showed mild leukocyturia (<75/µl). Moderate leukocyturia (> 75 leukocytes/µl) has been linked to IDV-associated nephrotoxicity by some investigators [13]. However, the relevance of this finding remains unclear, and there is no accepted definition or interpretation of urinalysis [13-15]. Gastrointestinal related symptoms were within the range of placebo. There were no significant changes in laboratory parameters. In addition, all observed AE were of mild nature as reflected by the calculated low toxicity scores. This finding of good tolerability is contrasted by the high discontinuation rate. However, reasons for discontinuation were not IDV-related and reflect rather "non-medical" reasons (i.e. lost to follow-up or personal reasons) than problems associated with the drugs under investigation. Only alopecia was regarded as an AE possibly related to IDV. Other groups examining boosted IDV in a dose of 400 mg BID found a good tolerability similar to our results [5, 6]. It is not possible to state from our results, whether the lower dose of 400 mg IDV was tolerated better than the higher dose of 600 mg. To our knowledge a formal comparison between different doses of IDV has not been performed so far.

The major drawback to our study is that only 14 patients could be included. Originally, 80 patients had been projected as necessary. However, with the availability of "newer" protease inhibitors such as lopinavir, fosamprenavir or atazanavir, the use of IDV decreased markedly in Germany. Thus, obviously an unforeseen selection bias occurred in addition to the low number of patients. This is illustrated by the fact of two patients imprisoned during the observation period. Although results have to be interpreted with great caution, the selection of such difficult to treat patients should strengthen the results, as e.g. efficacy would rather be underestimated.

In conclusion, although the number of patients is small, the use of reduced doses of boosted IDV (600 mg or 400 mg BID) as part of HAART regimens seems to be a safe, well tolerated and efficacious approach in treatment-naive HIV-infected patients. This could be of special interest in resource-limited settings as IDV currently is the protease inhibitor of lowest costs, and available as a generic drug in some countries.

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Address for correspondence:
Jan-Christian Wasmuth, MD
Department of Medicine I, University of Bonn
Sigmund Freud Str. 25
53105 Bonn
Germany