Ritonavir/saquinavir plus one nucleoside reverse transcriptase inhibitor (NRTI) versus indinavir plus two NRTIs in protease inhibitor-naive HIV-1-infected adults (IRIS study)

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Objectives: To compare the efficacy, tolerability and safety of a ritonavir 400 mg/saquinavir hard gel fomulation 400 mg twice daily versus an indinavir 800 mg once every 8 h containing first-line protease inhibitor (PI) treatment regimen.

Methods: Open, randomized, multicentre clinical trial. PI-naive patients received either ritonavir/saquinavir and one nucleoside reverse transcriptase inhibitor (NRTI) or indinavir and two NRTIs. Intention-to-treat (ITT) and on-treatment (OT) analyses were performed.

Results: The baseline characteristics of the study participants were similar in both arms, 67 patients (37%) were naive to antiretroviral treatment. The proportion of patients who achieved a plasma viral load below the level of detection of 400 copies/ml at week 48 was 43% (39/90) in the ritonavir/saquinavir arm and 63% (57/90) in the indinavir arm (*P*=0.005, ITT analysis). Using an OT analysis, these percentages were 84% and 88%, respectively (*P*=0.6). There were more drop-outs in the ritonavir/saquinavir arm than in the indinavir arm (35.6% (32/90) versus 15.6% (14/90), *P*=0.002), mainly due to gastro-intestinal side-effects. Abnormal liver tests and increased lipids levels were more frequently reported in the ritonavir/saquinavir arm than in the indinavir arm.

Conclusion: In PI-naive patients, indinavir in combination with two NRTIs was more effective and better tolerated than ritonavir/saquinavir plus one NRTI. Both treatments were very effective for patients who were able to tolerate them.

Introduction

The introduction of the protease inhibitors (PIs) in 1996 was a major step forward in the treatment of HIV infection. Nowadays, PIs in association with nucleoside reverse transcriptase inhibitors (NRTIs) remain the backbone of first-line therapy [1] even though other options, including PI-sparing regimens are also used [2,3].

Ritonavir is a specific and potent inhibitor of HIV-1 protease. This drug has a high oral bioavailability and a long plasma half-life, which allows twice daily dosing [4]. Saquinavir hard gel formulation is also a highly potent PI *in vitro* but has limited oral bioavailability due to its rapid metabolism by the cytochrome P450 [5,6]. The combination of ritonavir and saquinavir has a number of pharmacokinetic and virological advantages. Ritonavir inhibits cytochrome P450 so the area under the curve for drugs metabolized by this enzymatic system, such as saquinavir, is greatly increased, allowing greater efficiency [7,8]. An optimal antiviral effect is obtained with lower doses of each drug, thereby reducing the side-effects of ritonavir and saquinavir [8,9]. Finally, ritonavir and saquinavir do not share the same initial mutation pattern [10,11]. Indinavir is also a powerful PI [12,13,14] and a good first-line antiretroviral in association with two NRTIs.

This study was designed to compare the efficacy of two triple therapy regimens in PI-naive patients: a double PI combination plus one NRTI versus a single PI regimen plus two NRTIs.

Methods

Study design

This multicentre, open-label, randomized clinical trial compared two different types of tritherapy: two PIs plus one NRTI versus one PI plus two NRTIs. Patients were screened for participation 2 weeks before the start of the study. They were centrally randomized (ratio 1:1) and stratified for plasma viral load (threshold of 100 000 copies/ml) and previous exposure to NRTIs or non-nucleoside reverse transcriptase inhibitors (NNRTIs) (naive versus pretreated). Baseline data were obtained, including demographic characteristics, previous antiretroviral treatment and AIDS defining illnesses. Further evaluation took place at weeks 4, 12, 24, 36 and 48 with clinical evaluation and blood sampling. The latter was performed irrespective of fasting conditions. CD4 lymphocyte count, plasma viral load (pVL) and routine laboratory tests were assessed at baseline and at all follow-up visits. Changes in antiretroviral therapy and co-medication, adherence (assessed by questioning patients on drug intake at each study visit) and adverse events were recorded at every time point. All adverse events and their severity grade (1–4) according to AIDS Clinical Trial Group (ACTG) guidelines were recorded. PVL was measured by the Cobas Amplicor HIV-1 Monitor test version 1.5 of Roche (detection range 400–750 000 copies/ml); from 6 January 1999 the use of an ultrasensitive protocol of the same test was introduced (detection range of 50–50 000 copies/ml).

The protocol was later amended to allow the use of ritonavir syrup due to production problems with ritonavir capsules (1 August 1998). The ethics committee in each centre approved the study protocol and all patients gave written consent.

Study population

To be eligible for participation, patients had to meet all of the following criteria: seropositivity for HIV-1, no previous exposure to PIs, older than 18 years and a Karnofsky index of more than 50.

Exclusion criteria were any changes in antiretroviral therapy during the last 4 weeks before the start of the study, an active opportunistic infection, pregnancy or the use of contra-indicated drugs.

Treatment regimen

Patients were randomly assigned to one of two regimens. The first group received a combination of ritonavir (Norvir, Abbott, Ill., USA) 400 mg twice daily plus saquinavir hard gel formulation (Invirase, Roche, Basel, Switzerland) 400 mg twice daily, twelve hourly with one NRTI. NRTI-naive patients were prescribed stavudine (Zerit, Bristol-Myers Squibb, NJ, USA). The second group received a combination of indinavir (Crixivan, Merck Sharp & Dohme, NJ, USA) 800 mg once every 8 h with two NRTIs. NRTI naive patients were prescribed stavudine in association with lamivudine (Epivir, GlaxoSmithKline, UK).

Patients already pretreated with NRTIs at randomization were started on new NRTIs together with the PI, if no other therapeutic option was available then a recycling of the NRTI was allowed. Ritonavir was initiated according to a dose escalation schedule (300 mg twice daily for 3 days and then 400 mg twice daily). Saquinavir and indinavir were started on day 1 at the full dose. The standard dose of stavudine, 40 mg twice daily, was reduced to 30 mg twice daily for patients weighing less than 60 kg. When the allocated treatment had to be interrupted, for whatever reason, the patients were switched to the other study arm. All the study medications were registered and readily available on prescription.

Outcome parameters

The proportion of patients who achieved a reduction to below the level of quantitation (<400 copies/ml) after 48 weeks was used as the main end-point to assess efficacy of treatment. Secondary end-points were: (1) the decrease in log pVL. Measured by the 'area under the curve minus baseline' method (AUCMB), (2) the change in peripheral CD4 lymphocyte count, (3) the occurrence of side-effects (clinical and laboratory) and (4) major and minor HIV-related clinical events.

Statistical analysis

A 20% difference in the proportion of patients with undetectable pVL between the two study arms was considered to be relevant. With 80% power and a 95% confidence interval, 75 patients per study arm were needed to detect such a difference. A 25% premature withdrawal was expected, and an inclusion of 200 patients was therefore proposed. Statistical analyses were performed using the SPSS programme version 9.0 (SPSS Inc, Chicago, Ill., USA). Comparison between proportions was done using the difference in proportions test. Comparison between absolute numbers was done using the Pearson χ^2 statistic. When a cell had an expected count of less than five, Fisher's exact test was used. Comparison between means was done using the Student's *t* test. In order to use this test, the assumption of normality was checked. When the assumption of normality was not reached, the non-parametric Mann–Whitney–Wilcoxon test was performed to check for a difference between distributions. All *P* values were two-tailed and those <0.05 were considered to be significant. The AUCMB was the area

under the curve computed using the trapezoidal rule, divided by the length of time between initiation of treatment and the last known value, minus baseline level. The primary analysis was done according to the intention-to-treat (ITT) principle. In this analysis, all patients enrolled in the study were included, including those who were assigned to a regimen but never treated. Missing data and data from patients who discontinued their allocated treatment were counted as pVL >400 copies/ml. The virological response was also assessed in an 'on treatment' (OT) analysis, where patients remaining on their primary allocated treatment only were included. Adverse-event analysis was performed according to the ITT principle but patients had to have taken at least one dose of their allocated treatment.

Results

Characteristics of the patients

One-hundred-and-eighty patients were randomized between July 1997 and October 1998. Of these, 166 started randomized treatment. The baseline characteristics of the patients in the two treatment arms were comparable and are shown in Table 1. Almost 40% of the subjects had been treated with antiretroviral medications (NRTIs, NNRTIs, or both) before entry into the study, and they had taken two

Table 1. Baseline characteristics

Variable	RTV/SQV (*n*=90)	IDV (*n*=90)	*P* value
Age (years)			
Mean (95% CI)	38.8 (36.8–40.9)	37.3 (35.6–39.0)	0.25
Gender			
Men, *n* (%)	62.0 (68.9)	72.0 (80.0)	0.09
Women, *n* (%)	28.0 (31.1)	18.0 (20.0)	
Sex ratio (M:F)	2.2	4.0	
Race			
Caucasian, *n* (%)	53.0 (58.9)	58.0 (64.4)	0.43
Black African, *n* (%)	35.0 (38.9)	30.0 (33.3)	0.44
Asian, *n* (%)	1.0 (1.1)	1.0 (1.1)	1.0
Other, *n* (%)	1.0 (1.1)	1.0 (1.1)	1.0
BMI			
Mean (95% CI)	23.3 (22.5–24.2)	22.9 (22.2–23.6)	0.44
Previous NRTI and NNRTI treatment			
n (%)	35.0 (38.9)	32.0 (35.6)	0.64
CDC class			
A, *n* (%)	39.0 (43.3)	42.0 (46.7)	0.65
B, *n* (%)	31.0 (34.4)	26.0 (28.9)	0.42
C, *n* (%)	20.0 (22.2)	22.0 (24.4)	0.72
CD4 cell count at randomization (/mm^3)			
Mean (95% CI)	243 (206–280)	247 (208–285)	0.90
Median (Q1–Q3)	211 (106–366)	199 (98–346)	0.95
Log viral load at randomization			
Median (Q1–Q3)	5.05 (4.34–5.63)	5.13 (4.48–5.64)	0.48
Time since HIV diagnosis (years)			
Mean (95% CI)	3.86 (3.14–4.58)	3.41 (2.67–4.16)	0.39
Median (Q1–Q3)	2.77 (0.68–6.64)	2.16 (0.19–5.49)	0.18
Mode of infection			
Heterosexual, *n* (%)	54.0 (60.0)	57.0 (63.3)	0.65
MSM, *n* (%)	32.0 (35.6)	29.0 (32.2)	0.64
Blood transfusion, *n* (%)	1.0 (1.1)	0.0 (0.0)	
IVDU, *n* (%)	2.0 (2.2)	1.0 (1.1)	
Unknown, *n* (%)	1.0 (1.1)	3.0 (3.3)	

RTV/SQV, ritonavir/saquinavir; IDV, indinavir; *n*, number of observations; 95% CI, 95% confidence interval; Q1–Q3, interquartile range; MSM, men who have sex with men; BMI, body mass index; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; CDC, Centers for Disease Control; IVDU, intravenous drug user.

Table 2. Patient disposition by treatment assignment

	RTV/SQV, *n* (%)	IDV, *n* (%)	*P* value
Never started randomized treatment	7 (7.8)	7 (7.8)	NS
Drop-out after week 0	32 (35.6)	14 (15.6)	0.002
Adverse-event	24 (26.7)	7 (7.8)	<0.001
Altered dosage	0 (0)	4 (4.4)	NS
Drug interaction	2 (2.2)	0 (0)	NS
Death	2 (2.2)	0 (0)	NS
Lost to follow-up	0 (0)	2 (2.2)	NS
Patient's decision	4 (4.4)	1 (1.1)	NS
Completed 48 weeks of follow-up	51 (56.7)	69 (76.7)	0.004
Total	90 (100)	90 (100)	

RTV/SQV, ritonavir/saquinavir; IDV, indinavir; NS, not significant.

products on average for a median period of 12.1 months in the ritonavir/saquinavir arm and 19.4 months in the indinavir arm (*P*=0.2). Among those pretreated patients with NRTIs, 91% had used zidovudine, 40% lamivudine, 34% zalcitabine, 25% didanosine and 12% stavudine. Of the pretreated patients, 10% had taken an NNRTI before entry into the study. In the ritonavir/saquinavir arm, the patients received stavudine (95.2%), lamivudine (3.6%) or zalcitabine (1.2%), three patients (3.6%) had to receive one recycled NRTI. In the indinavir arm, the patients received stavudine (94%), lamivudine (96.4%), zidovudine (4.8%) or didanosine (4.8%), nine patients (10.8%) had to receive at least one recycled NRTI.

Follow-up and discontinuation of treatment

Seven patients (7.8%) in each arm never started the assigned treatment (Table 2). The proportion of patients who discontinued treatment for any reason was higher in the ritonavir/saquinavir arm (32/90, 36%) than in the indinavir arm (14/90, 16%; *P*=0.002). Four patients, all in the indinavir arm, were removed from the study because one of the co-investigators decided to give 1200 mg indinavir twice daily to simplify their treatment; two patients from the ritonavir/saquinavir group had to stop the allocated treatment due to drug interactions with antimycobacterial drugs. The adherence was good and similar in both arms with 78% of the patients taking their antiviral medications exactly as prescribed.

Suppression of plasma HIV-1 RNA to undetectable levels

In the ITT analysis (Figure 1a), the patients taking the combination of indinavir plus two nucleoside analogues began to show a higher response rate from week 24 onwards, but this was only statistically significant at the end of the follow-up period. The response rate at 48 weeks was 43.3% (39/90) for the patients in the ritonavir/saquinavir arm and 63.3% (57/90) for those in the indinavir arm (*P*=0.005). Using the ultrasensitive assay (limit of detection 50 copies/ml) the same trend was observed at week 48 with a response rate of 27/79 (34.2%) and 46/80 (57.5%), respectively (*P*=0.003).

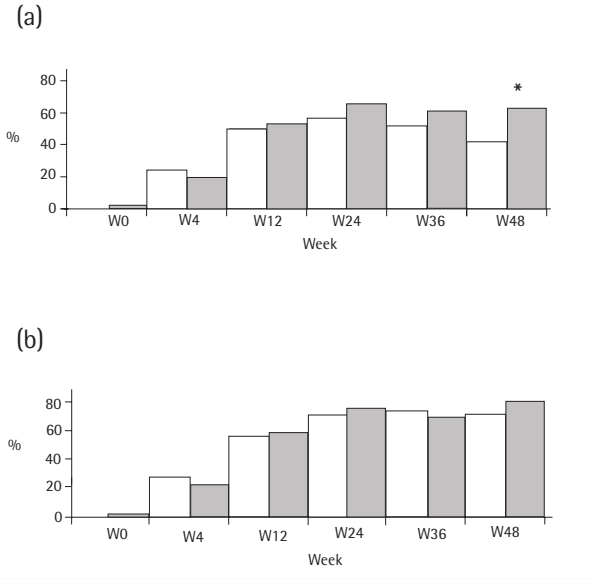
The superior virological response in the indinavir arm was only observed among the antiretroviral (ARV)-naive patients. After 48 weeks, 25 (45.5%) ARV naive patients from the ritonavir/saquinavir arm had an undetectable pVL, compared with 42 (72.4%) in the indinavir arm (*P*=0.004), while antiretroviral experienced patients had comparable responses in both arms (40.0% versus 46.9%; *P*=0.5). The difference in treatment response between the ritonavir/saquinavir (*n*=46) and the indinavir (*n*=51) arm was more pronounced among subjects with a pVL >5 log copies/ml at baseline (39.1% versus 68.6%; *P*=0.003).

OT analysis (Figure 1b), showed a treatment response above 70% in both arms at week 48 (*P*=0.19).

Decrease of the plasma viral load from baseline

There was a strong decrease from baseline in the median pVL in both arms throughout the 48 week

Figure 1. Proportion of patients with a viral load <400 copies/ml



The results for the ritonavir/saquinavir arm are represented by white columns and indinavir arm by grey. (a) Intention-to-treat analysis (NC=F); (b) on-treatment analysis.
NC=F, non-complier equals failure.
*$P<0.05$.

Table 3. Most frequent adverse events (toxicity grades II to IV)

	RTV/SQV, n (%)	IDV, n (%)	*P* value
Diagnoses			
Nauseau and/or vomiting	37 (44.6)	14 (16.9)	0.0001
Diarrhoea	26 (31.3)	7 (8.4)	0.0002
Paresthesia	13 (15.7)	9 (10.8)	0.36
Fatigue/weakness	12 (14.5)	5 (6.0)	0.07
Rash	3 (3.6)	10 (12.0)	0.04
Flu-like syndrome	3 (3.6)	10 (12.0)	0.04
Kidney stone/renal colic	0 (0.0)	9 (10.8)	0.02
Fever	7 (8.4)	9 (10.8)	0.59
Lipodystrophy	6 (7.2)	9 (10.8)	0.42

RTV/SQV, ritonavir/saquinavir; IDV, indinavir; n, number of episodes recorded during the first 48 weeks of follow-up.

observation period. Analysed according to the ITT-principle, the median AUCMB value was –1.97 log copies/ml [inter-quartile range (IQR) –2.44; –1.20] for the ritonavir/saquinavir arm and –2.37 log copies/ml (IQR –2.77; –2.07) for the indinavir arm after 48 weeks of treatment (P=0.016). However, the difference between the median AUCMB values was not significant in OT analysis [–2.08 log copies/ml (IQR –2.60; –1.47) for the ritonavir/saquinavir arm and –2.37 log copies/ml (IQR –2.77; –2.07) for the indinavir arm, respectively].

Change in CD4 lymphocyte count

A significant increase from baseline in CD4 lymphocyte count was found in both treatment arms, with a median CD4 lymphocyte count at week 48 of 364/mm^3 (IQR 238–490) in the ritonavir/saquinavir arm and 436/mm^3 (IQR 280–592) in the indinavir arm (P=0.09). At the end of the follow-up period, a median increase of CD4 lymphocyte count of 129/mm^3 (IQR 26–233) and 186/mm^3 (IQR 88–284) was observed in the ritonavir/saquinavir arm and the indinavir arm, respectively. This difference versus baseline was highly significant in each arm (P<0.001). The patients with a low CD4 lymphocyte count at baseline (<200/mm^3) experienced a greater increase in CD4 lymphocyte count in the indinavir arm (n=45) compared with those in the ritonavir/saquinavir arm (n=42) (201/mm^3 versus 129/mm^3; P=0.05).

Adverse events of the study medications

Sixteen (19.3%) patients in the ritonavir/saquinavir arm stopped their treatment because of gastrointestinal intolerance compared with three (3.6%) patients in the indinavir arm (P=0.002). Seven (8.4%) patients, included in the ritonavir/saquinavir arm, developed toxic hepatitis, defined as a rise in transaminase levels at least 10 times above the upper normal limit (other causes of hepatitis were excluded) and had to stop treatment. Lipodystrophy, clinically defined by physical examination and by patient report of fat wasting in the face or limbs with or without central obesity, was reported in six (7.2%) of the ritonavir/saquinavir patients and in 11 (13.3%) of the indinavir patients (P=0.2) (Table 3). Cholesterol, triglyceride and transaminase levels were significantly higher in the ritonavir/saquinavir arm. Total bilirubin and lactic dehydrogenase (LDH) were significantly higher in the indinavir arm (Table 4).

AIDS defining events

The incidence of AIDS defining events was low. During the 48 weeks of follow-up, five (5.6%) new AIDS defining events (one deep candidiasis, one cryptosporidiosis, one disseminated herpes simplex infection, one atypical mycobacteriosis and one recurrent bacterial pneumonia) were recorded among the patients included in the ritonavir/saquinavir arm. Twelve (13.3%) new AIDS defining events (three deep candidiasis, three atypical mycobacteriosis, two recurrent bacterial pneumonia, one cytomegalovirus infection, one pneumocystis carinii pneumonia, one pulmonary tuberculosis and one Kaposi's sarcoma) occurred during the same period among the patients included in the indinavir arm (P=0.07 for the difference between arms). No patient was forced to stop the assigned treatment due to an AIDS defining event but two patients, both included in the ritonavir/saquinavir arm, died of an AIDS defining event. The first, a 38-year-old woman, died of disseminated herpes simplex type 2 infection with involvement of the central nervous system and respiratory tract after 6 months of treatment, the CD4 lymphocyte count was then 28/mm^3 and the pVL was below 400 copies/ml. The second, a 31-year-old man, died of pulmonary Kaposi's sarcoma 3 months after the start of the treatment, the CD4 lymphocyte count was then 6/mm^3 and the pVL 551 copies/ml.

Discussion

This study compared the efficacy, safety and tolerability of two types of PI-containing treatment regimens. To our knowledge this is the first large-scale study comparing head-to-head ritonavir/saquinavir with indinavir in a triple therapy combination. The association between ritonavir/saquinavir plus two NRTIs (quadritherapy) has been previously compared with indinavir plus two NRTIs (triple therapy) [15,16]. The quadritherapy was found to be superior to the triple therapy after a follow-up period of 24 weeks [16], but this difference in response rate did not remain significant after 48 and 72 weeks of follow-up [15].

In our study the therapeutic response in the indinavir arm was better than in the ritonavir/saquinavir

Table 4. Laboratory abnormalities

		Toxicity Grading (TG)			Interarm difference	
Parameter	Study arm	TG 0, *n* (%)	TG I–II, *n* (%)	TG III–IV, *n* (%)	TG I–IV (*P*)	TG III and IV (*P*)
Cholesterol	RTV/SQV	40 (48.2)	37 (44.6)	4 (4.8)	0.003	0.65*
	IDV	58 (69.9)	21 (25.3)	2 (2.4)		
Triglycerides	RTV/SQV	27 (32.5)	53 (63.9)	1 (1.2)	<0.001	1*
	IDV	50 (60.2)	31 (37.3)	0 (0.0)		
Total bilirubin	RTV/SQV	68 (81.9)	14 (16.9)	1 (1.2)	<0.001	0.02*
	IDV	25 (30.1)	49 (59.0)	8 (9.6)		
AST	RTV/SQV	44 (53.0)	34 (41.0)	5 (6.0)	0.02	1*
	IDV	58 (69.9)	21 (25.3)	3 (3.6		
ALT	RTV/SQV	46 (55.4)	28 (33.7)	4 (4.8)	0.17	0.03*
	IDV	54 (65.1)	27 (32.5)	1 (1.2)		
LDH	RTV/SQV	48 (57.8)	31 (37.3)	4 (4.8)	0.006	0.43*
	IDV	30 (36.1)	49 (59.0)	3 (3.6)		

*One cell value was less than 5, Fisher's exact test was used.
RTV/SQV, ritonavir/saquinavir; IDV, indinavir; AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactic dehydrogenase.

arm (63.3% versus 43.3%, *P*=0.005). Baseline characteristics of the patients enrolled in both treatment arms were comparable. Drop-outs in the ritonavir/saquinavir arm, however, were significantly higher than in the indinavir arm. This difference in drop-out rates is probably the main explanation for the difference in response rate seen in the ITT analysis between the two treatment arms. Indeed, in the OT analysis, the virological response in both arms was high throughout the study period, with no significant difference between the two arms. The superior efficacy of indinavir at 48 weeks was only observed among antiretroviral-naive patients and among patients with a high pVL (>100 000 copies/ml) at baseline. Baseline characteristics of patients in subgroups analysis were not different between the two study arms. But the small sample size of certain subgroups may explain why differences in outcome were not detected. Antiretroviral-naive patients have more therapeutic options and are therefore more likely to switch to another treatment regimen in the case of side-effects than experienced patients. The drop-out rate for naive patients was 22/55 (40%) in the ritonavir/saquinavir arm and 6/58 (10%) in the indinavir arm (*P*=0.003), while it was 10/35 (28%) and 8/32 (25%) (*P*=0.7) for the experienced patients, respectively. This explains the difference in outcome between naive and experienced patients.

The antiretroviral activity was measured with a pVL assay with a detection limit of 400 copies/ml, which was the standard of care at the beginning of the study. This assay may have hampered the analysis of the efficacy of both regimens since it has been shown that measurements using ultra-sensitive assay can provide additional information on the long-term efficacy of combination therapy [17]. For this reason we re-assessed the samples collected at week 48 using an ultrasensitive protocol of the same test. Results were comparable with those obtained by the sensitive assay but treatment responses were obviously lower.

Antiretroviral regimens are considered to be able to delay disease progression and improve survival if they decrease pVL levels by at least 0.5 log [18]. In both treatment arms the median decrease in pVL was at least 2 log. Moreover, less than 8% of the study participants developed an AIDS defining event and only two patients (both included in the ritonavir/saquinavir arm) died from HIV-associated complications. Besides the decrease in pVL, a large majority of patients enrolled in this study showed a persistent and significant increase in their CD4 lymphocyte count after starting therapy. At the end of the follow-up period, 86% of the patients had a CD4 lymphocyte count above 200/mm^3. The extent of the immune reconstitution was comparable in both treatment groups and is in accordance with that found in other clinical trials of indinavir and ritonavir/saquinavir containing therapies [19,20,15].

In this study there was a high drop-out rate due to adverse events. This was higher than anticipated but is similar to what is observed in the 'real world' [21,22] where the occurrence of adverse events is still the main cause of treatment interruption.

The treatment response rate in the ritonavir/saquinavir arm was lower than that previously reported with similar treatment regimens. Gisolf *et al.* [20] reported a treatment response of 69% among 104 patients treated with a combination of ritonavir/saquinavir and stavudine. In a study by

Katzenstein *et al.* [15] among 104 patients treated with ritonavir/saquinavir and two NRTIs, the treatment response was 58%. In a dose finding study, Cameron *et al.* [19] reported a treatment response of 74% among 35 patients treated with ritonavir and saquinavir. There are several possible explanations for this difference. First, side-effects, such as nausea and diarrhoea, may influence patients' quality of life and adherence. In our study, when a patient experienced a side-effect which was thought to be caused by one of the study drugs, an early switch was made to maintain quality of life instead of prolonging a poorly tolerated treatment. Moreover, during the study some patients in the ritonavir/saquinavir arm had to switch from ritonavir capsules to ritonavir syrup due to manufacturing problems with the capsules. The ritonavir syrup was not used in the above mentioned studies. This syrup is known for its unpalatibility and many of the patients experienced difficulty tolerating it. Most of the drop-outs in the ritonavir/saquinavir arm (24/32) occurred before the switch to the ritonavir syrup. Only eight patients on ritonavir syrup switched. The drop-out rate of patients on ritonavir/saquinavir was only partially related to the use of ritonavir syrup.

The data were analysed using the ITT method considering patients with missing outcome data and those who interrupted the assigned treatment as treatment failures ('non-complier=failure' approach) [23]. We chose this method in order to include the treatment tolerability in the efficacy analysis of the primary outcome parameter, thereby assessing the effectiveness of both therapy arms instead of efficacy. With this method, a study arm with a higher drop-out rate may look virologically less effective [24]. Another analysis [15] which included all randomized subjects and where all missing values were considered as treatment failures ('missing=failure' approach) produced slightly different results (data not shown in the text). Using this method, the proportion of patients with an undetectable pVL after 48 weeks of follow up was 61% (55/90) in the ritonavir/saquinavir arm and 69% (62/90) in the indinavir arm (P=0.3).

In conclusion, a combination of indinavir plus two NRTIs seems slightly better than ritonavir/saquinavir plus one NRTI for PI-naive patients. This was mainly due to the high dropout rate in the double PI group. Both regimens seem very efficient for the patients who can tolerate them.

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