MAJOR ARTICLE

Randomized Trial to Evaluate Indinavir/Ritonavir versus Saquinavir/Ritonavir in Human Immunodeficiency Virus Type 1–Infected Patients: The MaxCmin1 Trial

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This trial assessed the rate of virological failure at 48 weeks in adult human immunodeficiency virus (HIV) type 1–infected patients assigned indinavir/ritonavir (Idv/Rtv; 800/100 mg 2 times daily) or saquinavir/ritonavir (Sqv/Rtv; 1000/100 mg 2 times daily) in an open-label, randomized (1:1), multicenter, phase 4 design. Three hundred six patients began the assigned treatment. At 48 weeks, virological failure was seen in 43 (27%) of 158 and 37 (25%) of 148 patients in the Idv/Rtv and Sqv/Rtv arms, respectively. The time to virological failure did not differ between study arms ($P = .76$). When switching from randomized treatment was counted as failure, this was seen in 78 of 158 patients in the Idv/Rtv arm, versus 51 of 148 patients in the Sqv/Rtv arm ($P = .009$). A switch from the randomized treatment occurred in 64 (41%) of 158 patients in the Idv/Rtv arm, versus 40 (27%) of 148 patients in the Sqv/Rtv arm ($P = .013$). Sixty-four percent of the switches occurred because of adverse events. A greater number of treatment-limiting adverse events were observed in the Idv/Rtv arm, relative to the Sqv/Rtv arm. In conclusion, Rtv-boosed Sqv and Idv were found to have comparable antiretroviral effects in the doses studied.

Cohort studies have shown that, among human immunodeficiency virus (HIV)–infected patients beginning highly active antiretroviral therapy (HAART) and achieving suppression of HIV-1 RNA to levels below detection, the annual rate of virological rebound is 15% [1, 2]. The main reasons for the failure of HAART are treatment-limiting toxicity, adherence problems, virological failure, and low potency of the drugs [3–5]. Other studies have shown long-term virus suppression to be dependent on safety, good adherence, and high plasma concentrations of antiretroviral drugs [6–10]. Ritonavir (Rtv) boosting (i.e., Rtv in doses of 50–200 mg), in combination with other protease inhibitors (PIs), results in higher plasma concentration of these other PIs [11]. This is due to inhibition of the *P450*CYP3A4 enzyme system in the intestine and liver and, possibly, inhibition of P-glycoprotein efflux [12, 13]. Other benefits of Rtv boosting are a reduction in the number of doses, from 3 times daily (t.i.d.) to 2 times daily (b.i.d.), fewer restrictions on food intake, and a lower pill burden, which is associated with better adherence. All these factors have been associated with a better treatment outcome [14, 15].

Indinavir (Idv)/Rtv (800/100 mg b.i.d.) was among the most commonly used Rtv-boosted PIs among an-

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tiretroviral regimens in use during 2000, when this trial was initiated. A switch from the recommended dose of Idv (800 mg t.i.d.) to the Rtv-boosted b.i.d. regimen was driven by relatively poor adherence to the t.i.d. regimen and by pharmacokinetic data suggesting that the dosing frequency could be diminished and the fasting requirement lifted [16]. However, it was shown recently that this switch led to an accelerated risk of treatment-limiting adverse events (AEs) among patients receiving a stable regimen that included Idv (800 mg t.i.d.) [17].

Relatively extensive studies have been made using saquinavir (Sqv)/Rtv, but mainly with a 400/400 mg b.i.d. dosing schedule. The Sqv/Rtv 400/400 mg b.i.d. regimen is associated with gastrointestinal AEs in most patients [18]. Some concern existed that, in a Sqv/Rtv regimen at a dose of 1000/100 mg b.i.d., only the Sqv element could be expected to have virological activity [19], whereas, with the 400/400 mg b.i.d. regimen, both drugs had virological activity.

Previous comparative studies of antiretroviral therapy (ART) including a Rtv-boosted regimen have shown a better virological outcome of the Rtv-boosted regimen (lopinavir/Rtv vs. nelfinavir) [20]. However, in clinical practice, it is important to establish whether Rtv-boosted regimens are comparable with regard to efficacy and safety. The MaxCmin1 trial is the first direct comparison of 2 Rtv-boosted PI regimens.

PATIENTS, MATERIALS, AND METHODS

This is a randomized (1:1), phase 4, open-label, multicenter trial involving 28 sites in 13 countries. The trial was conducted in accordance with the Helsinki II Declaration and the *Good Clinical Practice* guidelines (ICH-GCP Guideline [CPMP/ICH/135/95]; available at http://www.emea.eu.int), and local institutional review boards or independent ethics committees approved the protocol. Patients were assessed for eligibility at a screening visit and provided written informed consent before any trial-specific procedure was performed. Eligible patients were ⩾18 years old, had documented HIV-1 infection (ELISA), were not pregnant or breast-feeding, and did not have a serious medical condition at the time of screening. Furthermore, all laboratory values had to be without clinical significance according to the treating physician's judgment. A heterogeneous population was enrolled, including patients who were PI naive, PI intolerant, or for whom PI therapy had failed. PI-experienced patients with prior use of either of the study drugs were not precluded from participation; however, only patients with an equal chance of benefit from and/or risk of development of treatment-related AEs to the 2 study PIs at the time of screening could be randomized. This assessment was made by site physicians, and the final decision was made by the trial physician at the Copenhagen HIV Programme (CHIP) on the basis of ART history, prior virological and clinical failure, and available resistance tests. Before randomization, the treating physician decided the concomitant use of at least 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and/or non-NRTIs (NNRTIs). Computerized block randomization was done at CHIP. The randomization was stratified according to the geographic region of the site and the patients' virus load (VL). The countries were grouped in the following regions (sites from countries shown in italic type did not enroll patients): South America (Argentina and *Brazil*), North America (United States), Scandinavia (Denmark, Norway, and *Sweden*), Central Europe (Germany, Switzerland, and Austria), Northwest Europe (Belgium, *France,* United Kingdom, and The Netherlands), and Southern Europe (*Greece,* Italy, Portugal, and Spain). In the statistical analysis, the United States ($n = 3$ patients) was grouped with Northwest Europe.

Randomized patients, irrespective of whether they started receiving or switched from the assigned treatment, were followed up at baseline (first day of intake of assigned treatment) and at weeks 4, 12, 24, 36, and 48. During follow-up visits, the following procedures were performed: clinical evaluation, safety analyses (hemoglobin; white blood cell, lymphocyte, and platelet counts; and creatinine, aspartate aminotransferase and/or alanine aminotransferase, bilirubin, and amylase levels), and VL and CD4 cell count measurements. Fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, and total triglyceride levels were measured at baseline and at weeks 4 and 48. A case-report form was completed for each study visit and was faxed to CHIP, where real-time monitoring was performed by trained monitors (licensed nurses). In addition, CHIP monitors performed on-site monitoring at least twice at all participating sites.

Patients randomized to receive Sqv/Rtv were allowed to change from the Sqv soft-gel formulation (Fortovase; Roche) to the hard-gel formulation (Invirase; Roche) without this being considered a switch from the assigned treatment. During the trial, modification of the randomized treatment was allowed in the case of virological failure or treatment-limiting toxicities. If available, dose reduction was performed on the basis of therapeutic-drug monitoring. Of note, patients experiencing virological failure, according to the protocol's definition, were allowed to continue receiving the assigned treatment at the discretion of the treating physician.

Definition of virological, immunological, and clinical failure. For patients entering the study with a VL of <200 copies/mL, virological failure was defined as a VL of ⩾200 HIV-1 RNA copies/mL. For patients entering the study with a VL of ⩾200 copies/mL, virological failure was defined as any increase in HIV-1 RNA load of ⩾0.5 logs and/or a VL of ⩾50,000 HIV-1 RNA copies/mL at week 4, ⩾5000 copies/mL at week 12, or ⩾200 copies/mL at week 24 or thereafter. All cases of suspected virological failure were confirmed by a second VL determination performed at least 2 weeks later. Once reconfirmed, the

time of virological failure was defined as the time of the first VL measurement that met the failure criteria.

Immunological failure was defined as a decrease in the CD4 cell count of >50% from the baseline level, provided that the baseline CD4 cell count was >150 cells/μL. For patients with a baseline CD4 cell count of 100–150 cells/μL, immunological failure was defined as a CD4 cell count of <50 cells/μL and, for patients with baseline CD4 cell count of <100 cells/μL, immunological failure was defined as a CD4 cell count of <25 cells/μL. All cases of suspected immunological failure were confirmed by a second CD4 cell count measurement performed at least 1 week later. Once reconfirmed, the time of immunological failure was defined as the time of the first measurement that met the failure criteria. Clinical failure was defined as the development of a new AIDS-defining disease or as the relapse of an AIDS-defining disease that had been successfully treated previously.

Power calculation and statistics. The trial was powered to show equivalence between the study arms, with an 80% chance that the 95% confidence interval (CI) for the difference in virological failure rates would exclude a difference of >15% in either direction. This was based on a sample size of 150 patients/arm and an underlying failure rate of 20% in both arms.

Per study protocol, the primary population for analysis was the intention-to-treat/exposed (ITT/e) population, including all randomized patients who had taken at least 1 dose of the assigned treatment. This analysis is also termed the "ITT switch included" analysis. In the other protocol-stipulated analysis, switching from the assigned treatment constituted failure (ITT/e/switch = failure [ITT/e/s]). In both analyses, patients who withdrew consent, who were lost to follow-up, or who died constituted failure, and the time of failure was the time of the event (whichever came first). Some patients withdrew their consent during follow-up but permitted reporting of laboratory data measured as part of their routine care. For these patients, withdrawn consent did not constitute (virological) failure. Exploratory during-treatment efficacy and toxicity analyses were performed in accordance with Committee for Proprietary Medicinal Products guidelines regarding analysis of equivalence trials [21]. ITT analysis including all patients was done for the primary efficacy analysis, on the basis of recommendations from the Data Safety and Monitoring Board (DSMB).

All statistical analyses were performed using STATA software (version 7; StataCorp). The χ^2 test and Fisher's exact test were used for the comparison of categorical variables between treatment arms. Continuous variables were analyzed using Student's t or Kruskall-Wallis test, depending on the distribution. Cox analysis was performed, and Kaplan-Meier plots were produced for the "time-to-event" analyses containing sufficient numbers ($n > 25$). Multivariate models were developed to identify possible independent predictors of failure and the development of AEs. For the week-24 interim analysis presented to the DSMB, the Peto method of repeated significance testing was used to test for treatment difference, with $P = .001$ as the significance level, giving a significance level of $P = .05$ (2-sided) for the final, week-48 analysis.

Role of sponsor. CHIP developed the protocol and served as sponsor of the trial. Roche Pharmaceuticals provided financial support for the conduct of the trial. The conditions for this support were outlined in a contract between the 2 parties. This contract stipulates, among other issues, that the database will remain at CHIP at all times, only analyses approved by the trial Steering Committee are to be conducted, and such analyses will be performed by CHIP. Furthermore, the contract stipulates that Roche cannot veto the public presentation of any results from the trial.

RESULTS

Baseline parameters and follow-up. From September 2000 to March 2001, 317 patients were enrolled, 306 of whom initiated the randomized treatment. More patients in the Sqv/Rtv arm than in the Idv/Rtv arm did not initiate the assigned treatment (10 vs. 1). Of the 10, 4 knew and 4 did not know the result of the randomization, 1 was given the wrong treatment, and this information was not available for 1 patient. Patients who did not initiate the assigned treatment had lower VLs and higher CD4 cell counts, compared with patients who initiated the assigned treatment (data not shown).

No differences were observed at baseline, with regard to medical history, demographic, clinical, and laboratory parameters, or exposure to ART prior to baseline (table 1). Patients were primarily white (84%) men (78%) who engaged in homosexual- or bisexual-risk behavior (49%) with a median age of 39 years. The median CD4 cell count nadir was 110 cells/μL (interquartile range [IQR], 40–205 cells/μL), the median CD4 cell count was 277 cells/μL (IQR, 137–450 cells/μL), and the median VL was 3.9 $\log_{10}$ copies/mL (IQR, 1.7–5.1 $\log_{10}$ copies/mL); 39% of patients had a baseline VL of <400 copies/mL, and 30% had had a prior clinical AIDS-defining disease. At enrollment, 25% of patients were ART naive, 14% were ART experienced but PI naive, and 61% were PI experienced.

The status of patients at week 48 is shown in table 2. Complete week-48 follow-up data were available for 285 (93%) of the 306 patients who initiated the assigned treatment, 202 (66%) of whom continued to receive the assigned treatment. No difference was seen between the 2 study arms in the rate of patients lost to follow-up (7%). The 104 patients who prematurely switched from the assigned treatment did so primarily because of nonfatal, clinical AEs ($n = 67$). Among the 104 patients, no significant differences at the $P = .05$ level were observed between the study arms in the proportion of patients

Table 1. Demographic and baseline clinical characteristics of human immunodeficiency virus (HIV)–infected patients enrolled in the MaxCmin1 trial.

Characteristic	Idv/Rtv (n = 158)	Sqv/Rtv (n = 148)	Total (n = 306)
Male	117 (74)	122 (82)	239 (78)
Age, median years (IQR)	40 (34–46)	39 (34–48)	39 (34–47)
HIV exposure group			
Homosexual/bisexual	74 (47)	76 (51)	150 (49)
IDU	16 (10)	19 (13)	35 (11)
Hemophilic	6 (4)	2 (1)	8 (3)
Transfusion	0 (0)	4 (3)	4 (1)
Heterosexual	55 (35)	47 (32)	102 (33)
Unknown	7 (4)	0 (0)	7 (2)
Race			
White	129 (82)	127 (86)	256 (84)
Black	19 (12)	14 (9)	33 (11)
Asian	6 (4)	1 (1)	7 (2)
Other	4 (3)	6 (4)	10 (3)
CDC category C	45 (28)	48 (32)	93 (30)
PI naive	59 (38)	61 (41)	120 (39)
PI experienced			
Failure[a]	39 (25)	35 (24)	74 (25)
Intolerance[b]	59 (38)	52 (35)	111 (36)
VL, median $\log_{10}$ copies/mL (IQR)	3.9 (1.7–5.2)	4.0 (1.7–5.1)	3.9 (1.7–5.1)
VL <400 copies/mL	62 (39)	56 (38)	118 (39)
CD4 cell count, median 10^6 cells/L (IQR)	280 (139–453)	272 (135–420)	277 (137–450)
CD4 cell count nadir, median 10^6 cells/L (IQR)	119 (47–225)	107 (33–195)	110 (40–205)

NOTE. Data are no. (%) of patients, except where noted. IDU, injection drug user; Idv, indinavir; IQR, interquartile range; PI, protease inhibitor; Rtv, ritonavir; Sqv, saquinavir; VL, virus load.

[a] Defined as VL ⩾400 copies/mL.

[b] Defined as VL <400 copies/mL.

who switched treatment regimens, who received a mono or dual PI-, NNRTI-, or abacavir-based HAART regimen at week 48, or who discontinued treatment for any reason. Nine patients switched from Idv/Rtv to Sqv/Rtv, and 4 patients switched from Sqv/Rtv to Idv/Rtv. There was a significantly higher percentage of patients in the Idv/Rtv arm (41%) than in the Sqv/Rtv arm (27%) who prematurely switched from the assigned treatment ($P = .013$, χ^2 test). This difference was driven by patients who discontinued the randomized treatment because of a nonfatal, clinical AE (28% of patients assigned to Idv/Rtv arm vs. 15% in the Sqv/Rtv arm; $P = .004$, χ^2 test). Of the nonfatal, clinical AEs that led to patients' switching from the assigned treatment, 66% were of grade 1 or 2. More renal, skin and hair, and gastrointestinal AEs were observed in patients in the Idv/Rtv arm (data not shown). Twenty-two patients reduced the dose of the assigned treatment during follow-up (21 in the Idv/Rtv arm and 1 in the Sqv/Rtv arm).

Virological, immunological, and clinical outcome. The primary efficacy outcome, rate of virological failure, was seen in 77 (25%) of 306 patients, with no difference between the study arms ($P = .76$, log rank test; figure 1, *left*). The median VL at the time of failure was 2279 copies/mL, slightly higher in the Idv/Rtv arm (3857 copies/mL) than in the Sqv/Rtv arm (881 copies/mL) ($P = .40$). The difference between the 2 study arms in the proportion of patients experiencing virological failure was 2.2% (95% CI, −2.8% to 7.2%), with a higher proportion of protocol-defined virological failures in the Idv/Rtv arm. Using a Farrington-Manning equivalence test, we found sufficient evidence at the 5% level of significance to claim that the difference in success rates between the 2 treatments is <15% ($P < .0048$).

The higher discontinuation rate in the Idv/Rtv arm resulted in a significantly higher virological failure rate in this arm in the ITT/e/s analysis ($P = .009$, log rank test; figure 1, *right*). No difference was seen between the study arms in the during-treatment analysis ($P = .24$, log rank test). In the adjusted mul-

Table 2. Status of patients at week 48 of the MaxCmin1 trial.

Status	Idv/Rtv (n = 159)	Sqv/Rtv (n = 158)	Total (n = 317)
Randomized			
Initiated assigned PI Tx	158 (99)	148 (94)	306 (97)
Never initiated assigned PI Tx	1 (1)	10 (6)	11 (3)
Permanently switched from assigned PI Tx	64 (41)	40 (27)	104 (34)
Reason for switch			
Virological failure	3 (5)	2 (5)	5 (5)
Death	1 (2)	1 (3)	2 (2)
Nonfatal, clinical AE	45 (70)	22 (55)	67 (64)
Laboratory AE	4 (6)	2 (5)	6 (6)
Patient choice	3 (5)	5 (13)	8 (8)
Lost to follow-up	5 (8)	3 (8)	8 (8)
Other	3 (5)	5 (13)	8 (8)
Completed 48 weeks of assigned PI Tx	94 (59)	108 (73)	202 (66)
Patients with an outcome at week 48	148 (94)	137 (93)	285 (93)

NOTE. Data are no. (%) of patients. AE, adverse event; Idv, indinavir; PI, protease inhibitor; Rtv, ritonavir; Sqv, saquinavir; Tx, treatment.

tivariate Cox models, patients with a baseline VL of ⩾400 copies/mL had a higher hazard ratio of experiencing virological failure in the ITT/e, ITT/e/s, and during-treatment analyses (P < .001, for all comparisons), whereas being antiretroviral and PI naive failed to independently predict the risk of virological failure. Of importance, the hazard ratio for the comparison of Idv/Rtv versus Sqv/Rtv was not affected by adjusting for other risk factors. Similar trends were found when all randomized patients (ITT population, n = 317) were included in the analyses, rather than the ITT/e population (n = 306) (data not shown).

Figure 2 shows the proportion of patients with a plasma VL of <50 copies/mL during follow-up, stratified by different analytic approaches. At week 48, 203 (68%) of 306, 155 (51%) of 306, and 186 (93%) of 201 patients had a VL of <50 copies/mL in the ITT/e, ITT/e/s, and during-treatment analyses, respectively. Only when switching from the assigned treatment was counted as having a VL of >50 copies/mL (ITT/e/s) was a significant difference observed, with more patients in the Sqv/Rtv arm having a suppressed VL at week 48.

Only 6 patients experienced immunological failure (4 in the Idv/Rtv arm and 2 in the Sqv/Rtv arm). An increase of ⩾100 CD4 cells/μL at any time during follow-up was seen in 181 patients, at a median of 98 days. There was no significant difference between the study arms in the number of patients (P = .29, χ^2 test) or time to an increase of ⩾100 CD4 cell/μL (P = .47, log rank test). PI-naive patients were more likely to experience an increase of ⩾100 cells/μL than were PI-experienced patients (relative hazard, 0.50; 95% CI, 0.4–0.7; P < .0001).

Clinical failure was seen in 23 patients after a median of 80 days (13 patients classed as CDC category B, 7 patients classed as CDC category C, and 3 deaths); of these clinical failures, 14 (4 patients classed as CDC category C and 1 death) were observed in the Idv/Rtv arm, and 9 (3 patients classed as CDC category C and 2 deaths) were observed in the Sqv/Rtv arm. The low number of clinical failures precluded formal statistical analysis. In none of the fatal cases was the death directly related to the assigned treatment: the death in the Idv/Rtv arm was due to Castleman disease, and the 2 deaths in the Sqv/Rtv arm were due to *Pneumocystis carinii* pneumonia and hepatitis C end-stage liver failure.

AEs. Of the patients exposed to the study medication, 100 (33%) of 306 experienced at least 1 AE of grade 3 or 4 (65 [41%] in the Idv/Rtv arm vs. 35 [24%] in the Sqv/Rtv arm; P = .001, χ^2 test). Of these, the treating physician assessed the relationship to the assigned treatment as being at least possible in 46 (29%) in the Idv/Rtv arm versus 19 (13%) in the Sqv/

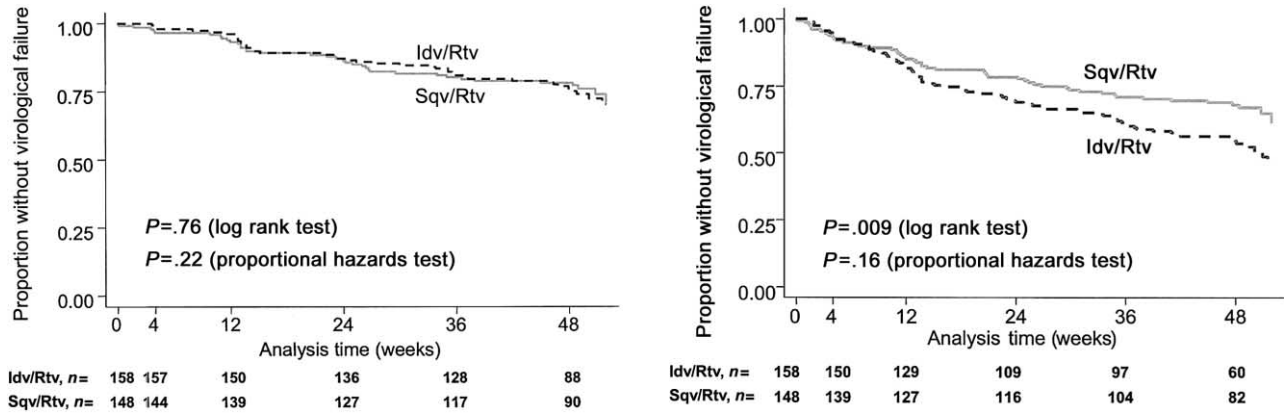

Figure 1. Rate of virological failure among patients enrolled in the MaxCmin1 trial. *Left,* Intent-to-treat/exposed (ITT/e) analysis. *Right,* ITT/e/switch = failure analysis. Idv, indinavir; Rtv, ritonavir; Sqv, saquinavir.

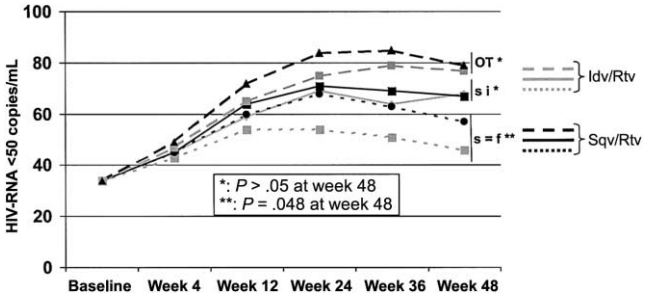

Figure 2. Proportion of patients enrolled in the MaxCmin1 trial with a plasma human immunodeficiency virus load of <50 copies/mL during follow-up, using different analytic approaches: intention-to-treat/exposed (ITT/e); ITT/e/switch = failure (ITT/e/s); and during-treatment analyses (DT). Idv, indinavir; Rtv, ritonavir; Sqv, saquinavir.

Rtv arm ($P = .001$, χ^2 test). There was a significant difference between the 2 study groups in the distribution by organ system of AEs grade 3 and 4, with a higher number of renal, dermatological, and gastrointestinal side effects in the Idv/Rtv arm (data not shown).

Laboratory results. The median fasting baseline lipid values were as follows: for total cholesterol, 4.7 mmol/L in the Idv/Rtv arm and 4.8 mmol/L in the Sqv/Rtv arm (normal range, 3.4–6.2 mmol/L); for LDL cholesterol, 3.1 mmol/L in the Idv/Rtv arm and 3.2 mmol/L in the Sqv/Rtv arm (normal range, 1.7–3.2 mmol/L); and, for total triglyceride, 1.6 mmol/L in the Idv/Rtv arm and 1.7 mmol/L in the Sqv/Rtv arm (normal range, 0.5–2.3 mmol/L). The median percentage change from baseline in fasting total cholesterol, LDL cholesterol, and total triglyceride is shown in figure 3. Significantly higher lipid elevations were seen in the Idv/Rtv arm, compared with the Sqv/Rtv arm, at weeks 4 and 48 (ITT/e analysis). These differences were even more pronounced when the actual median changes from baseline, rather than the median percentage change, were considered (data not shown). Similar differences were seen when restricting the analysis to patients who continued to receive their trial medication (data not shown).

No difference between the study groups was seen in hematological, renal, or hepatic laboratory parameters, except for bilirubin levels, which were 10 and 11 μmol/L at baseline in the Idv/Rtv and Sqv/Rtv arms, respectively (normal range, 4–22 μmol/L). In the Sqv/Rtv arm, the bilirubin level did not change over time, whereas, in the Idv/Rtv arm, it increased to 20 μmol/L at week 4, followed by a decline to 15 μmol/L at week 48.

DISCUSSION

The MaxCmin1 trial was designed in the early part of 2000 to assess whether equivalence exists in efficacy and safety between Idv/Rtv (800/100 mg b.i.d.) and Sqv/Rtv (1000/100 mg b.i.d.), in combination with at least 2 non-PI drugs, with the primary outcome being the incidence of protocol-defined virological failure. Equivalence was observed for efficacy, whereas Idv/Rtv lead to an increased risk of treatment-limiting AEs and AEs of grade 3 and/or 4. As a consequence of the safety profile of Idv/Rtv, fewer patients continued to receive this treatment throughout the 48 weeks, leading to differences in the efficacy analyses, in which continuation with study medication influence the outcome. In addition, Idv/Rtv was found to cause a higher risk of elevating blood levels of lipids and bilirubin.

The heterogeneous study population included introduces a serious limitation, because the trial would not have sufficient power to describe the outcome within each of the subgroups included if the outcomes of the treatments were affected by the stage of HIV infection or treatment. To address this limitation, multivariate models of the key efficacy outcomes were developed. Of importance, patients entering the trial with a VL of >400 copies/mL had a significantly increased risk of experiencing protocol-defined virological failure and of not achieving virological suppression (<50 or <400 copies/mL) at week 48, compared with patients who were virologically suppressed at baseline. However, being antiretroviral or PI naive at the time of enrollment did not independently affect the risk of a poor virological outcome. The hazards ratios for the comparison of virological failure in the Idv/Rtv versus Sqv/Rtv arm were comparable in univariate and multivariate models adjusting for other variables. To further elucidate whether baseline characteristics may have influenced the efficacy outcomes, 2 substudies are currently investigating genotypic-resistance mutations at baseline and at the time of virological failure and single-nucleotide polymorphisms in the multidrug resistance–1 locus of stored peripheral blood mononuclear cells. In addition, one substudy is investigating efficacy and safety in relation to trough levels (Cmin) of the study PIs at weeks 4 and 48.

In the analysis in which switching from the assigned treatment is equal to virological failure or lack of virological sup-

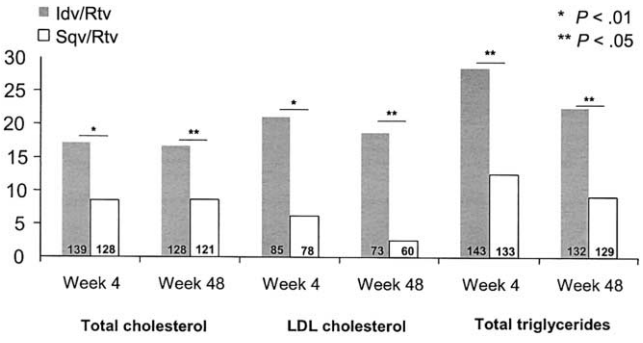

Figure 3. Median percentage change from baseline in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol, and total triglyceride levels in the intention-to-treat/exposed analysis. Nos. within the bars are the no. of measurements (i.e., patients) at each time point. Idv, indinavir; Rtv, ritonavir; Sqv, saquinavir.

pression, Sqv/Rtv tended to have superior virological activity than did Idv/Rtv. This result was to be expected, because a higher proportion of patients in the Idv/Rtv arm switched from the randomized treatment. The trial was not designed and did not have the statistical power to test whether there were differences in risk of protocol-defined immunological and clinical failures between the 2 study arms. No formal statistical analysis of these efficacy parameters was appropriate, because of the low number of such failures observed.

Finally, the efficacy and safety outcome of patients randomized to receive Idv/Rtv is comparable with data from the recently completed BEST trial [17]. The BEST trial randomized patients receiving a stable regimen, including Idv (800 mg t.i.d.), to either continue this regimen or switch to Idv/Rtv (800/100 mg b.i.d.). In the present trial, few patients were receiving IDV (800 mg t.i.d.) at the time of screening; hence, the patients who received Idv/Rtv in the 2 trials are not directly comparable.

In the present trial, 21 (13%) of 158 patients in the Idv/Rtv arm reduced the Idv dose. The present trial was not designed to evaluate whether this strategy lowered the risk of AEs or affected the efficacy of the treatment, nor was the sample sufficiently large for formal testing of these important questions. A randomized trial should be done to evaluate whether Idv/Rtv in lower dosing has a more favorable AE profile and maintained virological efficacy, compared with either Idv/Rtv (800/100 mg b.i.d.) or other commonly used Rtv-boosted PI regimens prior to the introduction of other Idv/Rtv dosing regimens in routine care.

Compared with patients in the Sqv/Rtv arm, patients in the Idv/Rtv arm had significant increases from baseline in total cholesterol, LDL cholesterol, and triglyceride levels at weeks 4 and 48. Other drugs (NNRTIs and stavudine) that could potentially influence these parameters were well balanced between the 2 groups at baseline. Therefore, these findings suggest that Idv/Rtv affects the lipid metabolism adversely, relative to Sqv/Rtv. Because the same Rtv dosing was used in both arms, it is likely that it is the Idv component that causes lipid levels to increase. However, another possibility is that the Rtv metabolism is affected differently by Idv, compared with Sqv. These mechanisms will be explored further by correlating drug levels at weeks 4 and 48 with lipid changes. Differences between PIs boosted by the same Rtv dosing has not been observed previously, whereas it was reported recently that lopinavir/Rtv lead to greater elevation of lipid levels, compared with nelfinavir [20].

In conclusion, we have found that, in this open-label study of a heterogeneous patient population—reflecting the real-life situation—Sqv/Rtv has antiretroviral effects comparable to those of Idv/Rtv in the doses studied. We observed more treatment-limiting AEs in the Idv/Rtv arm, relative to the Sqv/Rtv arm, and found that more patients in the Sqv/Rtv arm remained virologically suppressed at week 48, probably because of a better toxicity profile.

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References

1. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. Lancet **1999**; 353:863–8.
2. Paredes R, Mocroft A, Kirk O, et al. Predictors of virological success and ensuing failure in HIV-positive patients starting highly active antiretroviral therapy in Europe: results from the EuroSIDA study. Arch Intern Med **2000**; 160:1123–32.
3. Flandre P, Raffi F, Descamps D, et al. Final analysis of the Trilege induction-maintenance trial: results at 18 months. AIDS **2002**; 16:561–8.
4. D'Arminio MA, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. AIDS **2000**; 14: 499–507.
5. Havlir DV, Hellmann NS, Petropoulos CJ, et al. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. JAMA **2000**; 283:229–34.
6. Burger DM, Hoetelmans RM, Hugen PW, et al. Low plasma concentrations of indinavir are related to virological treatment failure in HIV-1–infected patients on indinavir-containing triple therapy. Antivir Ther **1998**; 3:215–20.
7. Phillips AN, Miller V, Sabin C, et al. Durability of HIV-1 viral suppression over 3.3 years with multi-drug antiretroviral therapy in previously drug-naive individuals. AIDS **2001**; 15:2379–84.
8. Tuldra A, Fumaz CR, Ferrer MJ, et al. Prospective randomized two-arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy. J Acquir Immune Defic Syndr **2000**; 25:221–8.
9. Clumeck N, Goebel F, Rozenbaum W, et al. Simplification with abacavir-based triple nucleoside therapy versus continued protease inhibitor–based highly active antiretroviral therapy in HIV-1–infected patients with undetectable plasma HIV-1 RNA. AIDS **2001**; 15:1517–26.
10. Veldkamp AI, Weverling GJ, Lange JM, et al. High exposure to nevirapine in plasma is associated with an improved virological response in HIV-1–infected individuals. AIDS **2001**; 15:1089–95.
11. Moyle GJ, Back D. Principles and practice of HIV-protease inhibitor pharmacoenhancement. HIV Med **2001**; 2:105–13.
12. Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet **2000**; 38:41–57.
13. Buss N, Snell P, Bock J, Hsu A, Jorga K. Saquinavir and ritonavir pharmacokinetics following combined ritonavir and saquinavir (soft gelatin capsules) administration. Br J Clin Pharmacol **2001**; 52:255–64.
14. Stone VE, Hogan JW, Schuman P, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the HERS study. J Acquir Immune Defic Syndr **2001**; 28:124–31.
15. Bartlett JA, DeMasi R, Quinn J, Moxham C, Rousseau F. Overview of the effectiveness of triple combination therapy in antiretroviral-naive HIV-1 infected adults. AIDS **2001**; 15:1369–77.
16. van Heeswijk RP, Veldkamp AI, Hoetelmans RM, et al. The steady-state plasma pharmacokinetics of indinavir alone and in combination with a low dose of ritonavir in twice daily dosing regimens in HIV-1–infected individuals. AIDS **1999**; 13:F95–9.
17. Arnaiz JA, Mallolas J, Podzamczer D, et al. Continued indinavir versus switching to indinavir/ritonavir in HIV-infected subjects with suppressed viral load. AIDS **2003**; 11:831–40.
18. Kirk O, Gerstoft J, Pedersen C, et al. Low body weight and type of protease inhibitor predict discontinuation and treatment-limiting adverse drug reactions among HIV-infected patients starting a protease inhibitor regimen: consistent results from a randomized trial and an observational cohort. HIV Med **2001**; 2:43–51.
19. Veldkamp AI, van Heeswijk RP, Mulder JW, et al. Steady-state pharmacokinetics of twice-daily dosing of saquinavir plus ritonavir in HIV-1–infected individuals. J Acquir Immune Defic Syndr **2001**; 27:344–9.
20. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. N Engl J Med **2002**; 346:2039–46.
21. Biostatistical methodology in clinical trials in applications for marketing authorizations for medicinal products. CPMP Working Party on Efficacy of Medicinal Products Note for Guidance III/3630/92-EN. Stat Med **1995**; 14:1659–82.