

# Quality of life in asymptomatic- and symptomatic HIV infected patients in a trial of ritonavir/saquinavir therapy

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**Objective:** To compare the impact on quality of life (QoL) of treatment with ritonavir (RTV)/saquinavir (SQV) versus RTV/SQV/stavudine (d4T) in asymptomatic [Centers for Disease Control (CDC) class A] and symptomatic HIV-infected patients (CDC B and C) who did or did not receive antiretroviral therapy (ARVT) before entry into the study.

**Design:** A multicenter randomized clinical trial.

**Patients:** Protease inhibitor- and d4T-naive patients were allocated to RTV/SQV (n = 84) versus RTV/SQV/d4T (n = 83).

**Main outcome measure:** Changes from baseline in QoL assessed by the Medical Outcomes Study Health Survey for HIV (MOS-HIV) and a symptom checklist administered at baseline and after 12, 24, 36 and 48 weeks.

**Results:** Changes in QoL were comparable in both treatments, although more neuropathy was reported in the RTV/SQV/d4T group. QoL improved significantly in both groups regarding health distress, energy/fatigue, mental health, health perceptions, physical function and overall QoL, despite an increase in reported symptoms. More favourable changes in cognitive and social function were observed in symptomatic compared with asymptomatic patients, with symptomatic patients showing an improvement and asymptomatic patients showing a decline in function after baseline. ARVT-naive patients showed more favourable changes in mental health, health distress and social function compared with patients with previous ARVT.

**Conclusion:** RTV/SQV and RTV/SQV/d4T were equally effective in improving the QoL of patients over 48 weeks, despite an increase in reported symptoms. Symptomatic patients reported more QoL benefit than asymptomatic patients, and ARVT-naive patients benefitted more than those with previous ARVT. The impact on patients' QoL should be considered in the search for the optimal management of HIV infection.

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## Introduction

Antiretroviral combination therapy consisting of two nucleoside reverse transcriptase inhibitors (NRTI) and a protease inhibitor (PI) has been shown to be effective with respect to viral suppression and to provide clinical benefits in terms of delaying disease progression and prolonging survival in the treatment of HIV infection [1–4].

Besides providing health benefits, PI-containing regimens may have a negative impact on patients' quality of life (QoL). PI require strict patient adherence in order to ensure a durable antiretroviral effect, which may interfere with the patients' daily activities. In addition, PI-containing regimens have the potential to cause short- and long-term toxicities. In patients with HIV-related symptoms or AIDS, these adverse effects of highly active antiretroviral therapy (HAART) may be offset by an evident clinical benefit. Several studies [5–7] have indeed demonstrated improved or stable QoL in patients with advanced HIV infection who were treated with PI-containing regimens. However, in patients who are still asymptomatic, the toxicities and constraints inflicted by HAART may reduce patients' QoL without providing an apparent short-term clinical benefit. This is the first study that reports on the impact of HAART on QoL in asymptomatic patients compared with symptomatic patients.

We studied the impact on patients' QoL of two ritonavir (RTV) and saquinavir (SQV)-containing regimens in a randomized clinical trial (RCT), the Prometheus Study [8]. Patients were stratified at randomization according to their use of antiretroviral therapy (ARVT) before entry into the study. We therefore additionally looked into the effect on QoL of previous ARVT.

The objective of this study was to compare the impact on patients' QoL of RTV/SQV versus RTV/SQV/stavudine (d4T), and to compare the changes in QoL in asymptomatic patients versus symptomatic patients with and without previous ARVT.

## Methods

### Patients

From January 1997 to January 1999, an open-label RCT was performed comparing RTV 400 mg/SQV

400 mg twice a day with RTV 400 mg/SQV 400 mg/d4T 40 mg twice a day in 10 hospitals in the Netherlands and four hospitals in Belgium. Eligible patients were HIV-infected individuals with an indication for initiation or change of antiretroviral treatment; they were PI and d4T naive. The primary outcome measure was the proportion of patients with a serum HIV-RNA below 400 copies/ml at week 48. In patients with a serum HIV-RNA above 400 copies/ml at week 12 and week 18, therapy was intensified with NRTI.

The impact on the QoL of patients was a secondary outcome. Patients were eligible for the QoL substudy if they were able to complete a Dutch, English, or French self-report questionnaire. Enrolment of the QoL substudy started on 25 February 1997. The study was approved by the Institutional Review Board of all participating centers. All patients gave written informed consent. Details of the design and clinical results of this trial have been reported separately [8].

### Quality of life measurement

QoL was assessed with a self-report questionnaire consisting of two parts: the Medical Outcomes Study Health Survey for HIV (MOS-HIV) and a symptom checklist.

The MOS-HIV is a widely used questionnaire of health-related QoL in HIV/AIDS with established reliability and validity [9–11]. It consists of 10 subscales: physical-, role-, social-, and cognitive function, mental health, energy/fatigue, health distress, health perceptions, pain, and overall quality of life [9–11]. Subscale scores range from 0 to 100, with higher scores indicating a better QoL.

The symptom checklist consists of 28 items referring to symptoms related to HIV infection or antiretroviral therapy. These items were derived from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30, and an HIV/AIDS-specific questionnaire [12,13]. The symptom checklist includes five subscales: fever (three items), neuropathy (two items), skin problems (two items), shortness of breath (two items), and nausea and vomiting (two items). The remaining single items pertain to: trouble sleeping, lack of appetite, diarrhoea, constipation, chest pain, headaches, abdominal pain, stomach pain, sore muscles, pain in legs, pain when urinating, pain when swallowing, dry mouth, tingling feeling around the mouth or tongue, taste disturbances, dizziness, and difficulty seeing. Symptoms were scored on a

four-point scale with the response categories 'not at all', 'a little', 'quite a bit', and 'very much'.

The QoL questionnaire was administered at the start of treatment and after 12, 24, 36 and 48 weeks of follow-up. Patients received the questionnaire from their AIDS counselling nurse or their physician when attending the outpatient clinic for scheduled study visits. The questionnaire was completed at the outpatient clinic or at home, depending on the choice of the patient and the outpatient clinic facilities. Completed questionnaires were returned in a sealed envelope.

### Statistical analysis

Patients were included in the analysis if a baseline measurement and at least one follow-up measurement was available. Baseline characteristics were compared between both treatment groups, and between patients included in the QoL substudy and patients not included in the QoL substudy, using Student's *t*-tests for continuous variables and chi-square- or Fisher's exact tests for categorical variables.

For the MOS-HIV subscales, we calculated changes from baseline by subtracting baseline scores from 12, 24, 36 and 48 week scores. Mean changes from baseline were compared between both treatment groups using repeated measures analysis of variance (ANOVA), including treatment group as a between-subject factor, and time as a within-subject factor, adjusting for baseline HIV-RNA, CD4 cell count and the use of ARVT before study entry (yes or no).

We dichotomized the responses on the symptom checklist into 'not at all' versus 'a little bit' to 'very much'. We computed the mean area under the curve minus baseline (AUCMB) to 48 weeks for the subscales and single items of the symptoms checklist, using the trapezoidal rule [14]. The AUCMB indicates the change in the proportion of patients reporting symptoms from baseline to 48 weeks. The mean AUCMB was compared between both treatment groups using ANOVA.

We categorized patients classified at baseline as category A, according to the 1993 Centers for Disease Control (CDC) classification system of HIV infection, as 'asymptomatic', and patients who were classified as category B or category C as 'symptomatic'. A second ANOVA was performed on the mean changes from baseline on the MOS-HIV subscales using two between-subject factors consisting of asymptomatic versus symptomatic, previous ARVT versus ARVT naive, and using time as a within-subject factor.

Two-sided *P* values < 0.05 were considered to indicate statistical significance. The individual between-

group or within-group effects were calculated in means and 95% confidence intervals (CI), and were interpreted only if the overall test statistic was found to be statistically significant.

For the handling of missing data we used the last observation carried forward approach. Analysis was by intention-to-treat. Data analysis was conducted using the SPSS software package (SPSS; Systat, Chicago, Illinois, USA).

## Results

### Patient accountability and response

A total of 208 patients were enrolled in the RCT, 104 patients were allocated to RTV/SQV and 104 patients to RTV/SQV/d4T. Forty-one of these patients (20 allocated to RTV/SQV and 21 to RTV/SQV/d4T), were not entered in the QoL substudy. Fifteen of these patients were enrolled in the RCT before the QoL substudy had started and therefore did not have a baseline QoL assessment. Nine patients were unable to complete questionnaires because of insufficient language skills (*n* = 8) or neurological impairment (*n* = 1). Seventeen others did not participate because they never started their allocated treatment (*n* = 5), they never returned a baseline questionnaire (*n* = 7), or were lost to follow-up after baseline (*n* = 5). A total of 167 patients were thus included in the QoL study, of whom 84 were allocated to RTV/SQV and 83 to RTV/SQV/d4T. For this sample, the response rates were: 96% (161/167) at week 12, 92% (154/167) at week 24, 87% (146/167) at week 36, and 92% (153/167) at week 48.

### Baseline characteristics

No statistically significant differences were found between both treatment groups of patients enrolled in the QoL study (Table 1). At baseline, participants in the

**Table 1.** Baseline characteristics.

	RTV/SQV ( <i>n</i> = 84)	RTV/SQV/d4T ( <i>n</i> = 83)
Male	76 (90%)	70 (86%)
Mean age (years) (SD)	39 (9)	38 (10)
Homosexual	62 (74%)	57 (69%)
Previous antiretroviral therapy	38 (45%)	35 (42%)
Median (IQR) log <sub>10</sub> HIV-RNA (copies/ml)	4.46 (3.98–5.00)	4.42 (3.86–4.81)
Median (IQR) CD4 cell count (cells/mm <sup>3</sup> )	260 (125–410)	260 (120–400)
HIV disease stage:		
CDC A	36 (43%)	39 (47%)
CDC B	28 (33%)	25 (30%)
CDC C	20 (24%)	19 (23%)

CDC, Centers for Disease Control; IQR, interquartile range; RTV, ritonavir; SQV, saquinavir; d4T, stavudine.

QoL study were comparable with patients not participating in the QoL study with respect to treatment allocation, median log<sub>10</sub> HIV-RNA (copies/ml), median CD4 cell count (cells/mm<sup>3</sup>), and baseline CDC classification of HIV infection (data not shown). QoL study patients were more likely to be ARVT naive (56 versus 39%,  $P = 0.05$ ), male (88 versus 63%,  $P < 0.01$ ), homosexual (73 versus 38%,  $P < 0.01$ ), and were older (39 versus 35 years,  $P = 0.02$ ).

### Comparison of changes in quality of life between both treatment groups

#### MOS-HIV

At baseline, MOS-HIV subscale scores were comparable for the treatment groups (Table 2). No statistically significant differences were found between both treatment groups in mean changes on the MOS-HIV subscales from baseline, and no statistically significant treatment group by time interaction was found, indicating a similar pattern of changes over time in both groups.

Combining the two treatment groups, statistically significant improvements were found from baseline with respect to: physical function, mental health, energy/fatigue, health perceptions, and overall QoL. QoL remained stable on the other MOS-HIV subscales.

#### Symptom checklist

A statistically significant difference was found between both treatment groups in the change in the proportion of patients reporting neuropathy (data not shown). In the RTV/SQV group, neuropathy decreased by 3% relative to the baseline, whereas in the RTV/SQV/

d4T group there was an increase from baseline by 12% (difference: 15%, 95% CI of difference: 2 to 28%).

There was an increase of at least 10% in both treatment groups in the proportion of patients reporting diarrhoea (RTV/SQV: 41% and RTV/SQV/d4T: 47%, difference 6%, 95% CI of difference: -10 to 21%), perioral tingling (RTV/SQV: 25% and RTV/SQV/d4T: 34%, difference 9%, 95% CI of difference: -6 to 25%), and abdominal pain (RTV/SQV: 15% and RTV/SQV/d4T: 13%, difference 2%, 95% CI of difference: -11 to 16%).

### Impact of HIV disease stage and previous antiretroviral therapy on changes in quality of life

As expected, asymptomatic patients (CDC A) had higher baseline MOS-HIV scores, indicating a better QoL, compared with symptomatic patients (CDC B and C) (Table 3). Baseline MOS-HIV scores were comparable in patients who had received ARVT before study entry and patients who were ARVT naive (data not shown).

No statistically significant interaction was found between disease stage and previous ARTV, indicating that previous ARTV had a similar impact on changes in QoL in asymptomatic compared with symptomatic patients.

We found a statistically significant difference in the changes from baseline in social and cognitive function in asymptomatic patients compared with symptomatic patients. Asymptomatic patients reported more limitations in social activities as a result of health problems

**Table 2.** Changes from baseline in quality of life in patients treated with ritonavir/saquinavir and ritonavir/saquinavir/stavudine.

MOS-HIV scales	MOS-HIV baseline scores <sup>a</sup>		Between-group difference (95% CI) <sup>b</sup>	Change from baseline (95% CI) <sup>c</sup>
	RTV/SQV (n = 84)	RTV/SQV/d4T (n = 83)		
Physical function	83.6 (2.3)	78.6 (2.4)	-4.4 (-10.1 to 1.3)	4.2 (1.4 to 7.0)*
Role function	79.5 (3.7)	72.3 (4.6)	-2.8 (-12.3 to 6.6)	2.1 (-2.5 to 6.7)
Social function	82.0 (2.6)	80.0 (2.5)	-3.5 (-9.5 to 2.5)	1.9 (-0.9 to 5.0)
Cognitive function	77.0 (2.2)	74.7 (2.2)	-3.7 (-8.2 to 0.7)	1.6 (-0.6 to 3.7)
Mental health	65.5 (2.3)	65.5 (1.9)	-0.4 (-4.7 to 4.6)	3.4 (1.5 to 6.2)*
Energy/fatigue	63.5 (2.1)	60.5 (2.1)	-2.5 (-7.5 to 2.6)	3.2 (0.7 to 5.7)*
Health distress	70.1 (2.8)	71.2 (2.3)	2.5 (-2.2 to 7.3)	6.4 (3.5 to 8.7)*
Health perceptions	51.7 (2.8)	47.6 (2.6)	-2.1 (-7.3 to 3.1)	4.3 (1.7 to 6.9)*
Pain	82.6 (2.0)	80.2 (2.3)	-2.5 (-8.7 to 3.6)	1.3 (-1.8 to 4.3)
Overall quality of life	66.3 (2.6)	66.5 (2.2)	2.4 (-4.4 to 9.1)	6.3 (2.9 to 9.6)*

CI, Confidence interval; MOS-HIV, Medical Outcomes Study HIV; RTV, ritonavir; SQV, saquinavir; d4T, stavudine.

\*  $P < 0.05$ .

<sup>a</sup>Values are means  $\pm$  standard errors.

<sup>b</sup>Values are mean differences between RTV/SQV compared with RTV/SQV/d4T in the change from baseline over all timepoints, adjusted for baseline HIV-RNA, CD4 cell count, and previous antiretroviral therapy. Scores below zero indicate a better quality of life (QoL) in the RTV/SQV/d4T group, whereas scores higher than zero indicate a better QoL in the RTV/SQV group.

<sup>c</sup>Values are mean changes from baseline over all timepoints for both treatment groups combined. Scores higher than zero indicate improvement in QoL compared with baseline, whereas scores below zero indicate decline in QoL.

**Table 3.** Effect of HIV disease stage and previous antiretroviral therapy on changes from baseline over 48 weeks in quality of life.

MOS-HIV scales	MOS-HIV baseline scores <sup>a</sup>		Asympt versus sympt (95% CI) <sup>b</sup>	Previous ARVT versus naive (95% CI) <sup>c</sup>
	Asympt (n = 75)	Sympt (n = 92)		
Physical function	85.8 (2.4)	77.3 (2.2)	-3.8 (-9.5 to 2.0)	-6.1 (-11.8 to -0.4)
Role function	80.3 (3.9)	70.1 (4.2)	-3.1 (-12.5 to 6.6)	-6.9 (-16.5 to 2.7)
Social function	87.3 (2.5)	75.8 (2.5)	-8.1 (-14.0 to -2.0)*	-6.2 (-12.2 to -0.2)*
Cognitive function	80.5 (2.0)	72.1 (2.2)	-8.5 (-12.7 to -4.0)*	-3.4 (-7.8 to 1.0)
Mental health	66.0 (2.6)	65.1 (1.7)	0.4 (-4.4 to 5.1)	-6.0 (-4.3 to -1.2)*
Energy/fatigue	64.7 (2.5)	59.8 (1.8)	-1.9 (-7.0 to 3.3)	-4.6 (-9.8 to 0.6)
Health distress	71.2 (2.8)	70.1 (2.4)	1.2 (-3.7 to 6.0)	-7.3 (-12.1 to -2.6)*
Health perceptions	56.8 (2.9)	43.9 (2.3)	-4.1 (-9.5 to 1.3)	-4.7 (-10.2 to 0.7)
Pain	84.9 (2.2)	78.6 (2.0)	-2.7 (-9.0 to 3.6)	-6.6 (-12.9 to -0.3)
Overall quality of life	68.7 (2.8)	64.5 (2.1)	-4.8 (-11.7 to 2.2)	-6.3 (-13.2 to 0.7)

Asympt, asymptomatic; sympt, symptomatic; ARVT, antiretroviral therapy; MOS-HIV, Medical Outcomes Study HIV.

\*  $P < 0.05$ .

<sup>a</sup>Values are means  $\pm$  standard errors.

<sup>b</sup>Values are mean differences between asymptomatic compared with symptomatic patients in changes from baseline in quality of life (QoL) over 48 weeks. Scores below zero indicate less favourable changes in QoL for asymptomatic patients compared with symptomatic patients.

<sup>c</sup>Values are mean differences between patients with previous ARVT compared with naive patients in changes from baseline in QoL over 48 weeks. Scores below zero indicate less favourable changes in QoL for patients with previous ARVT compared with naive patients.

relative to the start of treatment, whereas symptomatic patients reported fewer limitations. We found the same pattern for cognitive function: asymptomatic patients reported a worsening in cognitive function compared with baseline, whereas symptomatic patients reported an improvement.

We observed a statistically significant difference in changes from baseline in MOS-HIV scores in patients with previous ARVT compared with patients who were ARTV naive with respect to social function, mental health and health distress. These dimensions improved in the ARVT-naive patients. With respect to social function, there was an average decline from baseline in patients with previous ARVT. Mental health and health distress remained stable in patients with previous ARVT. The effects of disease stage and previous ARVT on the mean changes over 48 weeks in social function, cognitive function, mental health and health distress are illustrated in Fig. 1(a–d).

## Discussion

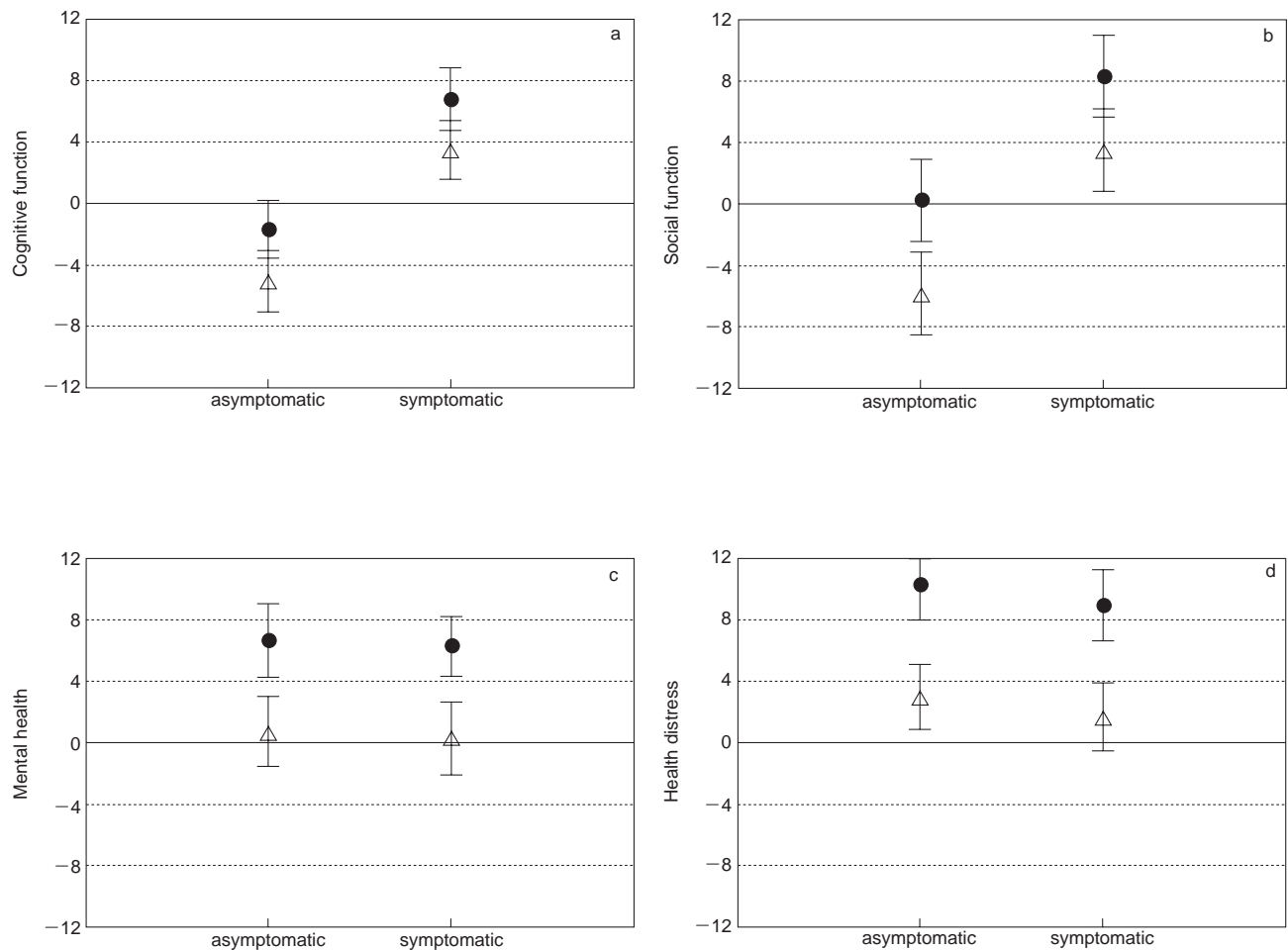
The QoL study was set up alongside a clinical trial, the Prometheus Study. This RCT showed no difference in the proportion of patients with a serum HIV-RNA below 400 copies/ml at 48 weeks between the group starting with RTV/SQV alone, and intensifying when indicated, versus those who were treated with immediate triple therapy [8]. The present study showed that both treatment strategies were equally effective in maintaining and improving patients' QoL, despite an increase in reported symptoms. Although patients allocated to RTV/SQV/d4T reported more neuro-

pathy, this did not result in a measurably diminished functioning or well-being. Taking the comparable impact into account, QoL is not a decisive factor in the choice between these two treatment strategies.

This is the first study that reports on the impact of HAART on the QoL of patients with an asymptomatic HIV infection. It has recently been called into question whether the potential advantages of initiating PI-containing regimens in early HIV infection outweigh the potential disadvantages [15,16]. There is a need for studies evaluating the long-term clinical effectiveness, adverse effects, adherence, and effects on QoL of ARVT in early HIV infection [17]. The present study showed a decline in functioning in asymptomatic patients after the start of therapy, and an improvement in functioning in symptomatic patients. Although this effect was limited to cognitive and social function, these may be considered highly relevant aspects of an individual's QoL.

We found more favourable changes in mental health, health distress and social function in ARVT-naive patients compared with patients with previous ARVT. The proportion of patients with HIV-RNA below 400 copies/ml was consistently higher after week 12 among patients who were ARVT naive compared with those who had had ARVT before entry into the study [8]. The more favourable QoL outcomes in ARVT-naive patients were probably associated with this better efficacy.

Forty-one patients enrolled in the RCT did not participate in the QoL study. Because baseline characteristics were equally distributed between both treatment groups in patients who participated in the QoL



**Fig. 1.** Effect of HIV disease stage and previous antiretroviral therapy on the mean changes from baseline over 48 weeks in quality of life. Changes in (a) cognitive function; (b) social function; (c) mental health; (d) health distress. ●, antiretroviral therapy naive; △, previous antiretroviral therapy. Values above the zero line indicate an improvement in quality of life, whereas values below the zero line indicate a worsening. Effects are adjusted for the other factor.

study, it is unlikely that this selection affected the comparison of the impact on QoL between both treatment groups. However, our results may not be generalized to populations with baseline characteristics that substantially diverge from our study sample. Furthermore, results from this study may not be unconditionally generalized to other antiretroviral combination therapies. Other regimens may be associated with different toxicities, and may differ with respect to the ease of administration. This study used a relatively convenient twice-daily dosing of the medication, taken together with food or after a meal. More or less convenient regimens may result in a different impact on patients' QoL. Finally, the follow-up of this study was only 48 weeks. Recently, long-term side-effects of ARVT, such as peripheral lipodystrophy, have been reported that usually occur after 48 weeks [18]. The impact of such long-term toxicities on QoL remains to be studied.

Information from the present study about the possible effects of treatment on QoL may be used to inform patients and clinicians when starting combination therapy with RTV and SQV is being considered, and may contribute to trade-offs between the potential burden and benefit of therapy.

## Conclusion

RTV/SQV and RTV/SQV/d4T were equally effective in maintaining and improving patients' QoL over 48 weeks despite an increase in reported symptoms. Symptomatic patients reported more benefits in QoL than asymptomatic patients, and ARVT-naive patients benefitted more than those with previous ARVT. The impact on patients' QoL should be considered in the search for the optimal management of HIV infection.

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## Appendix

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