

Quality of life outcomes of combination zalcitabine–zidovudine, saquinavir–zidovudine, and saquinavir–zalcitabine–zidovudine therapy for HIV-infected adults with CD4 cell counts between 50 and 350 per cubic millimeter

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Background: This double-blind study evaluated treatment with zalcitabine–zidovudine, saquinavir–zidovudine, or saquinavir–zalcitabine–zidovudine on the health-related quality of life of HIV-infected adults with CD4 cell counts between 50 and 350 cells/mm³.

Methods: Nine hundred and ninety-three HIV-infected male or female quality of life substudy patients aged 18 years or older, with CD4 cell counts between 50 and 350 cells/mm³ naïve to antiretroviral therapy or with less than 16 weeks of zidovudine therapy, were randomly assigned to one of three daily regimens: zalcitabine 0.75 mg and zidovudine 200 mg every 8 h (ddC/ZDV); saquinavir 600 mg and zidovudine 200 mg every 8 h (SQV/ZDV); or saquinavir 600 mg, zalcitabine 0.75 mg and zidovudine 200 mg every 8 h (SQV/ddC/ZDV). The health-related quality of life was measured using the Medical Outcome Study HIV (MOS–HIV) Health Survey subscale and physical and mental health summary scores, and a global visual analogue scale (VAS) score. The primary health-related quality of life endpoints were the MOS–HIV physical and mental health summary scores.

Results: After 24 weeks of treatment, no statistically significant differences were observed between the three treatment groups on physical health and mental health summary scores (global test $P = 0.118$). After 48 weeks of treatment, statistically significant differences among the groups were observed for physical health and mental health summary scores (global test $P = 0.020$); no change in physical health summary scores from the baseline were seen in the triple combination therapy, whereas the ddC/ZDV combination therapy group showed decreases from baseline in physical health summary scores ($P = 0.008$). Six of the 10 individual MOS–HIV subscale scores and the VAS scores showed results consistent with the physical health summary endpoints after 48 weeks of therapy. No statistically significant differences in baseline to 48 week changes in MOS–HIV subscale or summary scores were seen between the ddC/ZDV and SQV/ZDV groups ($P > 0.05$).

Conclusions: Patients on triple combination therapy maintained their quality of life over 48 weeks compared with significant decreases in the quality of life for ddC/ZDV combination therapy.

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Introduction

Combination antiretroviral therapy regimens including two nucleoside analogues, reverse transcriptase inhibitors and an HIV protease inhibitor have become the standard of care for HIV infection [1,2]. These potent regimens result in substantial reductions in plasma HIV RNA, improvements in CD4 cell counts and, most importantly, reductions in the risk of disease progression and death for persons with advanced immunodeficiency [3–9]. Clinical trials have demonstrated that combination antiretroviral therapy with a protease inhibitor reduces combined new opportunistic disease and death endpoints by 40–53% and death by 43–68% [7–9]. The quality of life impact of treatments for HIV-infected patients is an important consideration in treatment selection [10–14]. This is the first study to evaluate the impact of a triple therapy regimen, in this case the protease inhibitor saquinavir (SQV) plus two nucleoside analogues, on comprehensive measures of health-related quality of life (HRQL), as well as clinical endpoints, in HIV-infected persons with limited previous treatment with zidovudine (ZDV).

Clinical studies have demonstrated significant disease surrogate marker activity for combinations containing SQV. Collier *et al.* [5] found that triple combination SQV, zalcitabine (ddC), and ZDV therapy resulted in a greater impact on CD4 cell counts and plasma HIV RNA compared with SQV/ZDV or ddC/ZDV combination therapy in ZDV-pre-treated patients. In persons intolerant of or failed on ZDV, the combination of ddC plus SQV extends survival benefits to patients with symptomatic HIV disease and AIDS [7]. Quality of life measures in this study indicated that SQV monotherapy and combination SQV and ddC therapy resulted in benefits in physical functioning and well-being compared with ddC monotherapy in HIV-infected patients with previous ZDV treatment [15]. Few studies have evaluated the effect of protease inhibitors in combination with other antiretroviral therapy on patient functioning and well-being. Ritonavir combined with a variety of antiretroviral therapies demonstrated HRQL benefits in advanced AIDS patients [16]. The ritonavir study did not, however, specify any particular combination therapy regimen. The impact of combination therapies on improved surrogate markers and delayed disease progression may also result in improved patient HRQL, as long as the toxicity associated with triple combination therapy is not too great. HRQL outcomes are important for mildly symptomatic HIV disease patients treated with multiple antiretroviral drug regimens.

This report compares the effect of combination therapy with ddC/ZDV, SQV/ZDV, and SQV/ddC/ZDV on the HRQL of HIV-infected patients with CD4 cell counts between 50 and 350 cells/mm³. The PISCES

(SV14604) clinical trial found that SQV/ddC/ZDV combination therapy reduced combined new opportunistic disease and death endpoints by 50% compared with ddC/ZDV therapy (The PISCES (SV14604) Writing Committee, manuscript in preparation). It is important to examine whether these clinical benefits come at some cost to patient HRQL. The primary clinical efficacy and safety results from this clinical trial have been reported elsewhere (The PISCES (SV14604) Writing Committee, manuscript in preparation); therefore, this report focuses only on the HRQL outcomes.

Methods

This study was an international multicenter, four group, double-blind, randomized clinical trial involving advanced HIV-infected patients with CD4 cell counts between 50 and 350 cells/mm³ (The PISCES (SV14604) Writing Committee, manuscript in preparation). The clinical trial was conducted in 163 centers separated into two tiers: Tier 1 (intensive monitoring including all clinical efficacy, safety, and quality of life outcomes) and Tier 2 (monitoring clinical endpoints and serious adverse events only). Patients were randomly selected to receive: (1) ZDV; (2) ddC/ZDV; (3) SQV/ZDV; or (4) SQV/ddC/ZDV treatment. The study started in August 1994, and in October 1995 after the results of the DELTA and ACTG 175 clinical trials were reported [4,17], the study protocol was amended, at the request of the Data and Safety Monitoring Board, to transfer all ZDV monotherapy patients into the triple combination therapy group. No additional patients were randomly assigned into the ZDV monotherapy group. The quality of life component of the clinical trial included the Tier 1 patients (n = 1274), and patients randomly assigned to the ZDV monotherapy group (n = 273) were excluded from the quality of life data analysis and will not be considered further.

The 1001 Tier 1 patients included in the HRQL study were recruited from 55 clinical centers located in Australia, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Italy, Mexico, Spain, Switzerland, the United Kingdom, and the United States. Male or female patients with documented HIV infection were eligible to participate if they were aged 18 years or older, were naïve to reverse transcriptase inhibitor or protease inhibitor treatment or had been treated with ZDV for less than 16 weeks, and had Karnofsky Performance Status scores of 60 or over. Patients were excluded if they had a history or current evidence of peripheral neuropathy, evidence of malabsorption, severe laboratory abnormalities, active opportunistic infections, unexplained fever, malignancy, non-Hodgkin's lymphoma, were receiving radiation or

antineoplastic therapy, or were pregnant or breast-feeding women.

Eligible patients were randomly assigned to the treatment groups and randomization was stratified by previous ZDV treatment exposure (naïve or less than 8 weeks ZDV versus 8–16 weeks ZDV). The research protocol was approved by the appropriate ethics committee for each clinical center, and patients provided written informed consent before entering the study.

Treatment regimen

Patients were randomly assigned, in equal ratios, to one of three treatment groups: (1) zalcitabine 0.75 mg and zidovudine 200 mg every 8 h (ddC/ZDV); (2) saquinavir 600 mg and zidovudine 200 mg every 8 h (SQV/ZDV); or (3) saquinavir 600 mg, zalcitabine 0.75 mg and zidovudine 200 mg every 8 h (SQV/ddC/ZDV) for up to 80 weeks. ZDV was taken on an open-label basis and the other medications were double-blinded. Placebo medications were added to the therapy regimens so that each patient was required to take equivalent numbers of tablets or capsules. Study medications were taken orally every 8 h and all medication was taken within 2 h after a meal. The median time spent on blinded protocol therapy was 59.7 weeks for the ddC/ZDV group, 58.4 weeks for the SQV/ZDV group, and 63.3 weeks for the ddC/SQV/ZDV group. Therapy was stopped for AIDS-related events, treatment limiting toxicity, and patient or investigator preference. Concomitant medications were allowed, with the exception of the following: other antiretroviral agents, drugs with toxicities that overlap with ddC, SQV or ZDV, and other investigational drugs. Prophylactic and chronic maintenance therapies were allowed for *Pneumocystis carinii* pneumonia and other opportunistic diseases.

Health-related quality of life outcome measures

HRQL is a multidimensional construct that includes physical, psychological and social functioning, and general well-being [18,19]. For this study, the Medical Outcomes Study HIV Health Survey (MOS–HIV) [20] and a visual analogue scale (VAS) were selected to assess HRQL on the basis of their applicability for measuring HRQL in HIV-infected patients, match with study objectives, psychometric characteristics, availability of the necessary foreign language translations, and limited respondent burden.

The MOS–HIV subscales were selected to assess HRQL in patients with HIV disease [20]. They contain 10 subscales: general health perceptions, physical, social, role and cognitive functioning, pain, energy, mental health, health distress, and quality of life [20]. For each subscale, responses to questions are summed and scores are converted to a 0 to 100 scale, with 100 indicating better functioning and well-being. The subscales have demonstrated acceptable internal

consistency reliability and construct validity, are able to detect clinically important differences by HIV disease severity, and are correlated with HIV-related symptoms [14,15,20–22]. Internal consistency reliability (Cronbach alphas) for the MOS–HIV subscales range from 0.70 to 0.92, with most coefficients exceeding 0.80 (six of eight multi-item scales) [22]. The MOS–HIV has been translated into the major European and other languages, and international validation studies have demonstrated its reliability and construct validity [22,23]. Revicki and colleagues [24] developed physical health summary (PHS) and mental health summary (MHS) scores based on the 10 MOS–HIV subscales. The PHS measures physical functioning and activities and pain, and the MHS measures mental health and psychological well-being. The summary scores are transformed to a standardized scale with a mean of 50 and standard deviation of 10. Reliability (reliability coefficients over 0.90) and evidence of construct validity of the PHS and MHS have been demonstrated in three different studies of patients with HIV disease [24]. The PHS and MHS scores at 24 and 48 weeks were used as the primary HRQL outcomes in this study.

A VAS, adapted from the EuroQol measure [25], was used to obtain subjective ratings of the patient's global quality of life. The scale is anchored at 0, the worst imaginable health state, and 100, the best imaginable health state. Higher scores indicate more positive evaluations of quality of life. VASs have been used extensively to assess patient outcomes and are reliable, valid and easy to complete [21,26].

The HRQL instruments were administered at baseline and 24 and 48 weeks after enrollment. All evaluations were performed within 7 days of the scheduled follow-up visit. Patients who discontinued prematurely from the clinical trial were administered the HRQL measures at the time of discontinuation. For this report, only the baseline, 24 and 48 week assessments were analysed to remain consistent with the previous analysis of HRQL data for SQV [15].

Statistical methodology

Baseline MOS–HIV subscale and summary scores among the three treatment groups were compared using analysis of variance (ANOVA). Descriptive data on demographic and selected clinical characteristics (e.g. CD4 cell count, Karnofsky performance status scores) are summarized by treatment group.

The primary outcomes for the HRQL data analysis were baseline to 24 and 48 week endpoint changes in PHS and MHS scores. The study has greater than 90% statistical power to detect clinically meaningful differences (i.e. differences of 2 points, 0.20 standardized effect size) in PHS or MHS scores. Changes in PHS and MHS scores after 24 and 48 weeks of treatment

were identified *a priori* as endpoints for the HRQL data analysis to allow evaluation of both the short- and long-term impact of the treatments on HRQL. The 10 MOS-HIV subscale and VAS scores were designated secondary HRQL endpoints. Change scores were constructed at 24 and 48 weeks for all HRQL measures by subtracting baseline scores. Intention-to-treat principles, with the last observation carried forward, were used for the between-group analyses. Only patients with a baseline and at least one follow-up HRQL assessment were included in the statistical analysis.

Global test procedures using an ANOVA model [27] and a closed test procedure [28] were used to control for multiple endpoint comparisons. The closed test procedure first evaluates the hypothesis of no difference among treatments in global statistics for the two primary HRQL endpoints, and if the global test was statistically significant, tests of each primary endpoint were performed. Analysis of covariance (ANCOVA) was used to evaluate changes in the two primary HRQL endpoints. The ANCOVA models were specified *a priori* and included terms for the previous ZDV therapy stratum, treatment group, geographical region (country), the treatment group-ZDV stratum interaction, treatment group-geographical region interaction, and the relevant baseline HRQL score. Because there were statistically significant interaction terms in several of the ANCOVA models ($P < 0.15$), these terms were retained in the final models. Baseline HRQL scores were included because of differences observed between patients with and without follow-up HRQL scores (see below). Statistically significant differences in the primary HRQL endpoints were followed by pair-wise comparisons of treatment groups using a *t*-test for independent groups.

The baseline to 24 week and baseline to 48 week changes in secondary HRQL endpoints were also analysed using global statistics, closed test procedures and ANCOVA models. Statistically significant between-group differences in the HRQL endpoints were followed by pair-wise comparisons of treatment groups. A *P*-value of 0.05 was used for all statistical tests.

Results

A total of 993 patients in the HRQL component of the trial were randomly assigned to three treatment groups, with 327 in the ddC/ZDV treatment group, 324 in the SQV/ZDV treatment group, and 342 in the ddC/SQV/ZDV treatment group. There were no statistically significant differences among the three treatment groups on baseline demographic or clinical characteristics (Table 1).

Ninety-five per cent of the patients (947 of 1001) had baseline HRQL scores, and there were no statistically significant differences in baseline mean HRQL scores between the treatment groups (Table 2). Eighty-three to 84% of the patients (because of missing values for individual subscale scores) had a baseline and one or more follow-up MOS-HIV subscale scores, and 819 of 993 patients (82%) had a baseline and at least one follow-up PHS or MHS score. There were no statistically significant differences between the three treatment groups in percentage of missing endpoint HRQL scores ($P = 0.663$). At the 24 week assessment, 81–82% of patients were still receiving protocol treatment, and at 48 weeks 63–69% of patients were receiving protocol therapy. The demographic and clinical characteristics of patients with and without endpoint HRQL scores were comparable. For every HRQL scale, except pain ($P = 0.304$) and health distress ($P = 0.191$), the baseline scores of patients with missing endpoint HRQL outcomes were significantly worse than those of patients with endpoint scores ($P = 0.0002$ to $P = 0.032$).

Primary health-related quality of life outcomes: 24 weeks

Baseline to 24 week endpoint changes in PHS and MHS scores are summarized in Table 3. No statistically significant differences among the three treatment groups were seen for combined PHS scores and MHS scores (global test $P = 0.118$). The change in PHS scores was -1.7 in the ddC/ZDV group, -0.5 in the SQV/ZDV group, and 0.4 in the SQV/ddC/ZDV group ($P = 0.035$). The pair-wise treatment comparison between ddC/ZDV and SQV/ddC/ZDV for the change in PHS scores was statistically significant

Table 1. Baseline demographic and clinical characteristics*

Characteristic	ddC/ZDV	SQV/ZDV	SQV/ddC/ZDV
N [†]	312	308	324
Mean (± SD) age, years	37.4 ± 9.3	35.8 ± 8.9	36.3 ± 8.8
Male, n (%)	281 (86)	272 (84)	273 (80)
White, n (%)	280 (86)	297 (92)	298 (87)
8 to 16 week ZDV treatment, n (%)	52 (16)	56 (17)	61 (18)
Mean (± SD) HIV RNA, log ₁₀ copies/ml	5.0 ± 0.7	4.9 ± 0.7	4.9 ± 0.7
Mean (± SD) CD4 count cells/mm ³	199 ± 95	202 ± 90	198 ± 88
Mean (± SD) Karnofsky performance status score	95.8 ± 7.1	95.8 ± 6.9	96.2 ± 6.9

*There were no statistically significant ($P < 0.05$) differences among the three treatment groups. [†]The zalcitabine-zidovudine (ddC/ZDV) group sample size ranged from 312 to 327, the saquinavir-zidovudine (SQV/ZDV) group sample size ranged from 308 to 324, and the saquinavir-zalcitabine-zidovudine (SQV/ddC/ZDV) group sample size ranged from 324 to 342 because of missing data. SD, standard deviation.

Table 2. Baseline health-related quality of life by treatment group

Scale	ddC/ZDV Mean ± SD	SQV/ZDV Mean ± SD	SQV/ddC/ZDV Mean ± SD	<i>P</i> -value*
N [†]	309	306	332	
Primary outcomes				
Mental health summary	50.7 ± 9.3	49.7 ± 10.6	49.3 ± 9.5	0.292
Physical health summary	52.7 ± 9.2	52.7 ± 9.4	52.3 ± 9.5	0.932
Secondary outcomes				
Visual analogue scale	79.8 ± 16.1	77.7 ± 17.7	78.6 ± 17.7	0.465
Physical function	83.6 ± 21.7	84.5 ± 20.8	83.6 ± 22.0	0.843
Role function	79.5 ± 36.7	82.4 ± 35.3	83.1 ± 33.2	0.472
Social function	89.0 ± 19.8	86.6 ± 22.8	87.6 ± 21.0	0.519
Cognitive function	86.2 ± 17.5	82.7 ± 20.6	83.9 ± 17.9	0.119
General health	59.3 ± 25.0	57.1 ± 24.8	56.9 ± 24.6	0.562
Energy	66.9 ± 19.6	64.9 ± 21.5	63.4 ± 20.6	0.125
Pain	72.7 ± 30.0	74.2 ± 29.7	70.6 ± 30.2	0.346
Mental health	68.6 ± 18.8	67.0 ± 20.7	67.4 ± 18.9	0.643
Health distress	73.9 ± 22.4	74.6 ± 23.4	71.5 ± 23.1	0.351
Quality of life	68.2 ± 20.7	66.2 ± 21.6	65.5 ± 19.9	0.250

*Two-tailed *P*-value for treatment group from analysis of variance model. [†]The zalcitabine–zidovudine (ddC/ZDV) group sample size ranged from 309 to 323, the saquinavir–zidovudine (SQV/ZDV) group sample size ranged from 306 to 322, and the saquinavir–zalcitabine–zidovudine (SQV/ddC/ZDV) group sample size ranged from 332 to 342 because of missing data. SD, standard deviation.

(*P* < 0.05). No significant differences were seen in the changes in PHS scores between the ddC/ZDV and SQV/ZDV groups (*P* > 0.05). No statistically significant differences were observed in the changes in MHS scores at 24 weeks.

Secondary health-related quality of life outcomes: 24 weeks

No statistically significant differences between the three treatment groups were observed in baseline to 24 week changes in VAS, physical function, role function, social function, cognitive function, general health, energy, pain, mental health, health distress, and quality of life scores on the global statistical test (*P* = 0.152) (Table 3).

Primary health-related quality of life outcomes: 48 weeks

Baseline to 48 week endpoint changes in the PHS and MHS scores are summarized in Table 4. The global statistical test was statistically significant (*P* = 0.012). Statistically significant between-group differences in the changes in PHS scores (*P* = 0.008) were demonstrated after 48 weeks of follow-up. No between-group differences were seen in the changes in MHS scores after 48 weeks (*P* = 0.146). The triple combination therapy group showed minimal changes in PHS scores (−0.4), compared with decreases in the ddC/ZDV (−2.5) and SQV/ZDV (−2.2) groups. Pair-wise comparisons show that the ddC/ZDV group had larger decreases in PHS

Table 3. Baseline to 24 week endpoint change in health-related quality of life by treatment group

Scale	ddC/ZDV Mean ± SD*	SQV/ZDV Mean ± SD*	SQV/ddC/ZDV Mean ± SD*	Treatment <i>P</i> -value [†]	Previous ZDV interaction <i>P</i> -value [‡]
N [§]	255	255	278		
Primary outcomes					
Mental health summary	1.1 ± 8.7	1.2 ± 8.0	1.7 ± 8.9	0.315	0.095
Physical health summary	−1.7 ± 8.7 [¶]	−0.5 ± 8.6	0.4 ± 8.8 [¶]	0.035	0.342
Secondary outcomes					
Visual analogue scale	0.0 ± 16.2	−0.8 ± 14.8	0.6 ± 15.9	0.711	0.941
Physical function	−1.3 ± 19.5	−1.8 ± 20.1	1.8 ± 19.9	0.535	0.944
Role function	−0.0 ± 32.0	−1.8 ± 32.5	0.5 ± 31.9	0.344	0.280
Social function	−3.0 ± 20.3	0.2 ± 21.0	0.1 ± 24.9	0.090	0.189
Cognitive function	−1.0 ± 17.1	0.9 ± 14.5	−0.1 ± 16.4	0.480	0.146
General health	−0.4 ± 21.5	0.5 ± 20.7	2.0 ± 22.4	0.053	0.014
Energy	−0.8 ± 20.5	−0.0 ± 17.3	2.0 ± 18.6	0.474	0.515
Pain	−4.4 ± 37.4	−0.7 ± 32.2	0.8 ± 35.8	0.066	0.676
Mental health	3.2 ± 17.6	2.0 ± 17.1	1.2 ± 19.9	0.727	0.683
Health distress	5.1 ± 22.1	4.3 ± 18.2	6.2 ± 22.3	0.078	0.014
Quality of life	0.7 ± 22.1	0.6 ± 23.1	4.4 ± 22.6	0.133	0.163

*Mean change unadjusted for other covariates included in the analysis of covariance model. [†]Two-tailed *P*-value for treatment group from analysis of covariance model adjusting for baseline health-related quality of life score, region, previous zidovudine (ZDV) therapy strata, treatment group by previous ZDV interaction, and treatment group by region interaction. [‡]Two-tailed *P*-value for previous ZDV by treatment group interaction from analysis of covariance model adjusting for treatment group, baseline health-related quality-of-life score, region, previous ZDV therapy strata, and treatment group by region interaction. [§]The zalcitabine–zidovudine (ddC/ZDV) group sample size ranged from 255 to 273, the saquinavir–zidovudine (SQV/ZDV) group sample size ranged from 255 to 279, the saquinavir–zalcitabine–zidovudine (SQV/ddC/ZDV) group sample size ranged from 278 to 299. [¶]*P* < 0.05, pairwise *t*-tests between ddC/ZDV and SQV/ddC/ZDV. SD, standard deviation.

Table 4. Baseline to 48 week endpoint change in health-related quality of life by treatment group

Scale	ddC/ZDV Mean \pm SD*	SQV/ZDV Mean \pm SD*	SQV/ddC/ZDV Mean \pm SD*	Treatment <i>P</i> -value [†]	Previous ZDV interaction <i>P</i> -value [‡]
N [§]	249	257	280		
Primary outcomes					
Mental health summary	0.1 \pm 9.7	0.3 \pm 8.7	1.4 \pm 9.1	0.146	0.337
Physical health summary	-2.5 \pm 9.5 [¶]	-2.2 \pm 9.3	-0.4 \pm 9.1 [¶]	0.008	0.138
Secondary outcomes					
Visual analogue scale	-2.3 \pm 15.4 [¶]	-2.6 \pm 17.9	1.0 \pm 17.1 [¶]	0.002	0.174
Physical function	-2.5 \pm 22.2	-3.5 \pm 22.2	-0.6 \pm 21.1	0.179	0.447
Role function	-1.3 \pm 37.5	-3.7 \pm 33.4	0.3 \pm 34.3	0.276	0.683
Social function	-3.7 \pm 22.5 [¶]	-4.0 \pm 25.9	0.5 \pm 22.5 [¶]	0.004	0.366
Cognitive function	-1.5 \pm 16.9	-2.0 \pm 16.0	-0.0 \pm 17.5	0.027	0.061
General health	-3.4 \pm 24.2 [¶]	-2.7 \pm 22.4	0.8 \pm 21.7 [¶]	0.005	0.018
Energy	-1.9 \pm 22.1 [¶]	-1.8 \pm 18.2	1.6 \pm 19.9 [¶]	0.046	0.169
Pain	-8.1 \pm 36.2 [¶]	-4.3 \pm 34.1	-1.2 \pm 34.3 [¶]	0.022	0.243
Mental health	1.5 \pm 19.9	0.8 \pm 17.7	1.9 \pm 20.0	0.802	0.636
Health distress	3.8 \pm 23.3 [¶]	3.8 \pm 20.0	7.0 \pm 22.6 [¶]	0.015	0.080
Quality of life	-2.1 \pm 23.9	-1.3 \pm 22.5	1.9 \pm 22.5	0.058	0.139

*Mean change unadjusted for other covariates included in the analysis of covariance model. [†]Two-tailed *P*-value for treatment group from analysis of covariance model adjusting for baseline health-related quality of life score, region, previous zidovudine (ZDV) therapy strata, treatment group by previous ZDV interaction, and treatment group by region interaction. [‡]Two-tailed *P*-value for previous ZDV by treatment group interaction from analysis of covariance model adjusting for treatment group, baseline health-related quality-of-life score, region, previous ZDV therapy strata, and treatment group by region interaction. [§]The zalcitabine-zidovudine (ddC/ZDV) group sample size ranged from 249 to 274, the saquinavir-zidovudine (SQV/ZDV) group sample size ranged from 257 to 285, and the saquinavir-zalcitabine-zidovudine (SQV/ddC/ZDV) group sample size ranged from 280 to 297. [¶]*P* < 0.05, pairwise *t*-tests between ddC/ZDV and SQV/ddC/ZDV.

scores compared with the SQV/ddC/ZDV combination therapy group (*P* < 0.05) but not compared with the SQV/ZDV group (*P* > 0.05).

Secondary health-related quality of life outcomes: 48 weeks

The global test for baseline to 48 week endpoint changes in MOS-HIV subscale and VAS scores was statistically significant (*P* = 0.0009) (Table 4). Statistically significant between-treatment group differences were seen for VAS (*P* = 0.002), social function (*P* = 0.004), pain (*P* = 0.022), cognitive function (*P* = 0.027), general health perceptions (*P* = 0.005), energy (*P* = 0.046), and health distress subscale scores (*P* = 0.015) after 48 weeks of follow-up. Pair-wise treatment comparisons indicate statistically significant differences between triple combination therapy and ddC/ZDV combination therapy on VAS, social function, general health perception, pain, and health distress subscale scores (all *P* < 0.05). In general, the SQV/ddC/ZDV treatment group was observed to improve in most of the MOS-HIV subscale scores compared with the ddC/ZDV combination therapy group (see Table 4). No statistically significant differences in baseline to 48 week endpoint changes in MOS-HIV subscale scores were demonstrated between the ddC/ZDV and SQV/ZDV treatment groups.

Discussion

This randomized clinical trial evaluated the impact of ddC/ZDV combination therapy, SQV/ZDV combination therapy, and SQV/ddC/ZDV combination

therapy on HRQL outcomes in HIV-infected patients who were naïve to antiretroviral therapy or who had less than 16 weeks of ZDV treatment. The findings demonstrate that, over 24 weeks, patients treated with triple combination therapy showed small improvements in physical functioning and well-being compared with the other treatment groups. These effects were maintained over 48 weeks of therapy for the summary measure of physical functioning and well-being. The triple combination therapy group either improved or reported no change in measures of pain, social function, energy, cognitive function, and health perceptions over 48 weeks. For the two double combination therapy groups, decrements were observed in physical functioning and well-being and the other HRQL domains. This is the first evidence from a large clinical trial of the long-term quality of life benefits of SQV, a protease inhibitor, combined with two other antiretroviral medications.

Patients with HIV disease often experience chronic and progressive deterioration in their CD4 cell counts, and frequently experience opportunistic infections and malignancies that impact their HRQL [10-14,21-24, 29,30]. Although psychological well-being and distress scores may fluctuate, depending on the occurrence of opportunistic infections and adaptation to disease progression, physical functioning has been shown to decline over time [11-13,24,30]. SQV, combined with ddC and ZDV, maintained pre-treatment levels of physical functioning and well-being over 48 weeks of therapy. Patients in the triple combination therapy group demonstrated the maintenance of health status and quality of life compared with significant decreases in HRQL in the ddC/ZDV combination therapy group. The demonstrated

maintenance of HRQL in the SQV triple combination therapy patients represents an encouraging finding, especially when viewed in conjunction with its effects on delaying clinical progression in this patient population (The PISCES (SV14604) Writing Committee, manuscript in preparation). A previous SQV clinical trial [15] also demonstrated improvements in physical functioning and well-being over 48 weeks of combined SQV and ddC therapy. In contrast, Moyle *et al.* [31] found no differences in quality of life outcomes between HIV disease patients treated with ZDV or ddC/ZDV over 1 year.

The effects of triple combination therapy on HRQL were observed after 48 weeks of follow-up, with significant differences favoring the SQV/ddC/ZDV therapy on the physical health summary measure. These longer-term effects on HRQL were most apparent for triple combination therapy on measures on energy, general health perceptions, pain and social functioning. Therefore, triple combination therapy with SQV has a sustained beneficial impact on both clinical progression and HRQL outcomes in patients with HIV disease.

In general, patients with less than 8 weeks previous ZDV therapy experienced fewer improvements in physical functioning and well-being than those with a longer exposure, except in the triple combination therapy group. Previous ZDV therapy exposure appeared to have less influence on HRQL in the SQV/ddC/ZDV combination therapy group. There were, however, very few significant interactions between treatment group and previous ZDV exposure, and confirmation of these findings requires further research.

Previous studies have suggested that a 2 to 3 point change or difference in the MOS-HIV mental health and physical health summary scores is clinically significant [15,22,24,32]. In this clinical trial, physical health summary scores increased less than one-half point by 24 weeks and decreased less than one-half point after 48 weeks of SQV/ddC/ZDV treatment. Decreases of 1.7 points in PHS scores at 24 weeks and 2.5 points at 48 weeks were observed in the ddC/ZDV treatment group. The differences in PHS changes between triple combination therapy and ddC/ZDV therapy were 2.3 points at 24 weeks and 2.0 points at 48 weeks. Therefore, these differences in changes in physical functioning and well-being seen between the SQV/ddC/ZDV and ddC/ZDV treatment groups are clinically significant. It is important to note that the triple combination therapy group showed slight changes in physical health summary scores, whereas the ddC/ZDV combination therapy group showed significant decreases in physical health summary scores. These results are consistent with previous evaluations of HRQL in SQV-treated patients [15,33].

HRQL outcomes reflect both the impact of treatment and disease progression. The long-term quality of life

benefits of SQV in combination with ZDV and ddC may be attributable to lower rates of disease progression and fewer serious adverse events (The PISCES (SV14604) Writing Committee, manuscript in preparation). The differences in HRQL scores between the triple combination therapy and double combination therapy groups are attenuated somewhat because patients discontinuing the study without endpoint HRQL scores were more severely impaired compared with patients with endpoint HRQL scores. Other studies have suggested that patients experiencing an AIDS-related clinical endpoint have lower HRQL scores compared with those not experiencing an endpoint [15,22,32]. Slightly more ddC/ZDV (20%) than SQV/ddC/ZDV-treated patients (16%) did not have endpoint HRQL scores. Therefore, the differences in changes in patient function and well-being between ddC/ZDV and SQV/ddC/ZDV combination therapy may actually be larger than those observed in this study.

The strengths of this study for evaluating HRQL outcomes are the randomized assignment to treatment and systematic follow-up of large numbers of patients over 48 weeks. More than 80% of the patients entered into the study had at least one HRQL endpoint score. Although there are missing HRQL endpoints for some patients who experienced an AIDS-defining event, there was relatively complete HRQL follow-up of patients entered into the clinical trial. There were comparable percentages of patients on protocol therapy at 24 weeks, and slightly more patients on protocol therapy in the triple combination group (63 versus 69%). Patients discontinuing study therapy could be treated with other antiretroviral combination therapy. Despite this change in therapy, differences in HRQL between treatments based on the intention-to-treat analysis were still observed. The intention-to-treat and last observation carried forward approach taken in the statistical analysis is conservative (i.e. it attenuates between-treatment differences in HRQL outcomes).

The generalizability of these findings is limited to those patients starting therapy with CD4 cell counts below 350 cells/mm³. It is unknown whether these same HRQL effects would be observed in patients starting triple combination therapy at higher CD4 cell counts. In addition, the patient sample included mostly men (83%) and Caucasian patients (88%), therefore the results may not be generalizable to women and minority populations. There is some evidence supporting the validity of the MOS-HIV in women and minority populations [21–24]. The HRQL results did not differ by geographical region or country, despite differences in antiretroviral treatment patterns between the United States and other countries. This finding is most likely due to the comparable percentages of patients remaining on protocol therapy across treatment groups at 48 weeks (63–69%).

Conclusion

The beneficial effects on surrogate markers of HIV [5,9], clinical events and survival [5] and the absence of major toxicity [5,9] supports the benefits of SQV as part of combination therapy for patients with HIV disease (The PISCES (SV14604) Writing Committee, manuscript in preparation). This is the first clinical trial to examine the impact of a triple combination therapy regimen on HRQL outcomes in patients with limited exposure to ZDV. On the basis of these findings, the potent antiviral effects of this regimen result in significant benefits to patient physical functioning and well-being. The primary impact of triple combination therapy on HRQL outcomes was demonstrated over long-term treatment. SQV combined with nucleoside analogues with antiretroviral activity has clear clinical and HRQL benefits for HIV disease patients. In clinical practice, SQV is generally used in combination with other antiretroviral therapies including other protease inhibitors [1–3,34,35]. The current study is encouraging, because combination treatment with SQV, ZDV and ddC resulted in the maintenance of patient functioning and well-being over 48 weeks.

References

- Carpenter CJ, Fischl MA, Hammer SM, et al.: **Antiretroviral therapy for HIV infection in 1997.** *JAMA* 1997, **277**:1962–1969.
- BHIVA Guidelines Coordination Committee: **British HIV Association guidelines for antiretroviral treatment of HIV seropositive individuals.** *Lancet* 1997, **349**:1086–1092.
- Deeks SG, Smith M, Holodniy M, Kahn JO: **HIV-1 protease inhibitors: a review for clinicians.** *JAMA* 1997, **277**:145–153.
- Hammer SM, Katzenstein DA, Hughes MD, et al.: **A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter.** *N Engl J Med* 1996, **335**:1081–1090.
- Collier AC, Coombs RW, Schoenfeld DA, et al.: **Treatment of human immunodeficiency virus infection with saquinavir, zidovudine, and zalcitabine.** *N Engl J Med* 1996, **334**:1011–1017.
- CAESAR Coordinating Committee: **Randomized trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial.** *Lancet* 1997, **349**:1413–1421.
- Haubrich R, Lalezari J, Follansbee FE, et al., and the NV14256 Study Team: **Improved survival and reduced clinical progression in HIV-infected patients with advanced disease treated with saquinavir plus zalcitabine.** *Antiviral Ther* 1998, **3**:33–42.
- Cameron DW, Heath-Chiozzi M, Danner S, Cohen C, Kravcik S, Maurath C: **Randomized placebo-controlled trial of ritonavir in advanced HIV-1 disease.** *Lancet* 1998, **351**:543–549.
- Hammer SM, Squires KE, Hughes MD, et al.: **A controlled trial of two nucleoside analogs plus indinavir in persons human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less.** *N Engl J Med* 1997, **337**:725–733.
- Lenderking WR, Gelber RD, Cotton DJ, et al.: **Evaluation of the quality of life associated with zidovudine treatment in asymptomatic human immunodeficiency virus infection.** *N Engl J Med* 1994, **330**:738–743.
- DeBoer JB, van Dam FSAM, Sprangers MAG, et al.: **Longitudinal study on the quality of life of symptomatic HIV-infected patients in a trial of zidovudine versus zidovudine and interferon- α .** *AIDS* 1993, **7**:947–953.
- Revicki DA, Brown RE, Henry DH, et al.: **Recombinant human erythropoietin and health-related quality of life of AIDS patients with anemia.** *J Acquired Immune Defic Syndr* 1994, **7**:474–484.
- Stanton DL, Wu AW, Moore RD, et al.: **Functional status of persons with HIV infection in an ambulatory setting.** *J Acquired Immune Defic Syndr* 1994, **7**:1050–1056.
- Wu AW, Rubin HR, Mathews WC, et al.: **Functional status and well-being in a placebo-controlled trial of zidovudine in early symptomatic HIV infection.** *J Acquired Immune Defic Syndr* 1993, **6**:452–458.
- Revicki DA, Swartz C, Wu AW, Haubrich R, Collier AC: **Quality of life outcomes of saquinavir, zalcitabine and combination saquinavir-zalcitabine therapy for advanced HIV-infected adults with CD4 counts between 50 and 300 per cubic millimeter.** *Antiviral Ther* 1999, in press.
- Cohen C, Revicki DA, Nabulsi A, et al.: **A randomized trial of the effect of ritonavir in maintaining quality of life in advanced HIV disease.** *AIDS* 1998, **12**:1495–1502.
- Delta Coordinating Committee: **Delta: a randomized double-blind controlled trial comparing combination of zidovudine + didanosine or zalcitabine with zidovudine alone in HIV-1 infected individuals.** *Lancet* 1996, **348**:283–291.
- Revicki DA: **Health care technology assessment and health-related quality of life.** In *Health care technology and its assessment: an international perspective*. Edited by Banta D, Luce BR. New York: Oxford University Press; 1993:114–131.
- Testa MA, Lenderking WR: **Quality of life considerations in clinical trials of persons with HIV infection.** In *AIDS clinical trials*. Edited by Finkelstein D, Schoenfeld D. New York: Wiley-Liss; 1995:213–241.
- Wu AW, Rubin HR, Mathews WC, et al.: **A health status questionnaire using 30 items from the Medical Outcomes Study: preliminary validation in persons with early HIV infection.** *Med Care* 1991, **29**:786–798.
- Revicki DA, Wu AW, Murray M: **Change in clinical status, health status and health utility outcomes in HIV-infected patients.** *Med Care* 1995, **33**:AS173–S182.
- Wu AW, Revicki DA, Jacobson D, Malitz FE: **Evidence for the reliability, validity and usefulness of the MOS-HIV Health Survey.** *Qual Life Res* 1997, **6**:481–493.
- Scott-Lennox JA, Wu AW, Boyer JG, Ware JE: **Reliability and validity of French, German, Italian, Dutch, and UK English translations of the Medical Outcomes Study HIV Health Survey (MOS-HIV).** *Med Care* 1999, in press.
- Revicki DA, Sorensen S, Wu AW: **Reliability and validity of physical and mental health summary scores from the MOS HIV Health Survey.** *Med Care* 1998, **36**:126–137.
- Kind P: **The EuroQol instrument: an index of health-related quality of life.** In *Quality of life and pharmacoeconomics in clinical trials*, 2nd ed. Edited by Spilker B. Philadelphia: Lippincott-Raven; 1996:191–201.
- Froberg DG, Kane RL: **Methodology for measuring health-state preferences: II: scaling methods.** *J Clin Epidemiol* 1989, **52**:459–471.
- O'Brien PC: **Procedures for comparing samples with multiple endpoints.** *Biometrics* 1984, **40**:1079–1087.
- Lehmacher W, Wassmer G, Reitmeir P: **Procedures for two-sample comparisons with multiple endpoints controlling the experimentwise error rate.** *Biometrics* 1991, **47**:511–521.
- Lubeck DP, Fries JF: **Health status among persons infected with human immunodeficiency virus: a community-based study.** *Med Care* 1993, **31**:269–276.
- Lubeck DP, Fries JF: **Changes in quality of life among persons with HIV infection.** *Qual Life Res* 1992, **1**:359–366.
- Moyle GJ, Bouza E, Antunes F, Smith D, Harris R, Warburg M, Walker M: **Zidovudine monotherapy versus zidovudine plus zalcitabine combination therapy in HIV-positive person with CD4 cell counts 300–500 mm³: a double-blind controlled trial.** *Antiviral Ther* 1997, **2**:229–236.
- Chan K, Revicki DA: **Changes in surrogate laboratory markers, clinical endpoints and health-related quality of life in patients infected with the human immunodeficiency virus.** *Eval Health Professions* 1998, **21**:265–281.
- Testa MA, Lenderking WR, Fischer L, Revicki DA, Collier AC: **Effects of combination therapy with saquinavir, zidovudine and zalcitabine on quality of life.** *Abstracts of the 11th International Conference on AIDS*. Vancouver, BC, 7–12 July 1996 [abstract].
- Flexner C: **HIV-protease therapy.** *N Engl J Med* 1998, **338**:1281–1292.
- The Department of Health and Human Services (DHHS) Panel on Clinical Practices for the Treatment of HIV Infection: **Guidelines for use of antiretroviral agents in HIV-infected adults and adolescents.** *Ann Intern Med* 1998, **128**:1079–1100.