Quality of life improvement in resource-limited settings after one year of second-line antiretroviral therapy use among adult men and women

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Objective: We evaluated improvement of quality of life (QoL) after 1 year of second-line antiretroviral therapy (ART) use in resource-limited settings (RLS) among adult men and women, comparing two randomized treatment arms.

Design: The AIDS Clinical Trial Group A5273 was a randomized clinical trial of second-line ART comparing lopinavir/ritonavir (LPV/r) + raltegravir with LPV/r + nucleos(t)ide reverse transcriptase inhibitors (NRTIs) in participants failing a non-NRTI-containing regimen at 15 sites in nine RLS. Participants completed the AIDS Clinical Trial Group short-form-21 which has eight QoL domains with a standard score ranging from 0 (worst) to 100 (best).

Methods: Differences in QoL by randomized arm, as well as by demographic and clinical variables, were evaluated by regression models for baseline and week 48 QoL scores fitted using the generalized estimating equations method.

Results: A total of 512 individuals (49% men, median age 39 years) were included. A total of 512 and 492 participants had QoL assessments at baseline and week 48, respectively. QoL improved significantly from baseline to week 48 ($P < 0.001$ for all domains). There was no significant difference between treatment arms for any domain. Individuals with higher viral load and lower $CD4^+$ cell count at baseline had lower mean QoL at baseline but larger improvements such that mean QoL was similar at week 48.

Conclusion: Improvements in QoL were similar after starting second-line ART of LPV/r combined with either raltegravir or NRTIs in RLS. QoL scores at baseline were lower among participants with worse disease status prior to starting second-line, but after 1 year similar QoL scores were achieved.

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Introduction

Antiretroviral therapy (ART) has dramatically changed the course of the HIV/AIDS epidemic by reducing morbidity and mortality [1]. Once a terminal disease, HIV infection is now considered a chronic medical condition, with individuals on effective ART having life expectancies similar to those who do not have HIV [2].

Therefore, long-term complications of HIV infection and its treatment, including quality of life (QoL), are important considerations for HIV-infected individuals. QoL is a multidimensional concept and can be influenced by many factors such as income, housing, social support and life situation. Health-related QoL is a dimension of broader QoL that reflects the impact of disease and treatment on a person's well being and ability to carry out daily activities, taking into account the biological and psychological effects of the disease. It includes physical, social, cognitive and psychological functioning, as well as subjective sense of health, comfort and well being. QoL measurements are important to assess a person's perception of his/her own health [3,4].

Health-related QoL measures were introduced for HIV-infected individuals in higher income settings in the early 1990s [5] and were used to evaluate factors associated with QoL as well as effects of ART on the QoL [6–8]. Poorer immunological status, HIV-related symptoms, depression, lack of social support, unemployment and low adherence to ART were most frequently and consistently associated with low QoL in these rich settings [9].

QoL at first-line ART initiation in resource-limited settings (RLS) has varied with disease severity, demographic characteristics and country [3,10,11], and it improves over time after starting ART [10–13]. Previous studies have shown improvements in QoL among HIV-infected individuals taking protease inhibitor-containing regimens [14] and among individuals taking a raltegravir (RAL)-containing regimen [15,16].

We previously reported cross-sectional results of QoL among individuals with virologic failure on first-line ART before starting second-line ART [17]. However, QoL during second-line ART has not been extensively studied.

The WHO recommends boosted protease inhibitor and nucleos (t)ide reverse transcriptase inhibitors (NRTIs) as the preferred second-line ART and boosted protease inhibitor and RAL as an alternative regimen if NRTI toxicity is limiting [18]. Exploring QoL changes in individuals on these two regimens is important to support future recommendations.

The aim of this study is to assess changes in the QoL after 1 year of second-line ART in RLS in individuals on lopinavir/ritonavir (LPV/r) + NTRI vs. those on LPV/r + RAL. Associations of QoL with demographic and clinical variables at time of starting second-line ART (e.g. $CD4^+$ cell count and HIV-1 RNA viral load) were also assessed.

Methods

A5273 study

The AIDS Clinical Trial Group (ACTG) A5273 study, entitled 'Multicenter Study of Options for **SE**cond-**L**ine **E**ffective **C**ombination **T**herapy' was a phase III, open-label, randomized clinical trial comparing LPV/r + RAL with LPV/r + NRTIs in participants failing a nonnucleoside reverse transcriptase inhibitor (NNRTI)-containing regimen (ClinicalTrials.gov NCT01352715). Details of the study design have previously been described [19]. Participants were enrolled between March 2012 and October 2013 at 15 sites in nine countries: Brazil (one site), India (three sites), Kenya, Malawi (two sites), Peru (two sites), South Africa (three sites), Tanzania (one site), Thailand (one site) and Zimbabwe (one site). Eligible participants were HIV-infected men and women (≥18 years) who had virologic failure confirmed by two consecutive plasma HIV-1 RNA viral load at least 1000 copies/ml at least 1 week apart after at least 24 weeks on an NNRTI-containing first-line regimen. Participants were followed for at least 48 weeks at the end of study follow-up. The primary analysis of the trial showed no difference in virologic outcome between the two regimens [19]. The study was approved by the institutional review board at each participating site, and written informed consent was obtained from all study participants.

Quality of life measures

Participants were interviewed at weeks 0, 4, 24 and 48 using a modified version of the short-form-21 (SF-21) measure (ACTG SF-21) [3,20]. The ACTG SF-21 tool was originally adapted from the Medical Outcomes Study HIV Health Survey, an instrument with well established reliability and validity [21]. SF-21 and its short and long forms (SF-12, SF-36) have been widely used in HIV/AIDS research [3,22–26]. The ACTG SF-21 questions from eight domains: general health perceptions (GHPs), physical functioning, role functioning, social functioning, cognitive functioning, pain, mental health and energy/fatigue (Table 1). A standardized score ranging from 0 (worst QoL) to 100 (best QoL) was calculated for each domain using standard methods [3]. High scores for pain and energy/fatigue mean less pain and less fatigue, respectively. The ACTG SF-21 tool was administered in a face-to-face interview by study staff in the participant's local language.

Demographic and clinical factors

The following study entry demographic and clinical factors at the time of starting second-line ART were

Table 1. Information obtained using the short-form-21-item quality of life questionnaire.

Domains	Number of items	Summary of contents
General health perceptions	3	Participants rate their general health, resistance to illnesses and health outlook. It has been validated by Davies and Ware [27] and Stewart and Ware [28]. Two questions are reverse coded to control for response set effects
Physical functioning	4	It inquired about physical limitations ranging from severe to minor, including lifting heavy objects or running, walking uphill or climbing a few flights of stairs, and being able to eat, dress, bathe and use the toilet by oneself
Role functioning	2	Participants are asked if their health negatively impacts their ability to perform at a job/school or to work around the house in the past 4 weeks
Social functioning	2	Participants are asked to what extent their health in the past 4 weeks has limited their social activities [29]; one item is reverse coded to control for response set effects
Cognitive functioning	3	This domain measures the degree of difficulty participants have experienced in the past 4 weeks with respect to their cognitive abilities. It assesses a participant's level of difficulty with reasoning/solving problems, being attentive and remembering
Pain	2	This domain assess intensity of physical pain (e.g. headache, muscle pain, back pain, stomach ache) and degree of interference with daily activities in the past 4 weeks [30]; one item is reverse coded to control for response set effects
Mental health	3	This domain assesses anxiety, depression and overall psychological wellbeing in the past 4 weeks [31]. One item is reverse coded to control for response set effects
Energy/fatigue	2	This domain assesses vitality (feeling tired or fatigued and energy to do things the person wanted to); one item is reverse coded to control for response set effects

assessed: sex, age (years), plasma HIV-1 RNA viral load, $CD4^+$ cell count, BMI, country of enrollment (country), history of AIDS-defining events (ADE), number of comorbidities and years on first-line ART. History of AIDS was defined by a specified subset of diagnoses codes maintained by the ACTG (Appendix 60) [32] taking into account the WHO [33] and centers for disease control and prevention [34] classifications of ADE. Number of comorbidities was defined as number of diagnoses (other than ADE) included in ACTG Appendix 60 (considering all ongoing and previous comorbidities).

Statistical analysis

A regression model for baseline and week 48 QoL scores was fitted using the generalized estimating equations (GEE) method. Differences by randomized treatment arm (LPV/r + RAL vs. LPV/r + NRTI) in mean change in QoL, as well as QoL scores at week 48, were assessed.

In a previous cross-sectional analysis, participants with higher viral load and lower $CD4^+$ cell count at baseline (time of starting second-line ART) had lower QoL at this time-point for most domains. In addition, we previously showed that lower BMI, three or more comorbidities and history of AIDS were associated with lower QoL in some domains. No association with age and sex was observed [17]. To evaluate the impact of second-line ART, linear regression models for baseline and week 48 QoL scores were fitted using the GEE method to assess the variables (viral load, $CD4^+$ cell count, BMI, comorbidities, history of AIDS) by estimating the mean difference in QoL between groups at baseline, the QoL score change between baseline and week 48, and the QoL score at week 48. Furthermore, we fitted multivariable linear regression models for QoL scores at week 48 to assess if differences at week 48 remained after adjustment. These multivariable models included baseline viral load, $CD4^+$ cell count, BMI, comorbidities and history of AIDS as well as country and study arm (LPV/r + RAL vs. LPV/r + NRTIs).

In addition, we describe the temporal change in QoL by baseline viral load ($>$ vs. $\leq$100 000 copies/ml) and baseline $CD4^+$ cell count ($<$ vs. $\geq$50 cells/μl) over the first 48 weeks of second-line ART by plotting the mean [95% point-wise Wald confidence intervals (CIs)] of the QoL scores for each domain at baseline, week 4, 24 and 48.

Data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Five hundred and twelve eligible participants were enrolled into the A5273 study: 258 were randomized to the LPV/r + RAL arm and 254 to the LPV/r + NRTIs arm. Baseline demographic and clinical characteristics of participants by arm are depicted in Table 2. Median age was 39 years [interquartile range (IQR): 34–44], approximately half were women and approximately two-thirds were black African. Median $CD4^+$ cell count was 135 cells/μl, viral load 4.5 $\log_{10}$ copies/ml and BMI 22 kg/m^2. A total of 150 participants (29%) had a history of AIDS. Median duration of first-line ART was 4.2 years (IQR: 2.3–6.2).

Among 512 participants who had QoL assessment at baseline, 492 also had at week 48. Mean QoL score at baseline was 67 for the GHP, 91 for physical functioning,

Table 2. Baseline demographic and clinical characteristics of participants included in the analysis by arm.

Characteristic	LPV/r + RAL, $N = 258$	LPV/r + NRTIs, $N = 254$	Total, $N = 512$
Sex			
Male	124 (48%)	128 (50%)	252 (49%)
Female	134 (52%)	126 (50%)	260 (51%)
Age (years)			
Median (IQR)	39 (34; 44)	38 (33; 43)	39 (34; 44)
18–29	22 (9%)	29 (11%)	51 (10%)
30–39	111 (43%)	116 (46%)	227 (44%)
40–49	92 (36%)	86 (34%)	178 (35%)
50+	33 (13%)	23 (9%)	56 (11%)
Race			
Black African	163 (63%)	162 (64%)	325 (63%)
Others	95 (37%)	92 (36%)	187 (37%)
Country			
India	80 (31%)	78 (31%)	158 (31%)
Malawi	56 (22%)	55 (22%)	111 (22%)
South Africa	52 (20%)	51 (20%)	103 (20%)
Kenya	24 (9%)	24 (9%)	48 (9%)
Zimbabwe	24 (9%)	23 (9%)	47 (9%)
Tanzania	8 (3%)	9 (3%)	17 (3%)
Brazil	6 (2%)	6 (2%)	12 (2%)
Peru	5 (2%)	4 (2%)	9 (2%)
Thailand	3 (1%)	4 (2%)	7 (1%)
BMI (kg/m^2)			
Median (IQR)	23 (20; 27)	22 (19; 25)	22 (19; 26)
<18	24 (9%)	31 (12%)	55 (11%)
18–<25	145 (56%)	150 (59%)	295 (58%)
25–<30	56 (22%)	54 (21%)	110 (21%)
≥30	33 (13%)	19 (7%)	52 (10%)
Viral load (HIV-1 RNA copies/ml)	$N = 257$	$N = 253$	$n = 510$
Median (IQR) (log_{10})	4.6 (4.0; 5.2)	4.5 (3.9; 5.1)	4.5 (3.9; 5.1)
<10 000	68 (26%)	77 (31%)	145 (29%)
10 000–100 000	105 (41%)	101 (40%)	206 (40%)
>100 000	84 (33%)	75 (30%)	159 (31%)
$CD4^+$ cell count (cells/μl)	$N = 255$	$N = 252$	$n = 507$
Median (IQR)	138 (49; 268)	133 (56; 274)	135 (53; 271)
<50	65 (25%)	57 (23%)	122 (24%)
50–199	92 (36%)	102 (40%)	194 (38%)
200–349	67 (26%)	54 (21%)	121 (24%)
≥350	31 (12%)	39 (16%)	70 (14%)
History of AIDS			
Yes	70 (27%)	80 (31%)	150 (29%)
No	188 (73%)	174 (69%)	362 (71%)
Number of comorbidities			
0	83 (32.2%)	97 (38.2%)	180 (35%)
1	76 (29.5%)	72 (38.4%)	148 (29%)
2	45 (17.4%)	35 (13.8%)	80 (16%)
≥3	54 (20.9%)	50 (19.7%)	104 (20%)
Time on 1st-line ART (years)			
Median (IQR)	4.2 (2.2; 6.5)	4.1 (2.3; 6.0)	4.2 (2.3; 6.2)
<4	121 (46.9%)	124 (48.8%)	245 (48%)
4–<7	82 (31.8%)	95 (37.4%)	177 (34%)
≥7	55 (21.3%)	35 (13.8%)	90 (18%)

ART, antiretroviral therapy; IQR, interquartile range; LPV/r, lopinavir/ritonavir; NRTI, nucleos(t)ide reverse transcriptase inhibitor; RAL, raltegravir.

80 for role functioning, 91 for social functioning, 91 for cognitive functioning, 83 for pain, 85 for mental health and 80 for energy/fatigue. QoL improved significantly by week 48 on second-line ART; mean improvements from baseline were 7 for GHP, 4 for physical functioning, 9 for role functioning, 3 for social functioning, 4 for cognitive functioning, 5 for pain, 5 for mental health and 4 for energy/fatigue ($P < 0.001$ for all domains). There was no significant difference in the mean increase in QoL scores at week 48 between randomized treatment arms (Table 3, $P \geq 0.17$ for all domains).

Table 3 summarizes mean QoL scores for each domain at baseline and at week 48, as well as mean changes in QoL score between baseline and week 48 by selected stratification variables. Individuals with higher baseline viral load had lower mean baseline QoL in all domains but larger improvements throughout follow-up, such that mean QoL by baseline viral load was similar at week 48 (Fig. 1). Similarly, the differences in mean QoL at baseline by baseline $CD4^+$ cell count had disappeared by week 48 for all domains except role functioning (Fig. 2). For the role functioning domain, mean QoL was similar at week 0

Table 3. Quality of life at baseline (first-line failure) and mean increases (univariable model) at week 48 of second-line therapy by randomized treatment and baseline variables.

	Mean QoL at baseline (95% CI)		Difference in mean QoL at baseline	Mean increase in QoL from baseline to week 48 (95% CI)		Difference in mean increase	Mean QoL at week 48 (95% CI)		Difference in mean QoL at week 48
Randomized treatment	LPV/r + NRTIs	LPV/r + RAL	*P* value	LPV/r + NRTIs	LPV/r + RAL	*P* value	LPV/r + NRTIs	LPV/r + RAL	*P* value
General health perceptions	68 (66, 71)	66 (63, 69)	N/A	6 (4, 9)	8 (5, 11)	0.38	74 (72, 76)	74 (72, 76)	0.76
Physical functioning	93 (91, 95)	90 (88, 92)	N/A	4 (1, 6)	5 (2, 8)	0.42	96 (95, 98)	95 (93, 97)	0.33
Role functioning	82 (78, 86)	79 (75, 83)	N/A	9 (5, 12)	9 (5, 13)	0.85	91 (88, 93)	88 (85, 91)	0.19
Social functioning	92 (90, 94)	91 (89, 93)	N/A	4 (2, 6)	3 (1, 5)	0.40	96 (94, 97)	94 (92, 95)	0.03
Cognitive functioning	92 (90, 94)	90 (88, 92)	N/A	3 (1, 5)	5 (3, 8)	0.17	95 (94, 96)	95 (94, 97)	0.42
Pain	85 (82, 87)	81 (78, 84)	N/A	4 (1, 7)	5 (2, 8)	0.51	89 (86, 91)	86 (84, 89)	0.35
Mental health	86 (84, 87)	84 (82, 86)	N/A	4 (2, 6)	5 (3, 8)	0.28	89 (88, 91)	90 (88, 91)	0.66
Energy/fatigue	81 (79, 83)	79 (76, 81)	N/A	3 (1, 6)	5 (2, 8)	0.51	84 (82, 86)	84 (82, 86)	0.63
Baseline viral load (copies/ml)	≤100 000	>100 000	*P* value	≤100 000	>100 000	*P* value	≤100 000	>100 000	*P* value
General health perceptions	70 (69, 72)	60 (56, 63)	<0.001	3 (1, 5)	16 (12, 19)	<0.001	73 (72, 75)	75 (73, 77)	0.25
Physical functioning	94 (92, 95)	86 (83, 89)	<0.001	2 (0, 4)	10 (6, 14)	0.001	96 (94, 97)	96 (94, 98)	0.83
Role functioning	84 (81, 87)	72 (67, 77)	<0.001	5 (2, 8)	17 (12, 23)	<0.001	89 (87, 92)	89 (86, 93)	0.94
Social functioning	93 (90, 94)	87 (84, 90)	0.001	2 (0, 4)	7 (3, 10)	0.015	95 (94, 96)	94 (92, 96)	0.45
Cognitive functioning	92 (91, 94)	88 (86, 91)	0.022	3 (1, 5)	7 (4, 10)	0.010	95 (94, 96)	96 (94, 97)	0.41
Pain	85 (83, 87)	77 (73, 81)	0.001	2 (−1, 4)	11 (7, 15)	<0.001	87 (85, 89)	88 (85, 91)	0.58
Mental health	86 (85, 88)	82 (79, 84)	0.002	3 (2, 5)	8 (4, 11)	0.020	90 (88, 91)	89 (87, 91)	0.82
Energy/fatigue	82 (80, 84)	75 (71, 78)	0.001	2 (0, 5)	8 (5, 12)	0.006	84 (82, 86)	83 (80, 86)	0.42
Baseline $CD4^+$ cell count (cells/μl)	<50	≥50	*P* value	<50	≥50	*P* value	<50	≥50	*P* value
General health perceptions	55 (51, 59)	71 (69, 73)	<0.001	19 (15, 23)	3 (1, 5)	<0.001	74 (71, 77)	74 (73, 76)	0.99
Physical functioning	87 (83, 91)	93 (91, 94)	0.005	8 (4, 13)	3 (1, 5)	0.027	95 (93, 98)	96 (95, 97)	0.79
Role functioning	80 (75, 85)	80 (77, 83)	0.96	14 (9, 19)	7 (4, 11)	0.041	94 (91, 97)	88 (85, 90)	0.002
Social functioning	86 (82, 90)	93 (92, 94)	0.001	9 (4, 13)	2 (0, 3)	0.005	94 (91, 97)	95 (94, 96)	0.68
Cognitive functioning	88 (84, 91)	92 (90, 93)	0.016	8 (5, 12)	3 (1, 5)	0.007	96 (94, 97)	95 (94, 96)	0.33
Pain	78 (74, 83)	84 (82, 86)	0.016	12 (7, 17)	2 (0, 5)	0.001	90 (86, 93)	87 (85, 89)	0.10
Mental health	80 (77, 83)	87 (85, 88)	0.001	9 (6, 13)	3 (1, 5)	0.002	89 (86, 92)	89 (88, 91)	0.87
Energy/fatigue	72 (68, 76)	82 (81, 84)	<0.001	10 (5, 15)	2 (0, 4)	0.005	82 (78, 86)	84 (83, 86)	0.29
BMI (kg/m^2)	<18	≥18	*P* value	<18	≥18	*P* value	<18	≥18	*P* value
General health perceptions	59 (52, 65)	68 (66, 70)	0.007	15 (9, 22)	6 (4, 8)	0.007	74 (71, 77)	74 (73, 76)	0.96
Physical functioning	80 (73, 86)	93 (91, 94)	<0.001	15 (7, 22)	3 (1, 5)	0.002	95 (91, 98)	96 (95, 97)	0.52
Role functioning	63 (54, 71)	82 (80, 85)	<0.001	21 (10, 31)	7 (5, 10)	0.015	83 (76, 90)	90 (88, 92)	0.072
Social functioning	82 (76, 87)	92 (91, 94)	0.001	11 (4, 18)	3 (1, 4)	0.024	92 (88, 96)	95 (94, 96)	0.22
Cognitive functioning	85 (80, 90)	92 (90, 93)	0.008	9 (3, 15)	4 (2, 5)	0.07	94 (91, 97)	95 (94, 96)	0.53
Pain	71 (64, 78)	84 (82, 86)	0.001	15 (8, 22)	3 (1, 5)	0.001	86 (80, 92)	87 (86, 89)	0.62
Mental health	80 (76, 84)	85 (84, 87)	0.009	7 (2, 12)	4 (3, 6)	0.22	87 (83, 91)	90 (88, 91)	0.24
Energy/fatigue	72 (66, 78)	81 (79, 83)	0.008	4 (−5, 12)	4 (2, 6)	0.92	76 (70, 82)	85 (83, 86)	0.004
Number of comorbidities	<3	≥3	*P* value	<3	≥3	*P* value	<3	≥3	*P* value
General health perceptions	68 (65, 70)	65 (62, 69)	0.25	7 (5, 10)	6 (2, 9)	0.40	75 (73, 76)	71 (68, 74)	0.024
Physical functioning	92 (91, 94)	88 (85, 91)	0.026	4 (2, 6)	6 (3, 10)	0.29	96 (95, 97)	94 (92, 96)	0.15
Role functioning	84 (81, 87)	67 (60, 73)	<0.001	7 (4, 10)	15 (8, 21)	0.051	91 (89, 93)	81 (76, 86)	0.001
Social functioning	92 (91, 94)	87 (84, 91)	0.006	3 (1, 5)	6 (2, 9)	0.22	95 (94, 96)	93 (90, 95)	0.10
Cognitive functioning	91 (89, 92)	92 (90, 94)	0.29	5 (3, 7)	2 (−1, 4)	0.020	96 (95, 97)	94 (92, 96)	0.08
Pain	85 (83, 87)	74 (70, 78)	<0.001	4 (2, 6)	7 (1, 12)	0.39	89 (87, 91)	81 (76, 84)	0.001
Mental health	85 (83, 86)	85 (82, 87)	0.90	5 (3, 7)	2 (−1, 6)	0.17	90 (89, 91)	87 (85, 90)	0.048
Energy/fatigue	80 (78, 82)	79 (76, 83)	0.66	4 (1, 6)	5 (1, 9)	0.50	84 (82, 86)	85 (82, 87)	0.68

Table 3 (*continued*)

Randomized treatment	Mean QoL at baseline (95% CI)		Difference in mean QoL at baseline	Mean increase in QoL from baseline to week 48 (95% CI)		Difference in mean increase	Mean QoL at week 48 (95% CI)		Difference in mean QoL at week 48
	LPV/r + NRTIs	LPV/r + RAL	*P* value	LPV/r + NRTIs	LPV/r + RAL	*P* value	LPV/r + NRTIs	LPV/r + RAL	*P* value
History of AIDS	No	Yes	*P* value	No	Yes	*P* value	No	Yes	*P* value
General health perceptions	68 (66, 70)	65 (61, 69)	0.17	6 (4, 8)	10 (6, 13)	0.12	74 (72, 75)	75 (71, 77)	0.72
Physical functioning	93 (92, 95)	87 (84, 91)	0.004	3 (1, 5)	8 (4, 12)	0.029	96 (95, 97)	95 (93, 98)	0.64
Role functioning	80 (77, 83)	81 (76, 85)	0.90	8 (5, 12)	10 (5, 15)	0.60	89 (86, 91)	91 (87, 94)	0.36
Social functioning	92 (90, 93)	90 (87, 93)	0.37	3 (1, 5)	4 (1, 8)	0.54	95 (94, 96)	94 (92, 97)	0.81
Cognitive functioning	91 (89, 93)	91 (88, 93)	0.96	4 (2, 6)	5 (2, 7)	0.77	95 (94, 96)	95 (94, 97)	0.66
Pain	82 (80, 85)	84 (80, 87)	0.64	4 (2, 7)	6 (2, 10)	0.47	86 (84, 88)	89 (86, 92)	0.14
Mental health	85 (84, 87)	84 (81, 86)	0.25	4 (2, 5)	7 (4, 10)	0.063	89 (88, 90)	90 (88, 93)	0.23
Energy/fatigue	82 (80, 84)	75 (72, 79)	0.002	3 (1, 5)	6 (2, 11)	0.24	85 (83, 87)	81 (78, 85)	0.07

CI, confidence interval; LPV/r, lopinavir/ritonavir; NRTI, nucleos(t)ide reverse transcriptase inhibitor; QoL, quality of life; RAL, raltegravir.

for the two baseline $CD4^+$ cell count groups and improved over time in the baseline $CD4^+$ cell count less than 50 cells/μl group such that it was significantly higher in the baseline $CD4^+$ cell count at least 50 cells/μl group at week 48.

Participants with lower baseline BMI (<18 kg/m^2) had lower QoL at baseline in all domains than those with higher BMI (≥18 kg/m^2), but at week 48, both groups had similar QoL for all domains except for energy/fatigue. For energy/fatigue, mean QoL score was significantly lower at week 48 for those with baseline BMI less than 18 kg/m^2 (mean 76 vs. 85 for BMI ≥18 kg/m^2, $P = 0.004$). Individuals with at least three non-AIDS comorbidities had lower mean QoL score for some domains at baseline, notably role functioning, social functioning and pain, in comparison with those with less than three comorbidities. At week 48, the differences in role functioning and pain by number of baseline comorbidities persisted ($P = 0.001$ for both). At baseline, there was significantly lower mean QoL score for the physical functioning and energy/fatigue domains for individuals with vs. without a history of AIDS; these differences were reduced and NS at week 48.

In multivariable models, there was significant variation among countries in adjusted mean QoL score at week 48 for all domains ($P < 0.001$) except physical functioning ($P = 0.10$), but there were very few other significant associations. In particular, baseline viral load, $CD4^+$ cell count, BMI and history of AIDS were not significantly associated with QoL at week 48 ($P > 0.17$, for all domains), except that baseline $CD4^+$ cell count was significantly associated with mean energy/fatigue score (4 lower for <50 vs. ≥50 cells/μl, 95% CI: 0–8 lower; $P = 0.033$). In addition, higher number of comorbidities remained associated with lower mean role functioning score (6 lower for ≥3 vs. <3 comorbidities, 95% CI: 1–10 lower; $P = 0.031$) and lower mean pain score (7 lower for ≥3 vs. <3 comorbidities, 95% CI: 2–11 lower; $P = 0.004$) at week 48.

Discussion

In RLS, effective second-line ART with successful virologic suppression was associated with improvements in QoL following failure of first-line ART. Improvements in QoL were similar after starting second-line ART with LPV/r + RAL or LPV/r + NRTIs. Mean QoL scores were worse at first-line failure among participants with higher viral load, lower $CD4^+$ cell count, lower BMI and with a history of AIDS prior to starting second-line regimen, but after 1 year of second-line ART, similar QoL scores were achieved. Differences in mean QoL scores among countries and by number of comorbidities remained at week 48 for some domains, which likely reflects differences in QoL which are not directly impacted by ART.

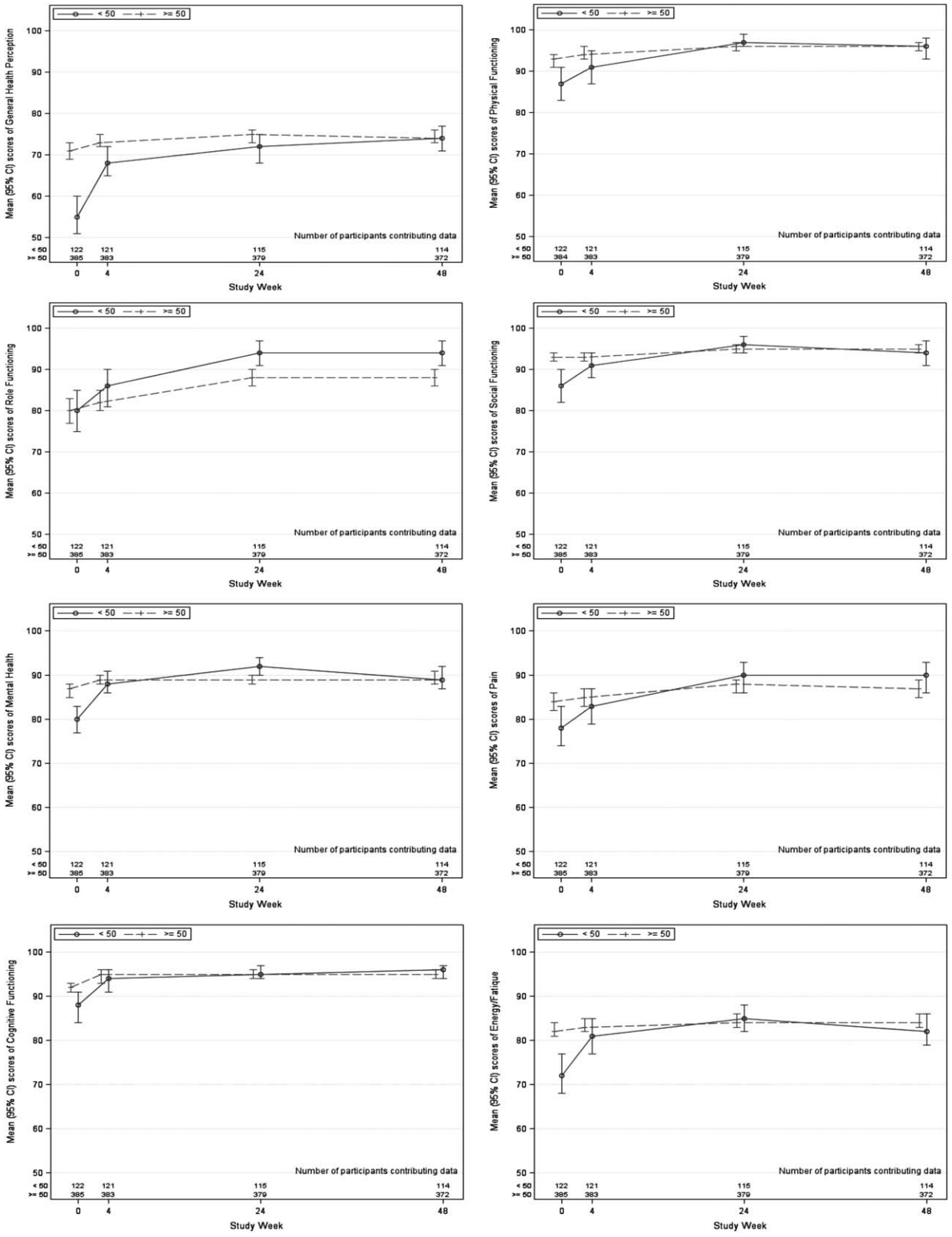

Fig. 1. Unadjusted mean quality of life from week 0 to week 48 by baseline viral load (>100 000 copies/ml vs. viral load ≤100 000 copies/ml) (bars are 95% confidence intervals).

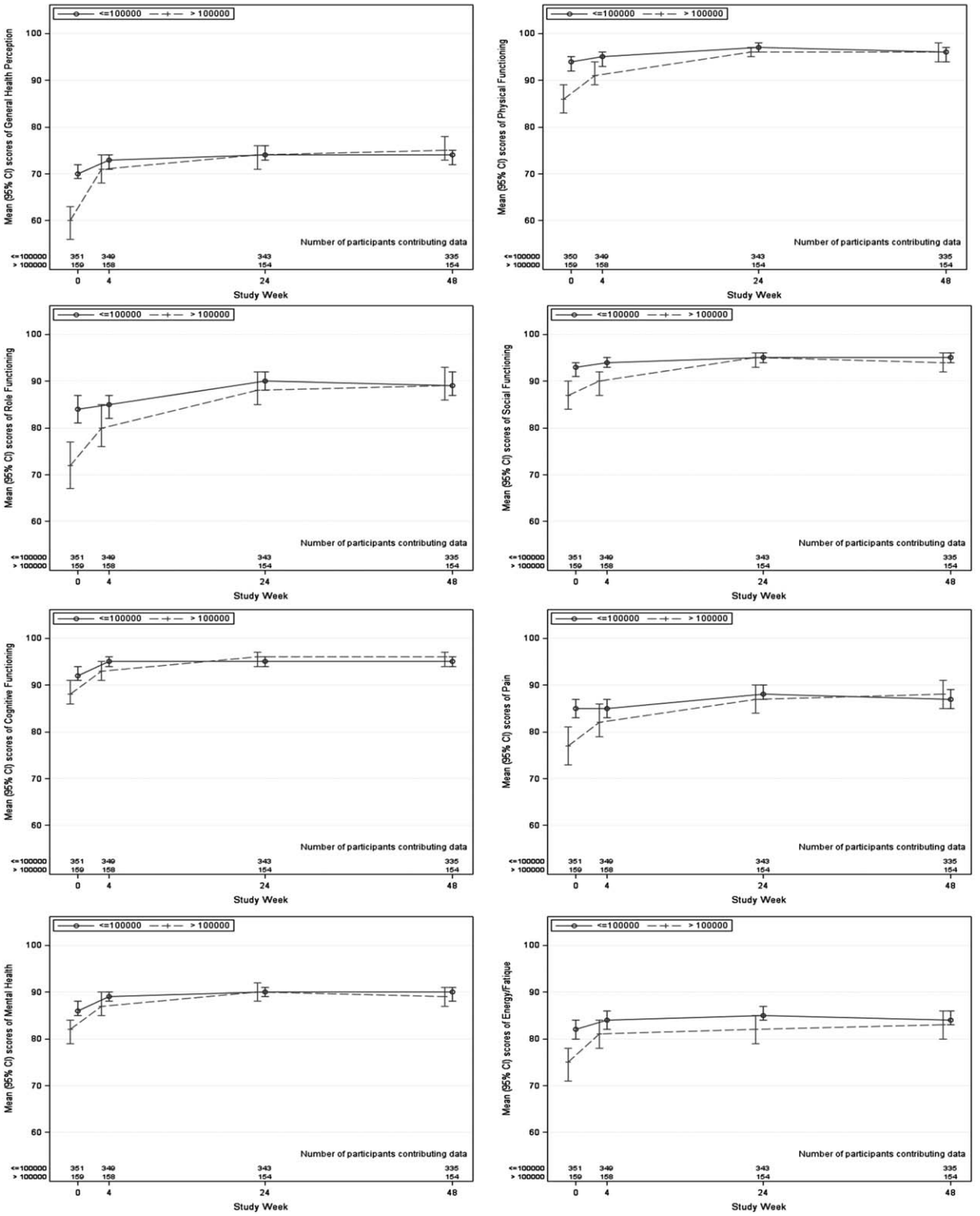

Fig. 2. Unadjusted mean quality of life from week 0 to week 48 by baseline CD4$^+$ cell count (<50 vs. ≥50 cells/μl) (bars are 95% confidence intervals).

In a study conducted in high and middle-income countries comparing LPV/r + RAL vs. LPV/r + NRTIs NRTIs for second-line ART, QoL (physical and mental domains) also improved in both treatment arms after 1 year with no difference between arms [16]. Other observational studies in high−income settings have described improvements in QoL after 1 year of protease-inhibitor-containing ART [14] and over a 24-

month period of treatment with a RAL-containing regimen [15]. In a randomized clinical trial conducted in Spain evaluating the use of either a protease inhibitor or efavirenz (EFV)-based second-line regimen among participants who failed a protease inhibitor-containing first-line regimen, QoL increased in both arms, although it increased more for those in an EFV-containing vs. protease-inhibitor-containing second-line regimen [35].

Our results and those of other studies provide reassurance that a switch to second-line ART is associated with improvements in QoL in settings in which viral load is less regularly monitored and HIV infected individuals may have experienced an extended period of time on a failing first-line ART. Although we found that QoL scores were worse among participants with higher viral load on the failing first-line regimen, within a year after starting a WHO-recommended second-line regimen, these differences had been resolved and there was no association of QoL score with baseline viral load.

Associations of lower role functioning and pain scores with higher number of comorbidities persisted even after 1 year of second-line ART. This might reflect the burden of comorbidities beyond HIV infection on an individual's daily activities and resultant increased pain. Chronic diseases were strong independent risk factors for low QoL in a study conducted in Tanzania with HIV-infected individuals on any ART for at least 2 years [36]. This is consistent with our findings, although the definition of comorbidities in our study was broader, including not only chronic diseases. As the HIV population is aging, the impact of comorbidities in QoL needs to be taken into account when a second-line ART is being initiated.

The highly significant heterogeneity in mean QoL scores among countries for all domains, even after 1-year effective second-line ART, may be related to different cultural perceptions of QoL. It could also be affected by differences in characteristics of participants being enrolled in different countries beyond those characteristics that we had data for (e.g. socioeconomic status, social support).

This study has limitations. Data were not collected on factors such as employment and educational status, depression or mental health disorders, sexual behavior and social stigma that might be associated with QoL. The population studied was from a clinical trial and so may differ from those in clinical practice. The improvements in QoL could reflect factors other than the initiation of second-line ART such as changes in care including participation in a clinical trial. Each clinical site may have selected participants for enrollment differently, with potential differences between countries and between sites. We do not have data on the length of time on first-line ART failure, which could have impacted QoL at baseline and its improvement. Caution should therefore be taken before generalizing our findings to other clinical and cultural settings.

In conclusion, QoL improved after second-line therapy initiation, with no difference between randomized treatments. These results are important to support the use of LPV/r with RAL or NRTIs in RLS as second-line regimens. QoL was poorer among participants with higher viral load and lower $CD4^+$ cell count at baseline, but these differences disappeared after 1 year of second-line ART use. Optimization of QoL is particularly important now that treated HIV infection is a chronic disease and individuals have long-term survival and expectations for near-normal life expectancy. Our findings support the need for ongoing effective ART with successful virologic suppression and immunologic recovery, to support improvements in QoL. This study provides important data for RLS, in which individuals may start or switch ART after longer periods of detectable viral load than in higher income settings.

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Author contributions

T.S.T. did the literature search. T.S.T., L.J.H., M.D.H. analyzed the data and generated the tables and figures. T.S.T., L.J.H., L.Z., M.D.H. interpreted the data. T.S.T., L.J.H., M.D.H. drafted the article. A.M.L.R., S.W.C., L.Z., M.N., F.S., U.G.L., T.M., A.C.C. revised the article and contributed intellectually. The members of the study group were responsible for study oversight and played other important roles for the study at their sites, reviewed the study results, article and provided input and other intellectual contributions.

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Conflicts of interest

There are no conflicts of interest.

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