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## Poor quality of life and incomplete self-reported adherence predict second-line ART virological failure in resource-limited settings

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### ABSTRACT

We evaluated health-related quality of life (QoL) and self-reported incomplete adherence as predictors of early second-line antiretroviral (ART) virological failure (VF). ACTG A5273 study participants completed the ACTG SF-21 measure which has 8 QoL domains. We used exact logistic regression to assess the association of QoL at baseline and week 4 with early VF adjusted for self-reported adherence. Of 500 individuals (51% women, median age 39 years) in this analysis, 79% and 75% self-reported complete adherence (no missing doses in the past month) at weeks 4 and 24, respectively. Early VF was experienced by 7% and more common among those who self-reported incomplete adherence. Participants with low week 4 QoL scores had higher rates of early VF than participants with high scores. After adjusting for self-reported adherence at week 4, VL and CD4 at baseline, cognitive functioning, pain and mental health domains were significantly associated with subsequent early VF. In this post-hoc analysis, poorer QoL adds to self-reported incomplete adherence after 4 weeks of second-line ART in predicting VF at week 24. Evaluation is needed to assess whether individuals with poorer QoL might be targeted for greater support to reduce risk of VF.

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## Introduction

Antiretroviral therapy (ART) is a key component in plans to end the HIV epidemic. Effective ART decreases the risk of AIDS-related and non-AIDS related events (The INSIGHT START Study Group, 2015) as well as HIV transmission, which is typically referred as treatment as prevention (TasP) (Smith et al., 2011). Efficacy of TasP has been shown among serodiscordant heterosexual and couples of men who have sex with men (Bavinton et al., 2018; Cohen et al., 2011; Rodger et al., 2019). In this context, the message “undetectable equals untransmittable” ( $U = U$ ) has been created to raise HIV prevention awareness and to reduce stigma (Rendina & Parsons, 2018; Torres et al., 2020), emphasizing the importance of suppressed viral load values. With availability of first-line ART increasing and prevailing challenges of non-adherence and drug resistance, the World Health Organization has projected an increasing

number of people on second-line ART (WHO, 2015). Consequently, it is essential to understand and identify the predictors of virologic success and failure, particularly on second-line ART.

Adherence to ART is closely linked to viral suppression (Arnsten et al., 2001). Although the monitoring of adherence to ART is highly recommended by health organizations, there is no gold standard for assessing adherence (WHO, 2016). An individual’s self-report is the easiest and most frequently used method to assess adherence in resource-limited settings (RLS) (Costa et al., 2018; Ortego et al., 2011).

Health-related quality of life (QoL) reflects the impact of disease and treatment on a person’s well-being and ability to carry out daily activities, taking into account biological and psychological effects of disease, including 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 (Wilson, 1995). Both poorer QoL and incomplete self-reported adherence have been found to be independent predictors of virologic failure (VF) among participants in a large clinical trial of initial ART undertaken in the U.S. (Schackman et al., 2007). In addition, in a large clinical trial of people starting first-line ART in RLS, worse QoL was found to predict incomplete self-reported adherence to ART (Safren et al., 2014). Furthermore worse QoL during treatment was found to predict treatment failure even after adjustment for self-reported level of adherence (Safren et al., 2014). Evaluating QoL early in treatment may therefore be an important marker of increased risk of VF separate from that identified by a person's self-report of incomplete adherence. In turn, this might help in identifying people in need of interventions to help improve QoL and potentially reduce the risk of subsequent VF.

We previously reported results about QoL among individuals from RLS who were failing first-line ART before starting second-line ART in the AIDS Clinical Trials Group (ACTG) A5273 study (Torres, Harrison, La Rosa, Lavenberg, et al., 2018), and subsequent improvement of QoL scores after one year of second-line ART with no difference between randomized treatments (lopinavir/ritonavir [LPV/r] + raltegravir compared to LPV/r + nucleos(t)ide reverse transcriptase [NRTI]-containing inhibitors) (Torres, Harrison, La Rosa, Cardoso, et al., 2018). Mean QoL scores were poorer among participants with higher plasma HIV-1 RNA viral load (VL) and lower CD4 cells count before second-line ART initiation (Torres, Harrison, La Rosa, Lavenberg, et al., 2018), but these discrepancies disappeared after one year of treatment (Torres, Harrison, La Rosa, Cardoso, et al., 2018). There was also no difference between randomized treatments in incidence of virologic failure (La Rosa et al., 2016). Our objective in this post-hoc analysis is to build upon the findings described above for people receiving first-line ART (Safren et al., 2014; Schackman et al., 2007) to explore whether poorer QoL predicts incomplete self-reported adherence to ART, and whether poorer QoL predicts VF independent of self-reported level of adherence among people starting second-line ART in RLS. We focused on predicting early VF defined as VL >400 copies/mL at 24 weeks of second-line ART with subsequent confirmation, as the majority of virologic failures occurred at 24 weeks, and because predictors of individuals experiencing VF after 24 weeks might differ from those individuals who have achieved virologic suppression at 24 weeks.

## Materials and methods

### A5273 study

ACTG A5273 was a randomized clinical trial, which enrolled and followed participants between January 2012 and October 2014, and showed non-inferior virologic efficacy of LPV/r + raltegravir compared to LPV/r + NRTIs as second-line ART in participants failing non-nucleoside reverse transcriptase inhibitor (NNRTI) based ART (clinicaltrials.gov NCT01352715). Details of study design and main results were described elsewhere (La Rosa et al., 2016).

Eligible participants were HIV-infected men and women ( $\geq 18$  years) who had first-line VF confirmed by two consecutive VL  $\geq 1000$  copies/mL at least one week apart after at least 24 weeks on an NNRTI-containing first-line regimen. Participants were enrolled at 15 sites in 9 RLS: Brazil (1 site), India (3 sites), Kenya (1 site), Malawi (2 sites), Peru (2 sites), South Africa (3 sites), Tanzania (1 site), Thailand (1 site) and Zimbabwe (1 site).

We included in the present analysis participants followed for at least 24 weeks (at which time early VF was determined) who had an assessment for QoL at week 4.

### Early second-line virological failure

Early second-line VF was defined as having VL > 400 copies/mL at week 24 with confirmation at the next VL measurement. Note that week 24 was the time of the first VL measurement at which VF was evaluated in the A5273 study.

### Self-reported adherence measure

We used the question "When was the last time you missed any of your ART medications?" for our assessment of self-reported adherence at 4 and 24 weeks after starting second-line ART. There were 6 potential responses: never skip medications, more than 3 months ago, 1–3 months ago, 2–4 weeks ago, 1–2 weeks ago, and within the past week. We dichotomized self-reported adherence as incomplete (self-report of missed doses within the past 4 weeks) and complete (self-report of never skip medications, or missed doses 1–3 months ago or more than 3 months ago) (R. A. Parker et al., 2017).

### Quality of life measures

Participants were interviewed at week 0 (baseline, just prior to starting second-line ART), and weeks 4 and 24 using a modified version of the SF-21 measure

(ACTG SF-21). The ACTG SF-21 questions cover eight domains: General Health Perceptions (GHP), Physical Functioning (PF), Role Functioning (RF), Social Functioning (SF), Cognitive Functioning (CF), Pain (P), Mental Health (MH), and Energy/Fatigue (E/F). A standardized score ranging from 0 (worst QoL) to 100 (best QoL) was calculated for each domain using standard methods previously described (Safren et al., 2012; Torres, Harrison, La Rosa, Cardoso, et al., 2018; Torres, Harrison, La Rosa, Lavenberg, et al., 2018). 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.

### Statistical analysis

For univariable analysis, we used exact logistic regression to evaluate the association of early second-line VF with self-reported adherence at week 4, age, VL and CD4 at baseline. Continuous variables were categorized as: age into 18–34, 35–49 or  $\geq 50$  years; VL into  $<10,000$ , 10,000–99,999 or  $\geq 100,000$  copies/mL and CD4 count into  $<50$ , 50–199 or  $\geq 200$  cells/mm<sup>3</sup>.

We calculated the mean change of QoL from baseline to week 4, and from week 4 to week 24, and tested whether the differences were significantly different from zero using paired t-test. Then, we calculated mean QoL scores at baseline according to self-reported adherence (complete or incomplete) at week 4 and mean QoL scores at week 4 according to self-reported adherence at week 24. We compared the self-reported adherence groups using the two-sample t-test.

We created three categories for QoL scores in each domain measured at baseline and week 4: high (score 100), medium (75–<100) and low (<75). Subsequently, we calculated the proportion of individuals with early VF and incomplete self-reported adherence at week 4 for each QoL category measured at baseline and week 4. We used exact logistic regression to assess whether QoL at baseline or week 4 as a quantitative variable was significantly associated with early VF taking into account self-reported adherence at week 4. Finally, we evaluated the association of early VF with QoL adjusted also for HIV disease status as measured by baseline VL and CD4 count as we had previously found an association of QoL scores for most domains (Torres, Harrison, La Rosa, Lavenberg, et al., 2018). Data is not publicly available or accessible, and was analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

### Results

Of the 512 participants who participated in the A5273 study, 500 individuals were included in this analysis. Twelve were excluded because of death ( $n = 4$ ), loss to follow-up ( $n = 4$ ), withdrawal of informed consent before 24 weeks ( $n = 2$ ), or missed study evaluations at week 4 ( $n = 1$ ) or week 24 ( $n = 1$ ). Median age was 39 years (interquartile range [IQR]: 34–44) and 51% of participants were women. Participants were predominantly from India (31%), Malawi (21%) and South Africa (20%). Median baseline CD4 count was 138 cells/mm<sup>3</sup> (IQR: 55–271) and VL 33,037 copies/ml (IQR: 7,963–137,925). Median duration of first-line ART was 4.1 years (IQR: 2.2–6.2).

At week 4, 79% (397/500) self-reported complete adherence during the past month. Incomplete self-reported adherence during the past month was reported by 103 (21%) participants: 23 (5%) within the past week, 49 (10%) 1–2 weeks ago and 31 (6%) 2–4 weeks ago. At week 24, 81% (401/497) had self-reported complete adherence during the past month. Incomplete self-reported adherence was reported by 19% (96/497) participants: 8 (2%) within the past week, 23 (5%) 1–2 weeks ago and 65 (13%) 2–4 weeks ago (percentages for the breakdown add to 20% rather than 19% because of rounding).

Thirty-seven (7.4%) of the 500 participants experienced early VF at 24 weeks after starting second-line ART (Table 1). Early VF was more common among participants who self-reported incomplete adherence at week 4 (14 [13.6%] of 103) versus complete adherence (23 [5.8%] of 397) (OR: 2.56; 95%CI: 1.16–5.42). Associations of early VF with sex, age, baseline VL and baseline CD4 count were not statistically significant (Table 1).

Table 2 summarizes mean QoL scores at baseline, week 4 and week 24, as well as mean changes in QoL scores from baseline to week 4 and from week 4 to week 24. Mean QoL scores improved for all domains during the first four weeks of second-line ART, though the mean change for the pain score was not statistically significant. Five of the 8 QoL domains improved significantly between week 4 and week 24. In general, these improvements were smaller in magnitude than those observed between baseline and week 4, though mean changes for the role functioning and pain scores were larger. In those with subsequent early VF, QoL did not improve from baseline to week 4 and from week 4 to week 24 ( $p > 0.1$ ; data not shown).

Lower QoL scores in role functioning and pain at baseline were associated with subsequent self-reported incomplete adherence at the week 4 and 24 evaluations (Table 3). QoL scores at week 4 were

**Table 1.** Association of early virologic failure (VF) on second-line antiretroviral therapy (ART) with self-reported adherence at week 4, demographic and baseline clinical factors.

Characteristic	Total <i>n</i>	Early VF <i>n</i> (%)	OR(95%CI) <sup>a</sup>	<i>p</i> - value
<b>Total</b>	500	37 (7.4)		
<b>Self-reported adherence at week 4</b>				
Complete	397	23 (5.8)	<b>Ref.</b>	<b>0.019</b>
Incomplete	103	14 (13.6)	<b>2.55 (1.16–5.42)</b>	
<b>Sex</b>				
Female	254	16 (6.3)	Ref.	0.43
Male	246	21 (8.5)	1.39 (0.67–2.92)	
<b>Baseline Age (years)</b>				
18–34	141	11 (7.8)	2.15 (0.45–20.6)	0.46 <sup>b</sup>
35–49	306	24 (7.8)	2.17 (0.51–19.5)	
50+	53	2 (3.8)	Ref.	
<b>Baseline Viral Load (HIV-1 RNA copies/mL)</b>				
<10,000	142	5 (3.5)	Ref.	0.24 <sup>b</sup>
10,000–99,999	202	17 (8.4)	2.51 (0.86–8.92)	
≥100,000	154	15 (9.7)	2.95 (0.98–10.6)	
<b>Baseline CD4 count (cells/mm<sup>3</sup>)</b>				
<50	115	9 (7.8)	Ref.	0.15 <sup>b</sup>
50–199	193	12 (6.2)	0.78 (0.29–2.17)	
≥200	187	16 (8.6)	1.10 (0.44–2.94)	

<sup>a</sup>Odds ratios (OR) and 95% confidence interval (95%CI) for early virological failure (VF) at week 24 from exact logistic regression.

<sup>b</sup>*p*-values from logistic regression considering the quantitative variable.

significantly lower in several domains (physical functioning, role functioning, social functioning, pain and mental health) in participants reporting incomplete adherence compared to those reporting complete adherence at the week 4 and 24 evaluations.

Table 4 provides a descriptive summary of the percentage of participants experiencing early VF by category of QoL score for each domain. Also shown are results from a trend test using the quantitative scores for the association between QoL score and proportion experiencing early VF. Only for the pain domain was early VF associated with lower QoL scores. This association was attenuated when adjusted for self-reported adherence at week 4 (Table 4).

In contrast, at week 4, participants with low QoL scores (<75) had higher rates of early VF than participants with high scores (=100) in all domains and were statistically significant for the general health perception,

cognitive functioning, pain, mental health and energy/fatigue domains (Table 5). Associations were slightly attenuated with adjustment for self-reported adherence at week 4, and with further adjustment for baseline VL and CD4 count, but remained significant for the cognitive functioning, pain and mental health domains. In the analyses adjusted for self-reported adherence at week 4, as well as baseline VL and CD4 count, across QoL domains, the odds of early VF were higher for participants with low scores compared with participants with scores of 100.

## Discussion

In RLS, QoL measured 4 weeks after second-line ART initiation adds to self-reported incomplete adherence in predicting early VF. The associations between low QoL scores and VF persisted with adjustment for self-reported adherence at week 4 and baseline HIV disease status as measured by baseline VL and CD4 count. These findings indicate that QoL and adherence assessments after 4 weeks of ART initiation could be implemented as real-time measurements to identify individuals at higher risk of subsequent VF in RLS. These individuals could benefit from interventions to improve QoL, such as social self-value empowerment (Bhatta & Liabsuetrakul, 2017) and yoga (Hari Chandra et al., 2019), or to optimize adherence, such as text-message reminders (Garofalo et al., 2016).

Different from QoL measured at week 4, most QoL domains measured prior to second-line ART initiation (baseline) could not predict early VF (except pain domain). This is consistent with a study conducted in Italy among multiexperienced individuals receiving raltegravir based-regimens, in which baseline characteristics, including QoL measures, did not predict VF after 48 weeks of ART initiation (Bucciardini et al., 2012). Our findings could be explained by significant QoL score improvements between baseline and week 4 for most domains. Thus, four weeks of second-line ART

**Table 2.** Mean QoL scores at baseline, week 4 and week 24 and mean change at weeks 4 and 24.

	Mean QoL score (95% CI)			Change in QoL score from baseline to week 4		Change in QoL score from week 4 to week 24	
	Baseline	Week 4	Week 24	Mean (95% CI)	<i>p</i> -value <sup>a</sup>	Mean (95% CI)	<i>p</i> -value <sup>a</sup>
General Health Perceptions (GHP)	67 (65, 69)	72 (71, 74)	74 (73, 75)	5 (3, 7)	<.001	2 (0, 3)	<b>0.030</b>
Physical Functioning (PF)	92 (90, 93)	94 (93, 95)	97 (96, 97)	2 (1, 4)	<b>0.003</b>	2 (1, 4)	<b>0.001</b>
Role Functioning (RF)	81 (78, 83)	84 (82, 86)	89 (88, 91)	3 (1, 6)	<b>0.008</b>	6 (3, 8)	<.001
Social Functioning (SF)	91 (90, 93)	93 (92, 94)	95 (94, 96)	2 (0, 3)	<b>0.013</b>	2 (0, 3)	<b>0.004</b>
Cognitive Functioning (CF)	91 (90, 93)	95 (94, 96)	95 (94, 96)	3 (2, 5)	<.001	0 (–1, 2)	0.60
Pain ( <i>P</i> )	83 (81, 85)	85 (83, 86)	88 (86, 90)	2 (0, 3)	0.13	3 (1, 5)	<b>0.001</b>
Mental Health (MH)	85 (84, 86)	89 (88, 90)	90 (89, 91)	4 (2, 5)	<.001	1 (0, 2)	0.10
Energy / Fatigue (E/F)	80 (78, 82)	83 (82, 85)	85 (83, 86)	3 (1, 5)	<b>0.001</b>	1 (–1, 3)	0.22

<sup>a</sup>*p*-value from Student's paired sample *t*-test. QoL: quality of life; CI: confidence interval. Possible scores for all domains ranged from 0 (worst) and 100 (best).



**Table 3.** Mean QoL scores at baseline and week 4 according to self-reported adherence at weeks 4 and 24.

	Mean QoL score at baseline (95% CI)					
	Participants self-reporting incomplete adherence at week 4 (n = 103)	Participants self-reporting complete adherence at week 4 (n = 397)	p-value	Participants self-reporting incomplete adherence at week 24 (n = 96)	Participants self-reporting complete adherence at week 24 (n = 401)	p-value
General Health Perceptions (GHP)	68 (64, 71)	67 (65, 69)	0.71	68 (65, 71)	67 (65, 69)	0.64
Physical Functioning (PF)	90 (87, 94)	92 (90, 94)	0.41	91 (88, 94)	92 (90, 94)	0.68
Role Functioning (RF)	67 (61, 74)	84 (81, 87)	<.001	64 (57, 72)	85 (82, 87)	<.001
Social Functioning (SF)	90 (87, 92)	92 (90, 93)	0.22	89 (87, 93)	92 (90, 93)	0.15
Cognitive Functioning (CF)	93 (91, 95)	91 (89, 92)	0.14	93 (91, 95)	91 (89, 92)	0.13
Pain (P)	76 (71, 81)	85 (83, 87)	<.001	77 (73, 82)	84 (83, 87)	0.003
Mental Health (MH)	85 (82, 87)	85 (84, 87)	0.56	86 (84, 88)	85 (83, 87)	0.22
Energy / Fatigue (E/F)	80 (77, 83)	80 (78, 82)	0.92	81 (78, 85)	80 (78, 82)	0.73
	Mean QoL score at week 4 (95% CI)					
General Health Perceptions (GHP)	70 (67, 73)	73 (71, 74)	0.15	71 (68, 74)	73 (71, 74)	0.35
Physical Functioning (PF)	89 (85, 93)	95 (94, 97)	0.003	89 (85, 93)	96 (94, 97)	0.002
Role Functioning (RF)	73 (68, 78)	87 (84, 89)	<.001	69 (63, 75)	87 (85, 90)	<.001
Social Functioning (SF)	88 (86, 91)	94 (93, 96)	0.001	89 (85, 92)	94 (93, 95)	0.001
Cognitive Functioning (CF)	93 (91, 95)	95 (94, 96)	0.19	92 (90, 95)	95 (94, 96)	0.08
Pain (P)	77 (72, 81)	87 (85, 88)	0.001	78 (74, 83)	86 (84, 88)	0.002
Mental Health (MH)	87 (85, 89)	89 (88, 90)	0.06	86 (83, 88)	89 (88, 91)	0.005
Energy / Fatigue (E/F)	80 (77, 84)	84 (82, 86)	0.09	81 (78, 85)	84 (82, 86)	0.25

p-values from Student's two sample t-test.

resulted in improvement of QoL among most individuals but not among those subsequently experiencing early VF.

Associations of low QoL at week 4 and early VF were more pronounced for cognitive functioning, pain and mental health domains. These domains aim to measure: (i) for cognitive functioning, the degree of difficulty participants have experienced with respect to their cognitive abilities; (ii) for pain, the intensity of physical pain (e.g., headache, muscle pain, stomach ache) and degree of interference with daily activities; (iii) for mental health, anxiety, depression, and overall psychological well-being (Torres, Harrison, La Rosa, Lavenberg, et al., 2018).

Cognitive dysfunction has been previously demonstrated to be associated with a higher risk of VF in resource rich-settings (Hinkin et al., 2002; Shahani et al., 2018), as it may impact ability to adhere to ART (Gorman et al., 2009). Pain symptoms are more prevalent among people living with HIV (PLWH) than the general population (Canan et al., 2019) due to multiple factors, including HIV infection, certain antiretroviral

drugs, co-existing psychiatric illness, and substance abuse (Krashin et al., 2012). Point prevalence of clinically significant pain among PLWH ranges from 54% (95% CI 51.14, 56.09) to 83% (95% CI 76, 88), considering a three-month recall period (R. Parker et al., 2014). Chronic pain has a negative impact on HIV status, including decreased adherence to ART (Surratt et al., 2015) and higher rates of unsuppressed HIV viral loads (Denis et al., 2019). However, chronic pain is undertreated in many settings, including in PLWH due to complexity of ART regimens, potential drug-drug interactions with pain medications, risk of side effects (Isenberg et al., 2017), psychiatric and substance use comorbidities (Miaskowski et al., 2011) and patient beliefs (e.g., no connection between pain and the disease or fear of what the pain may mean) (Breitbart et al., 1998). Mental health disorders are also reported more often by PLWH than the general population in RLS, including depression and posttraumatic stress disorders (Remien et al., 2019). Elevated depressive symptoms are correlated with a decrease of adherence to ART

**Table 4.** Associations of QoL domains at baseline with early virologic failure (VF) on second-line antiretroviral therapy (unadjusted and adjusted).

QoL domain	QoL Score Category <sup>a</sup>	N	Incomplete self-reported adherence at		OR for early VF (95%CI)	Trend p-value <sup>b</sup>	OR for early VF (95%CI) adjusted for self-reported adherence at week 4		Trend p-value <sup>b</sup>
			week 4 N (%)	Early VF N (%)			Ref	Ref	
General Health Perception (GHP)	High	31	5 (16.1)	2 (6.4)	Ref	0.87	Ref	Ref	0.84
	Medium	212	44 (20.7)	18 (8.5)	1.34 (0.30–12.5)		1.28 (0.28–12.0)		
	Low	257	54 (21.0)	17 (6.6)	1.03 (0.23–4.68)		0.97 (0.21–9.16)		
Physical Functioning (PF)	High	344	61 (17.7)	22 (6.4)	Ref	0.19	Ref	Ref	0.22
	Medium	114	37 (32.5)	11 (9.6)	1.56 (0.66–3.50)		1.34 (0.56–3.06)		
	Low	41	5 (12.2)	4 (9.8)	1.58 (0.38–5.02)		1.70 (0.40–5.44)		
Role Functioning (RF)	High	327	48 (14.7)	19 (5.8)	Ref	0.47	Ref	Ref	0.91
	Medium	27	5 (18.5)	5 (18.5)	3.66 (0.98–11.5)		3.57 (0.94–11.3)		
	Low	146	50 (34.2)	13 (8.9)	1.58 (0.70–3.49)		1.29 (0.55–2.93)		
Social Functioning (SF)	High	326	49 (15.0)	20 (6.1)	Ref	0.45	Ref	Ref	0.52
	Medium	125	47 (37.6)	13 (10.4)	1.77 (0.78–3.89)		1.43 (0.61–3.24)		
	Low	49	7 (14.3)	4 (8.2)	1.36 (0.32–4.32)		1.37 (0.32–4.39)		
Cognitive Functioning (CF)	High	275	53 (19.3)	20 (7.3)	Ref	0.67	Ref	Ref	0.53
	Medium	167	45 (26.9)	13 (7.8)	1.08 (0.50–2.35)		0.99 (0.43–2.17)		
	Low	58	5 (8.6)	4 (6.9)	0.94 (0.23–2.98)		1.08 (0.25–3.45)		
Pain (P)	High	249	38 (15.3)	16 (6.4)	Ref	<b>0.033</b>	Ref	Ref	0.08
	Medium	111	20 (18.0)	4 (3.6)	0.54 (0.13–1.74)		0.53 (0.12–1.70)		
	Low	140	45 (32.1)	17 (12.1)	2.01 (0.92–4.41)		1.73 (0.77–3.86)		
Mental Health (MH)	High	124	10 (8.1)	5 (4.0)	Ref	0.12	Ref	Ref	0.11
	Medium	263	74 (28.1)	20 (7.6)	1.96 (0.69–6.83)		1.56 (0.53–5.60)		
	Low	113	19 (16.8)	12 (10.6)	2.82 (0.89–10.6)		2.56 (0.80–9.66)		
Energy/Fatigue (E/F)	High	129	10 (7.7)	6 (4.6)	Ref	0.29	Ref	Ref	0.28
	Medium	234	73 (31.2)	19 (8.1)	1.81 (0.67–5.68)		1.39 (0.49–4.53)		
	Low	137	20 (14.6)	12 (8.8)	1.96 (0.66–6.58)		1.82 (0.60–6.13)		

<sup>a</sup>QoL score categories: high = 100; medium = 75–<100; low = <75; <sup>b</sup>p-values from logistic regression model including QoL score as a quantitative score.

**Table 5.** Associations of QoL domains at week 4 with early virologic failure (VF) on second-line antiretroviral therapy (unadjusted and adjusted).

QoL Domain	QoL Score Category <sup>a</sup>	N	Incomplete self-reported adherence at		OR for early VF (95%CI)	Trend p-value <sup>b</sup>	OR for early VF (95%CI) adjusted for self-reported adherence at week 4		Trend p-value <sup>b</sup>	
			week 4 N (%)	Early VF N (%)			Ref	aOR(95%CI) <sup>c</sup>		
General Health Perception (GHP)	High	35	5 (14.3)	1 (2.9)	Ref	<b>0.048</b>	Ref	0.063	Ref.	0.063
	Medium	256	52 (20.3)	17 (6.6)	2.41 (0.36–104)		2.27 (0.33–98.0)		2.30 (0.33–99.7)	
	Low	209	46 (22.0)	19 (9.1)	3.39 (0.50–145)		3.13 (0.46–135)		3.16 (0.46–136)	
Physical Functioning (PF)	High	382	57 (14.9)	22 (5.8)	Ref	0.08	Ref	0.18	Ref.	0.24
	Medium	95	39 (41.0)	12 (12.6)	<b>2.36 (1.02–5.22)</b>		1.91 (0.79–4.38)		1.87 (0.78–4.30)	
	Low	23	7 (30.4)	3 (13.0)	2.45 (0.43–9.24)		2.15 (0.38–8.27)		1.91 (0.33–7.44)	
Role Functioning (RF)	High	347	49 (14.1)	20 (5.8)	Ref	0.48	Ref	0.14	Ref.	0.17
	Medium	20	5 (25.0)	1 (5.0)	0.86 (0.02–6.00)		0.78 (0.02–5.51)		0.84 (0.02–5.98)	
	Low	133	49 (36.8)	16 (12.0)	<b>2.23 (1.04–4.71)</b>		1.84 (0.83–4.00)		1.77 (0.79–3.87)	
Social Functioning (SF)	High	342	51 (14.9)	21 (6.1)	Ref	0.13	Ref	0.28	Ref.	0.41
	Medium	131	41 (31.3)	12 (9.2)	1.54 (0.67–3.40)		1.32 (0.56–2.96)		1.28 (0.54–2.89)	
	Low	27	11 (40.7)	4 (14.8)	2.65 (0.61–8.82)		2.10 (0.47–7.23)		1.78 (0.39–6.31)	
Cognitive Functioning (CF)	High	332	55 (16.6)	19 (5.7)	Ref	<b>0.006</b>	Ref	<b>0.009</b>	Ref.	<b>0.014</b>
	Medium	137	41 (29.9)	12 (8.8)	1.58 (0.68–3.55)		1.38 (0.58–3.14)		1.35 (0.57–3.08)	
	Low	31	7 (22.6)	6 (19.3)	<b>3.93 (1.18–11.5)</b>		<b>3.75 (1.11–11.1)</b>		3.38 (0.99–10.1)	
Pain (P)	High	253	37 (14.6)	14 (5.5)	Ref	<b>0.001</b>	Ref	<b>0.006</b>	Ref.	<b>0.008</b>
	Medium	112	22 (19.6)	6 (5.4)	0.97 (0.30–2.77)		0.92 (0.28–2.65)		0.92 (0.28–2.65)	
	Low	135	44 (32.6)	17 (12.6)	<b>2.45 (1.10–5.58)</b>		2.10 (0.91–4.86)		2.00 (0.87–4.64)	
Mental Health (MH)	High	159	20 (12.6)	9 (5.7)	Ref	<b>0.015</b>	Ref	<b>0.023</b>	Ref.	<b>0.029</b>
	Medium	268	66 (24.6)	19 (7.1)	1.27 (0.53–3.28)		1.11 (0.46–2.90)		1.10 (0.45–2.88)	
	Low	73	17 (23.3)	9 (12.3)	2.33 (0.78–6.98)		2.09 (0.69–6.31)		2.07 (0.68–6.25)	
Energy/Fatigue (E/F)	High	161	20 (12.4)	6 (3.7)	Ref	<b>0.048</b>	Ref	0.07	Ref.	0.10
	Medium	232	58 (25.0)	17 (7.3)	2.04 (0.75–6.46)		1.80 (0.65–5.75)		1.79 (0.64–5.72)	
	Low	107	25 (23.4)	14 (13.1)	<b>3.87 (1.34–12.7)</b>		<b>3.49 (1.20–11.6)</b>		<b>3.30 (1.28–11.0)</b>	

<sup>a</sup>QoL score categories: high = 100; medium = 75–<100; low = <75; <sup>b</sup>p-values considering quantitative QoL domains scores; <sup>c</sup>adjusted for self-reported adherence at week 4, VL and CD4 count at baseline.

(Uebelacker et al., 2015) and VF (Anastos et al., 2005; Barfod et al., 2005).

In this study, a single question about self-reported adherence in the first 4 weeks of second-line ART was useful in predicting early VF in RLS. In the SECOND-LINE trial, which also evaluated a raltegravir-based regimen for second-line ART in RLS, poor adherence was a major determinant of VF (Boyd et al., 2015). Enhanced adherence counseling could be considered as a potential strategy to prevent VF; this intervention was effective in a Swaziland study to promote viral load suppression in PWLH with high VL (Etoori et al., 2018). Two-way mobile phone intervention might also be used to improve adherence, as it was shown to have a modest impact on VF rates in a multi-center study among individuals failing second-line ART in RLS (Gross et al., 2019).

We have also observed that low QoL scores measured at week 4 could predict incomplete self-reported adherence 24 weeks after starting second-line ART for most domains. Better QoL with respect to general health perception at baseline was associated with higher rates of complete self-reported adherence through 72-weeks of first-line ART in a multicentre trial conducted in RLS (Safren et al., 2014). Adherence over time was associated with greater QoL in prospective cohort studies (Geocze et al., 2010). This indicates that QoL measures could be useful to identify individuals at risk of incomplete adherence in RLS.

This study has limitations. Data were not collected on factors such as employment and educational status, 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 the routine clinical practice. We did not have sufficient number of early VFs to evaluate whether associations between QoL and VF might have varied among countries/cultures. Adherence data was self-reported by participants and may be subject to recall bias. First-line ART virological failure was identified at study entry and it is possible that participants may have had unidentified VF for an extended period of time, particularly in locations where VL testing was not part of routine care. It is also possible, therefore, that some PLWH experiencing unidentified VF might die or be lost from care and so not be represented in our study versus a study that was identifying VF proximal to its time of occurrence. Caution should therefore be taken before generalizing our findings to other clinical and cultural settings.

In this post-hoc analysis, poorer QoL adds to self-reported incomplete adherence after 4 weeks of second-line ART in predicting VF at week 24. Evaluation is needed to assess whether patients with poorer

QoL might be targeted for greater support to improve QoL and adherence, as well as to reduce risk of VF.

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