QUALITY OF LIFE AND ADHERENCE AS PREDICTORS OF SECOND-LINE ART VIROLOGICAL FAILURE

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ABSTRACT

Background. Poor adherence to antiretroviral therapy (ART) predicts virologic failure (VF). Self-reported adherence and health-related quality of life (QoL) have been associated with 1st line ART failure in resource-limited settings (RLS). Our objective was to assess whether QoL metrics add to self-reported adherence data at 4 weeks after starting 2nd-line ART in predicting early VF.

Methods. ACTG A5273 was a randomized clinical trial conducted between 2012 and 2014, which showed non inferior virologic efficacy of lopinavir/ritonavir (LPV/r) + raltegravir compared to LPV/r + nucleos(t)ide reverse transcriptase inhibitors as 2nd-line ART in participants failing non-nucleoside reverse transcriptase inhibitor ART at 15 sites in 9 RLS. Early 2nd-line VF was defined as HIV-1 RNA >400 c/mL at week 24 with subsequent confirmation. At baseline and week 4, participants completed the ACTG SF-21, which has 8 QoL domains each scored between 0 (worst) and 100 (best). Adherence was dichotomized as incomplete (self-report of any dose missed in the first 4 weeks of 2nd-line ART) and complete (no missed dose). Logistic regression was used to assess whether QoL at week 4, categorized in each domain as high (score 100), medium (75-<100) and low (<75), enhanced prediction of early 2nd-line VF in addition to adherence.

Results. 512 eligible adults (49% male, median age 39 years) were included including 500 with assessments for QoL and adherence at week 4. 7.4% (n=37/500) had early 2nd-line VF and 20.6% (103/500) reported incomplete adherence at week 4. Mean QoL improved (p<0.009) from baseline to week 4 in all domains: from 67 to 72 (general health perceptions), 92 to 94 (physical functioning), 81 to 84 (role functioning), 91 to 93 (social functioning), 91 to 95 (cognitive functioning, CF), 83 to 85 (pain), 85 to 89 (mental health), and 80 to 83 (energy/fatigue, E/F). Early VF was more common among participants who self-reported incomplete (14/103, 13.6%) versus complete adherence (23/397, 5.8%) at week 4 (OR: 2.56; 95%CI: 1.27-5.17; p=0.009). In analyses (both unadjusted and adjusted for adherence), lower QoL in CF and E/F categories at week 4 were associated with significantly higher odds of early 2nd-line VF (overall p<0.04). This association remained after additionally adjusting for sex, CD4 and number of comorbidities (**Table 4**).

Conclusions. Poorer QoL, particularly CF and E/F, adds to self-reported incomplete adherence after 4 weeks of 2nd-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 reduce risk of VF.

BACKGROUND

Poor adherence to antiretroviral therapy (ART) predicts virologic failure (VF). Self-reported adherence and health-related quality of life (QoL) have been associated with 1st line ART failure in resource-limited settings (RLS) (1)

QoL was poorer among participants with higher HIV-1 RNA and lower CD4 at first-line VF (2) but these differences disappeared after one year of second-line ART use (3).

Our objective was to assess whether QoL metrics add to self-reported adherence data at 4 weeks after starting 2nd-line ART in predicting early VF (at 24 weeks).

METHODS

ACTG A5273 was a randomized clinical trial conducted between 2012 and 2014, which showed non inferior virologic efficacy of lopinavir/ritonavir (LPV/r) + raltegravir compared to LPV/r + nucleos(t)ide reverse transcriptase inhibitors as 2nd-line ART in participants failing non-nucleoside reverse transcriptase inhibitor ART at 15 sites in 9 countries.

The primary analysis of the trial showed no difference in virologic outcome between the two regimens (4). In this analysis, early 2nd-line VF was defined as HIV-1 RNA >400 c/mL at week 24 with subsequent confirmation.

Adherence was dichotomized as incomplete (self-report of any dose missed in the first 4 weeks of 2nd-line ART) and complete (no missed dose).

At baseline and week 4, participants completed the ACTG SF-21, which has 8 QoL domains each scored between 0 (worst) and 100 (best) (**Table 1**).

We used exact logistic regression to assess whether QoL at week 4, categorized in each domain as high (score 100), medium (75-<100) and low (<75), enhanced prediction of early 2nd-line VF in addition to self-reported adherence. We also conducted adjusted multivariable models including variables associated with adherence and VF on univariate analysis (except country).

RESULTS

- 512 eligible adults started the study; 500 individuals with assessments for QoL and adherence at week 4 and for early VF were included in this analysis;
- 7.4% (n=37/500) had early second-line VF and 20.6% (103/500) reported incomplete adherence at week 4. Baseline characteristics of participants according to early VF and adherence at week 4 are depicted in **Table 2**.
- Early VF was more common among participants who self-reported incomplete (14/103, 13.6%) versus complete adherence (23/397, 5.8%) at week 4 (OR: 2.56; 95%CI: 1.27-5.17; p=0.009).
- Mean QoL improved significantly from baseline to week 4 in all domains. Mean QoL improved from week 4 to week 24 in most domains, except for CF and E/F (**Table 3** and **Figure 1**).
- In analyses (both unadjusted and adjusted for adherence), lower QoL in CF and E/F categories at week 4 were associated with significantly higher odds of early 2nd-line VF (overall p<0.04). This association remained after additionally adjusting for sex, CD4 and number of comorbidities (**Table 4**).
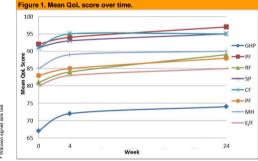
Table 1. Information obtained using the Short Form 21-item (SF-21) QoL Questionnaire.

Domains	# items	Summary of contents
General Health Perceptions (GHP)	3	Participants rate their general health, resistance to illnesses, and health outlook. It has been validated. Two questions are reverse coded to reduce or prevent response bias.
Physical Functioning (PF)	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 (RF)	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 (SF)	2	Participants are asked to what extent their health in the past 4 weeks has limited their social activities; one item is reverse coded.
Cognitive Functioning (CF)	3	This domain measures the degree of difficulty participants have experienced in the past four weeks with respect to their cognitive abilities. It assesses a participant's level of difficulty with reasoning/solving problems, being attentive, and remembering.
Pain (P)	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 four weeks; one item is reverse coded .
Mental health (MH)	3	This domain assesses anxiety, depression, and overall psychological wellbeing in the past 4 weeks. One item is reverse coded.
Energy/Fatigue (E/F)	2	This domain assesses vitality (feeling tired or fatigued and energy to do things the person wanted to); one item is reverse coded .

Table 2. Baseline demographic and clinical characteristics of participants according to early second-line VF and adherence at week 4

Characteristics	Total n(%)	Self-reported adherence (at week 4) Incomplete (%)	p-value	Early Second-line VF (at week 24) Yes (%)	p-value
Total	500	103 (20.6)		37 (7.4)	
Sex			0.006		0.34
Female	254 (50.8)	40 (15.7)		16 (6.3)	
Male	246 (49.2)	63 (25.6)		21 (8.5)	
Age (years)			0.69		0.41
<50	447 (89.4)	91 (20.4)		35 (7.8)	
50+	53 (10.6)	12 (22.6)		2 (5.4)	
Country			<.001		0.08
India	155 (31.0)	61 (39.3)		16 (10.3)	
Malawi	105 (21.0)	10 (9.5)		3 (2.9)	
South Africa	102 (20.4)	11 (10.8)		8 (7.8)	
Kenya	48 (9.6)	6 (12.5)		3 (6.2)	
Zimbabwe	47 (9.4)	10 (21.3)		1 (2.1)	
Other[a]	43(8.6)	5 (11.6)		6 (13.9)	
HIV-1 RNA (copies/mL)			0.49		0.19
≤100,000	344 (69.1)	74 (21.5)		22 (6.4)	
>100,000	154 (30.9)	29 (18.8)		15 (9.7)	
CD4 count (cells/mm³)			0.011		0.84
<50	115 (23.2)	14 (12.2)		9 (7.8)	
≥50	380(76.8)	88 (23.2)		28 (7.4)	
History of AIDS			0.58		0.19
Yes	147 (29.4)	28 (19.0)		7 (4.8)	
No	353 (70.6)	75 (21.2)		30 (8.5)	
Number of comorbidities			0.004		0.27
<3	400 (80.0)	72 (18.0)		27 (6.7)	
≥3	100 (20.0)	31 (31.0)		10(10.0)	

[a] countries with <20 participants: Brazil, Peru, Tanzania and Thailand

Table 3. Mean QoL (baseline, week 4 and week 24) and Mean Increases at weeks 4 and 24.

	Mean QoL at baseline (95% CI)	Mean QoL at week 4 (95% CI)	Mean QoL at week 24 (95% CI)	Mean increase in QoL from baseline to week 4 (95% CI)	p-value[a]	Mean increase in QoL from week 4 to week 24 (95% CI)	p-value[a]
General Heath Perceptions (GHP)	67 (65, 69)	72 (71, 74)	74 (73, 75)	5 (3, 7)	<.001	2 (0, 3)	0.055
Physical Functioning (PF)	92 (90, 93)	94 (93, 95)	97 (96, 97)	2 (1, 4)	0.001	2 (1, 4)	0.004
Role Functioning (RF)	81 (78, 83)	84 (82, 86)	89 (88, 91)	3 (1, 6)	0.009	6 (3, 8)	<.001
Social Functioning (SF)	91 (90, 93)	93 (92, 94)	95 (94, 96)	2 (0, 3)	<.001	2 (0, 3)	0.008
Cognitive Functioning (CF)	91 (90, 93)	95 (94, 96)	95 (94, 96)	3 (2, 5)	<.001	0 (-1, 2)	0.93
Pain (P)	83 (81, 85)	85 (83, 86)	88 (86, 90)	2 (0, 3)	0.008	3 (1, 5)	0.007
Mental Health (MH)	85 (84, 86)	89 (88, 90)	90 (89, 91)	4 (2, 5)	<.001	1 (0, 2)	0.058
Energy / Fatigue (E/F)	80 (78, 82)	83 (82, 85)	85 (83, 86)	3 (1, 5)	0.001	1 (-1, 3)	0.37

[a] Wilcoxon signed rank test

Table 4. Associations of QoL domains at week 4 with early 2nd-line VF (unadjusted and adjusted).

QoL Domain3	QoL Score Category[a]	N	Incomplete adherence N (%)	Early VF N (%)	OR(95%CI)	p-value	OR(95%CI) adjusted for adherence	p-value	aOR(95%CI)[b]	p-value
General Health Perception (GHP)	High	35	5 (14.3)	1 (2.9)	Ref		Ref			
	Medium	256	52 (20.3)	17 (6.6)	2.41(0.36-104.00)	0.67	2.27(0.33-97.98)	0.74	[c]	
	Low	209	46 (22.0)	19 (9.1)	3.39(0.50-145-37)	0.37	3.13(0.46-134.96)	0.44	[c]	
Physical Functioning (PF)	High	382	51 (14.9)	22(5.8)	Ref		Ref			
	Medium	95	39 (41.0)	12 (12.6)	**2.36(1.02-5.22)**	**0.044**	1.91(0.79-4.38)	0.16	[c]	
	Low	23	7 (30.4)	3 (13.0)	2.45(0.43-9.24)	0.32	2.15(0.38-8.27)	0.42	[c]	
Role Functioning (RF)	High	347	49 (14.1)	20 (5.8)	Ref		Ref			
	Medium	20	5 (25.0)	1 (5.0)	0.86(0.02-6.00)	1.00	0.78(0.02-5.51)	1.00	[c]	
	Low	133	49 (36.8)	16 (12.0)	**2.23(1.04-4.71)**	**0.038**	1.84(0.83-4.00)	0.10	[c]	
Social Functioning (SF)	High	342	51 (14.9)	21 (6.1)	Ref		Ref			
	Medium	131	41 (31.3)	12 (9.2)	1.54(0.67-3.40)	0.34	1.32(0.56-2.96)	0.60	[c]	
	Low	27	11 (40.7)	4 (14.8)	2.65(0.61-8.82)	0.20	2.10(0.47-7.23)	0.36	[c]	
Cognitive Functioning (CF)	High	332	55 (16.6)	19 (5.7)	Ref		Ref		Ref	
	Medium	137	41 (29.9)	12 (8.8)	1.58(0.68-3.55)	0.32	1.38(0.58-3.14)	0.52	1.34(0.57-3.08)	0.59
	Low	31	7 (22.6)	6 (19.3)	**3.93(1.18-11.48)**	**0.026**	**3.75(1.11-11.10)**	**0.033**	**3.46(1.01-10.34)**	**0.048**
Pain (P)	High	253	37 (14.6)	14 (5.5)	Ref		Ref			
	Medium	112	22 (19.6)	6 (5.4)	0.97(0.30-2.77)	1.00	0.92(0.28-2.65)	1.00	[c]	
	Low	135	44 (32.6)	17 (12.6)	**2.45(1.10-5.58)**	**0.028**	2.10(0.91-4.86)	0.08	[c]	
Mental Health (MH)	High	159	20 (12.6)	9 (5.7)	Ref		Ref			
	Medium	268	66 (24.6)	19 (7.1)	1.27(0.53-3.28)	0.72	1.11(0.46-2.90)	0.98	[c]	
	Low	73	17 (23.3)	9 (12.3)	2.33(0.78-6.98)	0.14	2.09(0.69-6.31)	0.22	[c]	
Energy/Fatigue (E/F)	High	161	20 (12.4)	6 (3.7)	Ref		Ref		Ref	
	Medium	232	58 (25.0)	17 (7.3)	2.04(0.75-6.46)	0.20	1.80(0.65-5.75)	0.32	1.77(0.63-5.70)	0.34
	Low	107	25 (23.4)	14 (13.1)	**3.87(1.34-12.72)**	**0.009**	**3.49(1.20-11.56)**	**0.019**	**3.45(1.18-11.48)**	**0.021**

[a] QoL score categories: high = 100; medium = 75-<100; low = <75; [b] adjusted for adherence, sex, CD4 and number of comorbidities; [c] not statistical significative

Figure 1. Mean QoL score over time.

CONCLUSIONS

- Early second-line VF was associated with early incomplete self-reported adherence in RLS.
- Effective second-line ART was associated with improvements in QoL after 4 weeks, with lower improvements after 24 weeks for some domains (CF and E/F).
- Poorer QoL, particularly CF and E/F, adds to self-reported incomplete adherence after 4 weeks of 2nd-line ART in predicting VF at week 24.
- Evaluation is needed to assess whether patients with poorer QoL might be targeted for interventions to reduce risk of VF.

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