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Relationship between adherence and health-related quality of life among HIV-patients in South Africa: findings and implications

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Greater access to highly active antiretroviral treatment (HAART) has increased the survival of people living with HIV and AIDS (PLWHA), and health-related quality of life (HRQoL) has emerged as an important indicator of treatment outcomes. However, the success of HAART depends on consistent and optimum adherence. Various cross-sectional studies and few longitudinal studies identified the relationship between HRQoL and HAART; however their association over time is still unclear. The objective of this study is to investigate the relationship between HRQoL and adherence to HAART over time. 431 PLWHAs were followed for one year at 4-monthly intervals. A descriptive adherence self-report rating scale and WHOQOL-HIV BREF were administered to collect adherence and HRQoL data respectively. Optimum adherence was set at ≥95%. Significant differences (p<0.05) in the overall mean HRQoL scores of the HAART adherent (≥95%) and non-adherent (<95%) patients were observed amongst patients on HAART for the periods of 9-28 months, 49-64 months and 81-120 months. This study established a strong relationship between adherence to HAART and HRQoL over time. Adherence to HAART is still a challenge and needs to be addressed through appropriate interventions.

Key words: Highly active antiretroviral therapy, health-related quality of life, medication adherence, interrupted time-series analysis, South Africa.

INTRODUCTION

HIV and AIDS has a devastating impact on morbidity and mortality across countries, with sub-Sahara Africa having the highest prevalence rates (WHO, 2014, 2018). Currently, 36.7 million people worldwide are living with HIV and AIDS, with 19.6 million people living in East and Southern Africa (Avert, 2017; US Department of Health

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and Human Services, 2018). Improved coverage and use of highly active antiretroviral treatment (HAART) has reduced morbidity and mortality in both children and adults with HIV and AIDS, with integrated approaches used to improve care and outcomes (Venter et al., 2017; Burrage et al., 2018). Improved care and an appreciable increase in access to HAART for people living with HIV and AIDS (PLWHA) have resulted in a 48% reduction in AIDS-related deaths since 2003, with the epidemic now declining (UNAIDS, 2017). Approximately 17 million PLWHA had access to HAART by end of 2015, and the global coverage of HAART has reached 46% (UNAIDS, 2016). South Africa has a high burden of infectious diseases (Statistics South Africa, 2018), with an estimated 7.52 million PLWHA (Statistics South Africa, 2018). Wider access to HAART through public health programs has resulted in life expectancy increasing from 54.9 years in 2002 to 64.2 years in 2018 among people with HIV in South Africa, which is encouraging (Statistics South Africa, 2018).

The evident effectiveness of HAART has resulted in an appreciable change in the patterns of mortality from HIV in South Africa, leading to increasing prevalence of HIV from 10.9% in 2002 to 12.6% in 2017 (Statistics South Africa, 2016). The increased life expectancy denoted by an ageing HIV-infected population is also impacting on the rate of non-communicable diseases (NCDs) in South Africa and other African countries, with increasing rates of patients with both HIV and NCDs (Meyer et al., 2017; Rwegerera et al., 2017). Several studies identified that PLWHA may have a higher prevalence and early age of onset of NCDs compared to the general population (Guaraldi et al., 2011; Althoff et al., 2014; Schouten et al., 2014). Treatment of NCDs poses challenges such as an increased pill burden impacting on adherence, increasing side-effects due to drug-drug interactions, as well as loss of treatment efficacy and subsequent virological breakthrough in patients with concomitant HIV, all of which may complicate HIV treatment (Deeks and Phillips, 2009; Althoff et al., 2016). With identified complexities relating to HAART and NCDs in PLWHA, coupled with reduced mortality, the focus over the last number of years has shifted to improving the health-related quality of life (HRQoL) of PLWHA (Oguntibeju, 2012; Van Tam et al., 2012; Balderson et al., 2013; Moorhouse, 2014; Owuor et al., 2014; Pasquau et al., 2018) as a key outcome measure.

Health-related quality of life (HRQoL) is one of the most used subjective aspects in assessing the impact of chronic disease conditions such as HIV, and is used as a key outcome variable for validating or reviewing current treatment approaches, assessing their effectiveness as well as in the approval of new therapeutic regimens (Geocze et al., 2010; Oguntibeju, 2012; Balderson et al., 2013; Smit et al., 2015; Etenyi et al., 2018). Strict or near perfect adherence to HAART (≥95%) is also a key determinant in optimal therapeutic outcomes of HAART, with non-adherence to HAART likely to lead to therapeutic failure, immune system deterioration, emergence of resistant strains and sub-optimal drug levels in the blood (Lyimo et al., 2012; Mghamba et al., 2013). This is a concern given still high prevalence rates for HIV and AIDS in sub-Saharan Africa, including South Africa. Published studies have also suggested that HAART potentially improves the HRQoL of patients, contributing to better adherence to HAART (Oguntibeju, 2012). Improved adherence will result in a greater suppression of the viral load and increased HRQoL (Campos et al., 2009). Although PLWHA experience the benefits of long-term use of HAART, various socio-demographic, clinical, psychological and behavioural determinants may negatively impact on their HRQoL (Degroote et al., 2014). On the other hand, greater adherence may lead to increased toxicities, resulting in decreased HRQoL (Mannheimer et al., 2008; Ncama et al., 2008; Airoldi et al., 2010). Tenofovir disoproxil fumarate (TDF) containing regimens for instance are associated with both liver and kidney toxicities and efavirenz has been associated with neuropsychiatric side-effects (Gaida et al., 2016; Kalemeera et al., 2016; Kalemeera et al., 2017; Mataranyika et al., 2017).

Although the initiative to improve the care of patients in the public health system in South Africa through the introduction of National Health Insurance (NHI) (Meyer et al., 2017) has increased HAART coverage; there are still concerns about the provision of clinical care, including issues of adherence to medicines for patients with chronic diseases affecting their HRQoL with or without HIV (Meyer et al., 2017; Rampamba et al., 2017).

It is known that a person's HRQOL is influenced by several determinants, and these determinants individually or simultaneously influence perceived HRQoL over time (Degroote et al., 2014). We are also aware that the relationship between HRQoL and HAART has been identified in high income countries. However, the relationship between HRQoL and long-term adherence to HAART is still unclear, especially in sub-Saharan African countries where the HIV population is very different to Western countries with a greater predominance of women (Gaida et al., 2016; Kalemeera et al., 2016). Furthermore, in these countries there is a high predominace of NCDs with high rates of obesity and hypertension (Cois and Day, 2015; Meyer et al., 2017; Rampamba et al., 2017), and resources are constrained. Consequently, we sought to investigate the relationship between aspects of HRQoL and adherence to HAART over time in South Africa to provide future guidance.

It is known that whilst a number of cross-sectional studies and longitudinal studies from various settings

have indicated a correlation between HRQoL and adherence to HAART (Mannheimer et al., 2005; Burgoyne and Tan, 2008; Ncama et al., 2008; Airoldi et al., 2010; Bello SI and Bello IK, 2013; Cohen et al., 2013; Silva et al., 2014; Vagiri et al., 2014), they have typically failed to establish a relationship over time due to the use of non-randomized convenience samples, insufficient sample size and use of HRQoL instruments not specific to PLWHA. They also failed to portray the HRQoL of patients according to the actual period of time they have been on HAART. We sought to address these deficiencies. Most HRQoL studies conducted globally using the WHOQOL-HIV BREF in PLWHA have also been cross-sectional in nature and predominantly focused on the perceptions about HRQoL or a specific HRQoL domain and adherence to HAART (Belak Kovaĉević et al., 2006; Peltzer and Phaswana-Mafuya, 2008; Fatiregun et al., 2009; Rüütel et al., 2009; Saddki et al., 2009; Hsiung et al., 2011; Imam et al., 2011; Tran, 2012; Bakiono et al., 2014; Vagiri et al., 2014; Tesfay et al., 2015; Surur et al., 2017).

Our study is different as it identified changes in HRQoL over time, and sought to ascertain if there was a relationship between HRQoL and adherence behaviour over time on HAART. Regular and repeated assessment of HRQoL can be used to track changes in functional status over time, especially in chronic illnesses like HIV, as well as to evaluate and monitor treatment effects (Grossman et al., 2003). Although ART can result in better clinical outcomes and potentially improved HRQoL, side effects of ART and change in adherence behaviour can negatively influence HRQoL (Oguntibeju, 2012).

Consequently, to our best knowledge, we believe this is the first longitudinal study to study the relationship between HRQoL and adherence to HAART considering the exact period of time the patient has been on HAART. In view of this, we believe our findings may be of interest not only to key stakeholders in South Africa but also to other sub-Saharan African countries with a high burden of HIV, greater predominance of women with HIV, and struggling to attain or retain universal access to healthcare, given increasing rates of NCDs.

MATERIALS AND METHODS

Study design and sample

This is a quantitative, longitudinal, cohort study conducted at Tshepang ARV Clinic at Dr George Mukhari Academic Hospital and the Tshwaraganang ARV Clinic at Phedisong 4 Community Health Centre between October 2013 and February 2015. Both study sites are in public sector settings situated north of Pretoria, are typical of such facilities throughout South Africa, and provide HAART for PLWHA.

A total of 563 patients (≥18 years) were sampled randomly from the register of patients scheduled for appointments at each of the two study sites on a daily basis and were enrolled within the following strata: i) newly-initiated on HAART; ii) 1 to 12 months on HAART; iii) 12 to 36 months on HAART; and iv) >36 months on HAART.

nQuery Advisor® 6 software was used for the calculation of sample size. Sample size estimates were based on the following assumptions: i) 80% of subjects will report high levels of adherence and 20% will report lower levels of adherence; ii) a two-group t-test with a 0.05 two-sided significance level will have 80% power to detect a difference in means of 6.0 in the HRQoL score between patients with high levels of adherence and those with lower levels of adherence will be clinically meaningful; and iii) an expected drop-out rate of 30%, based on experience from a previous studies conducted at study sites (Kadam and Bhalerao, 2010; Noordzij et al., 2010). Recruited patients were followed-up at 4-monthly intervals for a period of 12 months. At the end of the study period, 431 patients remained in the study and attended all study visits.

Data collection and instruments

Data were collected by four well trained data collectors, two at each clinic, while patients awaited consultation with heath care professionals. Most HRQoL questionnaires specific to HIV and AIDS are long forms with an in-depth analysis of well-being, resulting in PLWHA being burdened with a long and time-consuming QoL assessment. The WHOQOL-HIV BREF was identified as the most suitable HRQoL questionnaire for this study due to its HIV and AIDS specificity, provides a snap shot of HRQoL, has the ability to distinguish between different stages of HIV disease progression, has good psychometric properties and has discriminant validity (Meemon et al., 2016; Tesfaye et al., 2016). The completion and administration process of the questionnaire is simple, providing a quick measure of HRQoL; consequently, making it ideal for administration to PLWHA in busy clinics (O'Connell and Skevington, 2012). In addition, the WHOQOL-HIV BREF had already been translated into different languages and validated in different study and cultural settings across multiple countries (Belak et al., 2006; Peltzer and Phaswana-Mafuya, 2008; Fatiregun et al., 2009; Rüütel et al., 2009; Saddki et al., 2009; Hsiung et al., 2011; Imam et al., 2011; Tran, 2012; Bakiono et al., 2014; Vagiri et al., 2014; Tesfay et al., 2015; Surur et al., 2017).

The WHOQOL-HIV BREF is a multi-dimensional instrument comprising 31-items covering six domains; namely, physical, psychological, level of independence, social relationships, environment, and spirituality/religion/personal beliefs. The WHOQOL-HIV BREF is based on the shorter WHOQOL-BREF which is an abbreviated version of the WHOQOL-100. Each domain has a set of facets and denotes a description of a behaviour, a state of being, a capacity or potential, or a subjective perception or experience (O'Connell and Skevington, 2012). Individual items on the WHOQOL-HIV BREF were rated on a five-point Likert scale, ranging from one (low or negative perception) to five (high or positive perception).

Socio-demographic data, health-related characteristics and adherence data were obtained using an interviewer-administered questionnaire. Questions included in the socio-demographic questionnaire were based on previous studies conducted at Tshepang Clinic (Mapetla, 2007; Engelbrecht, 2010; Meyer et al., 2012), as well as with consideration of the literature (Belak Kovaĉević et al., 2006; Hasanah et al., 2010).

Adherence measures for this study were identified based on adherence measures reported in the literature and those used in previous studies conducted at Tshepang Clinic (Chesney et al., 2000; Mapetla, 2007; Amico et al., 2009; Wilson et al., 2009; Berg et al., 2010; Engelbrecht, 2010; Meyer et al., 2012). Recall on

adherence to HAART over the past 30 days was determined using a self-reported descriptive rating scale with six response options: excellent, very good, good, fair, poor, and very poor. This particular rating scale was used to measure adherence as previous research using cognitive testing indicated that respondents felt more comfortable and confident with words (adjectives and adverbs) compared to numbers. Cognitive estimation of adherence has also matched better with words than with numbers (Wilson et al., 2014; Phillips et al., 2017). Numeric values were assigned to patient-reported adherence ratings based on previous studies conducted at the study sites and published studies on adherence (Mapetla, 2007; Lu et al., 2008; Engelbrecht, 2010; Buscher et al., 2011; Vagiri et al., 2014). This was also supported by our previous study comparing patient-reported adherence ratings with assigned numeric values, which proved ideal in a cross-sectional study conducted with 110 PLWHA at one of the study sites (Tshepang HAART Clinic) (Vagiri et al., 2014). The cognitive process of adherence estimation matched better with the words, and assigned numeric values correlated with patient-reported adherence ratings, which supported the use of the rating scale as a self-report adherence measure in a resource-limited setting (Vagiri et al., 2014).

The data collection instruments were available in English and in Setswana, a local language predominantly spoken in the area where the study was conducted. Forward and back translation of the instruments was performed by two bi-lingual health professionals to provide cross-cultural equivalence. The questionnaires were pilot-tested for feasibility and administered to a sample of 110 PLWHA in an initial cross-sectional study previously conducted at one of the study sites (Tshepang HAART Clinic) (Vagiri et al., 2014). Based on the results of the pilot test, only the adherence questions were amended prior to the commencement of this longitudinal study.

Both the HRQoL and the self-reported adherence rating scale were administered to patients at baseline (Visit 1), and at follow-up visits after 4 months (Visit 2), 8 months (Visit 3) and 12 months (Visit 4). The self-reported adherence rating scale was not administered to patients who were still treatment-naïve at baseline. Socio-demographic and health-related characteristics data were obtained only at baseline. Patients who missed any, or all, of the follow-up study visits over the 12-month study period were excluded from the data analysis as each patient served as their own control.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutions. Permission to conduct the study was obtained from the management of the two study sites and ethical clearance was granted by the Medunsa Campus Research Ethics Committee of the University of Limpopo (MREC/H/160/2008:PG) and Tshwane Research and Ethics Committee (Project: 2012/16).

Data analysis

Data were captured into a Microsoft Office Excel™ spreadsheet, verified for correctness and cleaned, after which it was exported to Statistical Package for the Social Sciences (SPSS) Version 20.0 for analysis. Socio-demographic data, health-related characteristics data and adherence data were summarised and expressed as frequencies and percentages. The patient-reported adherence ratings were also converted to a percentage as follows: excellent (100%), very good (95%), good (90%), fair (80%), poor (70%), and very poor (<70%) in line with previous studies (Mapetla, 2007; Lu et al., 2008; Engelbrecht, 2010; Buscher et al., 2011, Vagiri et al., 2014). Optimal adherence was set at ≥95% in this study (Turner, 2002; WHO, 2006). Patients with adherence reported as 'very good' and 'excellent' on the rating scale were classified as adherent (≥95%) and those with adherence ratings of 'good', 'fair', 'poor' and 'very poor' were classified as non-adherent (<95%) (Feldman et al., 2013).

All HRQoL domain scores, ranging from one (low or negative perception) to five (high or positive perception), were multiplied by four to enable the scores range from four to 20 (All scores are multiplied by 4 so as to be directly comparable with scores derived from the WHOQOL-100). The mean HRQoL domain scores were then averaged to obtain an overall HRQoL score.

An interrupted time-series analysis was conducted to identify the association between adherence and mean HRQoL for the actual duration a patient had been on HAART (Velicer and Fava, 2003). The adherence and HRQoL responses of all patients for the four study visits were pooled to obtain a combined sample (n=1631, excluding 93 treatment-naïve patients). All scores were regrouped into 4-monthly intervals, according to the patient's exact duration on HAART (ranging from 1 to 120 months). Overall mean HRQoL was compared for patients classified as adherent (≥95%) and non-adherent (<95%) for each time interval, using an independent sample *t*-test, with statistical significance set at $p \leq 0.05$. *Cohen's d* test was employed to measure appropriate effect size of mean HRQoL scores between adherent and non-adherent patients.

RESULTS

Removing patients who missed any, or all, of the follow-up study visits over the 12-month study period resulted in a 23.6% (n=132) drop-out rate leaving a final sample size of 431 patients.

The majority of the participants were females (76.1%), completed secondary education (74.2%), lived in a family (87.9%), did not consider themselves ill (88.2%) and attended associations supporting HIV and AIDS (81.9%). More than half of the subjects were middle-aged (62.2%), Single (68.7%), unemployed (56.1%), asymptomatic (60.3%) and reported good health (54.0%). Just over a third of the patients did not have any income (36.4%) and 27.8% reported to be living with other HIV and AIDS patients. The mean age of the sample at baseline was 38.5 years (SD: 8.45) (Table 1).

From Table 2, it is evident that more than three-quarters (76.2%) of patients reported being highly adherent (≥95%) to HAART.

A gradual increase in the proportion of adherent (≥95%) patients was observed over time, from Visit 1 (69.5%) to Visit 4 (81.6%) after 12 months (Figure 1). Based on the self-reported adherence rating scale, all patient groups who reported ≥95% adherence, reported higher overall mean HRQoL compared to those <95% adherent, except for patients newly initiated on HAART (1-4 months) and those 41-44 months on HAART (Figure 2). Relatively low and very similar overall HRQoL was reported by adherent and non-adherent patients within the first 4 months of HAART (15.93 and 15.97

Table 1. Socio-demographic and health status characteristics of the study sample at baseline (n=431).

Socio-demographic and health status characteristics		Frequency (%)
Gender	Male	103 (23.9)
	Female	328 (76.1)
Age (in years)	≥18 - <31	76 (17.6)
	≥31 - <46	268 (62.2)
	≥46	87 (20.2)
Clinical status	Asymptomatic	260 (60.3)
	Symptomatic/AIDS	171 (39.7)
Education	Primary (Grade 0 – 7)	78 (18.1)
	Secondary (Grade 8 – 12)	320 (74.2)
	Tertiary	33 (7.7)
Employment	Unemployed	242 (56.1)
	Employed	189 (43.9)
Marital status	Single	296 (68.7)
	Married	87 (20.2)
	Divorced/Separated/Widowed	48 (11.1)
Income (in ZAR)	None	157 (36.4)
	R1 - R2000	187 (43.4)
	R2001 - R5000	63 (14.6)
	More than R5000	24 (5.6)
Self-rated health status	Good	362 (84.0)
	Neither poor nor good	59 (13.7)
	Poor	10 (2.3)
Consider oneself as ill	Yes	51 (11.8)
	No	380 (88.2)

respectively). This could potentially be explained by patients' clinical HIV status at the start of HAART. Although the overall mean HRQoL for adherent (≥95%) patients was lower than <95% adherent patients in the group 41-44 months on ART, this difference was not statistically significant (p=0.433) (Table 3).

Overall, a statistically significant difference in the mean HRQoL scores of HAART adherent (≥95%) and non-adherent (<95%) patients was observed amongst patients on HAART for the periods 9-28 months, 49-64 months and 81-120 months on treatment (Table 3; Figure 2). The significant differences in mean HRQoL scores between adherent and non-adherent patients was further confirmed by Cohen's d test, with effect sizes ranging from medium to large (Table 3).

DISCUSSION

The high percentage of women in our study confirms other studies showing higher rates of HIV among women in sub-Saharan Africa compared with men, which is different to the characteristics of patients with HIV in high income countries (Gaida et al., 2016; Kalemeera et al., 2016).

Encouragingly, three quarters of the patients (76.3%) in this study rated their adherence as "excellent" or "very good" on the descriptive patient-reported adherence rating scale; while very few patients (0.5%) rated their adherence as "poor" or "very poor". Although excellent adherence of ≥95% is required for HAART, a contributing factor to the appreciable number of patients in this study reporting good adherence could be the introduction of a fixed-dose combination (FDC) containing tenofovir, emtricitabine and efavirenz as a first-line regimen during 2013 by the National Department of Health (NDoH) in South Africa. Fixed-dose combinations are known to reduce pill burden, are convenient to take, and evidently promote adherence

Table 2. Levels of adherence (n=1629).

Adherence rating (%)	No. (%)[a]
Poor (70%)	8 (0.5)[b]
Fair (80%)	31 (1.9)
Good (90%)	347 (21.3)
Very Good (95%)	804 (49.4)
Excellent (100%)	439 (26.9)

[a]93 patients were treatment-naïve at Visit 1 (baseline), therefore could not rate their adherence; [b]Two of the 8 patients reported their adherence as very poor (<70%).

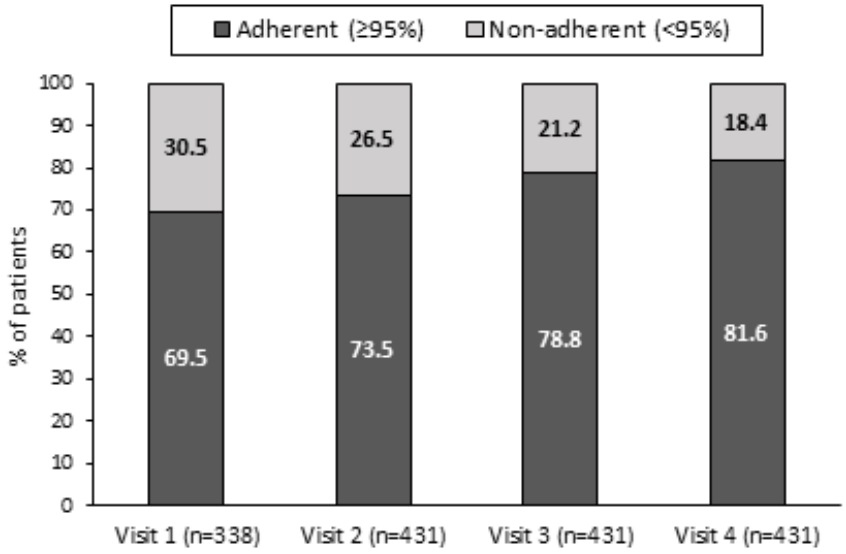

Figure 1. Level of adherence over time at different study visits (n=431).

(Farrel et al., 2013; Feldman et al., 2013; Vrijens et al., 2017). This though needs to be explored further before any definitive statements can be made especially as some of these patients will have co-morbidities increasing their pill burden. In our study, chronic co-morbidities and co-infections were not recorded, yet their treatment may have affected patients' adherence to HAART.

An improvement in HRQoL over time has been elucidated in a number of longitudinal studies; however, the results varied across different research settings. Mannheimer et al. (2005) reported a significant association between adherence and HRQoL in a 12-month prospective, longitudinal study conducted in the USA with 1050 HIV treatment-experienced patients. HRQoL was measured using the SF-12 Health Survey instrument and was administered at baseline, one, four, eight and 12 months respectively. The results described a significant improvement of HRQoL at the first, fourth and twelfth months. Participants who reported 100% adherence to HAART reported significantly higher HRQoL at 12 months compared to those with poorer adherence. As a result, this study also provided evidence that HAART, if taken as prescribed, has a positive effect on QoL similar to our findings (Mannheimer et al., 2008).

Another longitudinal study conducted in Brazil with treatment naïve patients included one baseline interview and three follow-up interviews at the first, fourth and seventh month thereafter. The baseline interview assessed socio-demographic, treatment-related and behavioural characteristics, while follow-up interviews evaluated adherence and HRQoL (assessed using WHOQOL-BREF). The results demonstrated a significant improvement in QoL after four months on HAART. Two-thirds (66.4%) of the patients reported good or very good QoL suggesting an improvement of HRQoL after initiating treatment (Campos et al., 2009). This study supports our study finding that better adherence results in increased QoL.

In our study, patients who reported ≥95% adherence reported better HRQoL compared to patients who reported

Table 3. Comparison of mean HRQoL scores between adherent (≥95%) and non-adherent (<95%) patients and their effect sizes.

Patient group	Adherence rate category	n	Mean HRQoL (SD)	T	p*	D
1-4 months	Adherent (≥95%)	38	15.93 (0.65)	-0.3	0.792	0.06
	Non-adherent (<95%)	58	15.97 (0.68)			
5-8 months	Adherent (≥95%)	54	16.09 (0.67)	0.5	0.594	0.09
	Non-adherent (<95%)	87	16.03 (0.66)			
9-12 months	Adherent (≥95%)	66	16.23 (0.91)	2.1	0.033	0.33
	Non-adherent (<95%)	102	15.94 (0.85)			
13-16 months	Adherent (≥95%)	46	16.46 (1.11)	2.7	0.007	0.53
	Non-adherent (<95%)	66	15.90 (1.01)			
17-20 months	Adherent (≥95%)	41	16.52 (1.21)	3.1	0.003	0.61
	Non-adherent (<95%)	62	15.82 (1.05)			
21-24 months	Adherent (≥95%)	39	16.52 (1.25)	3.2	0.002	0.67
	Non-adherent (<95%)	55	15.72 (1.14)			
25-28 months	Adherent (≥95%)	42	16.51 (1.06)	2.5	0.012	0.51
	Non-adherent (<95%)	65	15.95 (1.12)			
29-32 months	Adherent (≥95%)	38	16.35 (1.43)	1.4	0.162	0.27
	Non-adherent (<95%)	68	16.00 (1.12)			
33-36 months	Adherent (≥95%)	43	16.26 (1.41)	0.7	0.495	0.13
	Non-adherent (<95%)	63	16.10 (1.09)			
37-40 months	Adherent (≥95%)	39	16.29 (1.48)	0.6	0.575	0.12
	Non-adherent (<95%)	52	16.13 (1.19)			
41-44 months	Adherent (≥95%)	27	15.78 (1.92)	-0.8	0.433	0.19
	Non-adherent (<95%)	34	16.08 (1.03)			
45-48 months	Adherent (≥95%)	26	16.33 (1.64)	1.2	0.231	0.33
	Non-adherent (<95%)	26	15.87 (1.06)			
49-52 months	Adherent (≥95%)	17	16.56 (1.88)	2.1	0.041	0.65
	Non-adherent (<95%)	23	15.57 (1.06)			
53-56 months	Adherent (≥95%)	20	16.59 (1.92)	2.2	0.033	0.67
	Non-adherent (<95%)	22	15.53 (1.13)			
57-60 months	Adherent (≥95%)	19	17.04 (1.25)	4.0	0.000	1.25
	Non-adherent (<95%)	22	15.44 (1.30)			
61-64 months	Adherent (≥95%)	13	16.98 (1.28)	2.9	0.008	1.07
	Non-adherent (<95%)	16	15.52 (1.44)			
65-68 months	Adherent (≥95%)	13	16.32 (1.44)	1.3	0.205	0.48
	Non-adherent (<95%)	16	15.63 (1.42)			
69-72 months	Adherent (≥95%)	11	16.22 (1.06)	1.4	0.175	0.53
	Non-adherent (<95%)	20	15.63 (1.17)			
73-76 months	Adherent (≥95%)	15	15.98 (1.43)	0.9	0.396	0.32
	Non-adherent (<95%)	14	15.58 (1.03)			
77-80 months	Adherent (≥95%)	15	15.94 (1.44)	1.1	0.302	0.35
	Non-adherent (<95%)	20	15.46 (1.27)			
81-120 months	Adherent (≥95%)	43	16.48 (1.23)	4.2	0.000	0.79
	Non-adherent (<95%)	75	15.58 (1.04)			
All patient groups	Adherent (≥95%)	704	16.31 (1.26)	7.9	0.000	0.38
	Non-adherent (<95%)	1020	15.87 (1.03)			

*$p<0.05$, Independent sample t-test; SD: Standard deviation; *d*: *Cohen's d* for Independent sample t-test.

<95% over a period of 12 months (Table 2). We know HAART potentially improves HRQoL and contributes to enhanced treatment via better adherence to HAART (Smit et al., 2015; Mataranyika et al., 2018).

This finding was supported by a multi-site cohort study conducted in the USA where PLWHA who had a

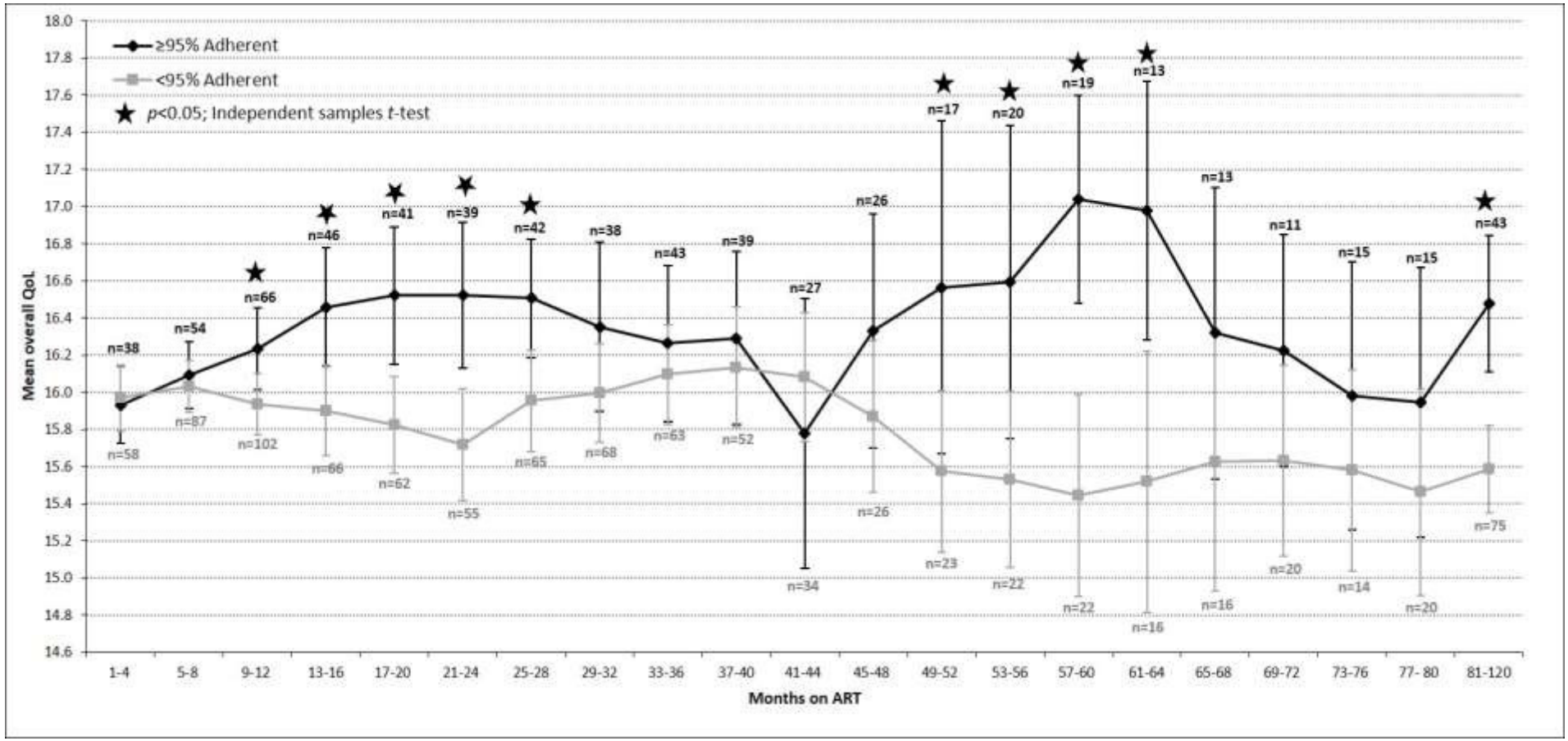

Figure 2. Time series analysis comparing level of adherence and mean HRQoL over time (n=1631).

meaningful, comfortable life, who were well cared for, and who used their time wisely, reported better adherence to their treatment (Liu et al., 2013). In addition, better adherence is known to result in greater suppression of the virus and results in increased HRQoL (Lyimo et al., 2012). This association between adherence to HAART and HRQoL is further confirmed by the results of our time-series analysis (Figure 2). Irrespective of the time on HAART, it was revealed that adherent patients (≥95%) consistently reported better HRQoL compared to the non-adherent patients.

It is recognise though that consideration of the role of social capital in adherence to HAART needs to be better understood in South Africa building on previous research (Binagwaho and Ratnayake, 2009; Jakovljevic and Milovanovic, 2015), and this will be investigated further in future

studies. It is also known that this study had some limitations. Firstly, it was conducted at only two treatment centres, hence the results cannot be generalised to the entire country, although we believe patients attending these two clinics are typical of those attending public health clinics throughout South Africa. Secondly, the drop-out rate over the 12-month follow-up period, as well as recall and social desirability bias due to patient self-report on adherence and HRQoL, could have inflated some of the data. Thirdly, numeric values were assigned to patient-reported adherence ratings, which may have influenced levels of adherence presented; although, this did not have an effect on actual categorisation of adherent (≥95%) and non-adherent patients (<95%) as optimal adherence for this study was set at ≥95% according to WHO adherence guidelines (WHO, 2006). However, despite these limitations, we believe our findings are robust in view of the methodology we employed.

Conclusion

Encouragingly, there were high adherence rates to HAART in this study, with this study establishing a significant relationship between HRQoL and adherence to HAART over time. Adherent patients consistently reported better HRQoL compared to the non-adherers irrespective of the period of time on HAART, underlining the importance of adherence in improving HRQoL in patients with HIV. Adherence to HAART is complex and it is a dynamic and biosocial process influenced by diverse factors influencing HRQoL in a positive or negative manner. As HAART is a lifelong treatment, assessing patients' adherence behaviour and improving adherence will maximise the benefits of HAART and enhance patients' HRQoL. This builds on the South African government's initiatives to improve adherence to HAART. Whilst HAART increases the lifespan of PLWHA, their HRQoL remains a concern. This can be improved with improved adherence. Understanding the social consequences of this disease, and making appropriate clinical interventions, can also improve HRQoL, and we will be exploring this further in future research.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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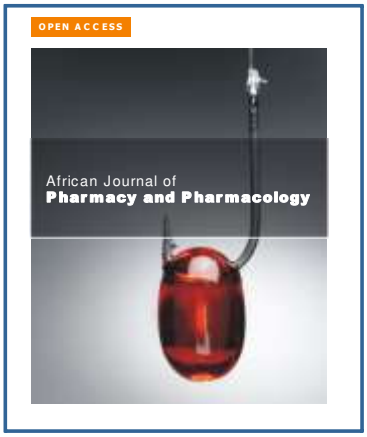

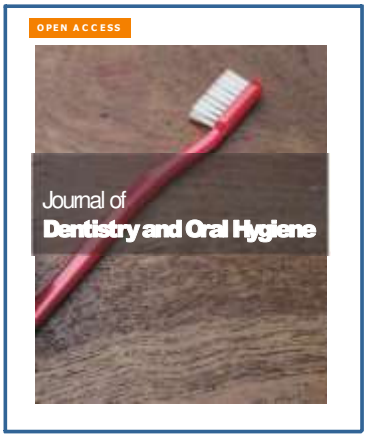

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