Quality of life and associated factors among people receiving second-line anti-retroviral therapy in Johannesburg, South Africa

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Abstract

Background: Studies which examine quality of life (QOL) provide important insights that are needed to understand the impacts of HIV/AIDS anti-retroviral treatment (ART), comorbid conditions and other factors on the daily activities of people living with HIV/AIDS (PLH). This study aimed to determine the inter-relationships between clinical factors, behavioural, socio-demographic variables and QOL among PLH.

Methods: The secondary analysis used data collected from 293 people living with HIV/AIDS (PLH) receiving second-line ART in Johannesburg in a clinical trial which evaluated the non-inferiority of ritonavir-boosted darunavir (DRV/r 400/100 mg) compared to ritonavir-boosted lopinavir (LPV/r) over a 48 week-period. Physical functioning, cognitive and mental QOL were measured using the Aids Clinical Trial Group questionnaire. Exploratory factor analyses were used to examine the structure, the relationships between and the construct validity of QOL items. Structural equation models which tested the a priori-hypothesised inter-relationships between QOL and other variables were estimated and goodness of fit of the models to the data was assessed.

Results: Patients on darunavir presented with lower pill burden. Older patients and women were more likely to report lower QOL scores. Pill burden mediated the effects of age, sex and treatment regimen on physical functioning QOL and adverse effects; the effects of age, sex, treatment regimen and adverse effects on cognitive QOL; and the effects of sex on mental QOL.

Conclusion: QOL among PLH is associated with socio-demographic and clinical factors. Therefore, QOL could be enhanced by considering PLH characteristics, clinical factors such as regimen side-effects profile, management of comorbid conditions and mitigating risks such as potential adverse drug-to-drug interactions among patients on ART.

Keywords: Quality of life, Anti-retroviral treatment, HIV drug effects, South Africa, Darunavir

Introduction

Quality of life (QOL) which encompasses an “individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns” [1], is an important measure in therapeutic research and practice. The concept of QOL is multi-faceted, reflecting...
different dimensions and experiences in a person’s life, such as their psychological, social and physical function. It focuses on assessing functional changes that may occur overtime in various illnesses [2, 3]. Measuring QOL and determining associated factors has become important for understanding patients’ experiences of living with chronic diseases, and how it affects daily activities [3].

Global advancements in the delivery of anti-retroviral therapy (ART) to people living with HIV/AIDS (PLH) has decreased mortality: PLH can live longer, albeit with their QOL negatively impacted by health-challenges related to the clinical manifestation of HIV, the adverse events of long-term exposure to treatment or emerging co-morbidities related to HIV [4–7]. Therefore, measuring QOL and determining associated factors are necessary for understanding impact of disease and targeting interventions that will mitigate the burden on individuals and the health system altogether [6, 8]. Additionally, findings from the study will assist healthcare practitioners and HIV programs to not only monitor the physical well-being of their patients but other QOL domains may be affected such as mental and social well-being [2].

Several studies have investigated worldwide factors that affect QOL among PLH [5, 9, 10]. Previous research has found concomitant medication administered for presence of co-morbidities impact QOL among PLH [11–13]. Co-morbid conditions increase the risk of adverse effects and complex medication regimens administered in attempts to manage these conditions may lead to additive toxicities and further increase adverse events and morbidity [14]. Moreover the compounded HIV-related challenges increase clinic visits and hospitalizations that lead to higher usage of healthcare resources by PLH [6, 15]. Other factors associated with QOL among PLH are behavioural in nature for example adherence to treatment [16, 17] and severe substance abuse [18, 19]. Lastly, biological sex of the patient, stigma and discrimination have also been reported to impact QOL [20, 21].

The QOL in HIV patients initiated on first-line ART varies according to disease severity, demographics and geography/country and for most patients tends to improve after starting ART [5, 22]. Consistent use of ART facilitates viral suppression which in turn improves QOL of PLH. However, sometimes patients develop resistance to treatment, making the virus unsuppressed and continuously replicating [23, 24]. In a study by Torres and colleagues, using the ACTG SF-21 tool, individuals failing first-line ART showed lower QOL in most domains except role function and social function [25]. The literature on first-line failures in South Africa is scanty, yet show that over 2% (which translates to over 10,000 of HIV patients) switch to second-line therapy annually [26].

While previous studies have investigated the factors associated with QOL among PLH, scholars used traditional regression models which are limited in elucidating the inter-relationships among the different factors. However, the application of novel structural equation modelling in understanding QOL allows the critical investigation of the direct and indirect pathways that affect QOL among PLH. This study was conducted to determine the inter-relationships among clinical factors, including severity of adverse events, pill burden (defined as medication taken in addition to the ART regimen) and ART treatment regimen, behavioural and socio-demographic variables and QOL among PLH receiving second-line ART in Johannesburg. Our a priori hypothesis assumed that adverse events [frequency and severity (clinical factor)] impacted on pill burden (clinical factor) and QOL; greater frequency and severity of adverse events increases pill burden (mediator) but would reduce QOL; treatment regimen (clinical factor) could impact on QOL through direct and indirect paths mediated by adverse events and pill burden and that socio-economic status could directly impact on QOL or this relationship could be mediated by substance use (behavioural).

Methodology

Study population: primary study
This secondary analysis used data collected from participants with HIV in a randomized control trial (RCT) conducted by the Wits Reproductive Health and HIV Institute (Wits RHI). The RCT investigated non-inferiority of ritonavir-boosted darunavir (DRV/r 400/100 mg) compared to the current standard second-line therapy ritonavir-boosted lopinavir (LPV/r) among 300 adults, HIV-1 positive patients receiving second-line ART in Johannesburg over 48 weeks (Protocol number: WRHI052). Ethics clearance was obtained from the I Human Research Ethic Committee (Medical) (M181001). A more detailed description on the participant selection criteria and procedures can be found elsewhere [27]. Of the 300 participants, this secondary data analysis included 293. We excluded seven participants due to early withdrawal (before week 48) (n = 4), relocation (n = 1), death (n = 1) and protocol deviation (n = 1).

Data collection and key measures
Variable measurement and recoding
This secondary data analysed was collected through the mentioned primary study whose methods and variable measurement are described in detail elsewhere [27]. The primary study measured explanatory and demographic variables namely age, sex, marital status, education, and employment status. Patient demographic and other details were collected at the screening visit and recorded...
on a screening form. Participants’ second-line therapy was informed by their randomisation to either the lopinavir (5 pills) or the darunavir (3 pills) treatment arm at enrolment visit. Pill burden counts were defined as medication taken additional to ART administered. The medication was taken from a concomitant medication source document that was regularly updated at every study visit. The number of co-medications was counted to give the total number of medications a participant self-administered over 48 weeks. Therefore, the co-medication/pill burden was used as a proxy indicator for co-morbid conditions that patients were facing. Adverse events were recorded at unscheduled and scheduled study visits. The total number of adverse events experienced over the 48 weeks period was categorised based on the Division of AIDS grading table used in the primary study (version 2.0, November 2014) [28] i.e., mild symptoms (causing no or minimal interference with usual social and functional activities), moderate (causing greater than minimal interference with usual social and functional activities), and severe or life-threatening (causing inability to perform basic self-care functions). If a patient presented with more than 1 adverse event, the highest grade was allocated to that patient. The events were then grouped together to form one variable. Data pertaining to alcohol, smoking tobacco, and illicit drug use were also extracted at the screening visit.

The primary study measured QOL using the standard ACTG-SF 21 (601-2) health survey questionnaire and manual administered by a research nurse at enrolment and at 5 follow up visits from Week 4 to Week 48, with Week 48 being the end of study visit (EOS) [29, 30]. In this study, QOL domains at Week 48 were used as the study outcomes. The original questionnaire consisted of eight domains and 17 questions which focused on general health perceptions, physical function, role function, pain, social function, mental health, energy, and cognitive function (Additional file 1: Appendix A). Table 1 shows how measured items in each domain were recoded by summing responses to create sub-domain scores before transforming each score to a scale ranging from 0 to 100 (Table 1). Higher transformed scores on the scales indicated better health.

### Data processing and analysis

All data were imported into STATA version 15® for cleaning and analysis. We conducted descriptive statistics to obtain frequency distributions of socio-demographic and clinical factors aggregated by sex. We tested the hypothesis of differences using Pearson’s Chi-Squared and Fisher’s Exact. The ACTG SF-21 questionnaire administered in the primary study included modifications that deviated from the validated tool as there was a reduction in the number of items scales used to comprehensively assess QOL dimensions. This resulted in the authors conducting an exploratory analysis to examine the structure and the relationship between items, as well as evaluate the construct validity of the item scales. A confirmatory factor analysis on measurement models was conducted by the authors, to confirm whether some of the items that were dropped in the EFA would load in the other factors. Additionally, we were interested in demonstrating fit indices for comparative purposes and to examine modification indices to further elaborate on the model. We acknowledge the use of both EFA and CFA in the same sample is contested and a subject of much ongoing expert

### Table 1 Description and transformation of the ACTG QOL domains

| Domains                  | Items | Item example                                                                 | Scale                          | Transformation equation          |
|--------------------------|-------|-----------------------------------------------------------------------------|-------------------------------|---------------------------------|
| General health perception | 1     | In general, would you say your health is?                                  | 1–5 (poor = 1 to excellent = 5) | \((100/5 - 1)\)* (general health perception raw score − 3) |
| Pain                     | 1     | How much bodily pain have you had in the past 4 weeks?                     | 1–5 (none = 1 to severe = 5)   | \((100/6 - 1)\)* (pain − 2)       |
| Physical function        | 3     | Does your health limit you are walking uphill/going stairs                 | 1–3 (yes limited a lot = 1; not limited at all = 3) | \((100/9 - 3)\)* (physical function raw score − 4) |
| Role function            | 2     | Does your health keep you from getting a job?                             | 1–3 (yes, all the time = 1; none of the time = 3) | \((100/9 - 3)\)* (role function raw score − 2) |
| Social function          | 2     | Has your physical or emotional health interfered with social activities? | 1–5 (not at all = 1, extremely = 5) | \((100/8 - 2)\)* (social function raw score − 2) |
| Cognitive function       | 3     | Difficulty reasoning or solving problems                                   | 1–3 (all of the time = 1; none of the time = 3) | \((100/9 - 3)\)* (cognitive function raw score − 3) |
| Mental Health            | 3     | In the past 4 weeks, have you felt downhearted and blue?                  | 1–3 (all of the time = 1; none of the time = 3) | \((100/(18 – 3))\)* (mental health raw score − 3) |
| Energy/fatigue           | 2     | In the past 4 weeks, how often have you felt tired?                        | 1–3 (all of the time = 1; none of the time = 3) | \((100/(6 – 2))\)* (energy/fatigue raw score − 2) |
debate in an article by Hurley et al. [31] particularly when a small sample size is used. Structural equation modelling (SEM) analysis guided by the pre-specified a priori framework, was conducted (Fig. 1). It assumed that (a) socio-economic status (SES) directly impacts physical, mental or cognitive QOL and indirectly through substance abuse; (b) adverse effects directly impact physical, mental or cognitive QOL and indirectly through pill burden; (c) treatment regimen directly impacts physical, mental or cognitive QOL and indirectly through pill burden or adverse events; (d) sex directly impacts physical, mental and cognitive QOL and indirectly through pill burden or adverse events or substance abuse; (e) age directly impacts physical, mental and cognitive QOL and indirectly through pill burden; (f) severity of adverse events directly impacts physical, mental and cognitive QOL and indirectly through pill burden; (g) pill burden directly impacts physical, mental and cognitive QOL and indirectly through adverse events or their severity. The SEM were estimated separately for the three domains. SEM models were estimated and modified by removing all statistically insignificant paths and applying modification indices where they improved model fit as shown in Additional file 1: Appendix B: Table S1 [32, p. 34].

Results
Socio-demographic and behavioural and clinical characteristics of PLH in the study
Sixty-eight percent (199/293) of the sample were women and participants were predominantly of Black African race (99%, 291/293), 92% (270/293) attained secondary education, 75% (220/293) were employed and 56% (164/293) were unmarried. Significantly higher proportions of women attained secondary education, however higher proportions of men were employed and were married, smoked, and consumed alcohol compared to women. There were no significant differences in the proportions of men and women by the different clinical characteristics (Table 2).

Exploratory factor analysis (EFA) and confirmatory factor analysis (CFA)
The factor analysis was conducted with the iterated principal axes option and retained three factors [factor (3) option]. Kaiser’s criteria were used to extract factors with eigenvalues greater than 1 as shown in Table 3 and scree plot in Additional file 1: Appendix C: Fig. S2 [35]. In the factor analysis with varimax rotation (minimal loading of 0.3), the 17 items covered 3 discrete dimensions as shown in Additional file 1: Appendix D: Table S2. Eleven items loaded onto Factor 1 and these were items of general health perception, pain, physical function, role function, social function and energy function. Factors 2 and 3 were defined by items measuring the cognitive and mental dimensions respectively. Therefore, the domains identified were physical/functional quality, mental and cognitive. In conducting the confirmatory factor analysis,

![Fig. 1](image-url)  
**Fig. 1** Conceptual model of interrelationships between factors affecting QOL among PLWHA
latent variables were created using factors associated with the specified subset of items during exploratory factor analysis. We used the measurement component of the output to verify that the observed variables load reasonably onto their corresponding latent constructs. In the fourth factor that was dropped, two energy items
had loaded and whilst creating the latent variables, collapsed the energy items with physical/functional items and they loaded successfully and items were not lost (Additional file 1: Appendix D). This analysis showed evidence of only one factor between the energy items and the physical/functional items [32, p. 32]. Reasonably, how energetic/fatigued you feel often affects your physical and functional capability. However, collapsing the mental and the cognitive with the physical/functional items was unsuccessful. Latent analysis resulted in three factors confirming the mental, cognitive, and physical/functional domains therefore they were analysed as three separate latent variables.

**SEM and pathway analysis of physical and functional QOL**

Figure 2 shows the final SEM path model that depicts the inter-relationships between variables and physical and functional QOL. Table 4 shows the statistical output of the model. Age, sex, and treatment regimen had in-direct effects on physical and functional QOL which were mediated by pill burden. The model had a moderate fit, as the likelihood ratio test did not meet the criteria for a well-fitted model. However, we proceeded based on the chi squared statistic having no longer completely relied upon as a bases of rejection or acceptance as it is shown to very sensitive to sample size and normality of data [33, 36, 37]. (CFI 0.982; TLI 0.980 RMSEA 0.038; RMSR 0.052 and LR chi2 0.002) (Table 4, Fig. 2).

**SE M and pathway analysis for cognitive QOL**

Figure 3 shows the final SEM path model that depicts the inter-relationships between variables and cognitive QOL. Table 5 shows the statistical output of the model. Age and treatment regimen had direct effects on cognitive QOL, and indirect effects mediated by pill burden. Pill burden also mediated the relationships of sex and severity of adverse effects on cognitive QOL. The model had a good fit as all the criteria for a well-fitted model were met (CFI 0.992; TLI 0.987; RMSEA 0.025; RMSR 0.034 and LR chi2 0.235).

**SEM and pathway analysis of mental QOL**

Figure 4 shows the final SEM path model that depicts the inter-relationships between variables and mental QOL. Table 6 shows the statistical output of the model. Severity of adverse events had a direct effect on Mental QOL. Sex had an indirect effect on mental QOL and

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**Table 3 Exploratory factor analysis**

| Factor      | Eigenvalues |
|-------------|-------------|
| Factor 1    | 6.208       |
| Factor 2    | 2.271       |
| Factor 3    | 1.310       |
| Factor 4 (dropped) | 0.7475   |

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**Fig. 2** Final model of factors influencing physical and functional QOL among PLH receiving second-line ART in Johannesburg
Table 4  Statistically significant latent structure, direct and indirect effects on physical QOL

| Latent variables                                      | Estimate | STD  | SE   | P-value |
|-------------------------------------------------------|----------|------|------|---------|
| General health perception → physical/functional QOL    | 1.220    | 0.452| 0.148| <0.001  |
| Pain → physical/functional QOL                         | 1.613    | 0.438| 0.206| <0.001  |
| Vigorous activities limited → physical/functional QOL  | 1        | 0.931|      |         |
| Normal activities limited → physical/functional QOL    | 0.953    | 0.925| 0.034| <0.001  |
| Daily activities limited → physical/functional QOL     | 0.659    | 0.836| 0.032| <0.001  |
| Role function limited → physical/functional QOL        | 0.959    | 0.974| 0.028| <0.001  |
| Role function at work → physical/functional QOL        | 1.008    | 0.999| 0.025| <0.001  |
| Interference of normal social activities → physical/functional QOL | 0.968 | 0.423| 0.120| <0.001  |
| Family activities limited → physical/functional QOL    | 0.525    | 0.413| 0.069| <0.001  |
| Fatigue → physical/functional QOL                      | 0.515    | 0.295| 0.114| <0.001  |
| Vitality → physical/functional QOL                     | 0.551    | 0.262| 0.105| <0.001  |
| Direct effects                                         |          |      |      |         |
| Sex → alcohol use                                      | 0.124    | 0.118| 0.061| 0.044   |
| Sex → adverse events                                   | 0.300    | 0.130| 0.122| 0.014   |
| Pill burden → physical/functional QOL                  | −0.020   | −0.219| 0.006| 0.001   |
| Age → pill burden                                      | 0.047    | 0.156| 0.020| 0.002   |
| Treatment → pill burden                                | 0.722    | 0.122| 0.311| 0.029   |
| Sex → pill burden                                      | 1.298    | 0.185| 0.401| 0.001   |
| Pill burden → severity of adverse events               | 0.059    | 0.356| 0.011| <0.001  |
| Indirect effects                                       |          |      |      |         |
| Age → pill burden → severity of adverse events         | 0.003    | 0.056| 0.001| 0.030   |
| Treatment regimen → pill burden → severity of adverse events | 0.043 | 0.043| 0.020| 0.032   |
| Sex → pill burden → severity of adverse events        | 0.077    | 0.066| 0.028| 0.006   |
| Age → pill burden → physical/functional QOL            | −0.0009  | −0.063| 0.004| 0.054   |
| Treatment regimen → pill burden → physical/functional QOL | −0.014 | −0.097| 0.007| 0.055   |
| Sex → pill burden → physical/functional QOL            | −0.025   | −0.034| 0.011| 0.019   |
| Correlations                                           |          |      |      |         |
| Number of adverse events ↔ severity of adverse events  | 0.325    | 0.537| 0.040| <0.001  |
| Number of adverse events ↔ pill burden                 | 1.351    | 0.513| 0.210| <0.001  |

Fig. 3  Final model of factors influencing cognitive QOL among PLH receiving second-line ART in Johannesburg
### Table 5  Statistically significant latent structure, direct and indirect effects on cognitive QOL

| Latent variables                      | Estimate | STD  | SE   | P-value |
|---------------------------------------|----------|------|------|---------|
| Reasoning → cognitive QOL             | 1        | 0.718|      |         |
| Attention → cognitive QOL             | 1.902    | 0.900| 0.180| 0.000   |
| Forgetfulness → cognitive QOL         | 1.937    | 0.635| 0.196| 0.000   |
| **Direct effects**                    |          |      |      |         |
| Pill burden → cognitive QOL           | -0.004   | -0.177| 0.001| 0.005   |
| Age → cognitive QOL                   | -0.001   | -0.133| 0.006| 0.046   |
| Treatment regimen → cognitive QOL     | 0.023    | 0.157| 0.009| 0.013   |
| Age → pill burden                     | 0.077    | 0.192| 0.019| 0.000   |
| Treatment regimen → pill burden       | 0.830    | 0.130| 0.320| 0.008   |
| Severity of adverse events → pill burden | 1.775   | 0.349| 0.266| 0.000   |
| Sex → pill burden                     | 1.080    | 0.158| 0.363| 0.003   |
| Sex → adverse events                  | 0.302    | 0.107| 0.124| 0.015   |
| Severity of adverse events → adverse events | 1.349   | 0.642| 0.093| 0.000   |
| Sex → alcohol                         | 0.110    | 0.114| 0.056| 0.049   |
| **Indirect effects**                  |          |      |      |         |
| Age → pill burden → cognitive QOL     | -0.0003  | -0.015| 0.0001| 0.023  |
| Treatment regimen → pill burden → cognitive QOL | -0.003 | -0.047| 0.002| 0.050   |
| Sex → Pill burden → cognitive QOL     | -0.004   | -0.019| 0.002| 0.042   |
| Severity of adverse events → pill burden → cognitive QOL | -0.007 | -0.005| 0.003| 0.010   |
| **Correlations**                      |          |      |      |         |
| Number of adverse events ↔ pill burden | 1.176   | 0.419| 0.258| 0.000   |

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**Fig. 4** Final model of factors influencing mental QOL among PLH receiving second-line ART in Johannesburg
was mediated by adverse events and pill burden. Age and treatment regimen had indirect effects on Mental QOL and were mediated by pill burden. The model had a good fit as all the criteria for a well-fitted model were met (CFI 1.000; TLI 1.008; RMSEA 0.000; RMSR 0.034 and LR chi2 0.673).

**Table 6** Statistically significant latent structure, direct and indirect effects on Mental QOL

| Latent variables                                      | Estimate | STD | SE  | P-value |
|-------------------------------------------------------|----------|-----|-----|---------|
| Serenity → mental QOL                                  | 1        | 0.912 |     |         |
| Despondent → mental QOL                               | 0.788    | 0.815 | 0.042 | <0.001 |
| Generally happy → mental QOL                          | 1.027    | 0.977 | 0.042 | <0.001 |
| **Direct effects**                                     |          |     |     |         |
| Sex → alcohol use                                      | 0.124    | 0.118 | 0.061 | 0.044   |
| Sex → adverse events                                   | 0.262    | 0.132 | 0.203 | 0.022   |
| Pill burden → mental QOL                               | −0.028   | −0.221 | 0.010 | 0.010   |
| Severity of adverse events → mental QOL                | −0.111   | −0.155 | 0.056 | 0.019   |
| Adverse events → mental QOL                            | 0.074    | 0.189 | 0.035 | 0.020   |
| Age → pill burden                                      | 0.049    | 0.161 | 0.020 | 0.014   |
| Treatment → pill burden                                | 0.682    | 0.118 | 0.313 | 0.029   |
| Sex → pill burden                                      | 1.300    | 0.184 | 0.402 | 0.001   |
| Pill burden → severity of adverse events               | 0.059    | 0.356 | 0.011 | <0.000  |
| **Indirect effects**                                   |          |     |     |         |
| Age → pill burden → mental QOL                         | −0.001   | −0.060 | 0.0009 | 0.072 |
| Treatment regimen → pill burden → mental QOL           | −0.021   | −0.103 | 0.012 | 0.092   |
| Sex → pill burden → mental QOL                         | −0.287   | −0.037 | 0.141 | 0.041   |
| Sex → adverse events → mental QOL                      | 0.014    | 0.025 | 0.018 | 0.435   |
| Pill burden → severity of adverse events → mental QOL  | −0.014   | −0.201 | 0.010 | 0.215   |
| **Correlations**                                       |          |     |     |         |
| Number of adverse events ↔ severity of adverse events   | 0.326    | 0.539 | 0.040 | <0.001  |
| Number of adverse events ↔ pill burden                 | 1.341    | 0.510 | 0.209 | <0.001  |

**Discussion**

Using 48-week data from an RCT, this study aimed to determine the inter-relationships between clinical factors, behavioural, socio-demographic variables and QOL among PLH receiving second-line ART. Confirmatory factor analysis yielded only three distinct domains: (a) namely physical and functional, (b) mental and, (c) cognitive, as opposed to the standard eight QOL domains. Socio-demographic factors of age and sex indirectly impacted on QOL. Treatment regimen, pill burden and severity of adverse events (all clinical factors) were important mediators, each of which differentially impacted on the different QOL domains.

PLH on lopinavir reported higher cognitive QOL compared to those on darunavir but there were no significant differences between the treatment groups on physical function and mental QOL. There is strong supportive evidence that darunavir has sustained high rates of viral suppression alongside a better side effect profile i.e., better metabolic profile, and lower impact on lipids [38]. In contrast, there have been studies that show that patients on lopinavir have commonly reported metabolic concerns [39–41]. Gupta et al., in a study observing the effect of lopinavir on mice, reported that these metabolic abnormalities largely contributed to decreases in cognitive function [40]. However, the relevance of this study to humans is currently unknown.

Treatment regimen was associated with pill burden but did not have effects on adverse effects—although pill burden covaried with adverse effects. The co-relations of pill burden and adverse events are consistent with existing literature [14]. Previous research found that treatment of adverse events secondary to ART increases pill burden [14, 42, 43]. Furthermore, since darunavir has lower dosage compared to lopinavir it is more tolerable and safer [39, 44]. This suggests a lower incidence of adverse events and consequently, less medication required to treat them. The CASTLE study in the United States reported that patients on darunavir had less gastrointestinal adverse events compared to patients on lopinavir [45]. However, in our study, we did not find an association between treatment regimen and adverse effects and could be a result of smaller sample size as compared to the CASTLE study.
Pill burden mediated the effects of age, sex, and treatment regimen on all three QOL domains. Increase in age was associated with increased pill burden and decreased QOL. The direct effects of age on pill burden and ultimately reduced QOL can be explained by the expected higher prevalence of co-morbidities among older PLH which in turn increases the number of medications, or pill burden, ultimately impacting on QOL [46]. In other studies, long-term exposure to treatment has been linked with increasing pill burden among older patients [42].

Sex impacted on QOL, but these relationships were influenced by clinical and behavioural factors. Women reported a higher number and severity of adverse events, higher pill burden and lower scores in all three QOL domains compared to men. This is consistent with Pereira et al.'s study which found that the incidence of HIV-related co-morbidities and associated pill burden was higher amongst women [3]. Moreover, the high number of adverse events reported amongst women had an unexpected positive association with Mental QOL scores. The findings of this current study do not support previous research [3, 47]. Wouters et al. conducted a structural equation model in South Africans on long-term changes in the physical and emotional QOL of patients on ART and reported that adverse events were negatively associated with emotional QOL [47]. It is difficult to explain this relationship between adverse events and mental QOL, however, it is possible that the response and care that a study participant receives in the event of an adverse effect, may paradoxically contribute positively to their mental QOL. This would mean that, in a study setting, a patient may feel more valued and supported, and as a consequence this would impact positively on their mental well-being.

Sex also had indirect impacts on QOL that were mediated by alcohol or substance use. Male PLH were more likely to engage in alcohol or substance use which lowered QOL. Previous studies have shown that alcohol (ab)use is associated with aggravating co-morbidities, delayed initiation to ART, adherence difficulties and decreased QOL [48, 49].

This study shows that a reduction in QOL may result from a myriad of factors including age, sex, HIV treatment, and pill burden which covary with adverse events and behavioural factors. These factors must be considered when reviewing treatment options and developing medication regimens. The public health implications of this study's findings should be contemplated because as PLH age, the impact of co-morbidities and pill burden as it related to QOL becomes compelling.

This study has several limitations. Firstly, the confirmatory analysis confirmed that data only loaded onto three QOL domains instead of the eight expected domains. It is possible that this could be the result of the primary study's used of a shorter version/fewer items of the ACTG SF-21 questionnaire instead of the full scale. The loading of data onto only three QOL domains limits the study's comparability to studies that used the full scale and eight QOL domains. Considering that the primary study was an open label RCT. There was potential for measurement biases including response bias i.e., a tendency for patients to report symptoms in a way they think is expected; as well as interviewer bias where a research assistants'/nurses' knowledge may influence the structure and manner with which questions are administered and may subtly influence responses.

The sample is a volunteer sample within a clinical trial setting therefore the external validity of the results is limited. The number of ART pills were not included as part of the pill burden but was adequately adjusted for in the SEM analysis through the inclusion of regimen as a variable. Lastly, as a secondary study there are limitations due to the reliance on only those variables collected as part of the primary study. Variables which may be important in understanding QOL for example psycho-social factors, family support, level of health education, stigma, and history of ART including time on first-line treatment, adherence data and frequency/dosage of alcohol and tobacco use were not measured therefore are not considered in analyses.

**Conclusions**

Our study showed that socio-demographic and clinical factors affect QOL among PLH in a South African trial setting. QOL was lower amongst participants with a higher pill burden, females and older age group. This study has implications for HIV management. It points to a need for considering the risk/benefit ratio of medications before initiating them. Furthermore, this study revealed the impact of co-morbidities and pill burden amongst the older participants with HIV, revealing the importance of guided functional and public health services that need to be tailored for the needs of the aging HIV population. The study supports the evidence that darunavir has a better side effects profile and should be considered when switching to second line therapy to improve QOL.

Females report a higher number of pill burden and adverse events as compared to males, as a result, are vulnerable in experiencing lower mental, physical and cognitive QOL. Therefore, to improve QOL of PLH, gender differences should be acknowledged.
Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-022-07429-9.

Additional file 1: Appendix A. QOL questionnaire. Appendix B: Table S1. Model fit before and after Modification Indices (MI). Appendix C: Figure S1. Eigenvalues Scree Plot. Appendix D: Table S2. Exploratory standardized factor loadings.

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Author contributions

The study was conceived by NOM, NC, MM and GA. NOM performed the data analyses with inputs from NC, MM and GA. NOM drafted the paper. NOM, MM and SL edited the paper. All authors read and approved the final manuscript.

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Availability of data and materials

The data that support the findings of this study are available from Ezintsha but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Ezintsha.

Declarations

Ethics approval and consent to participate

The primary study was approved by the drug regulator (the South African Health Products Regulatory Authority), local research authority (Johannesburg Health District Research Committee), and the local institutional review board (University of the Witwatersrand Human Research Ethics Committee), and overseen by an independent data safety monitoring board (DSMB) (1507058). This trial is registered with ClinicalTrials.gov, number NCT02671383, confirming that all experiments were performed in accordance with relevant South African regulatory guidelines and regulations. All participants provided written informed consent before the study. Ethical clearance was obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) for the secondary data analysis (M181001). All participants provided written informed consent before study commencement.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. WHO. Measuring quality of life. WHO-QOL. 1997. http://www.who.int/mental_health/media/68.pdf. Accessed 21 May 2015.
2. Mamo G, Chelkeba L, Chanie T. Health-related quality of life among people living with human immunodeficiency virus on highly active antiretroviral therapy in Ethiopia: PROQOL-HIV based survey Tsegaye Melaku.

Patient Relat Outcome Meas. 2020. https://doi.org/10.2147/PROM.S239429.
3. Pereira M, Canavarro MC. Gender and age differences in quality of life and the impact of psychopathological symptoms among HIV-infected patients. AIDS Behav. 2011;15(6):1857–69. https://doi.org/10.1007/s10461-011-9928-8.
4. Kharsany ABM, Karim QA. HIV infection and AIDS in sub-Saharan Africa: current status, challenges and opportunities. Open AIDS J. 2016;10(1):34–48. https://doi.org/10.2174/18746360166101000134.
5. Mutabazi-Mwesigire D, Katamba A, Martin F, Seeley J, Wu AW. Factors that affect quality of life among people living with HIV attending an urban clinic in Uganda: a cohort study. PLoS ONE. 2015;10(6):e0126810. https://doi.org/10.1371/journal.pone.0126810.
6. Arjun BY, Unnikrishnan B, Ramapurnam JT, Thapar R, Mithra P, Kumar N, et al. Factors influencing quality of life among people living with HIV in coastal South India. J Int Assoc Provid AIDS Care. 2017;16(5):247–53. https://doi.org/10.1080/17512433.2017.1377639.
7. Este J, Cihlar T. Current status and challenges of antiretroviral research and therapy. Antivir Res. 2010;85(1):25–33. https://doi.org/10.1016/j.antiviral.2009.10.007.
8. Jagannath V, Unnikrishnan B, Hegde S, Ramapurnam JT, Rao S, Achappa B, et al. Association of depression with social support and selfesteem among HIV positives. Asian J Psychiatry. 2011;4(4):288–92. https://doi.org/10.1016/j.ajp.2011.10.006.
9. Bujinirwe F, Tisch DJ, King CH, Arts EJ, Debanne SM, Sethi AK. Quality of life and social support among patients receiving antiretroviral therapy in Western Uganda. AIDS Care. 2009;21(3):271–9. https://doi.org/10.1080/09540120802241863.
10. Mafrikureva N, Dananjai B, Postma MJ, Van HM, Khoza S. Health-related quality of life in HIV/AIDS patients on antiretroviral therapy at a tertiary care facility in Zimbabwe: AIDS Care. 2016;28(7):904–12. https://doi.org/10.1080/09540121.2016.1173639.
11. Degroote S, Vogelaers DP, Vermeir P, Mariman A, De Rick A, Van Der Gucht B, et al. Socio-economic, behavioural, (neuro)psychological and clinical determinants of HRQoL in people living with HIV in Belgium: a pilot study. J Int AIDS Soc. 2013;16(1):18643. https://doi.org/10.7448/IAS.16.1.18643.
12. Glass TR, De GS, Weber R, Vernazza PL, Rickenbach M, Furrer H, et al. Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients the Swiss HIV cohort study. J AIDS. 2006;41(3):385–92. https://doi.org/10.1097/00018637.95301.52.
13. Sosoin M, Stanaway F, Mayanja HK, Namuleme T, Cumming R, Kyalimpa JL, et al. Polypharmacy among HIV positive older adults on anti-retroviral therapy attending an urban clinic in Uganda: BMC Geriatr. 2018;18:125. https://doi.org/10.1186/s12877-018-0817-0.
14. Chary A, Nguyen NN, Maiton KHM. A review of drug-drug interactions in older HIV-infected patients. Expert Rev Clin Pharmacol. 2017;10(12):1329–52. https://doi.org/10.1080/17512433.2017.1377610.
15. Cleary SM, McIntyre D, Bouille AM. The cost-effectiveness of antiretroviral treatment in Khayelitsha, South Africa—a primary data analysis. Cost Eff Resour Alloc. 2006;4:1–14. https://doi.org/10.1186/1475-7547-4-20.
16. Silva ACDO, Reis RK, Nogueira JA, Gir E. Quality of life, clinical characteristics and treatment adherence of people living with HIV/AIDS. Rev Lat Am Enfermagem. 2014;22(6):994–1000. https://doi.org/10.1590/0104-1169.3534.2014.
17. Lužcůvčyńska A, Sarkar Y, Knoll N. Received social support, self-efficacy, and finding benefits in disease as predictors of physical functioning and adherence to antiretroviral therapy. Patient Educ Couns. 2007;66(1):37–42. https://doi.org/10.1016/j.pec.2006.10.002.
18. Połcheln KL, Polcheln KG, Neupane SR. Harmful alcohol drinking among HIV-positive people in Nepal: an overlooked threat to anti-retroviral therapy adherence and health-related quality of life to threat to anti-retroviral therapy adherence and health-related quality of life. Glob Health Action. 2018;11(1):1441783. https://doi.org/10.1080/16549716.2018.1441783.
19. Levi-minzia MA, Suratt HL. HIV stigma among substance abusing people living with HIV/AIDS: implications for HIV therapy. AIDS Patient Care STDs. 2014;28(8):442–51. https://doi.org/10.1089/apc.2014.0076.
20. Earnshaw VA. Stigma, discrimination and living with HIV/AIDS. Dordrecht: Springer; 2013. p. 23–38. https://doi.org/10.1007/978-94-007-6534-1.
21. Gebremichael DY, Hadush KD, Kebede EM, Zegeye RT. Gender difference in health related quality of life and associated factors among people...
22. Choi SW, Podrabsky T, Mckinney N, Schalet BD, Cook KF, Cella D, et al. Fast, convenient online submission • Thorough peer review by experienced researchers in your field • Maximum visibility for your research: over 100M website views per year

23. Marins JR, Jamal LF, Chen SY, Barros MB, Hudes ES, Barbosa AA, Chequer P, Teixeira PRHN. Dramatic improvement in survival among adult Brazilian AIDS patients. AIDS. 2003;17(11):1675–82.

24. Burgoine RW, Tan DHS. Prolongation and quality of life for HIV-infected adults treated with highly active antiretroviral therapy (HAART): a balancing act. J Antimicrob Chemother. 2008;61:469–73.

25. Torres TS, Harrison LJ, LA RAM, Cardoso SW, Zheng L, Ngongondo M, et al. Quality of life improvement in resource-limited settings after one year of second-line antiretroviral therapy use among adult men and women. AIDS. 2017;32(5):583–93.

26. Keiser O, Tveta H, Boulle A, Braitsch P, Schechter M, Brinkhof MWG, Dabis F, Tubo S, Sprinz E, Pujades-Rodríguez M, Calmy A, Kumarasamy N, Nash D, Jahn A, Macphail P, Luthfy R, Wood R, Egger M. Switching to second-line antiretroviral therapy in resource-limited settings: comparison of programmes with and without viral load monitoring. AIDS. 2009;23(14):1867–74. https://doi.org/10.1097/QAD.0b013e32823e05b2.

27. Venter WDF, Mootoomoese M, Sokhela S, Serenata C, Akpomieemie G, Qavi A, et al. Low-dose ritonavir-boosted darunavir once daily versus ritonavir-boosted lopinavir for participants with less than 50 HIV RNA copies per mL (WRHI 052): a randomised, open-label, phase 3, non-inferiority trial. Lancet HIV. 2019. https://doi.org/10.1016/S2352‑3018(19)30081‑5.

28. Group ACT. Division of AIDS table for grading the severity of adult and pediatric adverse events . . . Allergy Infect Dis Div AIDS. 2004;(August):1–21.

29. Wu AW. ACTG QOL 601–602 health survey manual: adult AIDS Clin Trials Gr. 1996.

30. Saberi P, Neelands TB, Vittinghoff E, Johnson MO, Chesney M, Cohn SE. Barriers to antiretroviral therapy adherence and plasma HIV RNA suppression among AIDS clinical trials group study participants. AIDS Patient Care STDS. 2015;29(3):111–6. https://doi.org/10.1089/apc.2014.0255.

31. Hurley AE, Scandura TA, Schilder CA, Brannick MT, Seers A, Vandenberg RJ, et al. Exploratory and confirmatory factor analysis: guidelines, issues, and alternatives. J Organ Behav. 1997;18(6):667–83.

32. Harrington D. Confirmatory factor analysis. Pocket guides to social work. Oxford: Oxford University Press; 2009.

33. Schermelleh-Engel K, Moosbrugger H, Müller H. Evaluating the fit of structural equation models: tests of significance and descriptive goodness-of-fit measures. Methods Psychol Res Online. 2003;8(2):23–74.

34. Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equ Model. 1999;6(1):1–55.

35. Kaiser HF. The application of electronic computers to factor analysis. Educ Psychol Meas. 1960;20:141–51.

36. Vandenberg RJ. Statistical and methodological myths and urban legends. Organ Res Methods. 2006;9(2):194–201.

37. Bücher A, Dette H. Assessing model fit in structural equation modeling using appropriate test statistics. J Multivar Anal. 2010;101(3):749–63. https://doi.org/10.1016/j.jmva.2009.09.014.

38. Gakhar H, Kamali A, Holodniy M. Health-related quality of life assessment after antiretroviral therapy: a review of the literature. Drugs. 2013;73(7):651–72.

39. Hawkins T. Understanding and managing the adverse effects of antiretroviral therapy. Antivir Res. 2010;85:201–9.

40. Gupta S, Knight AG, Loasso BY, et al. Brain injury caused by HIV protease inhibitors: role of lipodystrophy and insulin resistance. Antivir Res. 2012;95:19–29.

41. Oguntibeju OJ. Quality of life of people living with HIV and AIDS and antiretroviral therapy. HIV/AIDS Res Palliat Care. 2012;4:117–24.

42. Marzolini C, Back D, Weber R, Furrer H, Cavassini M, Calmy A, et al. Ageing with HIV: medication use and risk for potential drug–drug interactions. J Antimicrob Chemother. 2011;66:2107–11.

43. Marzolini C, Elzi L, Gibbons S, Weber R, Lux C, Furrer H, et al. Prevalence of comedication and effect of potential drug–drug interactions in the Swiss HIV cohort study. Antivir Ther. 2010;15:413–23.

44. Mills AM, Nelson M, Jayaweera D, Ruxurungtham K, Cassetti I, Girard P-M, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. AIDS. 2009;23(13):1679–88.

45. Molina J-M, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 48-week efficacy and safety results of the CASTLE study. Lancet. 2008;372(9639):646–55.

46. Rodriguez-Penney AT, Ludicello JE, Riggs PK, Doyle K, Ellis RJ, Letendre SL, et al. Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. PLoS ONE. 2013;27(1):5–16.

47. Wouters E, Heunis C, van Rensburg D, Meulemans H. Physical and emotional health outcomes after 12 months of public-sector antiretroviral treatment in the Free State Province of South Africa: a longitudinal study using structural equation modelling. BMC Public Health. 2009;9(1):103. https://doi.org/10.1186/1471‑2458‑9‑103.

48. Bergenstrom AM, Abdul-Quader AS. Injection drug use, HIV and the current response in selected low-income and middle-income countries. AIDS. 2010;24(3):S20–9.

49. Thanh DV, Moland KM, Fylkesnes K. The context of HIV risk behaviours among HIV-positive injection drug users in Viet Nam: moving toward effective harm reduction. BMC Public Health. 2009;9:98.

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