Author's response to reviews

Title: Quality of life in individuals living with HIV/AIDS attending a public sector antiretroviral service in Cape Town, South Africa

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Author's response to reviews: see over
Dear Editor,

Thank you for offering us the opportunity to revise and re-submit our manuscript to BMC Public Health.

We are pleased that reviewers found our study findings to be important especially to those with closely related research interests.

We have revised the manuscript as requested and provide a point-by-point response to the comments below; a separate page for each referee.

We hope you find the revised manuscript suitable for publication in BMC Public Health.

Thank you for your time and consideration.

Yours sincerely,

Mweete Nglazi, on behalf of all authors
Reviewer 1: Lydia U Kaduka

- Major compulsory revisions

Comment 1:

The authors to provide a detailed sample size estimation and sampling procedure

Response 1:

We have provided this as suggested. Thank you. The corrected text is as follows:

**Sampling technique**

The broader study used convenient sampling technique. Patients were conveniently sampled consecutively from the day list at the Crossroad Community Health clinic; and all patients meeting the inclusion criteria were invited to participate in the study. Study recruitment began in February 2007 with a target sample size of 1650 (Note that the main objectives of the original study from which the study emanates were to estimate and compare the prevalence of metabolic complications in three ART regimen- hence to estimate the prevalence of lipodystrophy at 40% (an assumption derived from the literature) within an ART regimen with a precision of 4% a sample size of 557 per ART regimen is needed and to compare the prevalence of lipodystrophy between the three ART regimens using a chi-squared test with 90% power and 5% significant level a sample size of 552 was needed per ART regimen. A total target sample size of 1650 patients (consisting of 550 per ART regimen) was therefore needed to meet the requirements of both objectives). However, only 1035 patients (approximately 95% of patients approached) consented to participate in the broader study.

Comment 2:

Define HRQoL

Response 2

We have revised as recommended. Thank you. The amended text is as follows:

**Quality of Life**

HRQoL was assessed using a validated EQ-5D (five domains) tool and Visual Analogue Scale (EQ-5D VAS)[36-38]. The EQ-5D comprises of two components- a questionnaire and a visual analogue scale-EQ-5D VAS. The questionnaire part is a standardised measure of health status that includes five domains regarding quality of daily life, namely mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each domain has
three levels: no problems, some problems and severe problems. The EQ-5D VAS is used to assess overall current health. A score is recorded on a vertical, visual analogue scale with endpoints: 0 being “worst imaginable health state” to 100 being “best imaginable health state”.

**Comment 3:**

Provide the mobility indicators and their categorization to enable the reader follow the discussion

**Response 3**

Thank you. We have provided this as recommended. Please refer to response 2 as well as the text below:

*Each EQ-5D domain were categorised as “no problems” versus “problems” because the number of subjects that reported “severe problems” were very low, and therefore “some and severe problems” were combined to form one “problems” sub-category.*

**Comment 4**

Provide details of the anthropometric assessments done

**Response 4**

Thank you. We have provided this as advised. Please see the corrected text below:

**Body Composition Assessment**

The following anthropometric measurements were done in all subjects: weight, height, skinfolds (triceps, biceps, subscapular, supra-iliac, abdominal, thigh and calf), circumferences (waist, hip, arm and thigh) and sagittal abdominal diameter (SAD)[32, 33]. All measurements were performed by one trained investigator for consistency of data. All measurements were done in duplicate as previously described [31, 34, 35]. Sagittal abdominal diameter was measured as the distance between the blades of a portable sliding-beam caliper at the level of the iliac crest (L4-5) after a normal expiration with the subject lying in the supine position on a flat, standard, clinic examining bed.

-Minor essential revisions

**Comment 1:**

This having been a cross-sectional study done at a time when the eligibility criteria was still CD4 count<200cells/µL, the impression given by the authors in paragraph 4 of the discussion on possible impact in changing the eligibility criteria is misleading. The most would be to associate followed by recommendations in establish the true effects of the new criteria on HRQoL.
Response 1:

Thank you for pointing this important point. We have revised the CD4 count thresholds and only associated as advised. Please see the corrected text below:

-methods:

The CD4 count strata were categorized as ≤200 cells/µl, and 201 - 350 cells/µl, 351 - 500 cells/µl and >500 cells/µl according to the recent WHO recommendations and national guidelines for commencing ART [30, 39, 40].

-discussion:

We also found that, when subjects were grouped according to their baseline CD4 counts, EQ-VAS scores were significantly lower in ART-naïve patients with CD4 counts ≤200 cells/µL and 201-350 cells/µL. Our study findings corroborate recently reported studies. Mathews and colleagues found that EQ-5D VAS score improved with increasing CD4 cell count strata and were 65.4, 70 and 75 for CD4 counts <50, 50–199 and ≥200 cells/µL [41]. Anis and colleagues [42] showed that improvements in CD4 cell counts were associated with higher HRQoL scores (P=0.08). Bhargava and colleagues [13] found the HRQoL of patients receiving ART increased significantly with improvement in CD4 count. Igumbor and colleagues [7] found weak but significant associations between CD4 cell counts and HRQoL in a cohort of treatment-naïve patients and those who had received ART for 12 months.

Comment 2

In the limitations section, the author acknowledges the ungeneralizability of the current findings. The manuscript title should therefore be revised in view of this fact.

Response 2:

Thank you for this important point and we have revised the title as recommended. Please find below the revised text:

Quality of life in individuals living with HIV/AIDS attending a public sector antiretroviral service in Cape Town, South Africa

Concluding response to Reviewer 1: We thank the referee very much for the very pertinent and useful comments and suggestions. They have helped to improve the quality of our manuscript.
Reviewer 2: Joseph Sempa

-General comment

The authors describe health related quality of life in individual living with HIV/AIDS in South Africa. They highlight the impact of ART in improving the self-rated health state of individuals with HIV/AIDS and therefore the need to put people quickly of ART to improve their health.

Response:

Thank you for this comment

-Major Compulsory Revisions

Comment 1:

In the abstract, the authors mentioned results of Odds Ratios from a multivariate analysis. They are supposed to be reported as Adjusted Odds Ratios because at multivariable you have made adjustments of other variables.

Response 1:

Thank you. We have revised as suggested. The corrected text is as follows:

*Being ART-naïve (adjusted odds ratio (aOR) 3.08 95% confidence interval (CI) 1.63- 7.89) and obese 2.78 (95% CI 1.24- 6.22) were identified as predictors for increased mobility problems in multivariate analysis.*

Comment 2:

The authors need to present a case for using the cutoff of 200 cells/µl as opposed to 350 cells/µl or 500 cells/µl because 200 cells/µl is an old cutoff.

Response 2:

Thank you for this important point. We have revised the CD4 count thresholds and mentioned this in the text as follows:

*The CD4 count strata were categorized as ≤200 cells/µL, and 201 - 350 cells/µL, 351 - 500 cells/µL and >500 cells/µL according to the recent WHO recommendations and national guidelines for commencing ART [30, 39, 40].*

Comment 3:

In the analysis plan, the authors said that all the variables except waist to hip ratio were normally distributed. Why then do they use median and inter-quartile ranges instead of the mean?
Response 3:
Thank you. This was an error. We have corrected as advised. The amended text is below:

All continuous variables were not normally distributed (normality tested using Shapiro-Wilk test) except for waist-to-hip ratio.

Comment 4:
The authors need to cross check the p-values they got in some sections and confirm whether they are correct. Under subheading comparison of health related quality of life outcomes by ART status, the first sentence in the second paragraph the authors had median and IQR of two groups that were clearly overlapping but the P-value was statistically significant (P=0.0027) which I find is quite unusual. Cross check also other P-values for the score.

Response 4:
Thank you for this important point. We have cross checked the p-values and revised as suggested. The corrected text is below:

The ART-naïve group had a median VAS score of 80 (IQR 70-90), which was lower than that of the ART group (median 90, IQR 80-100; P<0.0001).

Comment 5:
The authors presented counter intuitive results by saying “…those unemployed were 4.76 times more likely to have a higher EQ-5D VAS score than those with some source of income…” please cross check with table 4 and also how this was coded to ensure that you are presenting the correct results.

Response 5:
Thank you for this pertinent comment. We have cross checked this with table 4 and how it was coded. We have revised text and table 4 as advised. Please see the revisions below:

Also, those with some source of income were 4.76 times more likely to have a higher EQ-5D VAS score than those unemployed (95% CI 1.63 -7.89).

Table 4 Multivariate analyses showing factors associated with Visual Analogue Scale score
<table>
<thead>
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<th>Variable</th>
<th>Coefficient</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
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<td>ART status</td>
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<tr>
<td>ART vs ART-naïve</td>
<td>5.61</td>
<td>2.50 - 8.72</td>
<td>&lt;0.001</td>
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<tr>
<td>CD4 count,</td>
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<td></td>
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</tr>
<tr>
<td>cells/µL &gt;200 vs ≤200</td>
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<td>-2.63 - 3.79</td>
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<td>-2.95 - 4.26</td>
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<tr>
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<td></td>
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<tr>
<td>≤ Grade 12</td>
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<tr>
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<td>-15.33 - 5.09</td>
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<tr>
<td>Full or part time or other</td>
<td>4.76</td>
<td>1.63 - 7.89</td>
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<td>Housing density</td>
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<td>1.00</td>
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<tr>
<td>≥ 2</td>
<td>1.76</td>
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<tr>
<td>Obese</td>
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</table>

Constant 82.04022, R-squared 0.0616, Root MSE 16.106

All differences were significant at P<0.05
- Minor Essential Revisions

Comment 1:
There are some typos in the paper so the authors are advised to read through it and make the necessary changes.

Response 1:
We have made the necessary changes as advised. Thank you.

Comment 2:
You need to add a reference to the second last sentence in the second last paragraph of the background that talks about increase in the CD4 count threshold.

Response 2:
Thank you. We have revised the background based on the comments of Reviewer 3 and therefore this sentence has been omitted from the amended text.

- Discretionary Revisions

Comment 1:
The authors are requested to see if there is a difference if the score if they used a CD4 count threshold of 350 cells/µl.

Response 1:
Thank you. We have revised the CD4 count thresholds. Please refer to response 2 in major compulsory revisions.

Comment 2:
The authors should consider adding to their study limitations generalizability of their findings due to the CD4 count initiation threshold used in this study.

Response 2:
We have stated this as advised. Thank you. The corrected text is as follows:

Furthermore, there may be limitations to the generalizability of study findings due to the CD4 count categories used in this study.
Concluding response to Reviewer 2: We thank the referee very much for the very pertinent and useful comments and suggestions. They have helped to improve the quality of our manuscript.
Reviewer 3: Ingrid Katz

-General comment:

This study performed by researchers in Cape Town South Africa provides a useful analysis of health related quality of life measures (HRQoL) for HIV-infected patients in a public sector service in Cape Town, South Africa, comparing individuals in treatment and those not in treatment. They used two well-validated measures of HRQoL to assess this outcome in a cross-sectional study. The authors found that certain measures within the HRQoL were improved with ART use, including those with immunocompromised status. They then conclude this may be relevant to the public sector ART program in South Africa. Overall, I believe this study has some important information, but appears to have rather dated information. If the authors choose to present this information, they will need to carefully explain how and why it is still relevant in the South Africa of 2014.

Response:

Thank you for your comment. Although the present study analyses dated information, we believe that the findings are relevant to South Africa and other developing countries that are still prescribing stavudine-based first-line regimens to patients.

-Major compulsory revisions

Comment 1:

Background: There are some statements made here that need references to support them (e.g., “The quality of life of people infected with HIV/AIDS, particularly in a resource-poor population, is a complex assemblage of poverty, disease, stigma and discrimination, and lack of healthcare services, combined with limited employment opportunities, family life and support”). The citations the authors do use are quite dated (some as far back as 2001), and may not even be relevant at a time in South Africa when first line treatment is generally not associated with the metabolic abnormalities such as lipodystrophy. This section needs to be stronger in order to justify the basis of this study. This section also gets bogged down with explaining in detail the scales used to measure HRQoL. This really belongs in the Methods section. In addition, the authors state “In resource-poor countries, in particular sub-Saharan Africa, few studies have examined the detrimental effects of the disease itself on HRQoL (measured using EQ-5D)...” They then spend the rest of the paragraph discussing the numerous studies that have done just
that (assessing the HRQoL using the EQ-5D) in the same country—South Africa. It leaves the reader feeling unclear as to the broader purpose of this study. This needs to be better explained and justified. Finally, the authors fail to cite the most recent literature regarding HRQoL in HIV-infected individuals in South Africa. There is literature from 2013 that needs to be cited, including a paper focused on a “Comparison of the health-related quality of life, CD4 count and viral load of AIDS patients and people with HIV who have been on treatment for 12 months in rural South Africa.” That study actually compared CD4 count, viral load and HRQoL between treatment-naïve AIDS patients and a cohort of people living with HIV who have been on treatment for 12 months. In order for readers to see what is novel in this study, the authors need to be up to date on the literature and cite the most recent studies to provide a context for their work.

Response 1:

Thank you. We have strengthened the background section and included the recent literature as advised. The revised text is below:

Background

Human immunodeficiency virus (HIV) is a global epidemic with 35 million people living with HIV/AIDS worldwide, the majority of whom reside in resource-poor countries. By 2012, sub-Saharan Africa accounted for 70% of the universal total, with South Africa home to the largest number of people living with HIV in the world (6.1 million)[1].

The roll out of antiretroviral therapy (ART) has profoundly improved the grave portrayal of this disease in South Africa. The national ART program commenced in 2004 and the latest WHO statistics show that, at the end of 2012, there were an estimated 2 150 881 HIV-infected people receiving ART in South Africa [2]. However, while ART prolongs the lives of HIV-infected individuals [1], it is associated with a variety of metabolic sequelae, including metabolic abnormalities and morphological body changes [3-5], that may adversely affect quality of life with long-term use [6]. There is, therefore, a growing need to understand the impact of ART use and on health-related quality of life (HRQoL).

Numerous studies have examined HRQoL in HIV-infected individuals the impact of ART on HRQoL in HIV infected adults in South Africa [7-12]. These studies have been either cross-sectional or longitudinal designs. A recent cross-sectional study demonstrated a significant association between ART use and improved HRQoL indicators [7]. A second cross-sectional study
found an improvement in physical health only [8]. Another study showed less pain and discomfort and fewer problems with self-care, daily activities and general mobility [10]. In addition, longitudinal studies have shown significant improvements in HRQoL during 7 months [9], 12 months [11] and 24 months [12] of follow-up after ART initiation.

There are, however, relatively fewer studies from South Africa that assessed the effect of higher CD4 cell counts on HRQoL [7, 13]. Bhargava and colleagues [13] found the HRQoL of patients receiving ART increased significantly with improvement in CD4 count. Igumbor and colleagues [7] found weak but significant associations between CD4 cell counts and HRQoL in a cohort of treatment-naïve patients and those who had received ART for 12 months.

Globally, there has been concern about how ART-related toxicities may adversely affect HRQoL of HIV-infected individuals. Non-nucleotide reverse transcriptase inhibitors such as stavudine (d4T) have been shown to be associated with metabolic complications such as dyslipidemias, lipoatrophy, peripheral neuropathy and lactic acidosis [14-25]. Owing to toxicity concerns, the World Health Organization (WHO) in 2010 recommended the replacement of d4T with tenofovir (TDF) or zidovudine (AZT)-based first-line regimens which have better safety profiles [26, 27].

Despite the World Health Organization recommendation to phase out d4T, the national ART programs of South Africa and other developing countries continue to use d4T as part of their first-line ART regimen. By the end of 2011, 1.1 million people were taking d4T regimens globally, the vast majority in resource limited settings in sub-Saharan Africa [28]. Progress in phasing-out d4T has been tampered by the higher cost of the alternative drugs AZT and TDF, uncertainties regarding whom to give priority to for phase out, the existence of stockpiles of d4T in several countries [28] and the failure of major donors to support the complete elimination of d4T [29]. With the lack of full elimination of d4T from first-line regimens in resource-poor countries, there is a need for studies on the impact of d4T-containing first-line ART regimens on HRQoL in order to inform their national ART programs.
Therefore, the objectives of this study were to establish whether there was a difference in the HRQoL in those patients who were not receiving ART compared to those who were on first-line ART (predominantly d4T-containing regimen for longer than 6 months) in public sector treatment program in Cross roads, Cape Town, South Africa. In addition, we aimed to examine the relationship between ART status and HRQoL according to CD4 count strata.

Comment 2:

Methods –The authors note these subjects were recruited before South Africa adopted the current ART treatment guidelines. Those guidelines were adopted in 2011- so therefore this cohort must be older than that. Given the rapid change that has occurred in SA in the past 3 years, relating not only to these CD4 initiation guidelines, but also to the first line medications being introduced, this cohort seems outdated. The authors will need to justify more why this cohort was chosen and how it is relevant in today's South Africa. Also, they do not mention how many people qualified for this study and how many actually enrolled – likely not the same number. Measurements are sound – both the body composition measures and the QOL measures.

Response 2:

Thank you for these important points. The methods section has been revised as suggested. Regarding study enrollment, we only documented those that consented to participate in the broader study but in general about 95% of those approached to participate in the study consented. The revised text is below:

**Study setting and population**

This study is a cross-sectional secondary analysis of a subset of data collected from a broader study examining the prevalence of metabolic complications of ART in HIV-infected patients, conducted by the Division of Diabetic Medicine and Endocrinology of the University of Cape Town in 2007. The study site was the Crossroads community health clinic in Cape Town which provides HIV care to over 5000 patients. As per national ART guidelines at the time of data collection, adult patients qualified for public sector ART if they had a CD4 count below 200 cells/µL and symptomatic, and/or WHO Stage four AIDS defining illness (World Health Organisation HIV/AIDS Staging System)[30]. The study population consisted of 435 not yet receiving ART (ART-naïve) and 468 on the South African National Department of Health first-line ART regimen (stavudine (d4T) or zidovudine (AZT), lamuvidine (3TC) and efavirenz (EFV) or nevirapine (NVP). At the time of data collection, patients in South Africa only qualified for public sector ART
if they had a CD4 count below 200 cells/µL and symptomatic, and/or WHO Stage four AIDS defining illness (World Health Organisation HIV/AIDS Staging System)[30]

The study cohort was selected due to the fact that d4T is still being used as part of first line regimens in South Africa and other resource-limited countries [2, 28] and it is, therefore, important to determine whether the drug has a negative impact on HRQoL.

Sampling technique

The broader study used convenient sampling technique. Patients were conveniently sampled consecutively from the day list at the Crossroad Community Health clinic; and all patients meeting the inclusion criteria were invited to participate in the study. Study recruitment began in February 2007 with a target sample size of 1650 (Note that the main objectives of the original study from which the study emanates were to estimate and compare the prevalence of metabolic complications in three ART regimen- hence to estimate the prevalence of lipodystrophy at 40% (an assumption derived from the literature) within an ART regimen with a precision of 4% a sample size of 557 per ART regimen is needed and to compare the prevalence of lipodystrophy between the three ART regimens using a chi-squared test with 90% power and 5% significant level a sample size of 552 was needed per ART regimen. A total target sample size of 1650 patients (consisting of 550 per ART regimen) was therefore needed to meet the requirements of both objectives). However, only 1035 patients (approximately 95% of patients approached) consented to participate in the broader study.

Inclusion criteria

To participate in the broader study, subjects were 18 years and older and were required not to have changed their ART in the past six months. Exclusion criteria included a history of diabetes mellitus or impaired glucose tolerance, active TB, active acute opportunistic infections, severe diarrhoea (>6 stools/day), known renal failure, pregnancy, or had received glucocorticoid therapy within the past six months.
Comment 3:

Results – The authors note the most common regimen used was Stavudine (d4T)/Lamividine(3TC)/Efavirenz (EFV). It would be helpful to understand how commonly this regimen is still prescribed, since my impression is that this regimen had been phased out due to known metabolic abnormalities associated with D4T.

Response 3:

Thank you. The reviewer is correct that stavudine-based regimens are being phased out in South Africa. However, progress of phasing out d4T has been hampered by several challenges in South Africa and other developing countries. We have stated this in the background and methods.

-background
Despite the World Health Organization recommendation to phase out d4T, the national ART programs of South Africa and other developing countries continue to use d4T as part of their first-line ART regimen. By the end of 2011, 1.1 million people were taking d4T regimens globally, the vast majority in resource limited settings in Africa (WHO, 2014). Progress in phasing-out d4T has been tampered by the higher cost of the alternative drugs AZT and TDF, uncertainties regarding whom to give priority to for phase out, the existence of stockpiles of d4T in several countries [28] and the failure of major donors to support the complete elimination of d4T[29]. With the lack of full elimination of d4T from first-line regimens in resource-poor countries, there is a need for studies on the impact of d4T-containing first-line ART regimens on HRQoL in order to inform their national ART programs.

-methods
The study cohort was selected due to the fact that d4T is still being used as part of first line regimens in South Africa and other resource-limited countries [2, 28] and it is, therefore, important to determine whether the drug has a negative impact on HRQoL.

Comment 4:

Discussion – It is not entirely clear how novel the findings related mobility problems and peripheral neuropathy (distal sensory polyneuropathy (DSP)) in the HIV-infected HAART-naïve patients are, since those are known to be associated with advanced HIV. What I believe may be the novel finding here
is the fact that despite being on outdated medications that have known toxic side effects, these participants EQ-5D VAS score was improved on HAART. In regards to CD4 differentials and HAART eligibility, the authors date themselves again by stating, “Our study findings support the notion that there would be a greater benefit of starting ART earlier, at higher CD4 cell counts (that is, above CD4 cell count of 200 cells/µL) within the public sector ART program in South Africa,” since that change was already made 3 years ago. The authors recognize this change has already occurred, but then do not attempt to put their findings in a modern context.

**Response 4:**

Thank you for your comment. We have removed the finding relating to mobility and peripheral neuropathy (distal sensory polyneuropathy (DSP) in the discussion and have highlighted the key findings as advised. The corrected discussion is below:

**Discussion**

In this study that compared HRQoL outcomes between ART-naïve and patients on ART for 6 months or longer (who were mostly using a d4T-based first-line regimen) the key findings were: Subject’s EQ-VAS scores (representing the subject’s self-rated health state) improved significantly on ART; and when subjects were grouped according to their baseline CD4 counts, EQ-VAS scores were significantly lower in ART-naïve patients with CD4 counts ≤200 cells/µL and 201-350 cells/µL.

Our finding that study subject’s EQ-5D VAS scores improved significantly on ART, suggests that drug toxicities, especially those related to d4T have little impact on subjects self-rated health. This study, therefore, support the findings of several studies [9-12] which report improved HRQoL outcomes on ART, despite participants being national first-line regimens containing d4T with known toxicities [14-25]. The study by Pitt and colleagues [9], for example, showed that drug toxicities, mainly those related to d4T, had little impact on mental health HRQoL scores during the first 48 weeks on ART.

We also found that, when subjects were grouped according to their baseline CD4 counts, EQ-VAS scores were significantly lower in ART-naïve patients
with CD4 counts ≤200 cells/µL and 201-350 cells/µL. Our study findings corroborate recently reported studies. Mathews and colleagues found that EQ-5D VAS score improved with increasing CD4 cell count strata and were 65.4, 70 and 75 for CD4 counts <50, 50–199 and ≥200 cells/µL [41]. Anis and colleagues [42] showed that improvements in CD4 cell counts were associated with higher HRQoL scores (P=0.08). Bhargava and colleagues [13] found the HRQoL of patients receiving ART increased significantly with improvement in CD4 count. Igumbor and colleagues [7] found weak but significant associations between CD4 cell counts and HRQoL in a cohort of treatment-naïve patients and those who had received ART for 12 months.

The strength of this study was the large sample size of HIV-infected individuals derived from a primary care clinic and it is one of the few studies that shed light on the impact of higher CD4 cell counts on HRQoL. However, the results of the study are not generalizable to the general population of people living with HIV/AIDS in the Western Cape Province of South Africa and South Africa as a whole. Our finding that the EQ-5D VAS was sensitive to ART use and ART eligibility (based on CD4 cell count) supports the use of this particular instrument in future assessments of HRQoL outcomes among HIV infected individuals in South Africa.

The study had the several limitations. Because this was a non-randomized study, the associations observed in the study are potentially biased due to residual confounding. We could not adjust for HIV-related symptom burden, duration on ART (among those on ART) and HIV-RNA viral load levels because all these factors known to influence HRQoL among HIV infected individuals [38] were not assessed in the present study. Furthermore, there may be limitations to the generalizability of study findings due to the CD4 count categories used in this study.

Concluding response to Reviewer 3: We thank the referee very much for the very pertinent and useful comments and suggestions. They have helped to improve the quality of our manuscript.