VALIDATION OF SELF-REPORTED MEASURES OF ADHERENCE TO ART AND FACTORS ASSOCIATED WITH ADHERENCE IN JINJA, UGANDA

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Johannesburg, 14th December 2016

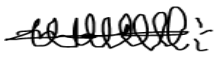
DECLARATION

I Felix Made declare that this research is my own work. I have acknowledged and referenced all sources where the work is solicited from somewhere else. I hereby submit this report for the partial fulfilment of Master of Science in Epidemiology and Biostatistics and this work has never been submitted before elsewhere or here in this university**.**

Name: Felix Made

Ethics Clearance Number: M151173

Signature:



Date: 14th December 2016

ABSTRACT

Background: Good adherence to ART prolongs survival and improves quality of life in people living with HIV/AIDS. Adherence is commonly assessed using self-reported measures, but these tend to over-estimate adherence. Viral load testing is the gold standard for measuring ART adherence but it is unaffordable in resource limited settings. Therefore, the aims of this small sub-study were to validate self-reported measures of adherence and to find factors associated with adherence to ART in Jinja, Uganda.

Methods: This study was a secondary analysis of data collected from a cluster randomized equivalence trial which was carried out to compare facility based ART care versus home based care. In the main study, 1453 participants aged 18 and above were enrolled. A total of 1276 men and women qualified for this sub-study. Receiver operating characteristic (ROC) was computed to see how well two self-reported measures of adherence predicted virological failure. The two self-reported measures were firstly a visual analogue score (VAS) where participants rated the number of doses that they had taken in the past month on a scale from 0 (meaning no ART taken) to 100 (meaning that all required doses had been taken) and secondly an adherence score based on the number of pills missed in the three days before the visit. Logistic regression models were fitted with survey estimator to find factors associated with virological failure. Tobit models were fitted to find factors associated with self-reported adherence measures, since these were restricted to the range of 0-100% and censored. We then compared associated factors among the three different outcome measures.

Results: There were 914 women and 362 men in this study. Home based care had larger number of patients (754) than facility based care (522). The median age of the patients was 38 years (IQR 32.0-44.0). Most of the participants were either married (518) or single (456). The majority of the trial participants had primary school education (n=713) and very few achieved tertiary education. A large number of participants had CD4 cell counts of less than 50 cells/mm^3 (n=351), and very few of the patients in the trial had CD4 counts greater than 200 cells/$mm^{3.}$ The median CD4 count of the study participants was 116 cells / mm^3 (IQR 43.0-167.0). A very large number of the patients were either in WHO clinical stage II or III (Stage II: n= 595; Stage III: n=577). A total of n=1079 (84.56%) and n=197 (13.44%) participants had no virological failure and failure respectively. The ROC methods showed that the

self-reported adherence measures estimated virological failure with a sensitivity that ranged between 35-65%. Female patients had lower odds of experiencing virological failure (odds ratio: 0.7; 95% CI: 0.485, 0.968; p=0.033). The odds of virological failure decreased with each one year increase in age (OR: 0.95; 95% CI: 0.928, 0.979; p=0.001). Participants who found adherence reminders very useful were less likely to experience virological failure (P=0.001).

Conclusion: This study show that self-reported measures are not good predictors of ART adherence since approximately only a half of the Jinja participants with virological failure were predicted by such measures. None of the factors associated with virological failure was also associated with both of the self-reported adherence measures. Viral load testing should be encouraged in place of self-reported adherence measures to ART. In addition, alternative methods of measuring adherence such as electronic medication monitoring, pharmacy refills and drug level detection should be investigated.

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LIST OF ACRONYMS AND ABBREVIATIONS

HIV: Human Immunodeficiency Virus

AIDS: Acquired Immune Deficiency Syndrome

ART: Antiretroviral Therapy

ARV: Antiretroviral drug

WHO: World Health Organization

TASO: The AIDS Support Organization (Uganda)

UNAIDS: United Nations Programme on HIV/Acquired Immuno-deficiency Syndrome

UAC: Uganda Aids Commission

ABC: Abstinence, Be faithful, Use a Condom

1. INTRODUCTION

1.1. Background:

Globally, HIV/AIDS remains a major cause of mortality and morbidity. An estimated 36.9 million people are living with HIV/AIDS and around 2 million were newly infected and about 1.2 million died globally due to the epidemic in 2015 (UNAIDS, 2016). The greatest burden of the disease is found in sub-Saharan Africa where almost 25.8 million (uncertainty interval 24.0 million - 28.7 million) are living with HIV/AIDS and the region is having 66% of all new infections in the world. In Uganda, an estimated 1.5 million are living with the virus; adults aged 15 and over account for about 1.4 million of the HIV positive people in Uganda, with a prevalence of about 7.1% by the end of 2014 (UAC, 2014). Nevertheless, sub-Saharan Africa has registered some improvement in HIV/AIDS management and Uganda is not an exception. For example, new HIV infections have remarkably reduced by 41% between 2000 and 2014. Deaths caused by AIDS fell by 48% between 2004 and 2014 in sub-Saharan Africa (UNAIDS, 2016). In Uganda, according to the HIV country progress report, new HIV infections declined considerably as did HIV/AIDS related deaths. New HIV infections decreased to about 95,000 in 2014 (down from 160,000 in 2010) and HIV/AIDS related deaths also dropped from 67,000 in 2010 to 31,000 in 2014 (UAC, 2014). Despite this, the East African nation is still regarded as a high burden country with a high number of people living with HIV/AIDS and a relatively large number of new infections.

In order to continue with the downward trend of new HIV infections and HIV/AIDS related deaths, UNAIDS in 2014 introduced a “Fast Track Strategy” which aims to step up the response to HIV in low and middle income countries and end the disease by the year 2020 (UNAIDS, 2014). The strategy set the “90 90 90” targets which stands for “90% of people living with HIV should know their status”, “90% of people who know they are HIV positive should have access to treatment” and “90% of people on treatment should have achieved viral load suppression”. For its part, Uganda has been using a more pragmatic approach which emphasizes the “Abstinence, Be faithful and always use a Condom” (ABC) slogan. The ABC approach and a system of voluntary counselling and testing and billboards awareness was promoted by the Ugandan government to prevent spread of HIV (UAC, 2014). The approach in Uganda led to a dramatic drop in HIV/AIDS infection

rates (Stoneburner and Low-Beer, 2004, Hearst and Chen, 2004). The billboards raising awareness of HIV and promoting voluntary counselling and testing led to people being more openly aware of the epidemic and had a positive impact as more people living with HIV/AIDS enrolled to receive ART. To achieve viral load suppression, the country took a more combative treatment effort by adopting the 2013 WHO guidelines. ART became available in the public sector from 2003 onwards. Access to ART in Uganda has increased up to about 751,000 in 2014. ART roll out has importantly enabled an estimated 76% of the people in Africa to achieve virological suppression (UAC, 2014).

Since it has been established that viral load suppression can be achieved by use of antiretroviral drugs, much emphasis within HIV/AIDS programmes has been on the roll out of ART. The need to monitor adherence to ART has not been given much-needed attention. That is why the government of Uganda has placed ART adherence and retention in care on the agenda as part of the planned remedial action for 2014 and 2015 (UAC, 2014). Good adherence to ART is important if we are to maintain the downward trend of HIV related deaths through slowing disease progression. In addition good adherence reduces the risk of HIV transmission through suppressing viral load. One way of measuring adherence to ART is by viral load testing. In 2013, WHO recommended routine viral load testing with viral loads tested 6 months after starting treatment and thereafter once a year to see if the treatment is working, to identify need for possible second-line drugs and above all, to distinguish between treatment failure and adherence failures (WHO, 2016). The WHO recommends that every patient must at least achieve an adherence score of 95% if viral resistance to the medication is to be prevented (Stone et al., 2001). According to Remor (2013) there are two different ways of measuring adherence to medication. For example, the direct methods which include examination of active drug in blood, and the indirect methods including clinical assessment, pill count and self-report.

Self-reported measures are defined by questions involving missed doses or by a visual analogue score where a mark is made on a line drawn from 0 to 100%, relating to the percentage of HIV drugs consumed and other assessment methods containing reasons for non-adherence (Giordano et al., 2004, Walsh et al., 1998). However, self-report has some shortcomings too; one of them is that it could be subjective as a patient may not want to be seen to be disobeying medical

recommendations. For a self-report based method of ART adherence to be reliable, feasible and valid, other approaches need to be employed to validate it. Therefore we conducted a validation of 2 self-reported measures (visual analogue scale and a measure based on the number of pills missed in the past 3 days) by comparing them to the results from viral load testing, and also investigating if they can be predicted using the same risk factors. While self-reported measures have not been fully evaluated to date, the relationship with plasma HIV ribonucleic acid (RNA) has been established (Simoni et al., 2006b). Virological failure is established using laboratory tests as a direct measure of effectiveness and outcome of ART adherence.

1.2. Literature Review:

ART adherence studies in Africa have mainly been carried out among adults. Adherence is usually measured as the percentage of required doses taken over a specified period of time, ranging from 0 - 100% (Miller and Hays, 2000, Catz et al., 2000). Studies in Africa found that 77% of individuals on ART achieved the WHO target of adherence (Mills et al., 2006b). There are many ways of measuring adherence. The best objective measure of adherence is HIV viral load testing, but its use is limited due to high costs (Bangsberg, 2008, Bova et al., 2005). In resource limited settings pharmacy adherence measures (PAM) which include pharmacy pill count, pill pick-up and medication or drug possession ratio are recommended since they are of a relatively lower cost and have been found to predict virological failure (Meyer et al., 2011). Self-reported measures are therefore the most widely used methods today because of low cost and ease of operation, which avoids the use of sophisticated equipment; in addition it is possible to validate these methods (Hawkshead and Krousel-Wood, 2007, Paterson et al., 2002). The objective is to see whether either (or both) of the self-reported adherence measures can be used as a proxy measure for virological failure However, past studies have found shortcomings with self-reported methods of adherence. One study indicated that the time frame used for recall could affect accuracy of the recall (Paterson et al., 2002). In order to get a more valid self-reported measure of adherence, it is important that self-reported recall periods are taken into consideration, since it is human nature to remember things that happened yesterday better than things that happened the day before yesterday. A systematic review found self-report recall periods to be associated with HIV-1 RNA viral load and CD4 count (Simoni et al., 2006a). Further

studies have also confirmed that self-reported adherence measures tend to exaggerate good adherence, since they reflect short term adherence that may give an over-estimate of overall adherence (Arnsten et al., 2001b, Liu et al., 2001, Wagner et al., 2004). One other disadvantage of self-reported measures may be that the respondent may give a response that he or she thinks the interviewer would want to hear.

Some of the possible factors contributing to poor adherence in Africa are related to socioeconomic factors, while others are behavioural. Various factors have been found to be associated with adherence to ART. Personal adherence reminders have been one of the most important predictors of adherence in previous studies. For instance, a study conducted in Laos in Asia, revealed that the major contributor to non-adherence to ART was forgetfulness (62.2% of 346 participants) (Hansana et al., 2013). Similar results were also found in Africa. For example, in Uganda, a study reported that 97% and 93% of the participants did not miss their doses and appointment respectively. The study also found that travel and forgetfulness were the reason for missing doses (Shumba et al., 2013). Similar findings were confirmed in Ethiopia where factors associated with poor adherence were also forgetfulness and travelling (Mitiku et al., 2013). Studies on the relationship between socioeconomic factors and ART adherence in Uganda are limited and it is not clear what effect these factors have on ART adherence. Available studies from middle and low income countries reported that income and level of education were significantly and positively associated with level of ART adherence in 15 and 10 studies (Peltzer and Pengpid, 2013).

When comparing achievement of ART adherence levels between low income regions and high income regions, (in this instance Africa and North America), a study showed that Africa had relatively higher adherence rates with about 20% more patients achieving over 80% adherence (Mills et al., 2006b). A few studies have reported on factors that are related to ART adherence in resource limited settings. Poor adherence was associated with age, in particular for young and old participants and also with missing clinic appointments in Tanzania; this study highlighted the importance of creating an adherence reminder protocol for clinic appointments, as studies elsewhere also reported forgetfulness as one of the predictors of poor adherence (Watt et al., 2010). Various factors have been found to contribute to poor

ART adherence, including cost, transport, stigmatization and lack of control over household materials (Braitstein et al., 2008, Gilks et al., 2006, Snow, 2009). Studies report that among many factors affecting adherence, demographic characteristics such as gender are important (Stone et al., 2001). Other studies indicate that factors such as side effects, pill burden, time on ART, and doctor-patient relationship may affect adherence (Schneider et al., 2004). A study found that 72% of patients at 12 and 24 months of ART had 75% and 72% undetectable HIV RNA and virological failure was associated with poor adherence, general clinical symptoms associated with WHO stage of the disease, and lower weight (Ahoua et al., 2009). Some factors affecting adherence may be similar across countries, while others may be country specific (Sabin et al., 2008, Weidle et al., 2006).

When reviewing literature to find out which self-reported adherence measures currently available are acceptable to patients, valid and reliable, the visual analogue scale and percentage of pills missed were identified. A visual analogue scale was found to be much easier to use than reporting the number of doses or pills missed (Garfield et al., 2011). In Europe, a higher visual analogue score was found to correspond with viral suppression with statistically significant association (Chkhartishvili et al., 2014). It is important to assess these 2 self-reported measures in a Ugandan context. Adherence to ART is widely regarded as one of the most important predictors of survival for people living with HIV/AIDS (Garcia de Olalla et al., 2002). Good ART adherence of 95% or more decreases the chances of opportunistic infections and reduces viral load (Hogg et al., 1999). In contrast, poor adherence leads to development of HIV viral resistance which quickens the development of HIV to AIDS, and decreases quality of life (Bangsberg et al., 2001). Strict adherence is difficult to maintain given the rapid replication rate of the virus, the complex nature of the ARV regimens and the combination of short and long term toxic effects (Thompson et al., 2012), all of which pose a challenge for individuals on ART. Nonetheless, patients must try to achieve the required level of ART adherence.

There is no universal method of self-report with many researchers using different periods of recall to assess adherence (Lu et al., 2008). The major challenges related to self-reported measures of adherence are concerns about their validity due to the potential for social desirability and memory bias. Many self-report methods such as response scale formats and time interval for recall are commonly used (Garfield et

al., 2011). A systematic review in 2006 suggested that measuring ART adherence using quantitative methods such as viral load was even more important in Africa than in the United States of America (Mills et al., 2006b). However the review fails to take into consideration the fact that sub Saharan Africa is a resource limited setting (Nahman et al., 2009). Self-reported measures of adherence therefore are the only methods available in many poor settings. Increased roll out of ART cannot be achieved fully without improving health systems which could emphasize retention, adherence and medication protocol compliance.

Few studies have empirical evidence to validate self-reported measures of ART adherence. Thus we evaluated two self-reported measures of adherence to ART and also investigated factors associated with adherence. This study used secondary data analysis of a cluster randomised trial in which participants were randomised by cluster to receive either home based ART or facility based ART in Jinja, South Eastern Uganda (Amuron et al., 2007, Jaffar et al., 2010). The secondary analysis presented here compares two self-reported measures of adherence by assessing how well they predict virological failure.

1.3. Problem statement:

While much emphasis has been placed on scaling up ART, the need to retain those already on treatment and to improve adherence has not been fully addressed in Ugandan government plans (Knodel et al., 2010). If we are to see suitable outcomes of scaling up ART as part of a universal effort towards eradicating the HIV epidemic, a measure of adherence should be part of HIV treatment policies. Viral load testing is the best measure of adherence, however Africa is a resource limited setting and many countries cannot afford routine viral load testing. Therefore there is a need for alternative measures of adherence, and self-reported measures are the cheapest available. One problem that has hindered the progress of ART adherence is the absence of a standard measure for self-reported adherence. As noted above, self-reported measures tend to over-estimate adherence. These measures also depend on the recall of participants, while the questions asked may not be properly communicated to the participants as the questionnaire may contain too many medical terms and recommendations (DiMatteo et al., 1992, Chesney et al., 2000).

1.4. Justification:

Viral load monitoring in most settings across Africa is unaffordable and requires sophisticated equipment (WHO, 2006). The clinically positive effects of ART in suppressing HIV virus and prolonging survival of people living with the infection are well documented (Kredo et al., 2009, Lohse et al., 2007, Vergidis et al., 2009), especially for patients who follow proper medication protocols and adhere to treatment modalities. Thus it is important that we evaluate self-reported measures of adherence. Finding a standard self-reported method is very important so that it can be used in place of viral load testing to monitor ART adherence. Self-reported measures may reveal risk factors for poor adherence to ART, including social, situational and behavioural factors and factors related to medicinal use (Hawkshead and Krousel-Wood, 2007). Many of these factors are particularly relevant in resource limited settings. The need to address these factors remains very important in improving ART adherence. This study will aid in strengthening health systems in HIV/AIDS treatment care and adherence.

1.5. Research questions

How valid are two self-reported measures of adherence to ART (visual ART score and number of pills missed) and what factors are associated with adherence to ART?

1.6. Aims and objectives

The aims of the study were to assess the two self-reported measures of adherence to ART and to identify factors associated with adherence to ART from a cluster randomised equivalence trial carried out in Jinja, South Eastern Uganda, from 2005 to 2009.

Objectives

The major objectives of this secondary analysis using data from a cluster randomised trial carried out from 2005 to 2009 in South East Uganda were the following:

1. To compare two self-reported measures of ART adherence by seeing how well each predicts virological failure.
2. To investigate factors associated with:
   a) Virological failure
   b) Adherence as defined by the two self-reported measurement scores
3. To compare which factors are associated with virological failure and also with both of the adherence measure (s).

2. METHODS

2.1. Study description

2.1.1. Study design:

This was a secondary data analysis of a cluster randomised equivalence trial on virological failure comparing facility based ART to home based ART care; 44 geographical clusters were randomized, with randomisation stratified by location and distance to the clinic in Jinja, south eastern Uganda (Jaffar et al., 2010). This secondary data analysis adopted the same study design.

2.1.2. Study setting/site:

The main trial was carried out in Jinja district, South Eastern Uganda. The facility based care was delivered at "The AIDS Support Organisation" (TASO), a clinic in Jinja town. TASO is the largest provider of ART in Uganda.

2.1.3. Study population

Participants were recruited from TASO clients who either had a "CD4 cell count less than 200 cells/µl or had WHO stage IV or late stage III disease and who initiated ART between 15 February 2005 and 19 December 2006" (Jaffar et al., 2010). A total of 1453 HIV-infected women and men aged 18 years or older were enrolled for the primary study. We included all participants who could potentially experience virological failure. Since virological failure was only measured from the 12 month visit onwards, this meant that we only included participants who had a visit at 12 months or later. A total of 1276 patients from the total number of the primary study qualified for this secondary study because they were observed at month 12 or beyond. See figure 1 for the CONSORT diagram for the main trial. In the CONSORT diagram, the number of patients analysed was lower than the one we used in this study because of different eligibility criteria for this secondary analysis. We decided to adjust the number of patients for analysis in the diagram for consistency.

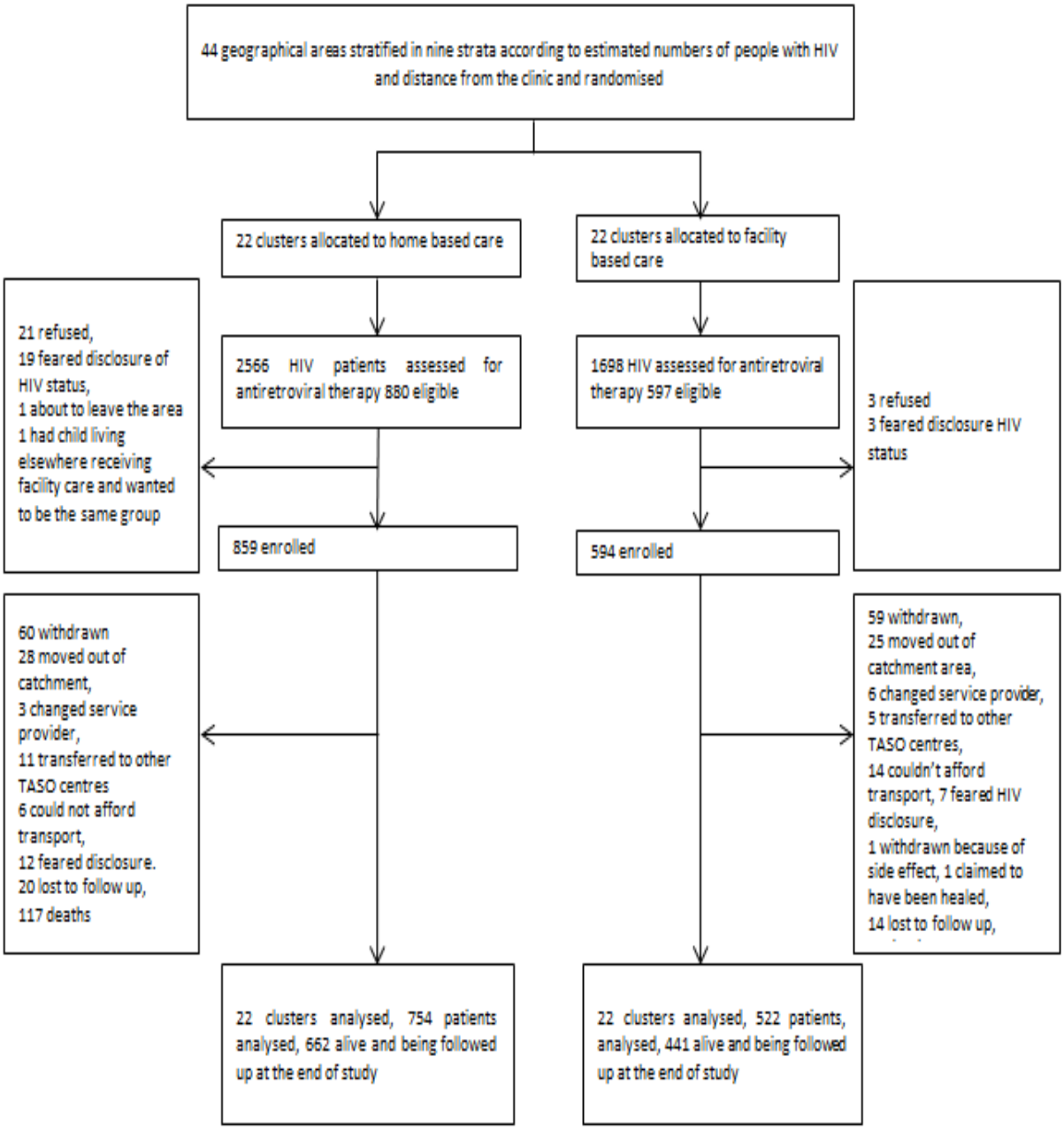

Figure 1: Jaffar et al. (2010). CONSORT diagram for cluster randomised trial

2.2. Intervention:

Participants were randomised by cluster to either receive hospital based ART care or home based ART care.

2.3. Main exposures, potential confounders and outcomes for each objective

Objective one: Comparing two self-reported measures of ART adherence by seeing how well each predicts virological failure. For this objective, adherence is an exposure but for objective 2b it is an outcome.

Outcome: Virological failure.

Exposures: Visual analogue score and number of pills missed (both exposures are measured as a percentage).

Objective 2a: Finding factors associated with virological failure.

Outcome: Virological failure.

Exposures: WHO stage for HIV, means of transport, usefulness of adherence reminders, CD4 cell counts, BMI, study arm and time taken to reach clinic.

Potential confounders: Education, sex, marital status and age.

Objective 2b Finding factors associated with self-reported measures (adherence measures). Only factors that were found to be statistically significantly associated with virological failure were considered as candidate explanatory variables for the models of the two self-reported measures of adherence.

Outcomes: The “visual analogue score” and the adherence score using “number of pills missed” (self-reported adherence measures).

Exposures: WHO stage for HIV, means of transport, usefulness of adherence reminders, CD4 cell counts, BMI, study arm and time taken to reach clinic.

Potential confounders: Education, sex, marital status and age.

Objective 3: Comparing factors associated with both virological failure and self-reported adherence measures scores

This objective involves a comparison of the findings for objective 2a and objective 2b so does not have its own outcome, exposures and potential confounders.

2.4. Selection of study population

2.4.1. Eligibility criteria

ART treatment requirements proposed by the Ministry of Health in Uganda were used to inform the inclusion criteria for the primary study. According to the guidelines, all people with HIV were eligible to start ART if they satisfied either of the following criteria.

1. WHO stage IV or late stage III disease
2. A CD4 cell count of less than 200 cells per microliter.

The inclusion criterion for this secondary study was to include all those participants who were followed up at month 12 or beyond.

2.4.2. Sampling

A total of 1453 participants were enrolled for the primary study. A total of 1276 participants in the primary study with at least one year of follow-up were included in this secondary analysis. All participants who satisfied the eligibility criteria for this secondary analysis were included. Since the eligibility criteria for this secondary analysis was different from that of the main paper, the number of patients for analysis in the CONSORT diagram was lower than the one we used in this study. In order to achieve some consistency, we adjusted the number of patients for analysis in the CONSORT diagram to match 1276, the number we used in this study.

2.4.3. Randomisation

A concealed box with cards containing either home based or facility based care were randomly drawn by two patient representatives, a TASO medical officer, TASO counsellor, and TASO field officer for each community, in order to determine the arm to which the community would be allocated (Jaffar et al., 2010).

2.5. Study procedures

2.5.1. Procedures at enrolment

Eligibility criteria were employed to screen patients for ART starting in August 2004 with enrolment which ended in 2006. Patients starting ART for the first time and were 18 years and older were allowed to join the study. All patients provided

informed consent. The right to autonomy, that is to say to refuse or withdraw from the trial at any time was conveyed to the participants. Questionnaires were written in English and translated into Luganda. Special persons not affiliated with the research were employed to help in translation. Luganda is a commonly spoken language in South Eastern Uganda. No financial incentives were used to motivate people to join the trial.

2.5.1. Follow-up

Patients in both arms of the study were followed up for interview at 2 months and again 6 months. From the main paper, enrolment began on 15 February 2005 and ended 19 December 2006. Thereafter they were followed up every six months. Follow-up continued until 31 January 2009, so participants were in the trial for 2-3 years. For follow-up visits, if a patient missed an appointment, the fieldworker went to his/her home, if the participant was not at home, the fieldworker left a message that the patient should come to the TASO clinic in Jinja. Under normal circumstances, patients who missed a follow-up visit were followed-up by research fieldworkers, and reminded to attend clinic and their consent was taken for possible consideration of home based care in case a participant was unable to make it to the clinic on the day of follow–up or review. Clinic visits were required by all patients from both arms for routine clinical check-ups by medical officers. The home based participants had 6-monthly clinic visits while the clinic based participants had monthly clinic visits. ART was dispensed on a monthly basis to both home based care and facility based care participants.

2.5.2. Measurement of variables

Virological failure

A viral load test result was used to define virological failure as a binary variable with 0 denoting no virological failure and 1 denoting virological failure. In the primary study, virological failure and associated time of failure was only assessed from 12 months onwards. If all viral load measurements for a subject from month 12 onwards were below 500 copies / ml, then the subject was deemed not to have failed. If a viral load measurement exceeded 1,000 copies per ml then the subject was considered a failure at the first visit at which this occurred. If the viral load was between 500 and 1,000 copies per ml at any visit, then the subject was considered a failure at that visit if at the next visit the viral load was 500 copies or higher. If at the second visit the

viral load was below 500 copies per ml, then the subject was not considered a failure. If the final viral load was between 500 and 1000 copies per ml, then a confirmatory viral load was done. Viral load was measured every six months, but virological failure was only assessed from month 12 onwards, as the viral load could take longer than six months after the initiation of ART to reach undetectable levels.

Adherence defined by visual analogue scale (VAS)

The visual analogue score was defined as the proportion of doses that a participant had taken and ranged between 0% (if the participant had not taken any drug) to 100% (if the participant had taken all the required doses). The participant rated his or her adherence at each adherence visit by marking a point on a line going from 0 to 100 (see appendix 8.3 for the main trial adherence questionnaire). For the analysis we used the mean value of the score calculated over all the adherence visits for each study participant. For those participants who experienced virological failure, data was included up to and including the visit at which the participant experienced the failure meaning that if a patient missed a visit, the adherence was not included in the adherence score. Also if an appointment or visit was missed from either arm, an effort was made to ensure that antiretroviral drugs were delivered to the patient. This was done by follow up at home by any of the trial team members especially if patients had consented to home visits.

Adherence based on number of pills missed

The adherence based on number of pills missed was calculated as a proportion by dividing the number of pills missed in the last 3 days by the total number of pills that should have been taken over the last three days, excluding the day of the visit (see appendix 8.3 for the main trial adherence questionnaire). The calculation was done at each visit and the mean score over all adherence visits for each participant was used. This was calculated as number of pills missed by the participant in the last 3 days excluding today as adherence percentage score. The higher score corresponds to fewer pills missed.

$$\frac{3 \text{ X number of pills taken every day} - \text{Number of pills missed over last 3 days}}{3 \text{ X number of pills taken every day}} \text{ X } 100\%$$

For those participants who experienced virological failure, data was included up to and including the visit at which the participants experienced the failure. Adherence measurement was taken every 6 months after ART roll out.

2.6. Laboratory methods

The TASO staff monitored CD4 cell counts every 6 months. TriTEST (Becton-Dickenson, Franklin Lakes, NJ, USA) reagents were used to measure CD4 cells according to an in-house dual-platform protocol and MultiSET and Attractors software (version 2.2) with a FACScan flow cytometer (Becton-Dickenson, Franklin Lakes, NJ, USA). In laboratory testing of RNA viral load, the storage temperature for the plasma was at – 80^{o}C. HIV-I RNA test was carried using VERSANT RNA 3.0 (Bayer, Bayer Healthcare, NY, and USA) assay "(with a lower limit of detection of 50 copies per mL)" for samples drawn at baseline. The Amplicor MONITOR 1.5 (Roche, Roche Molecular Systems, NJ, and USA) was used to test other samples (400 per copies per mL). The laboratory tests showed strong agreement between the results of the two assays (Jaffar et al., 2010).

2.7. Sample size considerations

The sample size for the primary Jinja Cluster Randomized Trial was calculated using the assumption that virological failure rate for participants in the ART facility based care would be 10 per 100 person-years at risk. A sample size of 1200 participants from 20 clusters per group gave over 95% power to show equivalence in virological failure in the two arms, with the assumption that the between cluster coefficient of variation was 0.2. A total of 4560 participants was screened, 2636 participants qualified for ART. From the 2636, 1889 (41%) were enrolled for ART. The remaining 59% did not return to clinic. A total of 1488 patients were started on ART, however, 11 patients didn't meet one of the eligibility criteria for the trial; a total of 1477 remained and were requested to join the trial, but 24 refused so finally 1453 were recruited to the study (Jaffar et al., 2010). This secondary study used a sample size of 1276 participants who were still in the trial at month 12 onwards, so that virological failure could be assessed.

2.8. Data management

In the primary study, all data were doubled entered to ensure consistency. Before performing the secondary analysis, the data were inspected for duplicates and obvious discrepancies. Missing values were checked. For every participant, a summary measure of adherence was obtained using all the adherence data. This was done separately for each of the two self-reported measures of adherence. Confidentiality and privacy of all participants was ensured by removing all identifiers and remaining with a coded study Identity number. All data cleaning and analysis was done using Stata 13.1

3. ETHICAL CONSIDERATION

Ethical approval for the primary study was acquired from the London School of Hygiene and Tropical Medicine, the Uganda Virus Research Institute and the Uganda National Council of Science and Technology. A data sharing agreement was obtained from the Uganda Virus Research Institute. Ethics clearance for this secondary study was obtained from Human Research Ethics committee (HREC), Faculty of Health Science, University of the Witwatersrand, Johannesburg.

4. DATA ANALYSIS

Explanatory variables: The categorical variables included study arm, coded as 1 for facility-based care and 2 for home-based care. Data on clinical, socio-demographic and behavioural characteristics were considered as potential risk factors for ART adherence. Socio-demographic factors included age, sex, educational status and marital status. Sex was coded as 1 for males and 2 for females. Marital status was coded as 1-4, (1: single, 2: married, 3: divorced and 4: widowed). Educational status coded as 1- 4, with 1: no formal education, 2: Primary education, 3: secondary education and 4 was tertiary education.

Clinical factors included BMI, CD4 and WHO stages. HIV WHO stage was coded as I-IV, with I: asymptomatic, II: Moderate weight loss and respiratory infections, III: Severe weight loss and unexplained persistent fever and diarrhoea, IV: HIV syndrome, pneumonia and meningitis (WHO, 2005). CD4 count x 10^6/l, and CD4 group10^6/l coded as I-5, 1: <50, 2: 50- 99, 3: 100-149, 4: 150-199, 5: >=200.

Many participants' adherence to ART might depend on behavioural characteristics; therefore behavioural characteristics included usefulness of adherence reminders, the form of transport used to reach the clinic and the time taken to reach clinic. The question on the usefulness of adherence reminders was included, as it is used in the tools of many health care providers who are trying to improve adherence. These tools include medicine companion and field officers who monitor patients using a check list as part of the trial procedures. The usefulness of the adherence reminder was coded as 1-3 with 1: very useful, 2: moderately useful and 3 as not useful (see appendix 8.3 for the main trial adherence questionnaire). We also believed that in this resource limited setting, the form of transport used to get to the clinics might have influenced ART adherence. The main form of transport was coded as 1 -5, with 1: walk, 2: public taxi, 3: Motorcycle taxi ("Boda-boda"), 4: Bicycle taxi ("Boda-boda") and 5 were other forms of transport. Continuous variables included CD4 count x 10^6/l, age measured in years, time taken to reach clinic in hours and body mass index (kg/m^2).

Statistical analysis

Descriptive analysis

A summary of the study population was given. Description of social, demographic and clinic characteristics of the participants stratified by the trial arm was illustrated. We also gave comparison of demographic and clinic characteristics of participants who qualified for this secondary analysis versus those who did not. For continuous variables, summaries consisting of medians and inter-quartile ranges were given stratified by study arm.

Analysis to address the objectives

Objective one: In order to assess which self-reported adherence measure is a better predictor of virological failure, we fitted separate univariable models using logistic regression and conducted receiver operator characteristic (ROC) curve analysis using virological failure outcomes and predicted probabilities from the logistic model. We used the ROC curve to get optimum cut-off points that give the best trade-off between sensitivity and specificity and area under curve (AUC) as a measure of predictive power, for the two self-reported measures of adherence. ROC models with two different ways of summarizing the results were employed to

estimate the AUC, sensitivity, specificity and cut-off points. In the first method, we estimated the AUC using parametric estimation. We also generated graphical sensitivity and specificity versus probability cut-off. The graph was used to get the best trade-off (cut-off point) to estimate sensitivity and specificity. Method two involved the non-parametric estimation of the ROC since the independent variables (self-reported measures) did not meet the assumption of following a normal distribution. We generated the ROC points by using possible outcomes of the viral load test result and tabulated the calculated sensitivities and specificities for each of the possible cut-off points including the area under the curve. The predictive accuracy of the two models was evaluated by considering the model with the largest AUC with the best sensitivity and specificity. Since neither of the adherence measures performed better than the other, both were used in objective 2b

Objective 2a: In order to find factors associated with virological failure, both univariable and multivariable logistic regression models were fitted. To take into consideration the effect of the clustering of participants, survey robust estimation of the standard errors were used for both univariable and multivariable regression models. The survey estimation was done taking into account the sampling design, namely stratification and clustering. We decided to use a liberal P-value of 0.20 in a univariable analysis as a screening requirement to include variables in the multivariable model with the exception of study arm. Study arm as a design variable was automatically included in all models. We then sequentially omitted variables which were not statistically significant at the 5% level in the multivariable analysis to produce a final model of variables associated with virological failure (this principle was also used in objective 2b). Goodness of fit was assessed for the adjusted model.

Objective 2b (Tobit model): In this objective, we investigated factors associated with self-reported adherence measurement scores. First, univariable Tobit analysis was done and then a final model which included significant predictors of virological failure as well as those from the Tobit model. In order to assess prediction of self-reported measures, we fitted Tobit regression models. Tobit regression models (sometimes referred to as censored regression models) were initially developed by Tobin (1958) and are used when the outcome variable is constrained to take a certain range of values by having either an upper limit or a lower limit or both. The

constraint is defined as either left or right censoring (censoring from below/lower limit and above/upper limit respectively) (Jeffrey, 2013). In our case, self-reported adherence measures were constrained to lie between a lower limit of 0 and an upper limit of 100% and therefore, most of our participants were censored at the upper limit. In the Tobit regression model, the variable y can be regarded as a latent or unobservable dependent variable. The coefficients β assist in determining the relation between y and the independent variables x_i in the same way as in ordinary least squares regression models. Random fluctuations in the relationship between y and x_i are captured by the "normally distributed error term" u_i. We can therefore interpret the coefficients of the Tobit regression model in the same way we would for ordinary least squares regression.

$$y = \beta x_i + u_i,\ u_i \sim N(0, \sigma^2)$$

When fitting the Tobit regression models we used robust survey estimation methods to take into account the effects of clustering and stratification.

Objective 3: Factors associated with virological failure and factors associated with self-reported adherence measurement scores were compared. The comparison considered whether the same factors that predicted virological failure were also associated with each of the two adherence measurements, and whether the estimated effects were consistent i.e. in the same direction. The "same direction" implies that if a risk factor predicted virological failure, we would expect the same variable to show a reduced self-reported adherence score, since poor adherence to ART is expected to lead to virological failure.

5. RESULTS

Table 1 present the distribution of social, demographic and clinical characteristics of the participants according to study arm. The main Jinja trial was a cluster randomised trial where 22 clusters were randomised to either home based care or facility based care with a total of 1453 participants. A total of 1,276 participants qualified for this study. The home based care arm had a higher number of participants (754 patients) while 522 patients were in the clusters that were randomly assigned to the facility based care. The majority of the participants were women (914) compared to 362 men.

The percentage distribution of men and women was similar between the two arms. Many of the participants had CD4 count of less than 50 cells/mm^3 (n=351), and very few of the patients in the trial had CD4 count greater than 200 cells/mm^3. The CD4 cell count was not well balanced between the two arms, in particular a higher proportion of participants in the facility based arm had CD4 count 150-199 (29.50%) compared to those in the home based arm (21.75%). The majority of the participants were in the HIV WHO clinical stage II or III (Stage II: n= 595; Stage III: n=577). The percentage distribution of participants in the HIV WHO clinical stages was similar between the two study arms. Many of the participants in the two arms were either single or married. The means of transport used by the majority of the participants to get to the TASO clinic was public taxi. About 95% of the study participants reported that adherence reminder tools were very useful. A large proportion of the participants reported reaching primary school education (n=713) and few reached tertiary level. The proportion of individuals without any formal education in the home based care (18.70%) was higher than in facility based care (13.60%).

The median age and BMI were similar between the study arms. The overall median age of the patients was 38 years (IQR 32.0-44.0), and that of BMI at enrolment was 21.8 kg/m^2 (IQR 19.1-23.6). The time taken to reach clinic and CD4 count has higher scores in facility based care than home based care. The median CD4 count of participants in the facility based care was 124 (IQR 46-169) compared to 105.5 (IQR 41-167) in the home based care. The overall median CD4 count was 116 (IQR 43.0-167.0). The large geographic area covered by the study meant that the time taken to reach the clinic would vary significantly among participants. The overall median time taken to get to the clinic was 1.0 hours (IQR 0.8-2.0).

Table 1: Socio-demographic and clinical characteristics by study arm				
Variables		**Facility based care (n=522)**	**Home based care (n=754)**	**Total (n)**
Sex	Male	164 (31.42%)	198 (26.26%)	362
	Female	358 (68.58%)	556 (73.74%)	914
CD4 group	<50	137 (26.25%)	214 (28.38%)	351
	50-99	66 (12.64%)	143 (18.97%)	209
	100-149	121 (23.18%)	158 (20.95%)	279
	150-199	154 (29.50%)	164 (21.75%)	318
	>200	44 (8.43%)	75 (9.95%)	119
HIV WHO stages	I	4 (0.77%)	14 (1.86%)	18
	II	236 (45.21%)	359 (47.61%)	595
	III	247 (47.31%)	330 (43.77%)	577
	IV	35 (6.70%)	51 (6.76%)	86
Marital status	Single	194 (37.16%)	262 (34.75%)	456
	Married	205 (39.27%)	313 (41.51%)	518
	Divorced	114 (21.84%)	168 (22.28%)	282
	Widowed	9 (1.72%)	11 (1.46%)	20
Means of transport	Walk	26 (4.98%)	26 (3.45%)	52
	Public Taxi	423 (81.03%)	638 (84.62%)	1061
	Boda/ Motorbike	16 (3.07%)	31 (4.11%)	47
	Boda Bicycle	29 (5.56%)	22 (2.92%)	51
	Others	28 (5.36%)	37 (4.91%)	65
Usefulness of reminder	Very useful	501 (97.09%)	719 (95.87%)	1220
	Moderately useful	14 (2.71%)	23 (3.07%)	37
	Not useful	1(0.19%)	8 (1.07%)	9
Education	None	71 (13.60%)	141 (18.70%)	212
	Primary	295 (56.51%)	418 (55.44%)	717
	Secondary	131 (25.10%)	170 (22.55%)	301
	Tertiary	25 (4.79%)	25 (3.32%)	50
Age median (IQR)		38 (33-44)	37 (32-44)	38 (32-44)
BMI median (IQR)		21 (19.2-23.4)	21.2 (19.2-23.8)	19.1 (21.8-23.6)
CD4 median (IQR)		124 (46-169)	105.5 (41-166)	116 (43-167)
Time median (IQR)		1.25 (1-2)	1 (0.5-2)	1 (0.8-2.0)
IQR= interquartile ranges				

Table 2 describes the comparison of clinical characteristics of patients who were eligible for this secondary analysis and those who were excluded. A higher percentage of individuals excluded from our study were males compared to the group included in this analysis. The proportion of female participants was higher (71.63%) in the group included in our analysis than the group of individuals excluded (66.10%). The median age was 38 (32-44) for the patients included in this study similarly to the individuals excluded from our analysis 36 (30-43). Education status was well balanced between the groups. Majority of the individuals not included in our study were in the WHO stage III (54.24%) and IV (18.08%) compared to 45.22% and 6.74% respectively for those included in this analysis. The median CD4 cell count for individual excluded was 37 (IQR 9-136), a very low value when compared to the participants included in our study 116 (IQR 43-167). A proportion of 52.54% of the excluded individuals were having CD4 cell count less than 50 cells/mm^3 compared to 27.51% of all the participants included in our study.

Table 2: Comparison of clinical characteristics of 1276 patients included in this study and 177 enrolled in the main trail but excluded from this secondary analysis.		
Characteristics	**Total (n)**	
	n = 1276 (%)	n = 177 (%)
Study arm		
Facility	522 (40.91%)	72 (40.68%)
Home	754 (59.09%)	105 (59.32%)
Sex		
Male	362 (28.37%)	60 (33.90%)
Female	914 (71.63%)	117 (66.10%)
Age median(IQR)	38 (32-44)	36 (30-43)
Education		
None	212 (16.61%)	22 (12.43%)
Primary	713 (55.88%)	103 (58.19%)
Secondary	301 (23.59%)	48 (27.12%)
Tertiary	50 (3.92%)	4 (2.26%)
WHO stage		
I	18 (1.41%)	2 (1.13%)
II	595 (46.63%)	47 (26.55%)
III	577(45.22%)	96 (54.24%)
IV	86 (6.74%)	32 (18.08%)
CD4 count median (IQR)	116.0 (43.0-167.0)	37 (9-136)
CD4 level		
<50	351 (27.51%)	93 (52.54%)
50-99	209 (16.38%)	23 (12.99%)
100-149	276 (21.87%)	27 (15.25%)
150-199	318 (24.92%)	21 (11.86%)
>200	119 (9.33%)	13 (7.34%)
IQR = Interquartile ranges; n=1276 :Included in this study; n=177: Not included in this study		

In table 3 we present the self-reported adherence measures categorized into two groups. One group consisted of those who reported less than 100% and the other group was those who reported 100% adherence to see if any of those who reported 100% adherence experienced virological failure at any time from month 12 onwards. The results revealed that 72 (13.87%) out of 519 participants who reported 100% adherence experienced virological failure for VAS. For adherence based on number of pills missed, 128 (12.80%) out of 1000 had virological failure.

Table 3: Distribution of adherence measurement scores according to virological failure status.			
	Virological failure		
Self-reported measures	**No failure**	**Failure**	**Total 1276 (n)**
VAS			
<100%	632 (83.49%)	125 (16.51%)	757
=100%	447 (86.13%)	72 (13.87%)	519
Adherence score based on number of pills missed			
<100%	207 (75.00%	69 (25.00%)	276
=100%	872 (87.20%)	128 (12.80%)	1000

Table 4 shows a description of adherence outcomes and treatment outcome. Assessment of virological failure at 12 months indicated that there were 1,079 (86.56%) participants who didn't have failure and 197 (15.44%) had virological failure. Self-reported adherence measures showed very high scores. The median VAS score was 98.8% (IQR 95.1-100) and median adherence score based on number of pills missed was 100% (IQR 100-100). The median number of pills taken per day was 4 (IQR 2-6).

Table 4: Description of outcomes measurements	
Variables	N (%)
Treatment outcome: Virological failure	
No failure	1079 (84.56%)
Failure	197 (15.44%)
Adherence outcome: VAS median(IQR)	98.8 (95.0-100.0)
Adherence outcome: Number of pills missed median (IQR)	100.00 (100.0-100.0)
Number of pills taken per day median (IQR)	4 (2-6)
IQR: Interquartile ranges	

Objective 1

The results of an analysis of the ability to predict virological failure by the two self-reported adherence measures is shown in tables 5a and 5b.

Table 5a: ROC analysis for adherence visual analogue score (VAS)		
ROC	**Visual analogue score**	
	Method 1	**Method 2**
Optimal cut-offs	0.127	0.982
Area under the curve	59.21%	40.00%
Sensitivity	56.00%	45.18%
Specificity	49.04%	43.73%

Table 5a showed that the optimal cut-off point to balance sensitivity and specificity is 0.127 and an area under the curve of about 60% using method 1 to analyse the ROC. The non-parametric analysis of the ROC using method 2 showed an optimal cut-off point of almost 100% with AUC at 40%. Method 1 predicted only 56% of the virological failures while the second method predicted only 45%.

Table 5b : ROC analysis for adherence based on number of pills missed		
ROC	**Adherence based on number of pills missed**	
	Method 1	**Method 2**
Optimal cut-offs	0.130	1.00
AUC	60.00%	40.36%
Sensitivity	35.50%	64.97%
Specificity	81.06%	19.26%

For the adherence based on number of pills missed, the two ways of summarising the ROC analysis gave contrasting results (table 5b). The predictive capacity of method 1 was 60% while for the other was 40%. Method 1 gave a cut-off point of 0.130 in order to achieve the highest sensitivity (35.50%) and this gave a specificity of 81.66%, while method 2 gave a cut-off of 100% with sensitivity of almost 65% and a very low specificity of 19%. Therefore prediction of participants with virological failure showed that adherence based on number of pills missed only predicted 36% for method 1 and 64.97% for the other method. The ROC analyses showed some similarities and differences between the two adherence measures. The AUC's were similar but sensitivity and specificity were different.

Objective 2a

Table 6 shows the results of the univariable analysis using robust survey estimation to predict possible risk factors associated with virological failure. In this objective, we first investigated whether the effect of CD4 counts on virological failure would be assessed as linear or non-linear. We used a linear term to model the effect of CD4 count, since there was no evidence of non-linearity. The majority of the variables were not associated with virological failure. Using a liberal p-value of 0.20 to screen for variables, age, sex, and usefulness of ART reminders and CD4 counts were confirmed statistically significant. Other than the significant variables, time taken to reach clinic was the only variable to have a p value less than the liberal value of 0.20.

The proportion of virological failure between the study arms was very similar. A higher proportion of males (20%) experienced virological failure than females (14%). Participants who were widows had the highest proportion of virological failure followed by those who were single. The participants with secondary school education had the highest proportion of virological failure compared to other education status. A large proportion of those who had virological failure used Motorbike boda to get to the ART clinic compared to participants who used other means of transport. The proportion of virological failure was low in participants who reported use of adherence reminder as very useful (14%) compared to those who reported reminder as moderately useful (46%) and not useful (67%). A relatively higher proportion of participants diagnosed with WHO clinical stage II and III have experienced virological than participants in other stages of the disease progression.

Table 6: Assessment of the association between factors and virological failure: Univariable model						
Factors	**Levels**	**Total n (%)**	**OR**	**P values**	**95% CI**	
Study arm	Facility	522 (15.33%)	1.00 (ref)			
	Home	754 (15.52%)	1.01	0.941	0.679	1.515
Sex	Males	362 (19.61%)				
	Females	914 (13.79%)	0.66	0.009	0.479	0.895
Age			0.96	0.004	0.940	0.987
Marital status	Single	456 (17.54%)	1.00 (ref)	0.921*		
	Married	518 (12.74%)	0.69		0.454	1.036
	Divorced	282 (13.60%)	0.87		0.537	1.405
	Widowed	20 (35.00%)	2.25		0.876	7.308
Education	None	212 (16.04%)	1.18		0.772	1.733
	Primary	717 (14.17%)	1.00 (ref)	0.592*		
	Secondary	301 (18.60%)	1.385			0.994
	Tertiary	50 (12.00%)	0.826		0.368	1.850
Means of transport	Walk	52 (11.54%)	0.70		0.296	1.668
	Public taxi	1061 (15.65%)	1.00 (Ref)	0.881*		
	Motorbike boda	47 (19.15%)	1.28		0.637	2.558
	Bicycle boda	51 (13.73%)	0.86		0.528	1.392
	Other	65 (13.85%)	0.86		0.455	1.647
Time taken to reach clinic			1.16	0.073	0.986	1.358
Usefulness of reminder	Very useful	1220 (14.04%)	1.00 (ref)	0.001*		
	Moderately useful	37 (45.95%)	5.87		2.535	13.613
	Not useful	9 (66.67%)	12.59		2.836	55.865
WHO clinical stage	I	18 (11.11%)	0.61	0.491*	0.145	2.263
	II	595 (16.97%)	1.00 (ref)		0.076*	
	III	577 (14.90%)	0.86		0.614	1.194
	IV	86 (9.30%)	0.50		2.338	1.076
CD4	Per 25 cell/mm3		0.94	0.010	0.893	0.984
BMI	Per 5 kg/m3		0.93	0.491	0.761	1.142
***Overall p value; CI: Confidence interval; n (%): Total number of participants (percentage of participants with virological failure; OR: Odds ratio**						

Table 7 indicates factors that were significantly associated with virological failure. Study arm and CD4 cell count were not statistically significantly associated with virological failure.

Table 7: Factors that are significantly associated with virological failure. Multivariable analysis				
Factors	**Odds Ratio**	**P values**	**95% CI**	
Study arm				
Facility	1.00 (ref)			
Home	1.05	0.807	0.700	1.579
Sex				
Males	1.00 (ref)			
Females	0.70	0.032	0.507	0.967
Age	0.95	0.001	0.930	0.980
Usefulness of reminder		0.001*		
Very useful	1.00 (ref)			
Moderately	5.28		2.311	12.071
Not useful	8.54		1.721	42.413
Time taken to reach clinic	1.15	0.095	0.974	1.361
CD4 per 25 cells/mm^3	0.96	0.175	0.918	1.016
CI = Confidence Interval *Overall p value				

Table 8 shows the final model assessment of factors associated with virological failure after fitting logistic regression models using the survey analysis approach to adjust for clustering. A Hosmer-Lemeshow test showed no evidence of lack of fit in the model (p=0.933). Participants who were in the home based care arm had about 7% higher odds of experiencing a failure compared to the facility care but the difference was not statistically significant.

Female participants and older participants were less likely to experience failure. Patients who reported finding the use of adherence reminders only moderately useful and not useful at all were more likely to experience virological failure compared to those who found the reminders very useful. The odds of having virological failure among female participants was about 0.70 times that of males (95% CI: 0.485, 0.968; p=0.033). The chances of having virological failure was also found to decrease by 5% as participants get older by one year (95% CI: 0.928, 0.979; p=0.001).

Overall, usefulness of adherence reminder was associated with virological failure (p=0.001). Participants who responded that usefulness of reminders were only moderate or not useful at all had about 6 and 9 times increased odds of developing virological failure respectively compared to those who found it very useful

Table 8: Odds ratios for association of factors with virological failure. Final model				
Factors	**Odds Ratio**	**P values**	**95% Confidence Interval**	
Study arm				
Facility	1.00 (Ref)			
Home	1.07	0.852	0.690	1.560
Sex				
Male	1.00 (Ref)			
Female	0.68	0.033	0.485	0.968
Age	0.95	0.001	0.928	0.979
Usefulness of reminder		0.001*		
Very useful	1.00 (Ref)			
Moderately	5.65		2.472	12.915
Not useful	8.88		1.828	43.108
***Overall p value; Goodness of fit = 0.933**				

Objective 2b

Figures 2 to 4 show a graphical representation of the self-reported adherence of participants. The graphs indicate that the average self-reported adherence score by the study participants was estimated to be about 95% with the majority reporting 100% adherence to ART.

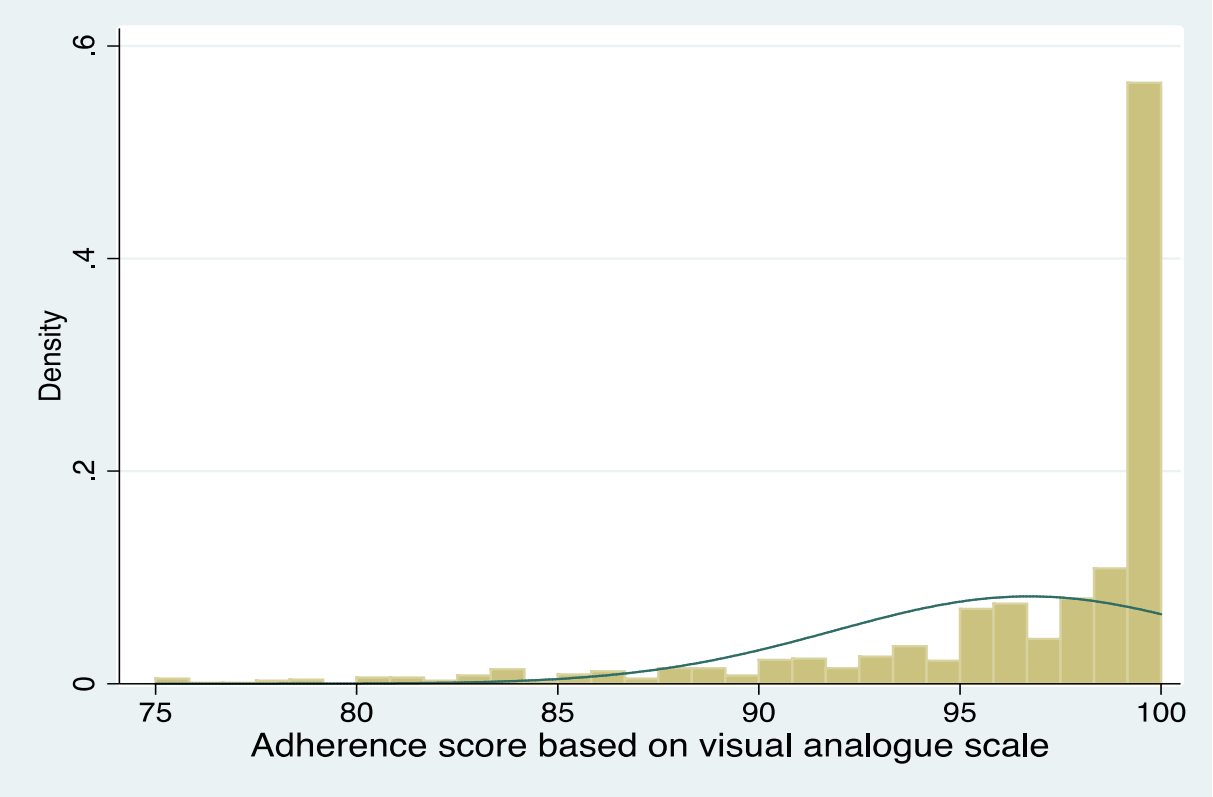

Figure 2: Distribution of adherence score based on VAS (%). The graph shows majority of the participants have reported VAS adherence score between 80 and 100%.

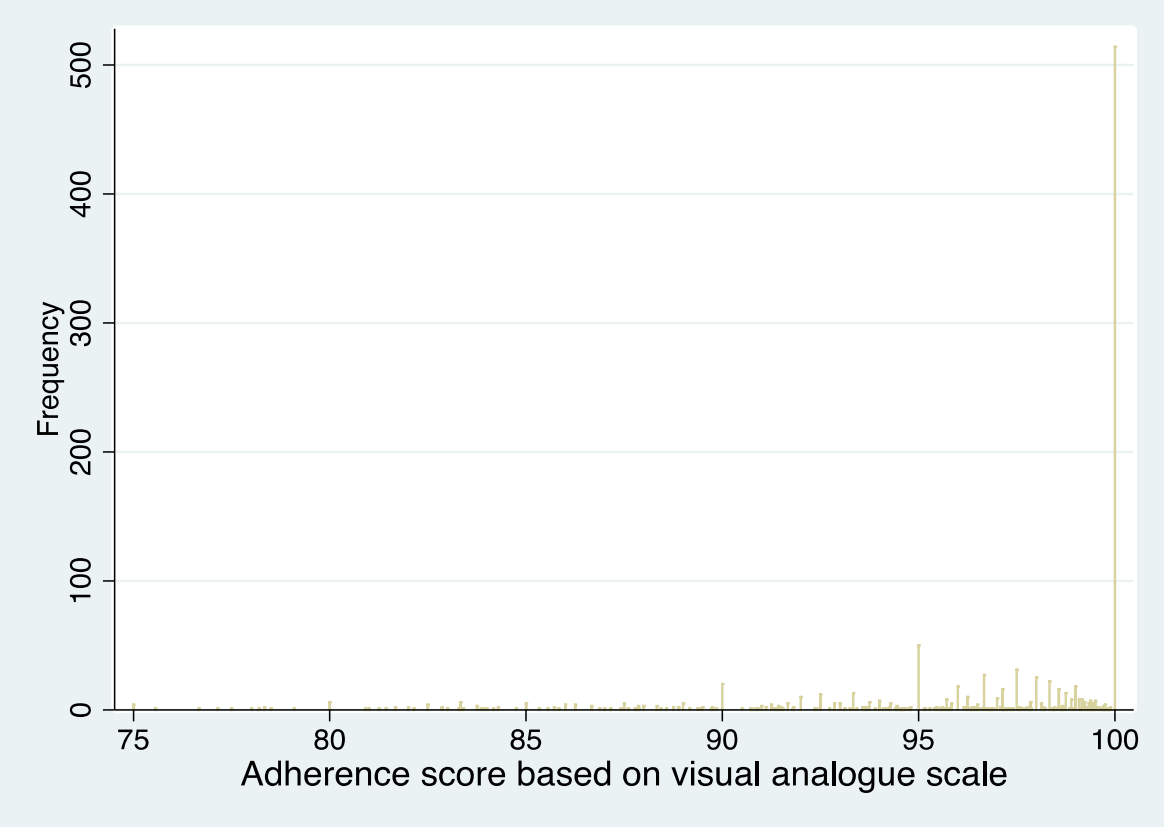

Figure 3 Highlights excess number of participants with VAS score equal = 100%. Due to continuous nature of the scores, most values are unique in the dataset. The height of the bar where VAS score = 100% when compared to other bars shows that the vast majority of participants have reported 100% adherence

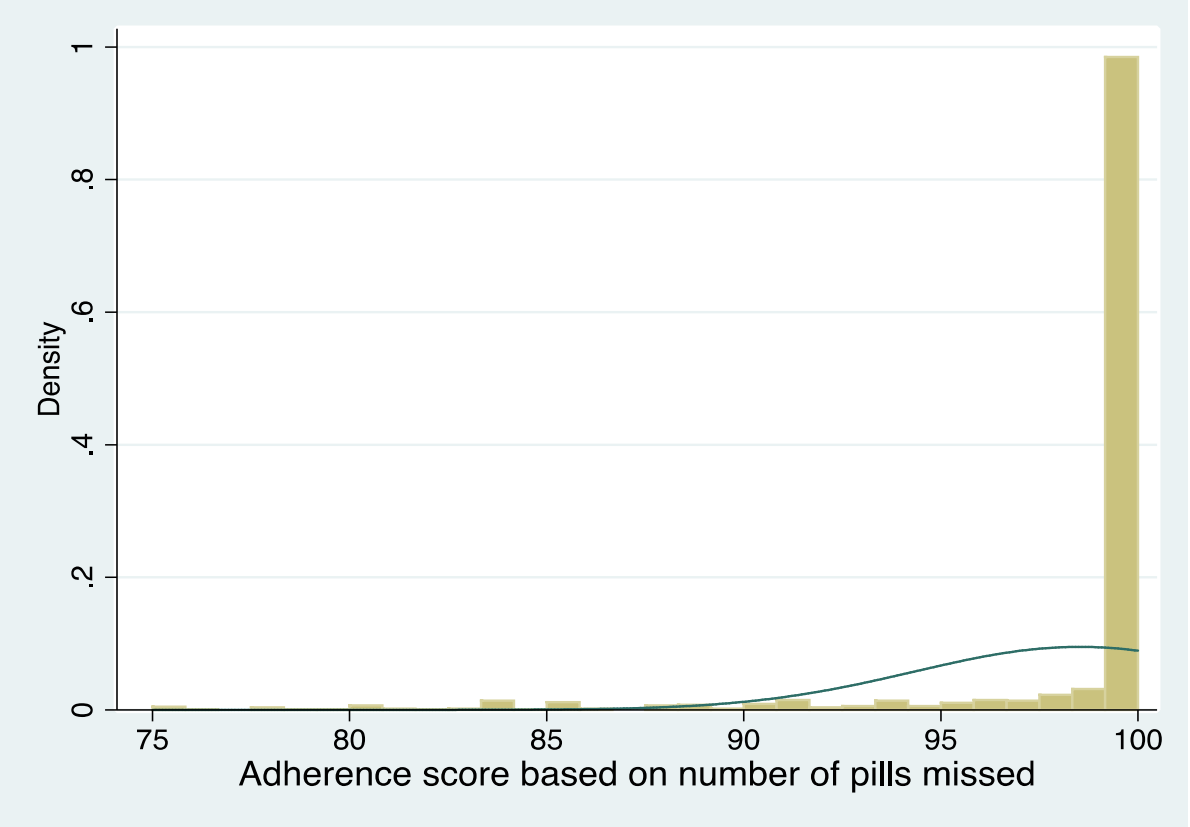

Figure 4: Distribution of adherence score based on the number of pills missed (%). It shows there were more participants with adherence based on number of pills missed score reported 100%.

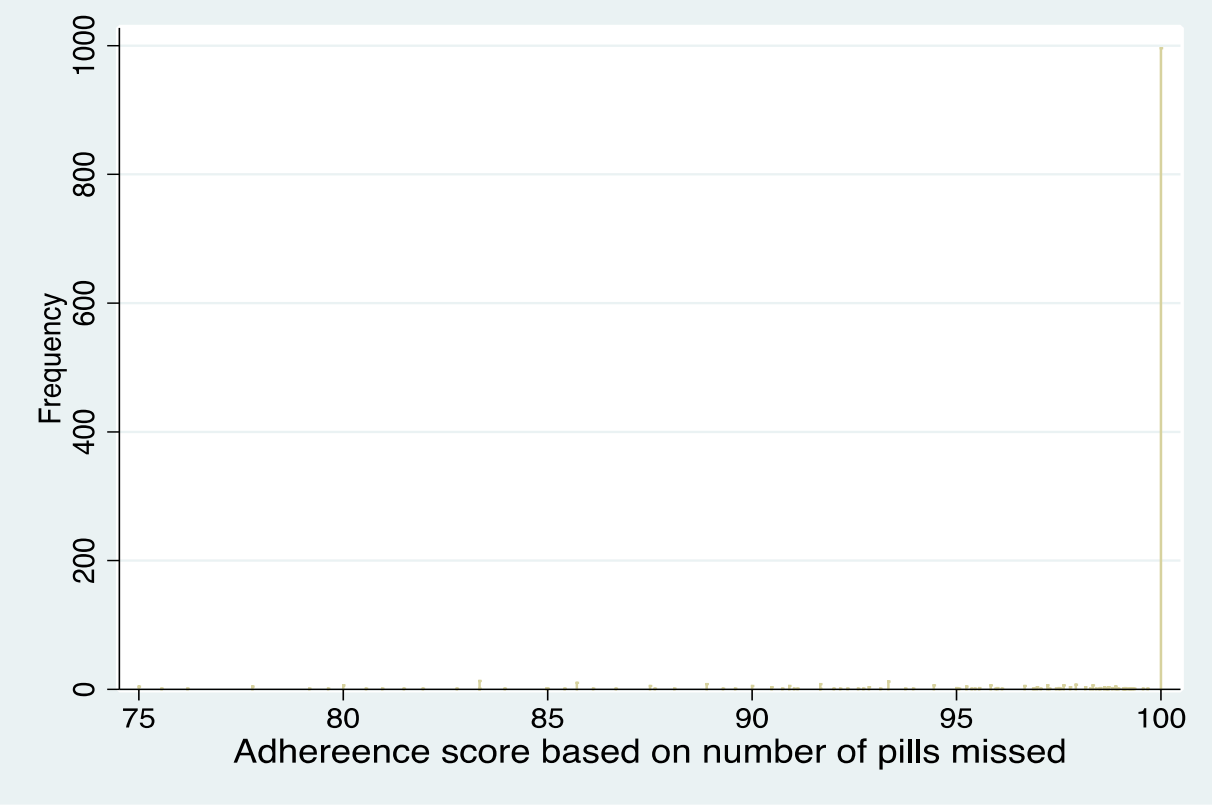

Figure 5 indicates the excess are participants where adherence score based on number of pills missed is equal to 100%. Due to continuous nature of adherence based on number of pills missed, most values are unique in the dataset. The height of the bar where adherence based on number of pills missed = 100% when compared to other bars shows the excess (too many) participants with the 100% value.

Visual analogue scale

In this objective, we fitted univariable Tobit models, using robust survey estimators, to find factors associated with VAS. Table 9 shows the results of a univariable analysis to assess possible risk factors associated with VAS. Here we also used a liberal p value (P=0.20) as a cut-off to consider variables for inclusion into the final model, the same principle was applied to adherence based on number of pills missed. Variables including education, time taken to reach clinic and usefulness of reminder have P-values less than 0.20.

Table 9: Assessment of the association between factors and VAS: Univariable model					
Factors	**Levels**	**Coeff**	**P values**	**95% Confidence interval**	
Study arm	Facility	1.00 (ref)			
	Home	0.792	0.408	-1.128	2.714
Sex	Males	1.00 (ref)			
	Females	2.822	0.014	0.597	5.048
Age		-0.026	0.556	-0.115	0.063
Marital status	Single	1.00 (ref)	0.006*		
	Married	2.516		0.223	4.809
	Divorced	2.504		0.303	4.705
	Widowed	5.447		-4.444	12.339
Education	None	0.763		-1.922	3.449
	Primary	1.00 (ref)	0.107*		
	Secondary	-1.794		-3.742	0.153
	Tertiary	-2.778		-8.972	3.414
Means of transport	Walk	-0.97		-5.505	3.106
	Public taxi	1.00 (Ref)	0.297*		
	Motorbike boda	-0.223		-4.060	3.613
	Bicycle boda	1.508		-2.251	5.268
	Other	-4.012		-9.906	1.882
Time taken to reach clinic		0.458	0.193	-0.241	1.158
Usefulness of reminder	Very useful	1.00 (ref)	0.135*		
	Moderately useful	-6.504		-14.376	1.367
	Not useful	-1.611		-13.404	10.180
WHO clinical stage	I	-7.652		-20.950	5.645
	II	1.00 (ref)	0.640*		
	III	-1.439		-3.921	1.043
	IV	3.439		0.224	7.156
CD4 count	Per 25 cells/mm^3	-0.060	0.727	-0.407	0.286
BMI	Per 5 kg/m^3	-0.092	0.834	-o.980	0.795
***Overall p value**					

In table 10, we ran Tobit models with robust survey estimation to see how significantly associated factors and factors that met the liberal p-value for inclusion would predict VAS. The results indicated that study arm, sex, marital status, usefulness of reminder and education were not statistically significantly associated with VAS. Time taken to reach clinic showed a marginally significant relationship with VAS.

Table 10: Factors that were significantly associated with VAS: Multivariable model				
Factors	**Coefficients**	**P values**	**[95% Confidence interval**	
Study arm				
Facility	1.00 (ref)			
Home	0.401	0.573	-1.027	1.830
Sex				
Male	1.00 (ref)			
Female	1.206	0.126	-0.357	2.770
Marital status				
Single	1.00 (ref)	0.070*		
Married	1.732		-0.274	3.739
Divorced	1.422		-0.483	3.327
Widowed	5.167		-1.296	11.631
Usefulness of reminder				
Very useful	1.00 (ref)	0.154*		
Moderately useful	-6.691		-14.036	0.654
Not useful	-0.718		-12.193	10.756
Time taken to reach clinic	0.598	0.055	-0.013	1.209
Education				
None	1.502		-4.331	3.437
Primary	1.00 (ref)	0.121*		
Secondary	-0.918		-2.569	0.731
Tertiary	0.941		-1.801	3.683
*** overall p value**				

Table 11 is the final model. Factors that were significantly associated with virological failure were included into the final model, since the interest of our study was to compare self-reported adherence with HIV viral load testing. The finding indicated that only sex was significantly predictive of visual analogue score while time taken to reach clinic showed a marginally significant effect. The visual analogue score was 2 points higher among female participants than males (coefficient: 2.218; 95% CI 0.681, 3.755; p=0.006). Time taken to reach clinic showed a marginally significant association with VAS. A unit increase in time taken to reach the clinic would increase VAS by 0.606 points (95% CI: -0.020, 1.233). The rest of the predictors of virological failure showed no association with visual analogue score.

Table 11: Prediction of VAS using factors associated with virological failure and factors associated with VAS: Final model analysis				
Factors	**Coefficients**	**P Values**	**95% Confidence Interval**	
Study arm				
Facility	1.00 (ref)			
Home	0.480	0.507	-0.974	1.936
Sex				
Males	1.00 (ref)			
Females	2.218	0.006	0.681	3.755
Age	-0.006	0.868	-0.086	0.073
Usefulness of Reminder		0.163*		
Very useful	1.00 (ref)			
Moderately useful	-6.244		-13.809	1.320
Not useful	-0.946		-12.777	10.885
Time taken to reach clinic	0.606	0.058	-0.020	1.233
*** = Overall p value**				

Adherence based on number of pills missed

Self-reported adherence based on the number of pills missed was modelled using Tobit analysis with robust survey estimation. Univariable analysis was conducted to screen significantly associated variables, the same principles applied in VAS analysis was also used for adherence based on the number of pills missed (table 12). The results showed that only the study arm was associated with adherence based on number of pills missed, while usefulness of reminders was marginally significant (p=0.08).

Table 12: Assessment of the association between factors and adherence based on number of pills missed: Univariable model					
Factors	**Levels**	**Coeff**	**P values**	**95% Confidence interval**	
Study arm	Facility	1.00 (ref)			
	Home	15.143	<0.001	8.719	21.566
Sex	Males	1 (ref)			
	Females	1.80	0.510	-3.695	7.304
Age		-0.017	0.926	-0.403	0.368
Marital status	Single	1.00 (ref)	0.789*		
	Married	0.2114		-5.489	5.912
	Divorced	-0.303		-7.659	7.052
	Widowed	-5.788		-24.298	12.721
Education	None	4.357		-3.406	12.120
	Primary	1.00 (ref)	0.810*		
	Secondary	1.435		-5.017	7.888
	Tertiary	2.389		-18.169	22.928
Means of transport	Walk	-6.637		-18.518	5.243
	Public taxi	1.00 (Ref)	0.409*		
	Motorbike boda	-4.427		-18.622	15.767
	Bicycle boda	1.939		-9.055	12.934
	Other	-10.544		-25.675	4.586
Time taken to reach clinic		-1.827	0.213	-4.749	1.095
Usefulness of reminder	Very useful	1.00 (ref)	0.080*		
	Moderately useful	-18.581		-34.987	-2.176
	Not useful	2.218		-37.378	41.815
WHO clinical stage	I	0.024		-39.857	39.907
	II	1.00 (ref)	0.982*		
	III	-2.609		-11.246	6.027
	IV	7.419		-5.105	19.944
CD4	Per 25 cells/mm^3	-0.330		-1.286	0.653
BMI/25	Per 5 kg/m^3	-1.094	0.452	-4.009	1.821
***Overall p value**					

Table 13 shows multivariable model for variables that were selected from table 10.

Both study arm and the usefulness of reminders were statistically significantly associated with adherence based on number of pills missed.

Table 13: Factors that were significantly associated with adherence based on number of pills missed: Multivariable model				
Factors	**Coeff.**	**P>t**	**95% Confidence interval**	
Study arm				
Facility				
Home	12.873	0.001	7.500	18.246
Usefulness of reminder		0.035		
Very useful	1.00 (ref)			
Moderately useful	-19.247		-35.099	-3.395
Not useful	-2.588		-42.052	36.874

Table 14 is a final model incorporating factors associated with virological failure including and those associated with number of pills missed. Participants' sex and age at baseline were not statistically significantly associated with adherence based on number of pills missed. Both study arm and the usefulness of reminders were statistically significantly associated with adherence based on number of pills missed. Patients who were getting their ART from home had 13% higher predicted adherence as measured by the reported number of pills missed than those who were using facility based care for treatment. (Coefficient: 12.921; 95% CI: 7.887, 17.954 and p = 0.001). The overall effect of usefulness of reminder was significant (p=0.036). Those who reported usefulness of reminder as only moderately useful had scores of about 20% lower than the scores of those who found reminders very useful.

Table 14: Prediction of adherence based on number of pills missed using factors associated with virological failure and factors associated with VAS: Final model analysis				
Factors	**Coefficient**	**P value**	**95% Confidence interval**	
Study arm				
Facility	1.00 (Ref)			
Home	12.921	0.001	7.887	17.954
Sex				
Male	1.00 (Ref)			
Female	-0.391	0.858	-4.813	4.030
Age	0.016	0.915	-0.289	0.321
Usefulness of reminder		0.036*		
Very useful	1.00 (Ref)			
Moderately useful	-19.310		-35.557	-3.064
Useful	-2.688		-43.040	37.663
***Overall p value**				

Objective 3:

Table 15 summarises the comparison of the prediction of self-reported measures in terms of the factors that were associated with virological failure. Correct direction of the prediction was that if a participant showed odds of experiencing of virological failure, then the same person should have also reported lower self-reported adherence score.

Table 15: Comparison between predictors of virological failure and self-reported adherence scores

Factors	**Virological failure**		**VAS**		**Number of pills missed**	
	Odds ratio	**P value**	**Coefficient**	**P value**	**Coefficient**	**P value**
Study arm						
Facility	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Home	1.07	0.852	0.480	0.507	12.921	0.001
Sex						
Male	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Female	0.68	0.033	2.218	0.006	-0.391	0.858
Age	0.95	0.001	-0.006	0.868	0.016	0.915
Usefulness of reminder		0.001*		0.163*		0.036*
Very useful	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Moderately useful	5.65		-6.244		-19.310	
Not useful	8.88		-0.946		-2.688	
Time taken to reach clinic	-	-	0.606	0.058	-	-
***overall p value**						

Overall, no single factor was associated with all three outcomes although sex and usefulness of reminders were associated with virological failure and one of the self-reported adherence measures. Participants in the home-based care arm had significantly better adherence by pill report than those in the facility based arm. There was no evidence that study arm was associated with virological failure and also no evidence that study arm was associated with the VAS adherence measure. Patients' sex showed same predictive direction with virological failure less likely for females and VAS higher for females, but lower for females using adherence based on number the pills missed. A similar finding was observed with age. Only the usefulness of reminders showed the same direction of prediction, that is to say, virological failure increased among those participants who found usefulness of reminders as moderate, the same patients also reported decreased self-reported scores. However, usefulness of reminder was not significantly associated with the VAS. Time taken to reach clinic showed a marginally significant relationship with VAS but it was not associated with other 2 outcomes.

6. DISCUSSION

The aims of this study were to assess two self-reported measures of adherence and also find factors associated with adherence.

Our summary measure indicated that median score for VAS and adherence based on number of pills missed was 98 and 100% respectively which was above WHO recommended 95% adherence expectation for people under ART medication (Stone et al., 2001). Despite having very high adherence scores, some patients who reported an adherence rate of 100% in our study still experienced virological failure, with an average of 14% of the participants who reported 100% adherence experiencing virological failure. Similarly, another study observed about 19% of those who reported 100% adherence to treatment having detectable virological failure (Côté et al., 2015, Dobbels et al., 2010). This finding tends to answer the dilemma posited by Wu et al. (2014) which questioned if self-reported measures, which tend towards "over-adherence", can be used as a surrogate marker for virological failure. Description of social and demographic and clinical characteristics by study arm showed a higher number of participants in home based care than facility based care. This finding is similar to that main paper of this study which also found that higher number of participants described by demographic and clinical character is in home based care (Jaffar et al, 2010). Percentage comparison between the arms was similar except for CD4 count which showed a lower median CD4 count in the home based care than in the facility based care, which could be due to chance. We also observed that the median CD4 count for individuals excluded from our study was lower than for those included. This difference in median CD4 count could be that the patients with very low CD4 counts were more likely to die before the 12 month follow-up visit, hence they were more likely to be excluded.

For objective one, we compared two self-reported measures of adherence by assessing how well each predicts virological failure. We used two ROC methods which gave different assessment of the predictive ability of self-reported measures. The first ROC method was a parametric estimation of AUC and graphical generation of sensitivity and specificity versus probability cut-off while the second method employed a non-parametric version which generated possible outcomes of viral load and tabulated calculated sensitivities and specificity for each cut-off point including AUC. A ROC curve is a common diagnostic method used in epidemiology to check

how well a marker discriminates between two disease states (Swets, 1986, Metz, 1978). In the case of our study, we were discriminating between having virological failure or no virological failure. Different criteria have been employed to summarize ROC results (Swets, 1979, Hanley and McNeil, 1982, Kramer, 1988). Based on these principles, we used AUC, sensitivity and specificity to evaluate the two self-reported measures in prediction of virological failure. Looking at AUC, we found that the two ROC methods give different results. Method 1 showed that the AUC was about 60% for both self-reported adherence measures, while method 2 had 40%. An AUC estimates the predicative power of the self-report measures in determining patients with virological failure. A perfect AUC is equal to 1 meaning that in our case, the adherence measures should be able to accurately differentiate between participants with virological failure and those without virological failure and an AUC of 0.5 is by chance. Our results indicated that the two methods are not good predictors of virological failure especially since method 2 which is an empirical ROC method, had less than 50% AUC, meaning the adherence rate performed worse than chance (Hanley and McNeil, 1982). Both VAS and number of pills missed showed lower predicative ability of participants with virological failure by the two ROC methods. The ability of the adherence measures was based on how well they predict virological failure. This low prediction of the participants with virological failure indicated that self-reported adherence does not adequately predict failure. Available studies compared adherence measurement methods such as pharmacy refill, electronic monitoring and self-report in prediction of virological failure. Our finding is consistent with these comparative studies. For example, a study conducted in Tanzania which showed that self-reported adherence was not a good predicator of virological failure as it was outperformed by pharmacy refill measures (Sangeda et al., 2014). Another comparison of adherence measures also revealed that self-reported adherence is less sensitive as the chances of having virological failure was higher than using electronically monitored adherence (Arnsten et al., 2001a). Our results differ from the finding of a study which reported that self-reported measures are valid when compared with viral load count values (Godin et al., 2003). Our results showed that self-reported measures cannot be used as a substitute for viral load measurement to determine virological failure because they predict virological failure poorly. Despite its widely known low cost and ease of operation, our findings have shown that self-reported adherence measures over-estimate actual adherence.

For objective 2a we investigated the risk factors associated with virological failure. Since a binary outcome was used in objective 1, we decided to also employ the same binary outcome for finding factors associated with virological failure in this objective. An alternative approach to the analysis would have been to use a time to event analysis to analyse the time to virological failure, but this was not done in this analysis.

Our findings showed that the risk factors associated with virological failure were sex; age, and usefulness of adherence reminders. Female participants were at a lower risk of having virological failure, indicating that females adhere better to ART treatment than males. It is not known why females experience less virological failure than males. We think that women's chance of experiencing lower virological failure than men could be due to being more careful about their personal wellbeing than males. Another possible explanation could be that women obey medication instructions much better. In Africa, one possible reason could be that men leave their home to work while women remain in the home settings which might lead to missed doses in the case of men. A similar study conducted in Burkina Faso also showed susceptibility to virological failure was higher among men than women (Penot et al., 2014). In contrast, a study conducted in Brazil showed that chances of poor adherence are much higher among females than males (de Fatima Bonolo et al., 2013). These conflicting results may be due to differences in adherence measurement tools and number of male and female participants enrolled. Gender effects might also vary between different cultures.

Another result showed that older people were at a lower risk of virological failure. We suggested that lower risk of virological failure in older participants might be due to their understanding or awareness of the HIV/AIDS effects. Our finding is consistent with a study conducted in Uganda which found that patients who were older than 35 years had 50% chance of having decreased virological failure compared to those who were below 35 years of age (Ahoua et al., 2009). The finding is also consistent with a study in Swaziland, Jobanputra et al. (2015) also confirmed that younger age group were more likely to have detectable viral load (virological failure) than adults. However some studies have contrasting results, for instance studies by Kilaru et al. (2006) and Moore et al. (2005) reported that participants of advanced age are at risk of treatment failure. Our finding can be attributed to the difference in knowledge

about the importance of ART and the lack of social support among the young compared to the older population.

We found that the odds of virological failure tended to increase by 6 fold among participants who found reminders as only moderately useful compared to participants who found reminders very useful, while participants who didn't think adherence reminders were useful had a 9-fold increased probability of virological failure. Typical example of adherence reminders could include timers/alarm and adherence support mechanism from family members. It could be argued that those who do not use reminders tend to forget taking medication in a timely fashion; this could lead to virological failure. The finding is supported by studies which found that forgetfulness is an important indicator of increasing virological failure (Watt et al., 2010, Mitiku et al., 2013, Shumba et al., 2013). Forgetfulness is confirmed by our study which stated that the use of a personal adherence reminder tool is an important part of ART administration as people who found use of reminders as useful experienced significantly decreased rate of virological failure compared to those who did not use reminders. Our findings support the fact that further studies in Africa also found forgetfulness is the main factor for non-adherence (Mthembu and Van Wyk, 2014, Odili et al., 2016). The use of adherence reminders is an important intervention to ensure adequate adherence to drug regimens. Failure to use reminders would make patients forget to take ART regimens.

For objective 2b, we determined the factors associated with self-reported measures of adherence using Tobit modelling. The Tobit model was used because the data is constrained to fall between two points (0 and 100%) and the data thus did not meet the assumptions for linear regression. From the Tobit model, females reported higher VAS adherence than males while study arm and usefulness of reminder were predictive of number of pills missed. There is gender disparity in access of ART and this could lead to better self-reported adherence reports among women than men. We also think that men might have poor access to HIV voluntary counselling and testing and ART clinics partly because of fear of stigmatization. Gender differences in access and adherence to ART may be related to several support services offered to women. For instance, in resource limited countries, there is increased maternal care comprising of mother to child HIV transmission programmes and counselling could have created such disparity between men and women (Braitstein et al., 2008).

Time taken to reach clinic was marginally significantly related to reporting VAS. Our study showed that participants who took a longer time had higher VAS score. Ideally, longer time taken to reach clinic means the distance to the clinic is far but some studies showed that the long distance to the ART clinic decreases adherence which is contrary to our findings (Mills et al., 2006a). We think that participants might feel they have worked so hard to get the medication by spending many hours to go to the clinic to get ART and this might have made them adhere well to the drugs. Also time taken to reach clinic might vary significantly between home based care and facility based care since those in the home based visited the clinic much less often. Patients who considered the usefulness of reminders as being only moderately useful had lower chances of high reporting scores for adherence based on number of pills missed than those who found it very useful. This is consistent with a study which found that adherence was higher among groups utilising reminder tools for uptake of ART doses than people who did not (Fenerty et al., 2012). Use of adherence reminders might have resulted in consistent uptake of ART which led to better self-reported adherence measurement scores. Patients receiving home based care of ART had a higher predicted value of adherence based on number of pills missed. Bringing HIV treatment services closer to the people or to the community might have importantly reduce the burden and cost of travelling to clinics to receive treatment thus such plans might have contributed to better chances of reporting adherence. Elsewhere in Brazil, similar comparison showed that participants from home based care reported better adherence than facility care (Gupta et al., 2005).

For objective 3, we directly compared results from objectives 2a and 2b. We could not find any particular variable that was associated with all three of the adherence measures. We observed that sex had the same direction of prediction of virological failure and VAS; the same was confirmed with usefulness of adherence and study arm in reporting adherence based on number of pills missed scores. We suggest that these findings support the assertion from objective one which confirmed self-reported method of evaluating ART adherence is not as good as viral load count.

Strength and limitations

The strengths of our study in the context of a randomised controlled trial are that our study had relatively large sample size; little missing data and rigorous data collection methods were employed. On the other hand, there are a number of limitations in this

study. The disparity in CD4 count between the study arms may be due to the weakness of the study design in achieving similarity through randomisation (Jaffar et al, 1999). One limitation of our study is that we used only two of the self-reported measures of adherence; there might be other measures of adherence that are better at predicting virological failure. The number of participants we used in this analysis was more than the number used in the main trial. Participants who did not have any viral load measurements after 12 months, or had a single viral measurement between 500-1000 copies/ml, but not confirmatory measurement were included in this study. Such participants were regarded as not having experienced virological failure, as this is the reason why including them could result in some bias. A liberal p value of <=0.20 in a univariable analysis was used to include variables in the multivariable analysis; some associations might have been missed if there was negative confounding. An alternative approach could have been used in this regard. Our results demonstrated there may be high social desirability bias where some participants tend to over-report adherence in order to be viewed favourably by the trial staff. This ultimately affects the ability of the self-reported adherence measures to correctly predict virological failure. We used only a 3-day period to measure adherence based on number of pills missed, with such an interval, it becomes difficult to group participants with better adherence over long period and those with better adherence maybe for just over short period of time yet they may be adhering poorly overall (Simoni et al., 2006b). As studies by Swets (1988) and Begg (1991) confirmed, our study used a single sensitivity and specificity value which was chosen by looking at cut-off points, thus such cut-off points is based on personal choice rather any reason or system. Some of our variables have very few individuals in some categories; this would affect the precision of the effect estimates and make it difficult to find statistical significance. The distribution of the adherence measures is extremely skewed; this might have affected the performance of the ROC curve in computing sensitivity and specificity.

Conclusion and recommendation

In conclusion, our study shows that self-reported measures are poor predictors of virological failure and therefore, are not good measures of ART adherence. We expected that self-reported adherence measures should be able to correctly predict at least 85% of patients with virological failure, but the measures only correctly

predicted between 35% to 65% of the participants with virological failure. No risk factor was associated with all the adherence measurement methods. Study arm and usefulness of adherence reminder was associated with adherence based on number of pills missed. Measuring ART adherence is one of the most important components in the fight against HIV and AIDS. Viral load testing should be highly encouraged even in resource limited settings.

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8. APPENDICES

8.1. APPENDIX 1

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I _Felix Made_____ (Student number: _____1239045_____) am a student registered for the degree of ____MSc Epidemiology and Biostatistics_____ in the academic year _2016_____.

I hereby declare the following:

I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.

I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.

I have followed the required conventions in referencing the thoughts and ideas of others.

I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature:

Date: **29 August 2016**

8.2. APPENDIX 2

R14/49 Mr Felix Made

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M151173

NAME: (Principal Investigator)	Mr Felix Made
DEPARTMENT:	Public Health Jinja, Uganda
PROJECT TITLE:	Validation of Self-Reported Measures of Adherence to ART and Factors Associated with Adherence in Jinja, Uganda
DATE CONSIDERED:	27/11/2015
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Janathan Levin
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/12/2015

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Secretary in Room 10004, 10th floor, Senate House, University.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**.

Principal Investigator Signature Date

8.3. Adherence questionnaire

TASO/MRC/CDC ART DELIVERY RESEARCH PROGRAMME

To be administered at a) 2, 6, 12, 18, 24, 30, 36 month routine visits, b) at any time a client presents with suspected treatment failure and c) at the unannounced home visit 6 months after recruitment.)

Interviewer to read:

We understand that many people on ART drugs find it difficult to take the drugs and often miss doses. We will not be surprised if you have missed lots of doses as well. We need to know how many doses you missed. The answers that you give shall not affect the services that you receive from TASO.

Tukimanyi nti abantu bangi abamira eddagala lya ART kibakaluubirira okumira eddagala lino nebatayosaamu. Tekijja kutwewunyisa singa naawe oba wayosaamu okumira amakerenda agawerako. Kyetwagala kwekumanaya obungi bw'eddagala lyewakayosa okumira. Kino tekija kukosa mungeri yonna obuyambi bw'ofuna okuva mu TASO.

SECTION 1. GENERAL

1.0	Client ID Number	*6 digits*	STUDY_ID	10

2.0	Today's date	*dd / mm / yyyy*	TDATE	20

3.0	Which type of visit is this?	*1-3 from codes below*	**If 2,3 >> 5.0**	VISTCAT	30

1=scheduled routine visit (at 2, 6, 12, 18, 24, 30, 36 months), **2**=client is unwell and has been referred or has self-referred. **3**=unannounced home visit by MRC

4.0	Interview round	*1-7 from codes below*	IROUND	40

1=2 monthly, **2**=6 monthly, **3**=12 monthly, **4**=18 monthly, **5**=24 monthly, **6**=30 monthly, **7**=36 monthly **8**=42 monthly, 9=48 monthly

5.0	Has any of your ART medication changed in the last 6 months ***Amakerenda g'omira aga ART gaali gakyuseemu mu myezi mukaga egiyise?***	*1 = yes, 2 = no*	TCHANGE	50

SECTION 2. VISUAL ART ADHERENCE SCORE

Interviewer to read: *Please put a cross on the line below at the point showing your best guess about how much ART medication you have taken in the <u>last 28 days:</u>*

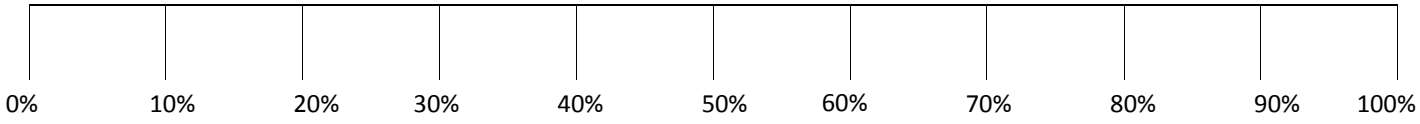
0% means you have taken no ART drugs

50% means you have taken half of your ART drugs

100% means you have taken all your ART drugs.

Tukusaba oteeke akasale kukasitaale kano wamanga akalaga w'olowooza nti wewasinga okulaga obungi bw'eddagala lya ART ly'omizze munaku abiri mumunaana (28) eziyise.

Awasooka (0%) walaga nti tolina ddagala lyonna elya ART ly'omizze,
Wakati (50%) walaga nti kuddagala elya ART lyolina okumira, omizeeko ebitundu ataano ku buli kikumi,
Awaseembayo (100%) walaga nti eddagala elya ART ly'olina okumira, lyonna olimizze.



6.0	Visual score	*Read from above*	VISUAL	60

SECTION 3. ART PILLS MISSED

7.0	How many ART pills (tablets) do you take per day? ***Omira amakerenda ga ART ameka olunaku?***	*Number of pills*	NOPILLS	70

8.0	Have you missed taking any of your ART pills in the last 3 days (excluding today)? ***Waliwo lwotamira amakerenda go aga ART munaku ssatu eziyise (ng'ogyeko olwaleero)?***	*1 = yes, 2 = no*	ANYMISS3 **IF 2 » 9.0**	80

8.1	**If yes** ***Oba Ye***	How many ART pills did you miss yesterday? ***Amakerenda ameka aga ART g'otamize jjo?***	*Number of pills*	NOMISS3	90

8.2	How many ART pills did you miss the day before yesterday? ***Amakerenda ameka aga ART g'otamira okwosa jjo?***	"	MISSM1	100

8.3	How many ART pills did you miss day before that (3 days ago)? ***Amakerenda ameka aga ART g'otamira enaku ssatu eziyise (enaku ssatu eziyise)?***	"	MISSM3	110

9.0	How many ART pills have you missed in the last 2 weeks? ***Amakerenda ameka aga ART g'otamira sabiiti bbiri eziyise?***	*Number of pills*		MISSM14	120

10.0	How many ART pills have you missed in the last 1-month? ***Amakerenda ameka aga ART g'otamira omwezi gumu oguyise?***	"		MISSM28	130

11.0	When was the last time you missed your ART pill? ***Ddi lwewasembayo okwosa okumira amakerenda go aga ART?***	*1-7 from list below*	**IF 6 or 7** **» 24.0**	LASTMISS	140

1=today, **2**=yesterday, **3**=earlier this week, **4**=last week, **5**=less than a month ago, **6**=more than a month ago, **7**=have never missed taking my ART pill.

SECTION 4. REASONS FOR MISSING ART PILLS

Interviewer to read: *People may miss taking their medicines for various reasons. Here is a list of possible reasons why you may miss taking your medicines. In the last month, did you miss taking your medicines because of the following?*

Abantu boosa okumira eddagala lyabwe olw'ensonga emu oba endala. Wamanga waliwo ensonga zetulowooza nti zezimu kwezo. Mumwezi oguwedde, wayosa okumira eddagala lyo olw'ensonga zino?

12.0	You were away from home ***Wali toliiwo awaka***	***1****=yes,* ***2****=no*	AWAYHOME **If 2 » 13.0**	150
12.1	If yes, how many times? ***Oba Ye, gyaali mirundi emeka?***		NAWAYHOME	160
13.0	You simply forgot ***Werabira bwelabizi***	***1****=yes,* ***2****=no*	FORGOT **If 2 » 14.0**	170
13.1	If yes, how many times? ***Oba Ye, mirundi emeka?***		NFORGOT	180

14.0	You had too many pills to take and could not swallow all ***Wali olina empeke nyingi ez'okumira, nezikuyitirirako.***	***1**=yes, **2**=no*	PILLBURDEN **If 2 » 15.0**	190

14.1	If yes, how many times? ***Oba Ye, gyali emirundi emeka?***	NPBURDEN	200

15.0	You had fear of side effects (e.g. felt drug was toxic or harmful?) ***Watya ebiyinza okuva mukukozesa eddagala (tugeze ng'okulowooza nti liyinza okuba nga lyabulabe)***	***1**=yes, **2**=no*	SEFFECT **If 2 » 16.0**	210

15.1	If yes, how many times? ***Oba ye, gyali emirundi emeka?***	NFEARAE	220

16.0	You fell sick ***Walwala***	***1**=yes, **2**=no*	FELLSICK **If 2 » 17.0**	230

16.1	If yes, how many times? ***Oba Ye, gyali emirundi emeka?***		NFELLSICK	240

17.0	You felt depressed/overwhelmed with issues of your illness ***Wawulira nga oli mweralikirivu nga ebikwata kubulwadde bw'olina bikuyitiriddeko***	***1**=yes, **2**=no*	FELTDEP **If 2 » 18.0**	250

17.1	If yes, how many times? ***Oba Ye, gyali emirundi emeka?***		NFELTDEP	260

18.0	You ran out of medicines ***Eddagala lyaggwawo***	***1**=yes, **2**=no*	RANOUT **If 2 » 19.0**	270

18.1	If yes, how many times? ***Oba Ye, gyali emirundi emeka?***		NRANOUT	280

19.0	You felt good or better and did not see the need to take pills ***Wawulira ossuuse n'otalaba nsonga lwaki olina okumira amakerenda.***	***1****=yes,* ***2****=no*	FELTGOOD **If 2 » 20.0**	290

19.1	If yes, how many times? ***Oba Ye, gyali emirundi emeka?***		NFELTGOOD	300

20.0	You were advised by someone else to stop taking medicines ***Waliwo eyakuwa amagezi nti oleker'awo okumira amakerenda***	***1**=yes, **2**=no*	ONADVISE **If 2 » 21.0**	310

20.1	If yes, how many times? ***Oba Ye, gyali emirundi emeka?***		NADVISE	320

21.0	Did not want others to notice you taking drugs ***Wali toyagala balala kumanya nti omira amakerenda***	***1**=yes, **2**=no*	ONOTICE **If 2 » 22.0**	330

21.1	If yes, how many times? ***Oba Ye, gyali emirundi emeka?***		NONOTICE	340

22.0	Other reason (1) ***Ensonga endala (1)***	***1**=yes, **2**=no*	OTHER1 **If 2 » 24.0**	350

22.1	Specify ***Nnyonnyola***		xx

22.2	How many times? ***Emirundi emeka?***		NOTHER1	360

23.0	Other reason (2) ***Ensonga endala (2)***	***1****=yes,* ***2****=no*	OTHER2 **If 2 » 24.0**	370

23.1	Specify ***Nnyonnyola***		xx

23.2	How many times? ***Emirundi emeka?***		NOTHER2	380

SECTION 5. TIMING OF ART DOSES

Interviewer to read: *We understand that many people on ART find it difficult to take the drugs on time. We need to know how many doses you took within the time that you were advised by TASO.*

Tukimanyi nti abantu bangi abamira eddagala lya ART kibakaluubirira okumira eddagala ku budde bwalyo. Twagala kumanya obungi bw'eddagala lyomizze ku budde bwalyo nga TASO bweyakusomesa.

24.0	What times in the day do you usually take your ART drugs: ***Bude kki mu lunaku bwotera okumira eddagala lyo erya ART?***	*Write time using 24 hour clock (e.g. 7pm should 1900)*		
	Dose 1:		DOSET1	390
	Dose 2:		DOSET2	400
	Dose 3:		DOSET3	410

25.0	In the last month, how many of your pills did you take within <u>half</u> an hour ***Mu mwezi oguwedde, amakerenda ameka aga ART gewamira mu <u>kitundu</u> ky'esaawa emu?***	*Codes 1-6 from list below*	TIME1	420

26.0	In the last month, how many of your pills did you take within <u>one</u> hour ***Mu mwezi oguwedde, amakerenda ameka aga ART gwewamira mu saawa <u>emu</u>?***	*Codes 1-6 from list below*	TIME2	430

27.0	In the last month, how many of your pills did you take within <u>two</u> hours ***Mu mwezi oguwuedde, amakerenda ameka aga ART gewamira mu saawa <u>bbiri</u>?***	*Codes 1-6 from list below*	TIME3	440

1=none, **2**=very little, **3**=less than half, **4**=about half, **5**=more than half, **6**=nearly all or all

SECTION 6. ART ADHERENCE REMINDERS AND SUPPORT

Interviewer to read: *People taking their medicines on a daily basis have things that help remind them to take their drugs on time. In the last month, what has helped you personally, to take your drugs on time?*

Abantu abamira eddagala erya ART buli lunaku balina ebintu ebibajjukiza okurimirira mu budde. Mu mwezi oguwedde, kiki ekikuyambye ng'omuntu okumira eddagala lyo erya ART mu budde?

28.0	Use of reminders (e.g. after brushing teeth, meal times) ***Okukozesa ebyeyambisibwa okujjukira (tugeze, nga wakamala okusenya, oba ebisera byemere)***	*Codes 1-4 from list below*	REMINDERS	450
29.0	Monthly contact with TASO staff ***Okulabagana naba TASO Jinja buli mwezi***	"	MVISIT	460
30.0	Support of medicine companion ***Okwewaayo kw'oyo eyeyama okkuyamba mu by'okumira eddagala***	"	SCOMPANION	470
31.0	Existence of personal adherence plan ***Entekateeka zewakola oleme kwerabira okumira eddagala lyo***	"	ADPLAN	480
32.0	Morning/evening prayers ***Essaala z'okumakya n'akawungezi***	"	PRAYER	490

33.0	Desire to improve health, self drive ***Nze kenyinni okwagala okubeera omulamu***	"	DRIVEN	500

34.0	Past experience with other medications ***Obumanyirivu bwennina mukumira eddagala edala***	"	PASTEXP	510

35.0	Support from other household members ***Obuyambi bwenfuna okuva mub'ennyumba yange***	"	HSUPPORT	520

1= very useful, **2** = moderately useful, **3** = not useful, **4** = not applicable

36.0	Other ***Ekirala…***	*“*	OTHER	530

36.1	Specify ***Nnyonnyola***		xx

1= very useful, **2** = moderately useful, **3** = not useful, **4** = not applicable

SECTION 7. ART DRUG SHARING

37.0	Many times it is difficult when our children or others fall sick in the household. Have you ever shared your ART drugs with others who need it? ***Ebiseera ebisinga kiba kiseera kizibu abaana baffe oba abalala betubeera nabo bwebalwara. Wali ogabanyeeko ku ddagala lyo erya ART n'abo abalyetaaga?***	***1**=yes, **2**=no*	SHARED **If 2 » 38.0**	540

37.1	If YES, how many ART pills did you share in the last month? ***Oba Ye, wabawaako empeke meka eza ART mu mwezi oguwedde?***	*Number of pills*	NOSHARED	550

38.0	Do any of your family members living with you need ART drugs but do not have them? ***Olina bobeera nabo abetaaga eddagala lya ART naye nga tebalifuna?***	***1**=yes, **2**=no*	ARTNEED	560

39.0	Are you under pressure to share your ART drugs with other people? ***Waliwo embeera yonna ekuwaliriza okugabana eddagala lyo erya ART n'abantu abalala bonna?***	***1**=yes, **2**=no*	PRESSURE **If 2 » 40**	570

39.1	If YES, from whom ***Oba ye, embeera eyo eva ku'ani?***	*Code 1-8 from list below*	WHOPRESS	580

1=Spouse, **2**=Parent, **3**=Sibling, **4**=Biological child, **5**= Other relative, **6**=Friend, **7**=Neighbour, **8**=Other

39.2	If other, specify ***Oba balala, nnyonnyola***	xx

SECTION 8. MISCELLANEOUS QUESTIONS

Please tell us how many times in the past month you did the following:

Tukusaba otubuulire mirundi emeka mu mwezi oguwedde gyewakola bino wammanga:

40.0	Saw your medicine companion for support/reminder? ***Okulaba oyo eyeyama okukuyamba okumira eddagala***	*Codes 1-7 from list below*	NMEDICINE	590
41.0	Drank alcohol ***Wanywa omwenge***	"	NALCOHOL	600
42.0	Took drugs such as marijuana ***Okweyambisa ebiragalalagala nga enjaga***	"	NDRUGS	610
43.0	Were away from home for at least one night ***Tewasula waka okumala olunaku lumu***	"	NAWAY	620
44.0	Came to TASO Jinja for counseling ***Wajja ku TASO e Jinja okufuna okubudabudibwa***	"	NCOUNSEL	630
45.0	Came to TASO Jinja or other clinic because you felt unwell ***Wajja ku TASO e Jinja oba ku ddwaliro eddala kubanga wali tewewulira bulungi***	"	NTREAT	640

46.0	Were admitted to hospital at Jinja or elsewhere for at least one night ***Walwala nebakuwa ekitanda mu dwaliro e Jinja oba mu dwaliro eddala lyonna okumala ekiro kimu***	"	NADMITTED	650

1 = not once in the month, **2** = once in the month, **3** = 2-3 times a month, **4** = 4-8 times per month **5** = 9-16 times per month, **6** = nearly every day, **7** = daily

INTERVIEWER'S SIGNATURE			xx

INTERVIEWER ID CODE	2 digit code	IPERSID	660

DATE FORM COMPLETED	*dd / mm / yyyy*	FDATE	670

FORM SEQUENCE NUMBER	*4 digits*	FSEQID	680

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