Adherence to antiretroviral therapy among HIV care and treatment patients in Rwanda: Report from a cross-sectional study

Implemented by:

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Acronyms and abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ACTG	AIDS Clinical Trials Group
ANOVA	Analysis of variance statistical test
ART	Antiretroviral therapy
CD4	Immunological blood test
CI	Confidence interval
CNLS	Commission Nationale Lutte Contre le SIDA
EDTA	Ethylenediaminetetraacetic acid (anticoagulant) used for storing blood specimens
GCP	Good Clinical Practice
GEE	Generalized estimating equation
GF	Global Fund to fight AIDS, Tuberculosis and Malaria
HIV	Human immunodeficiency virus
ICAP	International Center for AIDS Care Treatment Programs
IRB	Institutional Review Board
NEC	National Ethics Committee
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NPV	Negative predictive value
NRL	National Reference Laboratory
PBF	Performance-based financing
PCR	Polymerase chain reaction (DNA amplification technique)
PEPFAR	President's Emergency Plan for AIDS Relief
PLWHA	People living with HIV/AIDS
PMTCT	Prevention of mother-to-child transmission of HIV
PPT	Plasma preparation tubes
PPV	Positive predictive value
QDS	Questionnaire Design Software
RNA	Ribonucleic acid
SAS	Statistical Analysis Software
SID	Study identification number
SPSS	Statistical software program
STATA	Statistical software program
TDM	Therapeutic drug monitoring
TRACPlus/CIDC	Treatment and Research AIDS Center-Plus/Center for Infectious Disease Control
TRACnet	Health information system used by the Rwandan National Care and Treatment Program
UNAIDS	The Joint United Nations Programme on HIV/AIDS
UTAP	University Technical Assistance Program
VAS	Visual Analogue Scale
VCT	Voluntary counseling and testing
VL	Viral load
WHO	World Health Organization

Executive summary

In Rwanda, where an estimated 150,000 adults and children are currently living with HIV/AIDS, HIV care and treatment services are being scaled up rapidly. Currently, approximately 49,000 adults and children are receiving antiretroviral therapy (ART) at 165 facilities. Ensuring strict adherence to ART is required for optimal virological and immunological outcomes, prevention of drug resistance, and longer survival, yet limited information is available on ART adherence in Rwanda and other resource-limited settings. The cross-sectional study described in this report aimed to help build this literature by examining levels and patient- and site-level predictors of current ART adherence, and by validating low-cost measures of adherence among a nationally representative sample of adult patients remaining on ART 6, 12 and 18 months after initiation in the Rwandan national program.

Multistage sampling methods with stratification by time since ART initiation (i.e. 6, 12 or 18 months prior to study start) and type of site (i.e. public or faith-based) were used to randomly select a nationally representative sample of 1,798 adults ≥18 years of age across 20 sites. For simplicity, the time since ART initiation strata are referred to as "study groups" in this report (e.g. 6 months on ART study group, 12 months on ART study group, etc.). Four study assessments were done: a) a quantitative closed-ended patient questionnaire; b) abstraction of baseline and follow-up demographic and ART-treatment information from patient records; c) viral load assessments for a sub-sample of study participants; and d) a structured site assessment questionnaire that collected information about programmatic variation that could impact adherence at the patient level. Adherence was assessed using four key outcome measures: a) patient 3-day recall, b) patient 30-day recall, c) CD4 change, and d) viral load.

Results

Of the 1,798 patients selected for inclusion, 1,492 (83%) were confirmed to be eligible, and of those, 1,427 (96%) agreed to participate and had complete data, including 577 (40%), 495 (35%) and 355 (25%) who started ART 6, 12 and 18 months prior to data collection, respectively, and 842 (59%), who received viral load assessments among the 6 (40%) 12 (34%) and 18 (26%) months on ART groups.

Levels of adherence

Self-report: Self-reported measures of adherence indicated very high levels of adherence among study participants across all sites and did not vary by time on ART:

a. *3-day recall:* 93% (95% CI: 92-94%) of patients in the study reported perfect 3-day adherence with no statistically significant differences by time since ART initiation. Perfect three-day adherence ranged significantly across sites from 85% to 100%.
b. *30-day recall:* 77% (95% CI: 75-79%) of study participants reported perfect adherence in the 30 days preceding the interview. An additional 12% took 90% of all pills, 7% took 80%, and 4% took less than 80%. No statistically significant differences were observed by time since ART initiation at any of the adherence cut-off levels. Perfect 30-day adherence varied by site from 50% to 98%.
c. *Treatment interruption:* Respondents reported very infrequent treatment interruptions, defined as missing all pills for 3 or more consecutive days, with a rate of 1.2 per person-year on ART for both the 6- and 12- months on ART study groups and 0.7 in the 18-month group.

Immunological: Completeness of baseline and follow-up CD4 counts was very low for all participants, which limited our ability to examine immunological outcomes. Only 163 (28%), 140 (28%) and 68 (19%) patients on ART for 6, 12 and 18 months respectively had CD4 results at ART initiation and at interview documented in their charts. Among these patients,

as expected, the median change in CD4 count increased with time on ART: on average, the change in CD4 count was +118 cells/µl at 6 months, +160 cells/µl at 12 months and +204 cells/µl at 18 months.

Virological: Across the 842 patients selected for viral load assessments, 83% (95% CI: 80-85%) had undetectable (<40 copies/mL) viral loads and an additional 10% had viral loads between 40-500 copies/mL. The proportion of patients with undetectable viral varied significantly by site and ranged from 70% to 100%.

Reasons for non-adherence and side effects to ART

Among the 576 (40%) patients who ever missed ART, the most commonly cited reasons for missing a dose across all three study groups were forgetfulness (52%), being away from home (49%), and not having food (22%). Feeling well and therefore thinking the medication was unnecessary (1%), believing that ART is not helpful (<1%), not having water (3%), having consumed too much alcohol (4%), feeling that the medication was a reminder of one's HIV status (2%), being advised not to take ART by one's social network (1%), and being confused about when to take ART (1%) were the least commonly reported reasons for missing ART and all cited by less than 5% of respondents.

Headache (37%), fatigue (35%), insomnia (33%) nervousness/anxiety (31%) and muscle pain/joint aches (29%) were the most commonly reported side effects in the 30 days prior to interview. However, in most cases, respondents did not consider the side effects to be "severe": across all study groups and side effects, about 58% of participants who experienced a given side effect were either "not bothered" by it or "bothered a little". Participants who reported sexual dysfunction and insomnia experienced these side effects more "severely", with 60% and 55% of them, respectively reporting being "very bothered."

ART attitudes and beliefs

Participants reported largely positive attitudes about ART and a good understanding of the benefits of treatment with an overall knowledge and attitude "correctness" score of 85%. A substantial proportion of study participants, however, felt that HIV/AIDS is not a serious illness because of the availability of ART (40%), that ART can cure HIV (44%) and that people taking ART need to hide it (18%). Nearly all respondents (95%) believed that ART was very effective in keeping them healthy.

Patient- and site-level determinants of adherence

Reporting <100% adherence in the 30 days preceding interview: In multivariate models controlling for time since ART initiation and other patient- and site-level differences, patients who were younger, living in large households, experiencing severe side effects, missing a CD4 cell count assessment at ART initiation, believed ART is ineffective, using alcohol, receiving services at health centers, or sites with a high patient load, that have peer educator programs and do not regularly conduct supportive home visits for patients were significantly more likely to report <100% adherence in the 30 days preceding the interview.

Undetectable viral load:

In multivariate analyses, the overall odds of detectable viral load were significantly lower for older participants, males and patients participating regularly in PLWHA associations. The odds of having a detectable viral load were higher among patients enrolled at sites with a peer educator program.

Validation of 3-day and 30-day patient recall

Viral load results from a sub-sample were used as the referent measure to evaluate the validity of 3-day and 30-day self-reported perfect adherence. Assuming that adherent patients would have undetectable viral loads, results demonstrated a high sensitivity (93%

and 77%) and positive predictive value (84% for both measures) but low specificity (13% and 25%) and negative predictive value (29% and 19%) for the 3-day and 30-day recall measures, respectively. In all study groups, a greater proportion of those reporting <100% three-day adherence had detectable viral loads than those reporting perfect adherence, although this difference was only significant for the 12 months on ART study group. While no clear dose response emerged for 30-day self-reported adherence, participants who reported taking <80% of their pills in the 30 days prior to interview were more likely to have detectable viral loads than those who reported taking a greater proportion, although this difference was only significant for the 6-month study group.

Discussion, conclusion and recommendations

This study successfully estimated adherence using multiple indirect and direct measures among a nationally representative sample of patients remaining on ART for 6, 12 and 18 months in Rwanda; identified patient- and site-level predictors of sub-optimal adherence and virological failure which can be used to guide program and policy decisions; and for approximately half of the study participants, self-reported measures of adherence were compared against viral load, providing insights into the effectiveness of potential low-cost measures of adherence which can be incorporated into routine service delivery.

Very high levels of self-reported adherence and virological suppression were observed. When combined with the positive results from a previous evaluation of outcomes of the Rwandan national program that showed 92% and 93% of patients were retained on ART 6 and 12 months after ART initiation, this study provides further evidence of a successful national HIV treatment program. While time on ART was not significantly associated with self-reported adherence, there was substantial variability in the relationship between patient- and site-level determinants of adherence by time on ART, suggesting the need for evolving and targeted adherence support tools and strategies as patients gain experience with ART. Use of simple self-reported adherence measures had a high positive predictive value for detectable viral load, but there was significant lack of specificity, indicating further field testing and refinement of short adherence recall questions may be needed

Recommendations include the following:

- Further field test short adherence recall questions and integrate them into routine follow-up to identify patients in need of additional adherence support;
- Investigate systematic barriers to follow-up CD4 testing; implement strategies to optimally conduct and utilize repeated CD4 measures in routine patient monitoring;
- Where resources are limited, provide targeted counseling on adherence particularly focusing on patients who are younger, from large households, experiencing side effects, taking alcohol and those who have a negative perception of ART effectiveness. Provide clinical and psychosocial support to patients regarding the management of side effects, in particular those highlighted by this study as being bothersome to patients;
- Systematically address alcohol use in counseling sessions particularly soon after patients start ART;
- Utilize group and individual sessions to disseminate clear and accurate messages about HIV and ART (e.g. that HIV continues to be a serious disease regardless of the effectiveness and availability of ART, and that ART does not cure HIV); and
- Ensure that patients enrolled in HIV care are asked about the HIV status of their household members and strongly encouraged to bring them to the clinic for testing, care, and/or other appropriate services; also continue to encourage and support all patients to disclose their ART status to family members and others.

1.0 Background

HIV care and treatment programs in Africa and globally are quickly evolving from an emergency response with a focus on initiating the sickest HIV-infected individuals on antiretroviral therapy (ART) to building sustainable programs which provide lifelong treatment for a large number of patients across the HIV disease spectrum. One of the pillars of sustainable HIV treatment programs is the ability of patients to achieve and maintain high levels of adherence to ART. Limited data, however, are available on levels and predicators of adherence, as well as related-behaviors, in Rwanda and other resource-limited settings.

1.1 Significance of ART adherence

Studies from both resource-rich and resource-limited settings have repeatedly demonstrated that high levels of ART adherence are associated with better immunological and virological outcomes, decreased risk of developing an AIDS-defining illness, and improved survival (Shelton et al., 1998; Haubrich et al., 1999; Bangsberg et al., 2001c; Orrell et al., 2003; Glass et al. 2006; Abaasa et al., 2009; Nachega et al., 2009). Conversely, sub-optimal adherence has been associated with rapid disease progression, poor immunologic response, increased drug resistance, and increased risk of mortality (Sethi et al., 1999; Friedland & Williams, 1999; Paterson et al., 2000; Hogg et al., 2002; Hugen et al., 2002; Kent et al., 2003; WHO, 2006). Treatment interruptions, even when structured and monitored clinically, lead to significant adverse events, including an increased risk of morbidity and mortality (El-Sadr et al., 2006). Resistance to ART and treatment failure, documented consequences of sub-optimal adherence, are often difficult to diagnose and manage in routine clinical care in resource-limited settings (Kent et al., 2003; Mee et al., 2008). Since second-line ART is expensive and not often readily available in these settings, effective treatment of HIV becomes a challenge when first-line drug failure is detected (WHO, 2006; Boyd & Cooper, 2007). Transmission of drug-resistant HIV strains also poses a significant and growing public health challenge for national HIV treatment programs (WHO, 2006).

1.2 Methods of ART adherence measurement

There is currently no “gold standard” or consensus for measuring ART adherence. Previous studies have used a range of methods to assess adherence at the individual level with variable sensitivity and specificity, including: patient self-reports, pharmacy refill records, pharmacy insurance claims, pill counts, electronic pill bottle monitors, measurement of drug plasma levels (therapeutic drug monitoring or TDM), clinician estimation, changes in CD4 count, and viral load (Low-Beer et al., 2000; Golin et al., 2002; Spire et al 2002; Orrell et al.; 2003; Oyugi et al., 2004; Marazzi et al., 2005; Simoni et al., 2006; Muyingo et al., 2008; Uzochukwu et al., 2009).

Due to their relative low-cost and simplicity, the most commonly used measures of ART adherence are pill counts (Muyingo et al., 2008), pharmacy records of dispensed medication (Low-Beer et al., 2000; Orrell et al., 2003), and patient self-reports (Oyugi et al., 2004; Simoni et al., 2006). Although pill counts are often seen as objective measures of adherence, patient disposal of unused pills can lead to an overestimate of adherence when pill counts are scheduled in advance with the patient’s knowledge (Miller & Hays, 2000). Unannounced pill counts at the patient’s place of residence have been shown to more accurately estimate adherence (Bangsberg et al., 2001a). Pharmacy records are a convenient and low-cost source of ART adherence information. Assessment can be done in a variety of ways: by comparing the number of monthly medication insurance claims or ART pick-up dates against the number of months on ART (Miller & Hays, 2000; Bisson et al., 2008), or by measuring medication possession ratios using the number of pills dispensed in the pharmacy and patient pill count data (Muyingo et al., 2008). Patient self-report of ART adherence is generally elicited using either direct querying about the ingestion of pills each day over a specific and usually short time frame or a visual analogue scale (VAS) with a

numerical or pictorial anchor which the respondent uses to indicate the proportion of pills taken of the total prescribed during the indicated time period. Substantial variability exists in how these two approaches are implemented, including in the method of administration (self or by trained practitioner/interviewer); modality (in-person, by phone, on-line); recall period (2, 3, 7 or 30 days), number of questions (single vs. multiple items); and type of questions (open or closed-ended). Despite this variability, self-reported data on ART adherence have been shown to correlate with other objective measures of adherence including pill count and viral load (Bangsberg et al., 2001b; Oyugi et al., 2004; Simoni et al., 2006). Potential limitations of this method include social desirability and recall biases (Simoni et al., 2006; WHO, 2006; Boileau et al., 2008), although the impact of these biases on ART adherence estimation has yet to be assessed (Wagner & Miller., 2004).

Laboratory assays such as CD4 cell count and viral load are often used as indirect, but more objective, measures of ART adherence. However, changes in CD4 count can lag behind other clinical markers of therapeutic success or failure and have not correlated consistently with other measures of adherence (Simoni et al., 2006; Bisson et al., 2008). Viral load has demonstrated a strong association with patient self-report of ART adherence (Fletcher et al., 2005; Nieuwkerk & Oort, 2005) but viral load tests are costly and not part of routine care in most resource-limited settings. Similarly, TDM of plasma drug concentrations can be a valuable tool to directly measure adherence, though results can vary between patients based on rates of absorption and drug interactions (Back et al. 2001). Cost constraints have also prevented TDM from being incorporated into routine patient management even in resource-rich settings. Rather than serving as routine measures of adherence in resource-limited settings, laboratory measures—TDM and viral load, in particular—are used most frequently to validate other non-invasive, less expensive, and more subjective measures of adherence (Grossberg et al., 2004; Godin et al., 2005; WHO, 2006).

Most measures of ART adherence were developed and validated in resource-rich settings and, to date, limited validation has been done in resource-limited settings (Simoni et al., 2006). Most studies of ART adherence have used multiple subjective and low-cost measures of adherence, generally with some triangulation and/or assessment of correlation between measures as means of validation (Golin et al., 2002; Orrell et al., 2003; Simoni et al., 2005; WHO, 2006; Amberbir et al., 2008).

1.3 ART adherence estimates and prevalence of non-adherence

Studies conducted in resource-rich and resource-limited countries have examined ART adherence in a range of populations and settings. A recent meta-analysis of 58 studies from sub-Saharan Africa and North America that used varying ART adherence measures suggested significantly higher levels of adherence in Africa than in North America: pooled estimates of 77% (95% CI: 68-85%) versus 55% (95% CI: 49- 62%) (Mills et al., 2006a). However, the 27 African studies included in the analysis were conducted during a very early phase of HIV care and treatment scale-up, were limited to patients who had recently initiated ART, and for the most part had small sample sizes, all factors which likely limit their generalizability to the current context of national ART scale-up in resource-limited settings. More recently, a few larger studies have been conducted in routine service-delivery settings in sub-Saharan Africa and have reported optimal adherence (defined as ingestion of ≥95% or 100% of prescribed doses) among 25% to 94% of patients (Amberbir et al., 2008; Chi et al., 2009; Nachega et al., 2009; Uzochukwu et al., 2009; Unge et al., 2009).

1.4 Reasons for non-adherence to ART

Mills and colleagues (2006b) systematically reviewed patient-reported barriers and facilitators of ART adherence reported in qualitative and quantitative studies conducted in both resource-rich countries (n=72), including North America, Western Europe, and Australia, and resource-limited settings (n=23), including sub-Saharan Africa, Latin America,

Asia, and Eastern Europe. A similar set of factors were found to negatively impact adherence in both settings, including fear of disclosure, forgetfulness, lack of understanding of treatment benefits, regimen complexity, side effects, and work and family responsibilities. Issues of access, including financial constraints and problems with drug stock-outs, were more commonly reported as barriers to adherence in the studies from resource-limited settings. Studies included in a WHO (2006) compilation suggested additional barriers to ART adherence across Botswana, Tanzania, and Uganda, including transport costs, waiting times at the health facility, hunger caused by ART, food restrictions associated with different medications, and stigma. Results from other small studies conducted in African settings have echoed some of these findings (Hardon et al., 2007; Murray et al., 2009; Ware et al., 2009).

1.5 Study justification

In Rwanda—where an estimated 150,000 adults and children are currently living with HIV, including 49,000 who are receiving ART at approximately 165 facilities (UNAIDS, 2008)—only two studies on ART adherence have been published. The first, a cross-sectional study of 95 patients who initiated ART one to four months prior to data collection at the main reference hospital in Kigali, used patient recall and TDM for the non-nucleoside reverse transcriptase inhibitor (NNRTI) portion of the prescribed regimen to assess adherence (Demeester et al., 2005; Omes et al., 2005). High ART adherence rates were observed with 95% of patients reporting taking all doses in the three days preceding data collection and 87% reporting perfect adherence for the preceding month. Results from TDM correlated with patient self-reports: 85% of patients on an Efavirenz-based regimen reporting perfect adherence and 93% on a Nevirapine-based regimen reporting perfect adherence had therapeutic levels of the NNRTI in their serum. The second study, a cross-sectional survey of 71 adult ART patients receiving services in a research clinic in Kigali, found that the majority (76%) of respondents feared ART would increase their appetite as poverty prevented them from obtaining additional food (Au et al, 2006). About one quarter (23-29%) of these patients also cited the interruption of routine activities, accepting HIV as a life-threatening disease, and feeling sick from treatment as obstacles to ART adherence.

While an increasing number of studies on ART adherence have been conducted in resource-limited settings in recent years, data on adherence among a nationally representative sample with an assessment of site-level predictors of adherence is still lacking in the literature. It is also essential to validate and standardize simple, low-cost measures of ART adherence in resource-limited settings so that they can be implemented as part of routine care to help patients achieve and maintain high levels of adherence. In the Rwandan context, in particular, more information is needed about ART adherence behaviors in multiple settings, including in rural areas and those outside of Kigali, and among patients who have been on ART for more than four months to reflect the maturity of the country's HIV care and treatment program. The study described in this report aimed to add to the existing literature by examining levels and patient- and site-level predictors of ART adherence among a nationally representative sample of patients remaining on ART 6, 12 and 18 months after initiation using multiple adherence measures.

2.0 Methods

2.1 Objectives

The objectives of the study were developed collaboratively by all study partners in order to produce rapid results to inform the scale-up of comprehensive HIV care and treatment services in Rwanda and other resource-limited settings. Among adults remaining on ART 6, 12 and 18 months after treatment initiation in the Rwandan national HIV care and treatment program as of September 2008 – April 2009, we aimed to:

1. assess current adherence to ART;

2. identify patient-level factors that are associated with current sub-optimal adherence to ART;

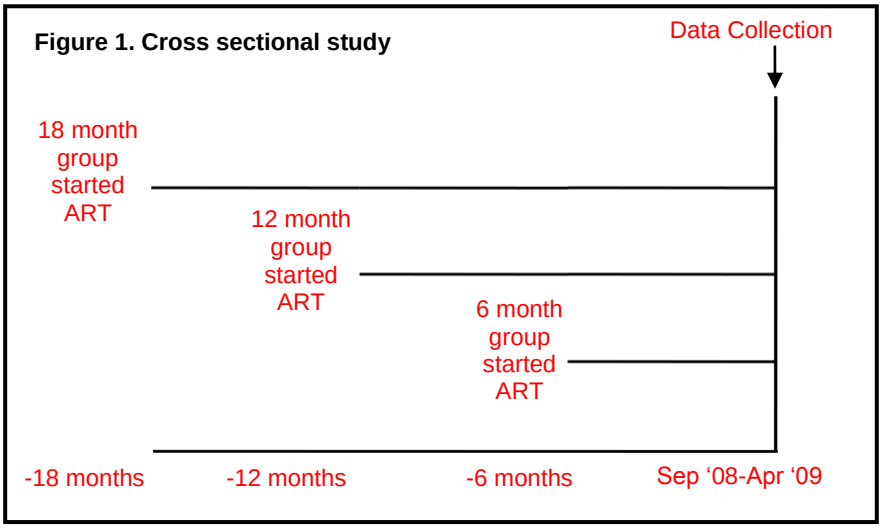
3. identify site-level and contextual factors that are associated with current sub-optimal adherence, after adjusting for patient-level factors; and

4. validate current self-reported ART adherence as a measure of ART adherence against the referent measure of viral load.

2.2 Design

A nationally representative cross-sectional study (Figure 1) was conducted to assess ART adherence among patients remaining on ART 6, 12 and 18 months after treatment initiation at public and faith-based care and treatment sites.

Figure 1. Cross sectional study



2.3 Sampling

Multistage sampling methods with stratification by time since ART initiation (i.e. 6, 12 or 18 months prior to study start) and type of site (i.e. public or faith-based) were used. For simplicity, the time since ART initiation strata are referred to as "study groups" in this report (e.g. 6 months on ART study group, 12 months on ART study group, etc.).

2.3.1 Sample size and power calculations

Sample size calculations were based on the expected proportion of patients reporting perfect adherence 18 months after ART initiation as that proportion was expected to be lower than those at 6 and 12 months after ART initiation (thus providing a more conservative sample size estimation). Assuming an 18-month perfect adherence rate of 85% (based on a Mills et al, 2006a), a precision of ±5%, a design effect of 1.5 and a non-response rate of 20%, we required a sample size of 2,206 adults on ART, split evenly across the six sampling strata

(i.e. public sites/6 months since ART initiation, faith-based sites/6 months since ART initiation, public sites/12 months since ART initiation, etc). As aggregate TRACnet data on the number of adults who initiated ART in each stratum suggested that the calculated sample size was >5% of the total population—and thus no longer considered to be a small proportion of the total population size—and we intended to sample without replacement, we applied a finite population correction factor to the total estimated sample size, resulting in a revised total sample size of 1,798 patients. In order to ensure an accurate proportional distribution of the total sample size across the six sampling strata, we reviewed patient registers and charts at each site to generate lists of the number of patients meeting study eligibility criteria (see below) per stratum. This resulted in the target sample size per stratum shown in Table 1. This sample was further divided by site using probability proportionate to size techniques. Budget constraints limited viral load assessments to approximately 50% of the total sample as shown below.

Table 1: Target sample size per strata

Type of clinic	Time since ART initiation (+/- 2 months)	Target sample size for patient interview and data abstraction	Target sample size for viral load
Faith-based	6 months	241	120
	12 months	188	94
	18 months	149	75
Public	6 months	460	230
	12 months	414	207
	18 months	346	173
Total		1798	899

2.3.2 Site inclusion criteria and selection

Based on logistical considerations and the expected site effect, systematic random sampling was used to select 20 care and treatment sites from the 113 public or faith-based sites active as of February 28, 2007[1] (approximately 18 months prior to study start) stratified by type of site. Fourteen public (70%) and six faith-based (30%) sites were selected to represent the relative contribution of those sectors to the total number of active sites.

2.3.3 Patient inclusion criteria and selection

Participation was restricted to adults aged ≥18 years at study enrolment who had initiated first-line ART at one of the study sites 6, 12 and 18 months (+/- 2 months) prior to data collection and were still receiving ART at their initiating site, or transferred into one of the study sites within 30 days of ART initiation, and were still receiving ART at that site. Patients who died, were lost to follow-up, transferred to another clinic before study start or transferred into one of the study sites on ART more than 30 days after initiating ART were excluded, as were those who continued in care at their initiating site but had stopped ART prior to data collection.

As described above, patient registers and charts were used to create site-specific sampling frames of all eligible patients by time since ART initiation. Simple random sampling techniques were used to select potential participants by time since ART initiation at each site. Every alternate patient was selected for inclusion in the viral load sub-sample. Site staff otherwise unaffiliated with the study contacted selected patients at home and invited them to return to the clinic to learn more about the study. The study team confirmed the eligibility of patients who returned to the clinic, provided them more details about the study, and if

[1] Six private sites were also active as of February 28, 2007 but were excluded from the sampling frame. According to TRACnet, these sites accounted for 1% of all patients who started ART 18 months prior to study start.

patients consented, completed an interview. If a patient was found to be ineligible after selection, s/he was replaced when possible by another eligible patient with the same duration on ART. Patients who refused to participate or could not be located were not replaced. Those in the viral load sub-sample had their blood drawn after their interview. Data abstraction was completed either prior to or after the patient interview depending on the flow of participants at each site. Participants received 2,500 Rwandan Francs for their travel to the clinic to complete the study interview.

2.4 Study assessments

Four different study assessments were done: patient interviews, abstraction of clinical and medication data from patient charts and pharmacy records, viral load assessments and site assessments.

2.4.1 Patient interviews

Trained interviewers conducted face-to-face interviews which lasted approximately 30 minutes using a closed-ended 163-item questionnaire (available upon request) which was drafted in English and translated into Kinyarwanda. The questionnaire had nine main sections which covered socio-demographics, adherence, side effects, knowledge of and attitudes towards ART, quality of life, utilization and satisfaction with services, disclosure and social support, use of herbal, traditional and other medicines, and risky behaviors.

2.4.2 Data abstraction

Interviewers used a structured 46-item tool (available upon request) to abstract data from patient charts and pharmacy records. Information was gathered on patient demographics, the initiating ART regimen and drug substitutions or regimen switches, the number of pills dispensed at the last refill, the number and type of clinic visits made since ART initiation, and all CD4, weight and WHO stage assessments since enrollment into care. The abstraction tool was available in French and English.

2.4.3 Viral load assessments

Viral load assessments were done for approximately half of the study participants alternately selected from the list of participating patients. Upon completion of the interview, selected patients had five cc of blood drawn in either PPT or EDTA tubes (Becton Dickinson, San Jose, CA, USA). Following guidelines from the National Reference Lab (NRL) and depending on the distance of the site from the NRL in Kigali, samples were either transported directly to the NRL within four hours of being drawn for centrifuging, or centrifuged at the site or a nearby District Hospital within four hours and then transported to the NRL within 18 hours. Non-centrifuged samples were transported in a cool box (either to NRL or to the District Hospital where centrifuging was done) and centrifuged samples were transported on ice in a cool box. At the NRL (after centrifugation as needed), all centrifuged samples were aliquoted and stored at −70°C. Real-time PCR was conducted on specimens using a Cobas TaqMan 48 machine (Roche Diagnostic Systems, NJ, USA) with a detection limit of 40 RNA copies/mL.

2.4.4 Site assessments

A 53-question structured site assessment questionnaire (available upon request), modeled on an ICAP site survey tool (http://www.socialtext.net/icap_data_dissemination_/index.cgi?icap_data_dissemination#pfacts_reports), was drafted in English, translated to French and completed for each study site. Information about programmatic variation (e.g. provider-to-patient ratio, availability of various adherence support tools and services) that may impact adherence at the patient level was obtained from the Director of the health facility, the Director of the HIV care and treatment clinic, the ART or site pharmacist, the clinic social worker and other relevant staff.

2.5 Outcome measures

Adherence was assessed using four key outcome measures as shown in Table 2.[2] For each outcome measure, we defined optimal adherence *a priori* and these definitions guided the primary analyses. Additional analyses were conducted using other thresholds and classifications.

Table 2: Study outcome measures

Measure	Description	Optimal adherence cut-off	Data source
Patient 3-day recall	3-day recall was assessed using an abbreviated form of an ART questionnaire developed by the AIDS Clinical Trials Group (ACTG) which has been previously validated in the United States (Chesney et al., 2000) and used successfully in resource-limited settings (Oyugi et al., 2004). For each medication prescribed, patients were asked to indicate whether they took the required doses during each of the three days preceding the interview. These questions were preceded by a statement that many people do not take their medication perfectly all of the time in an effort to elicit accurate reporting.	100% vs. ≤99% adherence	Patient interview
Patient 30-day recall	An ordinal visual analogue scale (VAS) modeled on a continuous numeric scale validated in the United States (Walsh et al., 2002) and a categorical pictorial scale developed by ICAP staff in Mozambique (Brambatti, 2007) was used to document the percentage of doses of all ART medications taken relative to that prescribed for the 30-day period prior to the interview. Patients were presented with a line anchored with cups at 0 (empty cup) and 10 (full cup), provided with examples of what 0, 50 and 100% adherence would represent and asked to assess their own adherence for all of their ART medications over the past 30 days.	100% vs. ≤99% adherence	Patient interview
CD4 change	Change in CD4 count was calculated for each patient as the difference between CD4 count at ART initiation (+/-2 months) and the CD4 count at the time of interview (+/-2 months).	Increase of ≥50 cells/µl vs. increase of ≤ 50 for every 6 months of treatment	Chart abstraction
Viral load	The amount of plasma viral load copies at the time of interview was measured using the procedure described in Section 2.4.3	≤40 copies/mL vs. >40 copies/mL	Viral load assessments

2.6 Data collection, management and analysis

2.6.1 Data collection

Three data collection teams comprised of four Interviewers, one Interviewer Supervisor and a Research Coordinator conducted all data collection. Interviewers documented patient

[2] Using a similar approach to Muyingo et al (2008) and Orrell et al (2003), drug possession ratios will also be calculated in the future.

eligibility, provided interested patients with information about the study, obtained informed consent, and completed patient interviews and chart abstraction. Interviewer Supervisors maintained recruitment logs and reviewed all completed patient questionnaires and chart abstraction forms for completeness and consistency on a daily basis. The three Research Coordinators, all medical doctors, reviewed a sample of completed patient questionnaires and chart abstraction forms, accompanied patients selected for the viral load sub-sample to their blood draw, ensured specimens were appropriately labeled and prepared for transport, provided study participants with their compensation, and completed the Site Assessment Questionnaire. Study monitoring was done by one of the Principal Investigators and two Co-Investigators at regular intervals.

All Research Coordinators, Interviewer Supervisors and Interviewers participated in a five-day training led by several of the Co-Investigators using standard operating procedures and a training manual developed for the study (available upon request). The training covered good clinical practice with an emphasis on patient confidentiality, standard consent, interviewing and data abstraction techniques, a detailed review of all of the study procedures and data collection tools, and practical exercises using the tools. A three-day refresher training was conducted immediately before data collection began. Pilot testing of the study tools and procedures was done at four sites not included in the study sample.

2.6.2 Data management

Signed informed consent forms and completed questionnaires and data abstraction forms were maintained by Interviewer Supervisors while in the field and transported to ICAP's Kigali office on a weekly basis, where they were maintained in locked cabinets. Trained Data Entry Clerks double-entered data into Questionnaire Design Software (QDS) databases developed for each study tool (e.g. patient interview, chart abstraction, etc). Data cleaning was done by a dedicated Database Manager and one of the Co-Investigators using Access 2007, SAS Version 9.2 and SPSS Version 15 for each QDS database separately, as well as on a merged database. Inconsistent or unusual values were flagged and corrected when possible.

2.6.3 Data analysis

Analysis was conducted using STATA Version 10 and SAS Version 9.2. Sampling weights accounting for the probability of selection and inclusion in the study at the site- and patient-levels were used in all descriptive analyses to obtain nationally representative figures. Chi-square and ANOVA tests were used to compare baseline clinical and demographic characteristics, ART regimen information, reasons for missing ART, self-reported side effects, ART knowledge and attitudes, disclosure and risky behaviors, and ART adherence levels for each of the primary outcome measures (see Table 2 above) by time since ART initiation. Crude odds ratios for sub-optimal self-reported 30-day adherence and detectable viral load were estimated to examine the association between various patient- and site-level factors and adherence using a maximum-likelihood logistic model. After removing variables with insufficient variability and collinear variables, all remaining patient- and site-level factors significant at the bivariate level were introduced in multivariate models. Backward stepwise selection based on a 5% level of significance was used to determine the multivariate models presented in this report, after forcing time since ART initiation, CD4 at ART initiation, age and sex into the models. For the self-reported adherence outcome, models were developed for each duration on ART study group separately and for all study participants together, controlling for time since ART initiation. Due to limited statistical power for the viral load outcome, the model was not stratified by time since ART initiation. Bivariate and multivariate analyses were not conducted for other outcomes due either to a lack of variability in (e.g. 3-day self-reported adherence), or availability of (e.g. CD4 response), the data. To validate self-reported recall as a measure of ART adherence at 6, 12 and 18 months against the referent measures of CD4 count and viral load, we estimated the sensitivity, specificity, positive predictive value and negative predictive value of 3- and 30-day self-reported

adherence. We also examined the proportion of patients reporting optimal 3- and 30-day adherence with undetectable viral loads.

Several indices were used in these analyses.

- *Poverty index:* Household-level information on dwelling conditions (i.e. availability and source of water, availability of electricity, sanitation facilities, type of floor) and assets ownership (i.e. radio, television, refrigerator, bicycle, motorcycle, car, cell phone) was used to construct a poverty index by using principal components analysis. A three-level categorical poverty variable (i.e. poorest, middle and least poor) was then created by dividing participants into tertiles with the first tertile comprised of those in the lowest third of the poverty index and the third tertile comprised of those in the highest third of the poverty index.
- *Side effects index:* An index of side effects was generated by summing scaled responses to whether each of 19 different side effects were experienced and if so, their severity, in the 30 days prior to interview (0=did not experience side effect, 1=experienced side effect but not bothered by it, 2=experienced side effect and bothered somewhat by it, 3=experienced side effect and bothered a lot by it). This index had a possible range of 0 to 76. We also created a three-level categorical side effect variable based on the 25^{th} and 75^{th} percentile cut-offs of this index representing whether the respondent experienced no or few side effects, moderate side effects or severe side effects.
- *ART knowledge and beliefs index:* An ART knowledge and beliefs index ranging from 0 to 100% was created by summing responses to eight binary questions which assessed various aspects of ART literacy and attitudes, dividing that number by the total number of questions and multiplying by 100. Zero percent represented poor knowledge of and negative attitudes towards ART, while 100% represented high ART literacy and positive attitudes.

2.7 Ethical considerations

The study protocol was approved by the Institutional Review Board of the Columbia University Medical Center (New York, USA), the Rwandan National Ethics Committee and the Rwandan Commission Nationale de Lutte Contre le SIDA.

3.0 Results

3.1 Map of and description of sites

The 20 study sites, covering 16 of the 30 districts in Rwanda, are shown in Figure 2 and represent 18% of the 113 sites which initiated ART services at least 18 months prior to study start. As shown in Table 3 and as per the study design, there were 14 public and six faith-based sites. Both urban (n=9) and rural (n=11) sites were included. The majority of study sites were health centers (n=14). Sixteen sites received funding from the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and four from the Global Fund (GF) to Fight AIDS, Tuberculosis and Malaria, three of which also received external technical support. The sites initiated ART services between 2003 and 2007, with most starting in 2005 and 2006. Three sites began implementing performance based financing (PBF) in 2004-2005, seven sites in 2006, nine sites in 2007 and one site in 2008. Cumulative adult (≥15 years of age) enrollment in care and on ART varied widely among study sites (range for care: 265-4,903; and for treatment: 152-2,065) but nine sites had enrolled more than 1,000 adults in HIV care and eight sites had initiated more than 500 patients on ART.

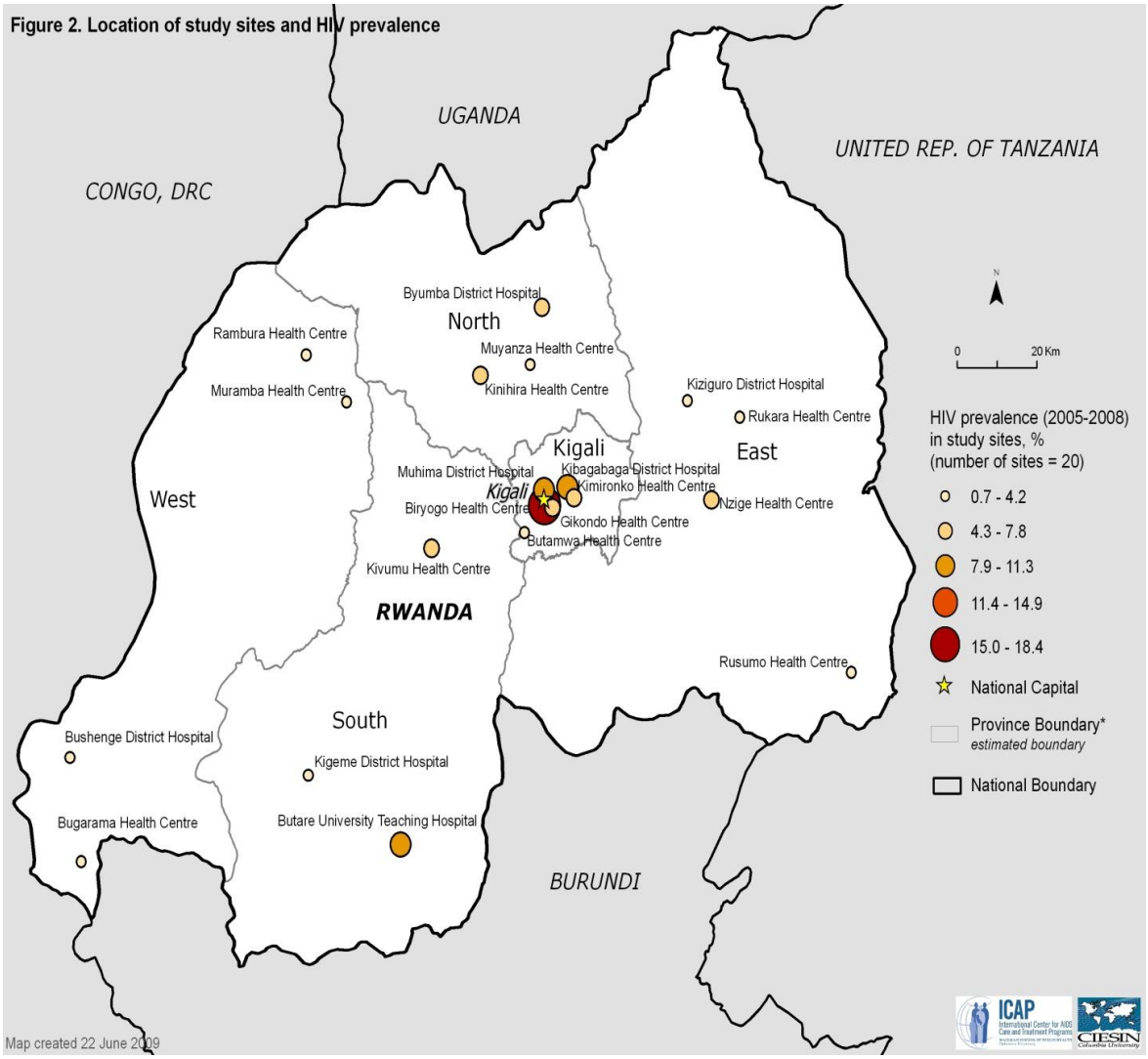


Table 4 shows the ART adherence support services, nutritional services and other services available at the 20 study sites. All sites routinely used at least one tool or approach to support ART adherence, including providing patients with appointment cards (n=17), pill boxes (n=9), paper tools such as calendars or checklists (n=9), conducting routine pill counts in the pharmacy (n=17) or doing home visits when patients miss appointments (n=18). Sixteen of the 20 sites routinely conducted nutritional counseling for ART patients and nine did routine nutritional evaluation. Vitamin and/or minerals distribution (n=1), food support (n=4) and income generation activities (n=2) were rarely done. Seventeen sites had support groups for HIV care and treatment patients and five had support groups specifically for ART patients. Peer educator programs were available at six sites and ten sites conducted supportive home visits regardless if patients missed their appointments.

3.2 Eligibility and response rates by duration on ART

As shown in Figure 3, according to TRACnet data and a review of the medical records available at site, a total of 1,951 patients were believed to have initiated ART at the 20 study sites 6, 12 and 18 months prior to the start of the study. Of these, 1,798 (92%) were randomly selected for participation, 1,492 (83%) of whom were confirmed to be eligible to participate in the study. The 306 (17%) ineligible patients included 50 who died prior to study start; 70 who were lost to follow-up; 113 who transferred to another site; 36 who initiated ART at another site and transferred to the study site more than one month after ART initiation; 13 who had taken ART for prevention of mother to child transmission (PMTCT) of HIV rather than for therapeutic purposes; and 24 who were on ART but close review of patient files indicated that they did not fall within the 6, 12 or 18 months duration on ART study groups. Of the 1,492 patients who were eligible for the study, 18 (1%) declined to participate and 36 (2%) could not be located by the study team resulting in a total of 1,438 (96%) patients enrolled into the study. Eleven (1%) of those patients had incomplete data (i.e. missing either a data abstraction form or patient questionnaire) and thus 1,427 (99%) of all eligible patients are included in the analyses in this report, including 577 (40%), 495 (35%) and 355 (25%) who started ART 6, 12 and 18 months prior to data collection, respectively. These 1,427 patients represent 96% of all patients confirmed to be eligible for the study. As per the study design, 842 (59%) had viral load assessments done, including 335 (40%), 286 (34%) and 221 (26%) in the 6, 12 and 18 months on ART study groups, respectively. No statistically significant differences in ineligibility, non-participation or incomplete information were observed by time since ART initiation (data not shown).

3.3 Geographic and socio-demographic characteristics of sample

As per the sampling design, 68% and 33%, respectively of the 1,427 study participants were receiving services at public-sector and faith-based sites, with no difference by time since ART initiation (Table 5). The majority of participants in all study groups (≥52%) were enrolled in sites in Kigali, with patients in Kigali and the Western region comprising a greater proportion of study participants in the 6 months on ART study group than in the 12- and 18-month on ART study groups. Individual sites contributed 1-12% of study participants.

Table 6 shows the socio-demographic characteristics of the 1,427 participants by time since ART initiation. There were no statistically significant differences across the three study groups in age, sex, education, marital status, employment, number of children, household size, and poverty levels. The majority of participants were female (65%). On average, they were 37.4 years old and had completed 5.5 years of school. One-third of participants were working for cash or other payment at the time of interview. Respondents reported having relatively few ever born children (mean: 3.6 children) and living children (mean: 3.1 living children) and living in relatively large households (mean: 5.0 household members). As described in Section 2.6.3, participants were evenly divided into poverty tertiles. A statistically significant difference was observed in the religious affiliations of participants by time since ART initiation. While most participants were Catholics (42%) or other Christian denominations (49%), and few were Muslims (6%) or reported no religious affiliation (3%), there were significantly fewer Muslims in the 18 months on ART study group (3%) when

compared to the 6 and 12 months on ART groups (7%).

Table 3: Facility type, location, funding information, and cumulative, and study enrolment by site

Site name	District	Type of facility	Location	Funding	Year ART services began	Year PBF[§] introduced	Cumulative number of adults enrolled		Number enrolled in study by time since ART initiation		
							In care	On ART	6 months	12 months	18 months
Biryogo HC*	Nyarugenge	Faith-based	Urban	PEPFAR[†]	2003	2007	2856	1296	60	49	22
Bugarama HC	Rusizi	Public	Rural	GF[‡]	2007	2006	449	204	13	8	10
Bushenge DH**	Nyamasheke	Public	Rural	PEPFAR	2004	2006	2010	594	59	42	17
Butamwa HC	Nyarugenge	Public	Urban	PEPFAR	2005	2007	383	156	16	8	7
BUTH***	Huye	Public	Urban	GF	2004	2006	1059	914	6	8	11
Byumba DH	Gicumbi	Public	Urban	PEPFAR	2005	2007	1142	1106	65	43	22
Gikondo HC	Kicukiro	Faith-based	Urban	PEPFAR	2004	2007	2168	1234	83	52	37
Kibagabaga DH	Gasabo	Public	Urban	PEPFAR	2007	2006	736	275	22	14	24
Kigeme DH	Nyamagabe	Public	Rural	PEPFAR	2004	2006	2051	954	29	51	30
Kimironko HC	Gasabo	Public	Urban	GF	2003	2008	4903	2065	36	52	25
Kinihira HC	Rulindo	Public	Rural	PEPFAR	2005	2007	640	358	24	12	20
Kivumu HC	Muhanga	Faith-based	Urban	PEPFAR	2005	2005	845	357	25	26	14
Kiziguro DH	Gatsibo	Public	Rural	PEPFAR	2005	2006	1100	293	13	8	6
Muhima DH	Nyarugenge	Public	Urban	PEPFAR	2004	2006	2968	1669	66	42	49
Muramba HC	Ngororero	Public	Rural	PEPFAR	2006	2007	374	207	14	18	8
Muyanza HC	Rulindo	Faith-based	Rural	PEPFAR	2006	2007	265	164	4	8	8
Nzige HC	Rwamagana	Public	Rural	PEPFAR	2005	2005	519	220	10	6	7
Rambura HC	Nyabihu	Faith-based	Rural	PEPFAR	2007	2007	312	152	11	13	17
Rukara HC	Kayonza	Faith-based	Rural	PEPFAR	2005	2004	573	177	9	11	15
Rusumo HC	Kirehe	Public	Rural	GF	2006	2007	855	380	12	24	6

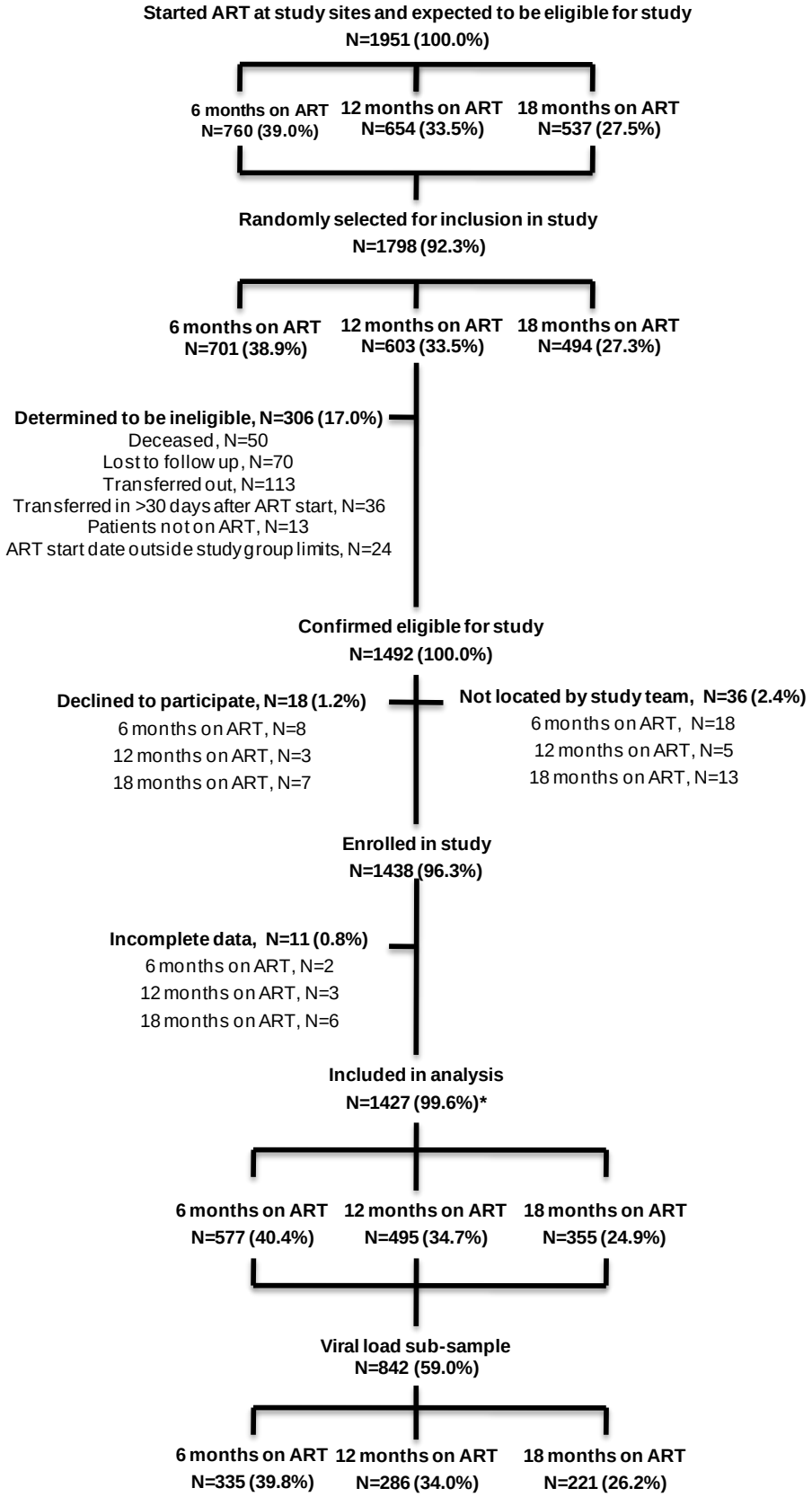
*HC: Health Centre
**DH: District Hospital
***BUTH: Butare University Teaching Hospital
[†] President's Emergency Plan for AIDS Relief
[‡] Global Fund
[§] PBF: Performance based financing

Table 4: Availability of ART adherence support services, nutritional services and other services by site

	ART adherence services available					Nutritional services available					Other services available			
Site name	Appt[†] card	Pill boxes	Paper tools[‡]	Pill counts	Home visits after missed visit	Nutritional counseling	Nutritional evaluation	Vitamins and/or minerals distribution	Food support	Income generation activities	Patient support group	ART-specific patient support group	Peer educators	Supp. home visits[§]
Biryogo HC*	X		X	X	X	X	X		X	X	X	X		X
Bugarama HC	X			X	X						X		X	X
Bushenge DH**	X			X	X	X	X				X			X
Butamwa HC	X					X					X		X	
BUTH***	X			X	X						X			
Byumba DH	X				X	X					X			
Gikondo HC	X	X	X	X	X	X	X							
Kibagabaga DH	X	X	X	X	X	X	X		X	X	X		X	X
Kigeme DH	X			X	X	X								
Kimironko HC	X		X	X	X	X	X				X	X		X
Kinihira HC		X		X	X	X					X			
Kivumu HC	X	X		X	X						X			
Kiziguro DH	X		X	X	X						X			
Muhima DH	X	X	X	X	X	X	X				X	X	X	X
Muramba HC					X	X					X	X	X	
Muyanza HC		X		X	X	X								
Nzige HC	X	X	X	X	X	X	X				X			X
Rambura HC	X	X	X	X		X	X		X		X		X	X
Rukara HC	X		X	X	X	X					X			X
Rusumo HC	X	X		X	X	X	X	X	X		X	X		X

*HC: Health Centre
**DH: District Hospital
***BUTH: Butare University Teaching Hospital
[‡] Paper tools include calendars and checklists
[§] Supportive home visits are unrelated to outreach services for missed appointments
[†] Appt: appointment

Figure 3: Participant selection and recruitment



***Note:** The 1427 patients included in the analysis represent 95.5 % of the 1493 patients confirmed to be eligible for the study.

Table 5: Site characteristics of participants by time since ART initiation

	6 months		12 months		18 months		Total			
	N	%	N	%	N	%	N	%		
	577	40	495	35	355	25	1427	100	df	p-value
Facility ownership										
Public	385	66.7	336	67.9	242	68.2	963	67.5	2	0.658
Faith-based	192	33.3	159	32.1	113	31.8	464	32.5		
Location										
Urban	198	34.3	201	40.6	144	40.6	543	38.1	2	0.017
Rural	379	65.7	294	59.4	211	59.4	884	61.9		
Province										
East	44	7.6	49	9.9	34	9.6	127	8.9	8	0.001
Kigali City	348	60.3	260	52.5	186	52.4	794	55.6		
North	34	5.9	28	5.7	39	11.0	101	7.1		
South	68	11.8	95	19.2	52	14.7	215	15.1		
West	83	14.4	63	12.7	44	12.4	190	13.3		
Administrative district										
Gasabo	58	10.1	66	13.3	49	13.8	173	12.1	30	<0.001
Gatsibo	13	2.3	8	1.7	6	1.7	27	1.9		
Gicumbi	65	11.3	43	8.7	22	6.2	130	9.1		
Huye	6	1.0	8	1.6	11	3.1	25	1.8		
Kayonza	9	1.6	11	2.2	15	4.2	35	2.5		
Kicukiro	83	14.4	52	10.5	37	10.4	172	12.1		
Kirehe	12	2.1	24	4.9	6	1.7	42	2.9		
Muhanga	25	4.3	26	5.3	14	3.9	65	4.6		
Ngororero	14	2.4	18	3.6	8	2.3	40	2.8		
Nyamagabe	29	5.0	51	10.3	30	8.5	110	7.7		
Nyamasheke	59	10.2	42	8.5	17	4.8	118	8.3		
Nyarugenge	142	24.6	99	20.0	78	22.0	319	22.4		
Nyabihu	11	1.9	13	2.6	17	4.8	41	2.9		
Rulindo	28	4.9	20	4.0	28	7.9	76	5.3		
Rusizi	13	2.3	8	1.6	10	2.8	31	2.2		
Rwamagana	10	1.7	6	1.2	7	2.0	23	1.6		
Health facilities										
Biryogo Health Centre	60	10.4	49	9.9	22	6.2	131	9.2	38	<0.001
Bugarama Health Centre	13	2.3	8	1.6	10	2.8	31	2.2		
Bushenge District Hospital	59	10.2	42	8.5	17	4.8	118	8.3		
Butamwa Health Centre	16	2.8	8	1.6	7	2.0	31	2.2		
Butare University Teaching Hospital	6	1.0	8	1.6	11	3.1	25	1.8		
Byumba District Hospital	65	11.3	43	8.7	22	6.2	130	9.1		
Gikondo Health Centre	83	14.4	52	10.5	37	10.4	172	12.1		
Kibagabaga District Hospital	22	3.8	14	2.8	24	6.7	60	4.2		
Kigeme District Hospital	29	5.0	51	10.3	30	8.4	110	7.7		
Kimironko Health Centre	36	6.2	52	10.5	25	7.0	113	7.9		
Kinihira Health Centre	24	4.2	12	2.4	20	5.6	56	3.9		
Kivumu Health Centre	25	4.3	26	5.3	14	3.9	65	4.6		
Kiziguro District Hospital	13	2.3	8	1.6	6	4.7	27	1.9		
Muhima District Hospital	66	11.4	42	8.5	49	13.8	157	11.0		
Muramba Health Centre	14	2.4	18	3.6	8	2.2	40	2.8		
Muyanza Health Centre	4	0.7	8	1.6	8	2.2	20	1.4		
Nzige Health Centre	10	1.7	6	1.2	7	2.0	23	1.6		
Rambura Health Centre	11	1.9	13	2.6	17	4.8	41	2.9		
Rukara Health Centre	9	1.6	11	2.2	15	4.2	35	2.5		
Rusumo Health Centre	12	2.1	24	4.9	6	1.7	42	2.9		

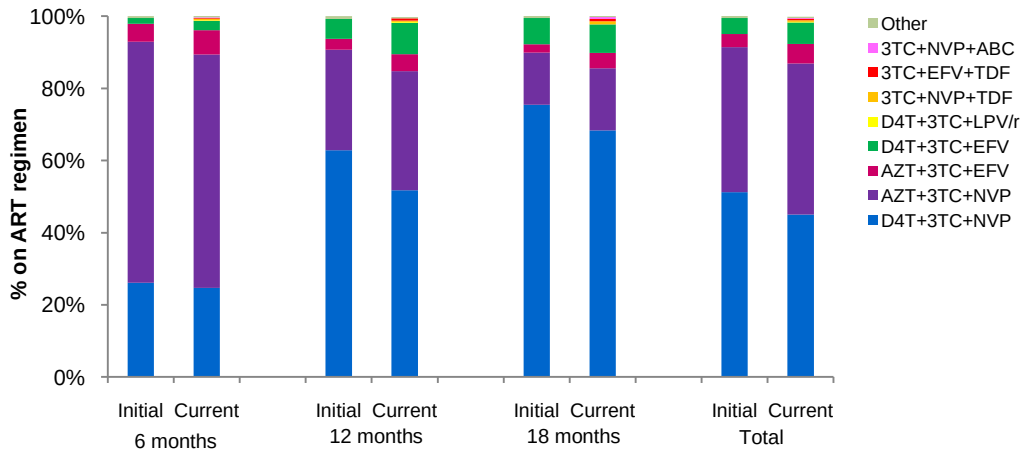
Table 6: Sociodemographic characteristics of participants by time since ART initiation

	6 months		12 months		18 months		Total			
	N	%	N	%	N	%	N	%		
	577	40	495	35	355	25	1427	100	df	p-value
Sex										
Male	205	35.5	171	34.6	127	35.8	503	35.3	2	0.918
Female	372	64.5	323	65.4	228	64.2	923	64.7		
Missing			1							
Age										
Mean years, SD	37.5	9.3	37.6	9.5	37.1	9.4	37.4	9.4	NA	0.748
Age groups										
18-25 years	50	8.7	45	9.1	32	9.0	127	8.9	2	0.974
26-35 years	205	35.5	173	35.0	137	38.5	515	36.1	2	0.518
36-45 years	199	34.5	175	35.4	130	36.5	504	35.3	2	0.795
46-55 years	101	17.5	77	15.4	42	12.1	220	15.4	2	0.075
56 years+	19	3.8	23	5.1	14	3.9	56	4.3	2	0.544
Missing	3		2		0		5			
Education										
Mean years, SD	5.5	4.3	5.2	4.1	5.8	4.6	5.5	4.3	NA	0.174
Education levels										
None	130	22.5	115	23.3	78	21.9	323	22.6	8	0.321
Primary	329	57.0	288	58.1	189	53.4	806	56.5		
Secondary	87	15.1	65	13.2	62	17.4	214	15.0		
Tertiary	9	1.6	5	1.0	11	3.1	25	1.8		
Other	22	3.8	22	4.5	15	4.2	59	4.1		
Religion										
No religion	10	1.7	23	4.7	7	2.0	40	2.8	6	<0.001
Catholic	238	41.2	186	37.7	181	50.8	605	42.4		
Other Christian	289	50.1	252	50.8	155	43.8	696	48.8		
Muslim	40	6.9	34	6.9	12	3.4	86	6.0		
Marital status										
Married/living with partner	310	53.8	277	55.9	189	53.5	776	54.5	6	0.444
Separated/divorced	81	14.1	56	11.3	53	14.9	190	13.3		
Widowed/not living with partner	127	22.0	124	25.1	80	22.5	331	23.2		
Never married	58	10.1	38	7.7	32	9.0	128	9.0		
Missing	1		0		1		2			
Working for cash or other payment	192	33.3	152	30.7	127	35.8	471	33.0	2	0.325
Missing	2		0		0		2			
Number of children ever born										
Mean number, SD	3.5	2.6	3.6	2.7	3.6	2.5	3.6	2.6	NA	0.659
Missing	1		0		1		2			
Number of living children										
Mean number, SD	3.1	2.0	3.1	2.1	3.1	1.9	3.1	2.0	NA	0.950
Missing	51		39		31		121			
Number of household members										
Mean number, SD	4.9	2.3	5.1	2.3	5.0	2.3	5.0	2.3	NA	0.749
Missing	3		0		0		3			
Household poverty index										
Poorest	200	34.7	180	36.4	114	32.1	494	34.6	4	0.776
Less poor	185	32.1	155	31.3	118	33.2	458	32.1		
Least poor	191	33.2	160	32.3	123	34.7	474	33.2		
Missing	1		0		0		1			

3.4 Point of referral, baseline WHO stage and CD4, ART regimens and visit frequency

The majority of patients entered care and treatment from VCT (70%) and PMTCT (17%) clinics with no statistically significant differences between study groups (Table 7). Time since HIV diagnosis varied significantly between study groups and, as expected, increased from 18 months for patients on ART for 6 and 12 months to 22 months for patients on ART for 18 months. WHO stage at enrolment into care and at ART initiation varied by time since ART initiation, and indicated that patients on ART for a longer period of time entered care and started ART in a more advanced disease stage: 27% of patients on ART for 6 months had WHO stage III/IV at enrolment into care compared to 43% of patients on ART for 12 months and 39% of those on ART for 18 months (p<0.001). Among patients on ART for 6, 12, and 18-months, respectively, 36%, 47%, and 42% had WHO stage III/IV at ART initiation. The median CD4 count at enrolment into care and at ART initiation varied by time since ART initiation, and were higher for patients who started ART more recently: 277 cells/µl at enrolment into care and 250 cells/µl at ART initiation in the 6 months on ART group, 218 cells/µl at enrolment into care and 197 cells/µl at ART initiation in the 12 months on ART group and 189 cells/µl at enrolment into care and 185 cells/µl at ART initiation in the 18 months on ART group (p<0.001 for the difference in CD4 at enrolment into care and for the difference in CD4 at ART initiation by time on ART).

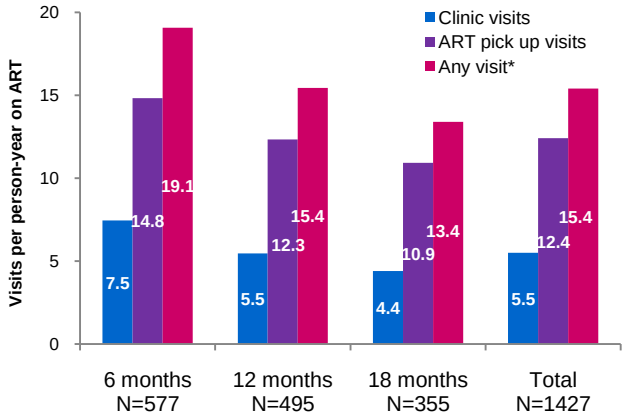
Figure 4. Current and initial ART regimen by time since ART initiation



Differences across time since ART initiation groups in initial regimens and current regimens significant (p <0.001).

Most patients on ART for 6 months started with an initial regimen of AZT+3TC+NVP (67%) while most patients who began ART earlier started with D4T+3TC+NVP: 63% in the 12 months on ART group and 76% in the 18 months on ART group (p<0.001). These secular changes in first-line ART prescribing patterns remained evident in the distribution of the ART regimens patients were on at the time of the interview across the three study groups (Figure 4): 65% of patients on ART for 6 months were still on AZT+3TC+NVP, while 52% of those on ART for 12 months and 68% those on ART for 18 months remained on D4T+3TC+NVP (p<0.001). All patients were on regimens which required an average of two pills per day. Rates of drug substitutions were low and varied by

Figure 5. Number of visits per person-year on ART by visit type and time since ART initiation



Differences across time since ART initiation groups in number of clinical, ART, and any visits significant (p <0.001).
* "Clinic visits" + "ART pick up visits" ≠ "any visits"

time since ART initiation (p<0.001), with 0.151, 0.201 and 0.107 substitutions recorded per person-year on ART for the 6-, 12- and 18-months on ART study groups.

Only three patients had documentation of switching to second-line therapy, resulting in a rate of resulting in a rate of 0.002 per person-year on ART with no difference by time since ART initiation. The number of clinic visits (during which the patient saw a nurse or physician) and ART pick-up visits per person-year on ART both decreased significantly as patients remained on ART (Figure 5): Patients on ART for 6, 12 and 18 months made 7.4, 5.5 and 4.4 clinic visits per person-year on ART (p<0.001), respectively, and 14.8, 12.3 and 10.9 ART pick-up visits per person-year on ART (p<0.001).

Table 7: ART-related characteristics of the study population by time since ART initiation

	6 months		12 months		18 months		Total			
	N	%	N	%	N	%	N	%		
	577	40	495	35	355	25	1427	100	df	p-value
Patient admission mode										
Voluntary counseling and testing	416	72.4	345	69.7	239	67.3	1000	70.2	12	0.386
PMTCT	91	15.8	78	15.8	70	19.7	239	16.8		
Hospitalisation	12	2.1	13	2.6	13	3.7	38	2.7		
Out-patient consultation	19	3.3	11	2.2	10	2.8	40	2.8		
Tuberculosis consultation	5	0.9	6	1.2	4	1.1	15	1.1		
Transferred in ≤30 days of starting ART	8	1.4	15	3.0	5	1.4	28	2.0		
Other	24	4.2	27	5.5	14	3.9	65	4.6		
Missing	2		0		0		2			
Time (months) since HIV diagnosis										
Mean, SD	27.9	27.4	29.2	27.1	33.7	27.0	29.9	27.3	NA	0.031
Median, IQR	18.0	8-39	18.0	13-35	22.0	18-41	19.0	13-38		
Missing	220		187		110		517			
WHO stage at enrolment										
WHO stage I	225	40.4	145	30.9	108	31.6	478	34.9	1	<0.001
WHO stage II	182	32.7	125	26.6	101	29.5	408	29.8		
WHO stage III	136	24.4	183	38.9	119	34.8	438	32.0		
WHO stage IV	14	2.5	17	3.6	14	4.1	45	3.3		
Missing	20		25		13		58			
WHO stage at ART initiation										
WHO stage I	96	34.4	90	27.4	79	28.4	265	29.9	1	0.037
WHO stage II	84	30.1	85	25.5	79	29.1	248	28.1		
WHO stage III	86	31.2	138	42.0	101	36.3	325	36.8		
WHO stage IV	12	4.4	17	5.2	17	6.1	46	5.2		
Missing	299		165		79		543			
CD4 count (cells/µL) at enrolment into care										
Mean, SD	284	151.8	242	146.5	207	142.2	248	150.4	NA	< 0.001
Median, IQR	277	183-349	218	140-315	189	117-281	231	144-323	NA	< 0.001
Missing	150		87		58		295			
CD4 count (cells/µL) at ART initiation										
Mean, SD	236	96.0	200.9	97.2	189	109.7	212	102.0	NA	<0.001
Median, IQR	250	180-300	197.0	130-273	185	122-256	209	143-288	NA	<0.001
Missing	97		60		46		203			
Initial ART regimen										
D4T+3TC+NVP	150	26.1	310	62.9	268	75.5	728	51.2	8	< 0.001
AZT+3TC+NVP	384	66.8	137	27.8	51	14.4	572	40.2		
AZT+3TC+EFV	29	5.0	15	3.0	8	2.3	52	3.7		
D4T+3TC+EFV	9	1.6	27	5.5	26	7.3	62	4.4		
Other	3	0.5	4	0.8	2	0.6	9	0.6		
Missing	2		2		0		4			

Table 7: ART-related characteristics of the study population by time since ART initiation (cont'd)

	6 months		12 months		18 months		Total			
	N	%	N	%	N	%	N	%		
	577	40	495	35	355	25	1427	100	df	p-value
Current ART regimen										
D4t+3TC+NVP	141	24.7	251	51.8	242	68.4	634	45.0	16	<0.001
AZT+3TC+NVP	369	64.7	160	33.0	61	17.2	590	41.9		
AZT+3TC+EFV	38	6.7	23	4.7	15	4.2	76	5.4		
D4T+3TC+EFV	15	2.6	42	8.7	28	7.9	85	6.0		
3TC+NVP+TDF	2	0.4	2	0.4	3	0.9	7	0.5		
3TC+EFV+TDF	1	0.2	3	0.6	2	0.6	6	0.4		
3TC+NVP+ABC	1	0.2	0	0.0	2	0.6	3	0.2		
D4T+3TC+LPV/r	1	0.2	1	0.2	0	0.0	2	0.1		
Other	2	0.4	3	0.6	1	0.3	6	0.4		
Missing	7		10		1		18			
Number of daily pills										
Mean, SD	2.15	0.5	2.24	0.7	2.23	0.7	2.20	0.6	NA	NA
Median, IQR	2	2-2	2	2-2	2	2-2	2	2-2	NA	NA
Missing	35		32		32		99			
Drug substitutions per person-year on ART										
Rate, SD	0.151	0.023	0.201	0.020	0.107	0.015	0.152	0.011	NA	<0.001
Missing	2		2		0		4			
Regimen switches per person-year on ART										
Rate, SD	0.007	0.005	0.002	0.002	0.000	0.000	0.002	0.001	NA	0.532
Missing	1		0		0		1			

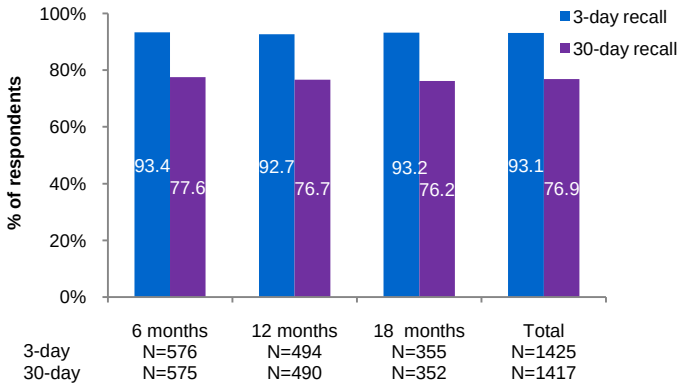
3.5 Levels of adherence

Adherence estimates for the various measures included in the study are shown in Table 8 and Figures 6-13.

3.5.1 Self-reported adherence and treatment interruptions

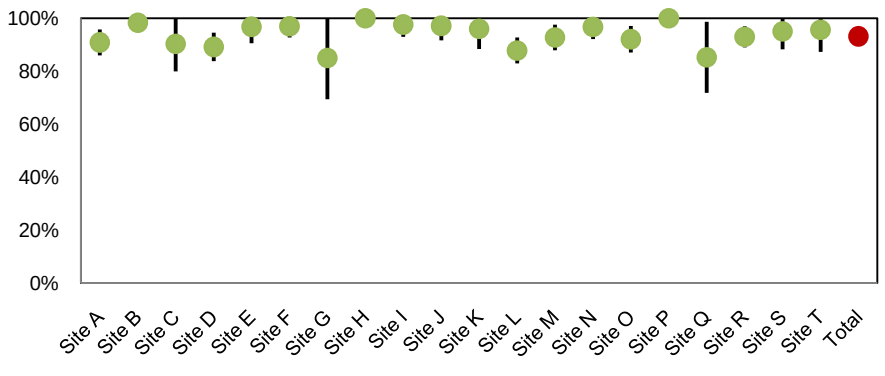
3-day recall: When asked whether participants had missed any ART doses in the preceding three days, 93% (95% CI: 92-94%) of patients in the study reported 100% adherence, with no statistically significant differences by time since ART initiation (Figure 6). However, perfect three-day adherence ranged across sites from 85% (95% CI: 72%-99%) to 100% (95% CI: 100%-100%), with a small but significant difference across sites (Figure 7).

Figure 6. 100% self-reported adherence during 3 and 30 days by time since ART initiation



No significant differences by time since ART initiation

Figure 7: Proportion (and 95% CI) of patients reporting 100% adherence during 3 days preceding interview by site



30-day recall: Perfect (100%) adherence in the 30 days preceding the interview was reported by 77% (95% CI: 75-79%) of respondents, with no statistically significant differences by time since ART initiation (Figure 6). An additional 12% took 90% of all pills, 7% took 80%, and 4% took less than 80% (Table 8). No statistically significant differences were observed by time since ART initiation at the 90%, 80% and less than 80% adherence cut-off levels. Perfect 30-day adherence varied by site, however, as shown in Figure 8, and ranged from 50% (95% CI: 31-69%) to 98% (95% CI: 93-100%).

Figure 8. Proportion (and 95% CI) of patients reporting 30-day 100% adherence by site

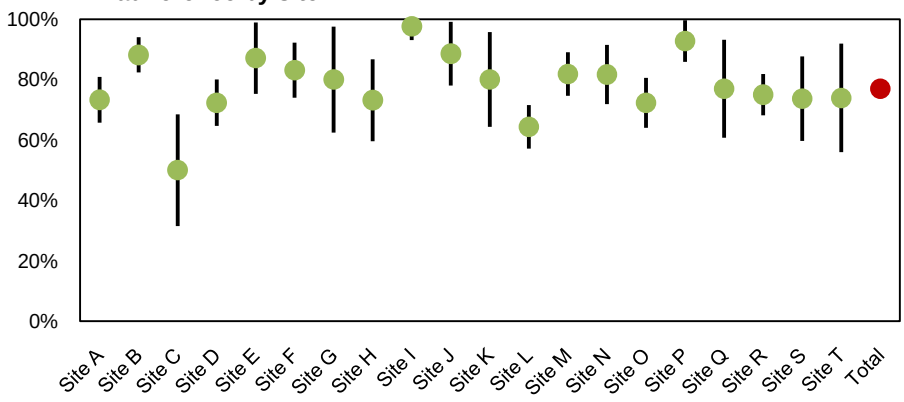
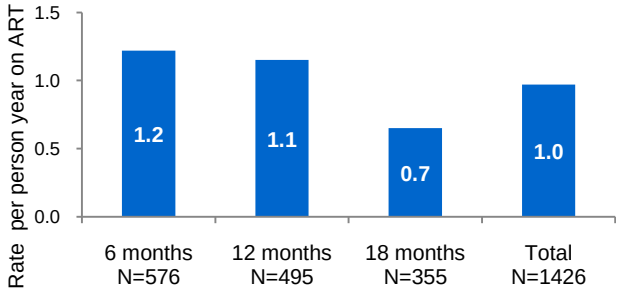


Table 8: Adherence by time since ART initiation

	6 months		12 months		18 months		Total			
	N	%	N	%	N	%	N	%	df	p-value
	577	40	495	35	355	25	1427	100		
Primary outcomes										
Patient 3-day recall										
100% adherent	538	93.4	458	92.7	331	93.2	1327	93.1	2	0.942
90-99% adherent	22	3.8	23	4.7	13	3.7	58	4.1	2	0.754
80-89% adherent	6	1.0	10	2.0	6	1.7	22	1.5	2	0.412
<80% adherent	10	1.7	3	0.6	5	1.4	18	1.3	2	0.201
Mean, SD	98.4	7.8	98.8	5.2	98.4	8.4	98.6	7.2	2	0.552
Median, IQR	100	100-100	100	100-100	100	100-100	100	100-100	2	0.918
Missing	1		1		0		2			
Patient 30-day recall										
100% adherent	446	77.6	376	76.7	268	76.2	1090	76.9	2	0.873
90% adherent	65	11.3	57	11.6	45	12.8	167	11.8	2	0.747
80% adherent	39	6.8	34	6.9	30	8.5	103	7.3	2	0.596
<80% adherent	25	4.4	23	4.7	9	2.6	57	4.0	2	0.289
Mean, SD	95.1	13.4	95.3	11.7	95.7	10.8	95.3	12.2	2	0.809
Median, IQR	100	100-100	100	100-100	100	100-100	100	100-100	2	0.919
Missing	2		5		3		10			
CD4 count (cells/µL) at interview										
Median, IQR	367	259-445	347	248-501	366	272-543	NA	NA	2	0.641
Missing	373		332		274					
CD4 change between ART initiation and interview										
Number with CD4 data at ART initiation and interview	163	28.2	140	28.2	68	19.2	NA	NA		
Change ≥50 cells/µl for every 6 months on ART	125	76.7	102	72.9	44	64.7	271	73.1	2	0.173
Median change, IQR	118	52-196	160	89-252	204	116-345	NA	NA	2	<0.001
Missing	414		355		287					
Viral load (copies/mL)										
Number with viral load	335	58.1	286	57.8	221	62.3	842	59.0		
Undetectable/≤40	279	83.3	234	81.8	185	83.7	698	82.9	2	0.816
41 - 500	35	10.5	28	9.8	18	8.1	81	9.6	2	0.641
>500	21	6.3	24	8.4	18	8.1	63	7.5	2	0.588
Mean, SD	6274	64429	4858	38060	9857	82418	6734	62612	NA	0.664
Median, IQR	40	40-40	40	40-40	40	40-40	40	40-40	NA	0.810

Treatment interruption: The rate of treatment interruption (i.e. missing all pills for 3 or more consecutive days) was 1.2 per person-year on ART for both the 6 and 12 months on ART groups and 0.7 in the 18 months on ART group, but this difference was not statistically significant (Figure 9).

Figure 9. Rate of treatment interruptions (missing ART for ≥3 days) per person year on ART by time since ART initiation

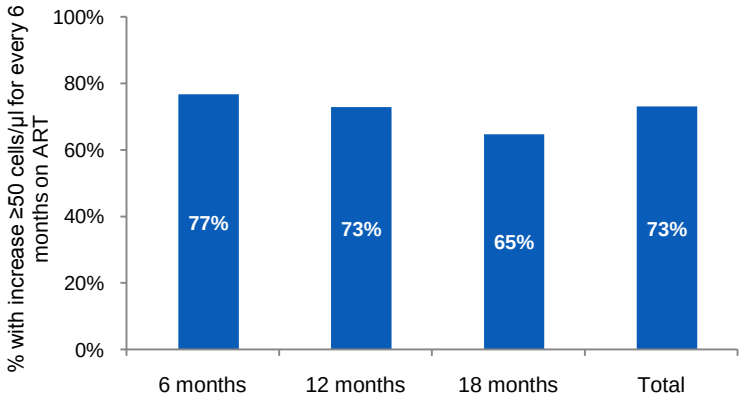


No significant differences by time since ART initiation

3.5.2 Immunological

Only 163 (28%), 140 (28%) and 68 (19%) of patients on ART 6, 12, and 18 months, respectively, had CD4 results on record at both ART initiation (+/- 2 months) and at the time of interview (+/- 2 months), which corresponded to their 6, 12 and 18 month CD4 assessments (depending on their duration on ART group). Of those with available data, the majority experienced large increases in CD4 count: 77% of patients on ART for 6 months had an increase of at least 50 cells/µl; 73% of patients on ART for 12 months had an increase of at least 100 cells/µl; and 65% of patients on ART for 18 months had an increase of at least 150 cells/µl (Figure 10).

Figure 10. Percent of patients with increase of ≥50 cells/µl per 6 months on ART by time since ART initiation

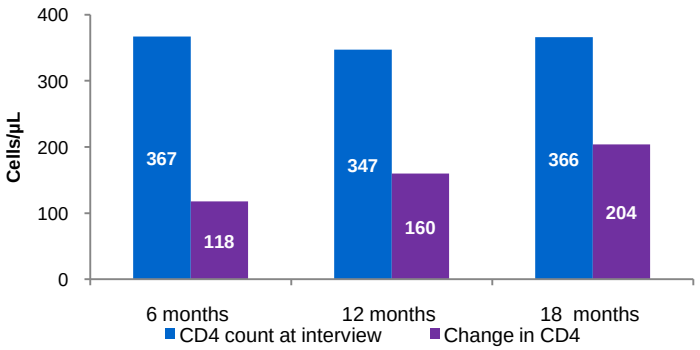


As expected, the median change in CD4 count increased with time on ART: on average the change in CD4 count was +118 cells/µl at 6 months, +160 cells/µl at 12 months and +204 cells/µl at 18 months on ART (Figure 11).

3.5.3 Virological

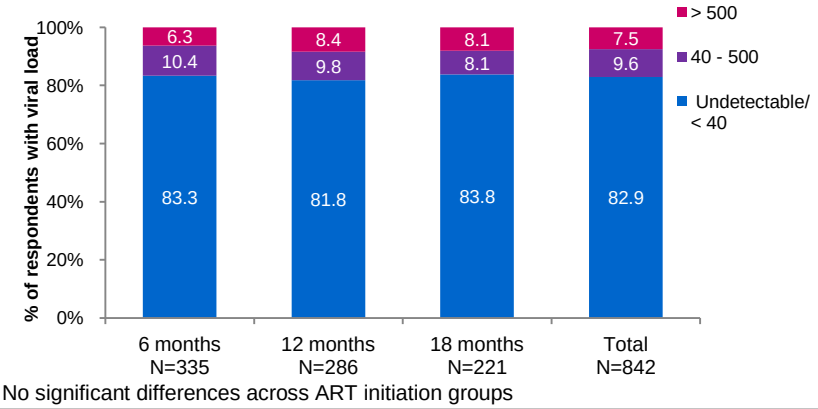
Among the 842 patients selected for viral load assessments, the majority, 83% (95% CI: 80-85%) had undetectable (<40 copies/mL) viral loads, with no statistically significant differences by time since ART initiation (Figure 12). An additional 10% had viral loads between 40-500 copies/mL and 8% had over 500 copies/mL with a maximum of 1,150,000 copies/mL. The proportion of patients with undetectable viral varied significantly by site and ranged from 70% (95% CI: 56-84%) to 100% (95% CI: 100-100%) as shown in Figure 13.

Figure 11. Median CD4 count (cells/µL) at interview and change in median CD4 count between ART initiation and interview by time since ART initiation



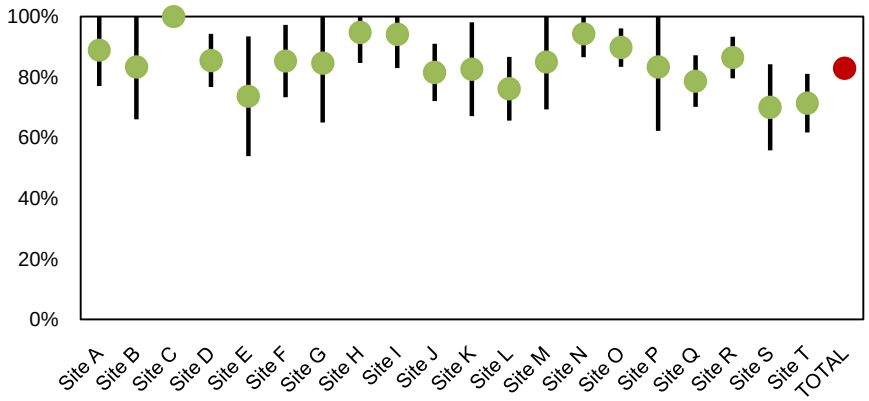
Differences across time since ART initiation in change in median CD4 count between ART initiation and interview significant (p <0.001)

Figure 12. Viral load (copies/mL) by time since ART initiation



No significant differences across ART initiation groups

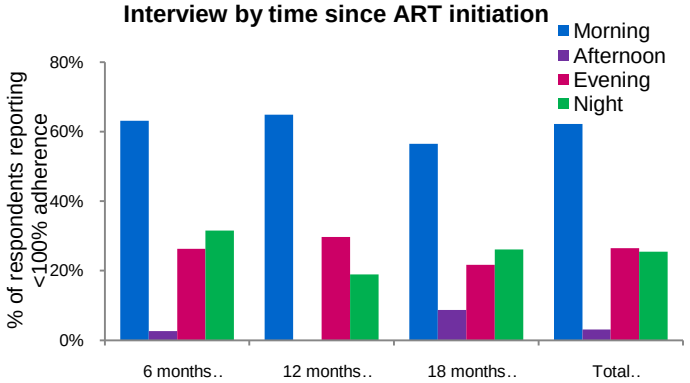
Figure 13. Proportion of patients with undetectable viral load by site



3.6 Time of ART ingestion

The 98 study participants who reported missing at least one pill in the three days prior to interview were asked about the timing of their non-adherence (Figure 14). The majority (62%) reported missing a morning dose, with no difference by time since ART initiation. About one-quarter (26-27%) also reported missing pills in the early evening and at night. As most patients were on regimens requiring morning and evening ingestion, very few participants noted problems with afternoon dosing.

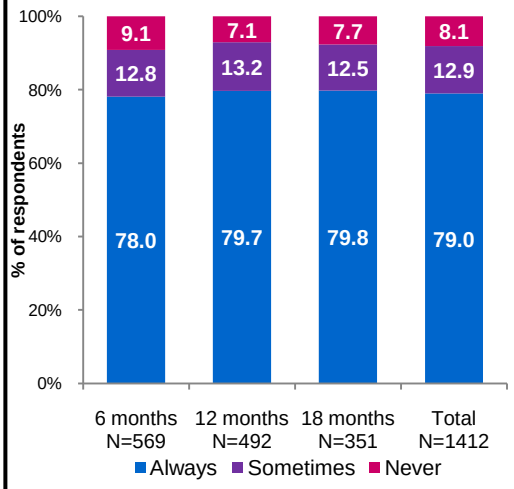
Figure 14. Timing of missed pills among patients reporting <100% adherence in three days preceding Interview by time since ART initiation



No significant differences by time since ART initiation

As shown in Figure 15, nearly 80% of all respondents, regardless of time since ART initiation, reported “always” following the instructions they had received about when and how (e.g. food related instructions) to take their medication in the three days preceding the interview. Between 7% and 9% reported “never” following the instructions in the three days before the interview.

Figure 15. Fidelity to food and timing instructions for ART ingestion in three days preceding interview by time since ART initiation

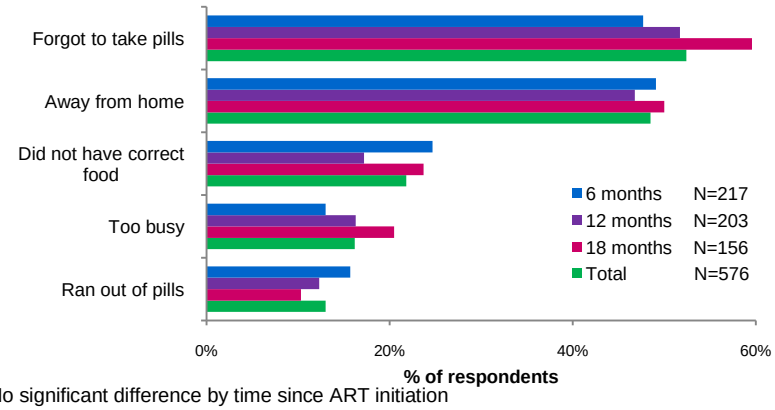


No significant difference by time since ART initiation

3.7 Reasons for non-adherence

The 576 (40%) patients who reported ever missing ART were read a list of 21 reasons why people may miss taking their medication which included health issues or health-beliefs, logistical issues, psychosocial issues, and other reasons (Table 9). Respondents were asked whether each of these reasons had ever contributed to their non-adherence. Overall, health-related beliefs and psychosocial issues were rarely mentioned as reasons for missing ART doses. As shown in Figure 16, the most commonly cited reasons for missing a dose, and the only reasons reported by more than 15% of respondents, were forgetfulness (52%), being away from home (49%), not having food (22%) and being too busy (16%), with no statistical difference by time since ART initiation. Feeling well and therefore thinking the medication was unnecessary (1%), believing that ART is not helpful (<1%), not having water (3%), having consumed too much alcohol (4%), feeling that the medication was a reminder of one's HIV status (2%), being advised not to take ART by one's social network (1%), and being confused about when to take ART (1%) were the least commonly reported reasons for missing ART and all cited by less than 5% of respondents (Figure 17). A statistically significant difference by time since ART initiation was observed in only one of the 21 potential reasons read to patients — timing inconveniences— which was cited as a reason for non-adherence by 15% of the patients on ART for 18 months, 6% of those on ART for 12 months and 7% of those on ART for 6 months.

Figure 16. Most common reasons for ever missing ART among participants who ever missed ART by time since ART initiation



No significant difference by time since ART initiation

Figure 17. Least common reasons for ever missing ART among participants who ever missed ART by time since ART initiation

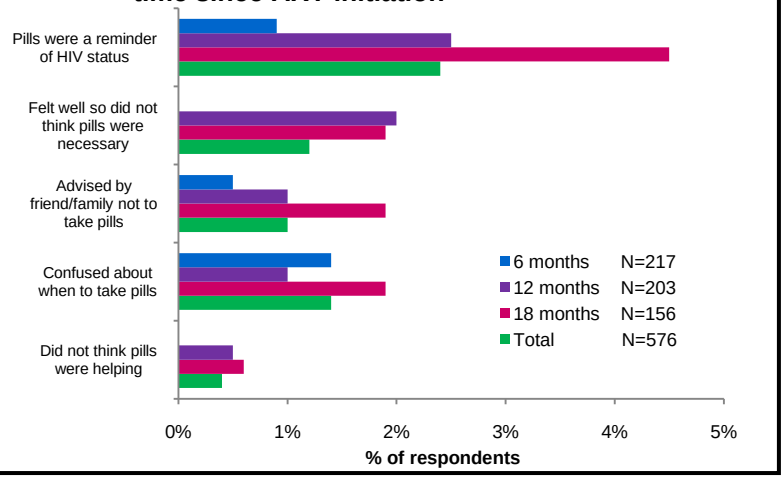


Table 9: Reasons for missing ART among patients who ever missed ART by time since ART initiation

	6 months			12 months			18 months			Total			
	N	%		N	%		N	%		N	%		
	217	38	Missing	203	35	Missing	156	27	Missing	576	100	Missing	p-value
Health or health-belief related reasons													
Scared pills were harmful	20	9.3	1	18	8.9	0	19	12.2	0	57	9.9	1	0.556
Too sick to take pills	18	8.3	1	23	11.3	0	15	9.6	0	56	9.7	1	0.592
Felt sick when took pills	22	10.2	1	13	6.4	0	15	9.6	0	50	8.7	1	0.396
Felt well so did not think they were necessary	0	0.0	2	4	2.0	1	3	1.9	0	7	1.2	3	0.105
Did not think pills were helping	0	0.0	1	1	0.5	0	1	0.6	0	2	0.4	1	0.530
Logistical reasons													
Away from home	106	49.1	1	95	46.8	0	78	50.0	0	279	48.5	1	0.821
Did not have correct food	53	24.7	2	35	17.2	0	37	23.7	0	125	21.8	2	0.151
Too busy	28	13.0	1	33	16.3	0	32	20.5	0	93	16.2	1	0.164
Ran out of pills	34	15.7	1	25	12.3	0	16	10.3	0	75	13.0	1	0.228
Timing was inconvenient	15	6.9	1	12	5.9	0	23	14.7	0	50	8.7	1	0.009
Too many pills to take	3	1.4	1	9	4.5	1	7	4.5	0	19	3.3	2	0.155
Did not have water	6	2.8	1	4	2.0	0	6	3.9	0	16	2.8	1	0.511
Psychosocial reasons													
Did not want others to see	10	4.6	1	8	3.9	0	8	5.1	0	26	4.5	1	0.883
Could not afford to come to clinic to pick up pills	9	4.2	1	13	6.4	0	3	1.9	0	25	4.4	1	0.128
Had too much alcohol/was drunk	4	1.9	1	9	4.4	0	7	4.5	0	20	3.5	1	0.230
Pills were reminder of HIV status	2	0.9	1	5	2.5	0	7	4.5	0	14	2.4	1	0.091
Other reasons													
Forgot to take pills	103	47.7	1	105	51.7	0	93	59.6	0	301	52.4	1	0.072
Pills made patient hungry	13	6.1	2	15	7.4	0	19	12.2	0	47	8.2	2	0.109
Fell asleep	14	6.5	1	9	4.4	0	11	7.1	0	34	5.9	1	0.519
Confused about when to take pills	3	1.4	1	2	1.0	0	3	1.9	0	8	1.4	1	0.903
Advised by friend/family not to take pills	1	0.5	1	2	1.0	0	3	1.9	0	6	1.0	1	0.456

3.8 Side effects to ART

All participants were read a list of 19 side effects associated with ART and for each side effect, asked whether they had experienced it in the 30 days preceding the interview, and if so, whether it bothered them a little bit, somewhat or a lot. As shown in Tables 10-11 and Figure 18, headache (37%), fatigue (35%), insomnia (33%) nervousness/anxiety (31%) and muscle pain/joint aches (29%) were the most commonly reported side effects. The side effects reportedly experienced the least often in the 30 days prior to interview (Figure 19) were nausea/vomiting (21%), bloating/stomach pain/gas (20%), diarrhea (11%), lipodystrophy (10%), and alopecia/changes in hair texture (5%). Significant differences by time since ART initiation were observed in the prevalence of nausea/vomiting which was experienced by 24% of patients on ART 6 months, 20% of those on ART for 12 months and 16% of those on ART for 18 months (p=0.009); nervousness / anxiety which increased over time—26% in the 6 months on ART study group, 34% in the 12 months on ART study group and 33% in the 18 months on ART study group (p=0.013); sadness and depression which increased over time from 23% in the 6 months on ART study group to 29-30% in the 12 months on ART study group (p=0.024); and diarrhea which was experienced by 10% of the participants on ART 6 and 18 months and 15% of those on ART for 12 months (p=0.019).

Figure 18. Most common side effects experienced in 30 days preceding interview by time since ART initiation

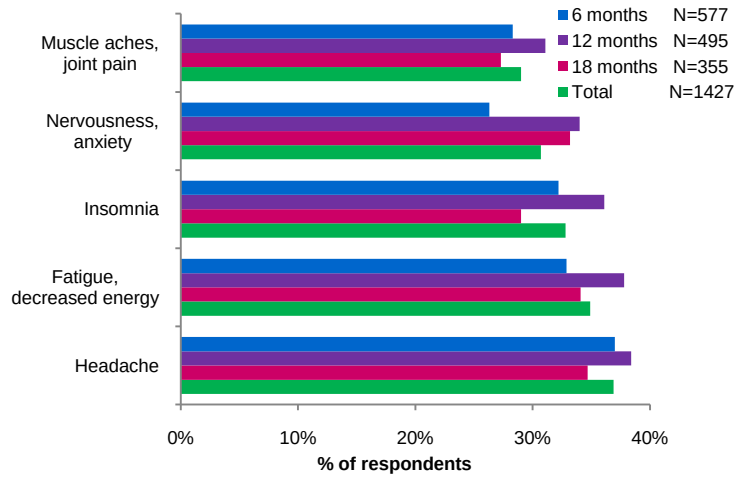
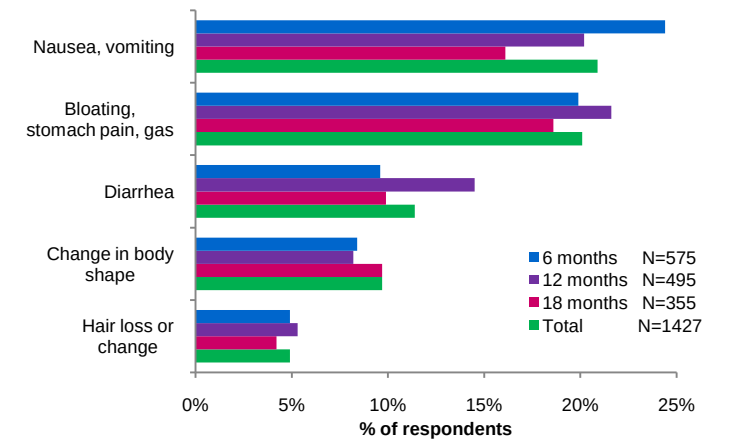


Figure 19. Least common side effects experienced in 30 days preceding interview by time since ART initiation



The severity of the side effects experienced by study participants is shown in Figure 20. Overall, across all groups and side effects, about 17% of participants who experienced a given side effect were “not bothered” by it. Participants who reported sexual dysfunction and insomnia experienced these side effects more “severely”, with 60% and 55% of them, respectively reporting being “very bothered.” Conversely, hair loss or change and loss of appetite or change in the taste of food did not appear to bother study participants, with 43% and 24%, respectively, of those who experienced those side effects reporting that they were “not bothered” by them.

Figure 20. Severity of side effects for all participants

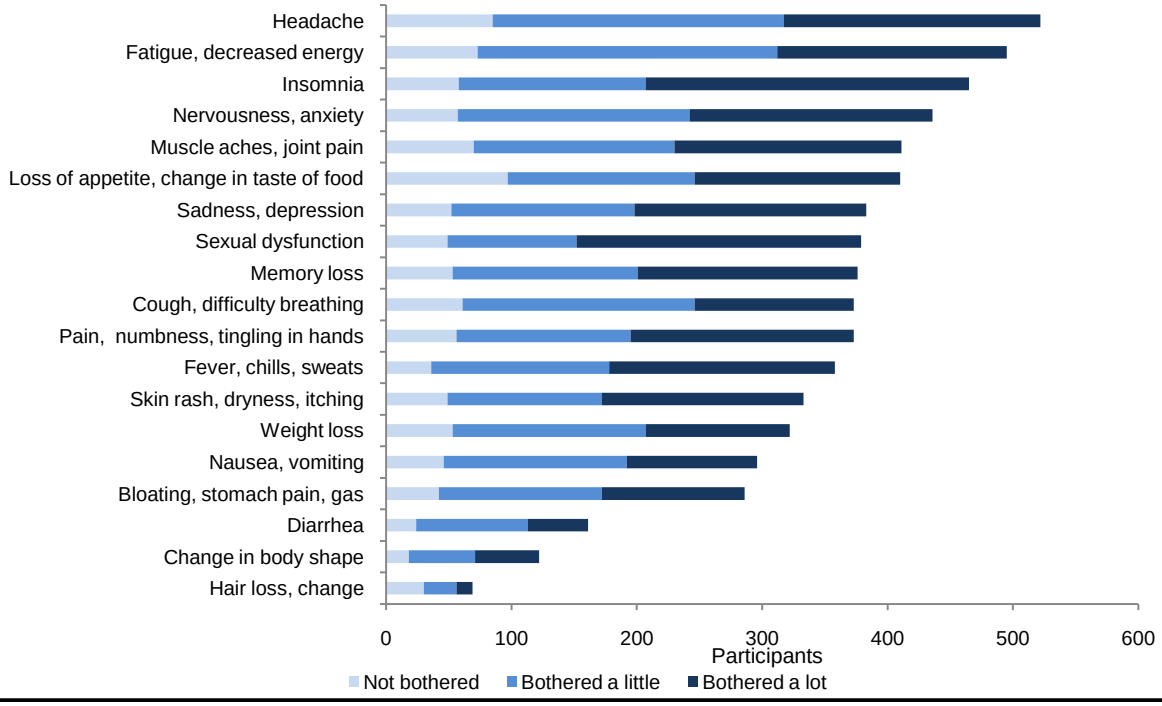


Table 10: Side effects experienced in the 30 days preceding interview by time since ART initiation

	6 months			12 months			18 months			Total				
	N	%		N	%		N	%		N	%			
	577	40	Missing	495	35	Missing	355	25	Missing	1427	100	Missing	df	p-value
Whole body, musculoskeletal, skin/connective tissue														
Headache	211	37.0	7	188	38.4	4	123	34.7	1	522	36.9	12	2	0.529
Fatigue, decreased energy	189	32.9	3	185	37.8	4	121	34.1	1	495	34.9	8	2	0.236
Muscle aches, joint pain	162	28.3	4	152	31.1	5	97	27.3	1	411	29.0	10	2	0.433
Fever, chills, sweats	151	26.4	4	121	24.7	5	86	24.2	1	358	25.3	10	2	0.744
Skin rash, dryness, itching	133	23.2	3	130	26.5	4	70	19.7	1	333	23.5	8	2	0.065
Hair loss, change in way hair looks, feels	28	4.9	5	26	5.3	5	15	4.2	2	69	4.9	12	2	0.722
Nervous system														
Insomnia	185	32.2	3	177	36.1	3	103	29.0	1	465	32.8	7	2	0.082
Nervousness, anxiety	151	26.3	3	167	34.0	3	118	33.2	1	436	30.7	7	2	0.013
Sadness, depression	132	23.0	4	147	29.9	3	104	29.3	1	383	27.0	8	2	0.024
Sexual dysfunction	151	26.5	8	138	28.9	6	90	25.6	4	379	26.9	18	2	0.678
Memory loss	151	26.4	4	129	26.3	4	96	27.2	2	376	26.5	10	2	0.971
Gastrointestinal														
Loss of appetite, change in taste of food	166	28.9	3	154	31.4	3	90	25.4	1	410	28.9	7	2	0.176
Nausea, vomiting	140	24.4	4	99	20.2	4	57	16.1	1	296	20.9	9	2	0.009
Bloating, stomach pain, gas	114	19.9	3	106	21.6	3	66	18.6	1	286	20.1	7	2	0.570
Diarrhea	55	9.6	5	71	14.5	4	35	9.9	1	161	11.4	10	2	0.019
Metabolic														
Weight loss	129	23.0	16	118	24.7	17	75	21.4	5	322	23.2	38	2	0.492
Change in body shape	48	8.4	8	40	8.2	6	34	9.7	4	122	9.7	18	2	0.803
Respiratory														
Pain, numbness, tingling in hands and feet	159	27.7	3	130	26.5	3	84	23.7	2	373	26.3	8	2	0.389
Cough, difficulty breathing	132	23.0	4	146	29.7	3	95	26.8	1	373	26.3	8	2	0.052

Table 11: Index of side effects experienced in 30 days preceding interview by time since ART initiation

	6 months N=577		12 months N=495		18 months N=355		Total N=1427		df	p-value
Side effect index continuous										
Mean, SD	10.5	9.9	11.2	10.0	10.0	9.7	10.6	9.9	NA	0.209
Median, IQR	8	2-16	9	3-17	7	2-16	8	2-16	NA	0.201
Missing	3		3		1		7			
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**df**	**p-value**
Side effect index categorized										
No or few side effects	154	26.8	115	23.4	104	29.4	373	26.3	4	0.379
Moderate side effects	280	48.8	247	50.2	166	46.9	693	48.8		
Severe side effects	140	24.4	130	26.4	84	23.7	354	24.9		
Missing	3		3		1		7			

3.9 ART attitudes and beliefs

All participants were asked whether they agreed or disagreed with eight statements about HIV and ART in order to assess their disease and treatment literacy and beliefs. The majority of participants had correct information about and a positive attitude towards ART with an overall "correctness" score of 85% (out of 100%) and no statistically significant differences were observed by time since ART initiation in the overall score or agreement/disagreement with any individual statement (Table 12). More than 90% of respondents agreed that ART can help people live longer (99%); result in improved health if taken as prescribed (99%); and if people stop taking ART, their illness will worsen (98%); and disagreed that ART is not worth taking due to side effects (98%); and ART does not work as well as doctors and nurses say it will (97%). A substantial proportion of study participants, however, felt that HIV/AIDS is not a serious illness because people living with HIV/AIDS (PLWHA) can take ART (40%), that ART can cure HIV (44%) and that people taking ART need to hide it (18%). Respondents were also asked how effective they felt ART had been in keeping them healthy. Nearly all (95%) believed it was "very effective", 5% said it was "somewhat effective" and <1% indicated it was "ineffective", with no significant difference by duration on ART.

Table 12: ART knowledge and attitudes by time since ART initiation

	6 months			12 months			18 months			Total			
	N	%		N	%		N	%		N	%		
	577	40	Missing	495	35	Missing	355	25	Missing	1427	100	Missing	p-value
Proportion agreeing with statement													
ART can help people live longer	568	99.3	5	491	99.6	2	352	99.2	0	1411	99.4	7	0.765
If people follow instructions about how to take ART, they will be healthier	568	99.0	3	494	100.0	1	350	98.9	1	1412	99.3	5	0.068
If people stop taking ART, their illness will worsen	550	97.2	11	471	98.3	16	345	98.3	4	1366	97.9	31	0.370
Proportion disagreeing with statement													
ART is not worth taking because it has a lot of side effects	559	97.2	2	483	98.4	4	346	97.7	1	1388	97.7	7	0.503
ART does not work as well as doctors and nurses say it will	548	96.5	9	476	97.0	4	343	97.4	3	1367	96.9	16	0.740
People taking ART need to hide it from others	464	81.1	5	404	82.8	7	283	80.2	2	1151	81.5	14	0.607
HIV/AIDS is not a serious illness because PLWHA can take	327	57.1	4	303	61.5	2	223	62.8	0	853	60.0	6	0.146
ART can cure HIV	298	56.7	51	249	54.9	41	180	55.4	30	727	55.7	122	0.831
Index of correct* knowledge and attitudes about ART (0-100%)													
Mean score (%), SD	84.4	12.1	2	85.3	12.0	1	85.3	11.2	0	84.5	11.9	3	0.365
Scored 100%	137	23.9	2	133	27.0	1	89	25.1	0	359	25.2	3	0.546
Perception of ART effectiveness in keeping respondent healthy													
Very effective	536	93.2	2	472	95.7	2	335	94.9	2	1343	94.5	6	0.442
Somewhat effective	36	6.3		20	4.1		17	4.8		73	5.1		
Not effective at all	3	0.5		1	0.2		1	0.3		5	0.4		

*Patients were considered to have "correct" knowledge and attitudes if they agreed with the first 3 statements above and disagreed with the subsequent 5 statements.

3.10 Household HIV and ART status, disclosure, stigma, use of traditional medicine, alcohol and ART adherence reminder tools, and satisfaction with services

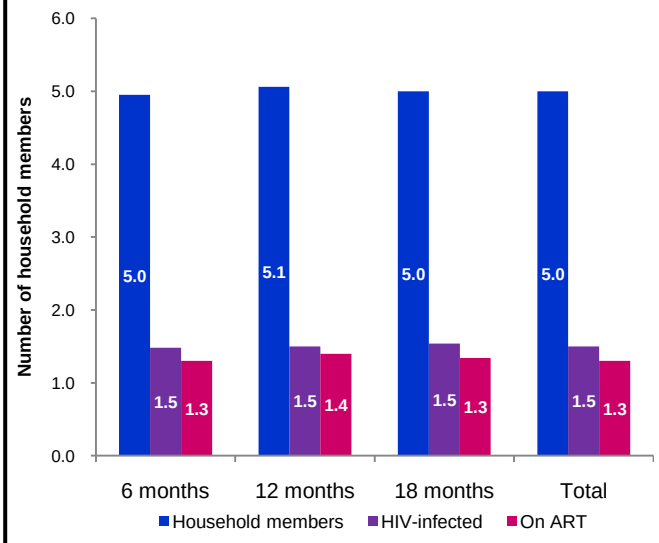


Figure 21. Median number of household members with HIV and on ART by time since ART initiation

No significant differences by time since ART initiation

As shown in Figures 21 and 22, 30% of respondent's household members were HIV-infected and 27% were on ART. Not surprisingly, then, fully 80% of study participants reported having disclosed their HIV status to at least one family member (Table 13) and many (42%) also said they had shared this information with at least one person outside of their family, with no difference by duration on ART. Participation in a support group for PLWHA was also common and increasingly common the longer one was on ART with 43%, 48% and 52% of patients on ART for 6, 12 and 18 months, respectively, participating in such support groups (p=0.010). The majority (79%) of respondents had ever experienced stigma related to their HIV status in their community with 63% reporting that they experienced "a lot" of stigma and small but significant differences by time since ART initiation (p=0.010). Use of traditional medications while on ART was extremely rare and reported by only 1% of all respondents. Use of alcohol and drunkenness in the seven days prior to the interview was far more common, reported by 25% and 16% of study participants, respectively, with no difference by time since ART initiation.

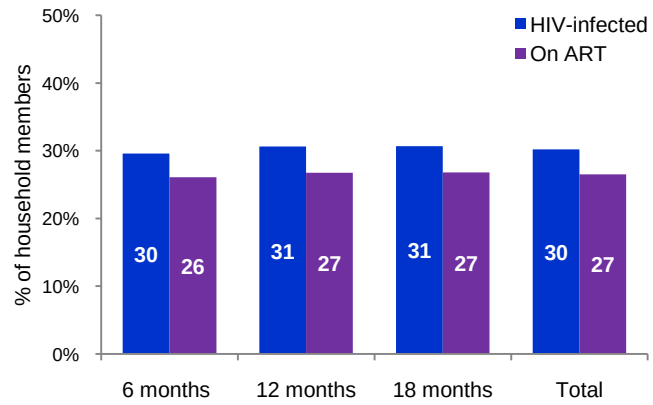


Figure 22. Percent of household members with HIV and on ART by time since ART initiation

No significant differences by time since ART initiation

About two-thirds of participants (62%) used at least one tool to remember to take their ART, namely alarm clocks (26%) and cell phones (17%), with no difference by duration on ART. When asked how satisfied they were with the services they received in the care and treatment clinic, the vast majority (90%) reported being "very happy" with no difference by duration on ART (Table 13).

Table 13: Disclosure, stigma, use of traditional medicine and reminder tools, and satisfaction with services at the clinic alcohol, by time since ART initiation

	6 months		12 months		18 months		Total			
	N	%	N	%	N	%	N	%		
	577	40	495	35	355	25	1427	100	df	p-value
Disclosed HIV status to ≥1 family member	462	80.2	384	77.6	296	83.4	1142	80.1	2	0.1
Missing	1		0		0		1			
Disclosed HIV status to ≥1 non-family member	231	40.0	225	45.5	142	40.0	598	41.9	2	0.139
Missing	0		0		0		0			
Participates regularly in in PLWHA meeting	246	42.7	238	48.3	184	51.8	668	46.9	2	0.01
Missing	1		1		0		2			
Experienced stigma in community										
Never	121	22.7	95	20.3	62	18.0	278	20.7	4	0.01
Some	70	13.1	81	17.3	76	22.1	227	16.9		
A lot	343	64.2	292	62.4	206	59.9	841	62.5		
Missing	43		27		11		81			
Took herbal medicine since starting ART	7	1.2	3	0.6	1	0.3	11	0.8	2	0.230
Missing	4		2		0		6			
Drank alcohol in the past seven days										
A lot (4-7 days)	20	3.5	17	3.5	10	2.8	47	3.3	4	0.766
Some (1-3 days)	123	21.4	112	22.8	68	19.2	303	21.3		
Never	432	75.1	363	73.8	276	78.0	1071	75.4		
Missing	2		3		1		6			
Was drunk in the past seven days, among those who consumed alcohol										
A lot (4-7 days)	4	2.8	1	0.8	2	2.6	7	2.0	4	0.668
Some (1-3 days)	17	12.1	21	16.4	11	14.3	49	14.2		
Never	120	85.1	106	82.8	64	83.1	290	83.8		
Missing	436		367		278		1081			
Reminder tools to take ART										
No tools	205	35.6	188	38.2	143	37.9	527	37.0	2	0.739
Cell phone	99	17.5	79	15.8	65	18.2	243	17.1	2	0.752
Alarm clock	160	28	122	24.5	89	25.1	371	26.1	2	0.492
Paper diary	12	2.1	9	1.8	11	3.2	32	2.3	2	0.292
Radio	116	20.2	93	18.7	64	18.0	273	19.1	2	0.632
Other	14	2.4	17	3.6	10	2.8	41	2.9	2	0.664
Use any tool	365	63.7	297	59.7	218	61.2	880	61.7	2	0.593
How happy with services at the clinic										
Very happy	517	89.8	450	91.1	312	87.9	1279	89.8	4	0.645
Somewhat happy	53	9.2	38	7.7	38	10.7	129	9.1		
Not happy	6	1.0	6	1.2	5	1.4	17	1.2		
Missing	1		1		0		2			

3.11 Bivariate and multivariate associations of patient- and site-level predictors of self-reported non-adherence during the past 30 days

Bivariate (Tables 14-15) and multivariate (Table 16) analysis of patient- and site-level of participants reporting <100% adherence during the 30 days preceding the interview on the VAS was conducted separately for each ART duration group and for all study participants together. Time since ART initiation was not significantly associated with self-reported non-adherence in either the bivariate or multivariate models.

In bivariate analysis, patient-level risk factors (Table 14) for non-adherence at the 0.10 level included: being male (12-month group and total), having some education (6- and 18-month groups and total), higher socio economic status (all groups), moderate/severe side effects (6- and 12-month groups and total), missing a CD4 cell count measurement at ART initiation (6-month group and total), using a reminder tool to take ART (6-month group and total), experiencing stigma (12-month group only), believing ART is ineffective (all groups), and alcohol use in the past week (6- and 18-month groups and total). Patient-level factors associated with decreased odds of reporting non-adherence in bivariate analysis included: increasing age (6- and 12-month groups and total), living in a household with a high proportion of household members on ART (18-month group only), living more than 30 minutes from the HIV clinic (6- and 12- month groups and total), and participating regularly in PLWHA meetings (6- and 12-month groups and total). At the site level (Table 15), receiving services in faith-based sites (6-month group and total), in urban areas (all groups) and at sites with a high patient volume (6- and 12-month groups and total) significantly increased the odds of non-adherence in bivariate analysis, while enrolling in a site that initiated ART services more recently (6- and 12-monthgroups and total) and that regularly conducts supportive home visits to PLWHA (18-months on ART group and total) significantly decreased odds of self-reported non-adherence.

At the multivariate level, Type I and Type II errors and complex confounding and casual pathways may mask associations in some study groups (e.g. associations are observed in the 6-month group but not the 12-month group), making it difficult to assess whether risk factors for non-adherence differ by time since ART initiation. For this reason, we summarize below the results for the entire study sample, controlling for time since ART initiation. Model results for each duration on ART group are presented in Table 16; readers are cautioned to examine whether confidence intervals for point estimates overlap across study groups before concluding that a variable is a risk factor for non-adherence in one ART duration group but not another.

In multivariate analysis, after controlling for time since ART initiation, and other patient- and site-level differences (Table 16), several socio-demographic, treatment-related, psychosocial and site-level factors were associated with reporting <100% adherence during the 30 days preceding the interview for the entire study sample. Residing in a large household, experiencing moderate to severe side effects, missing a CD4 count at ART initiation, believing ART is ineffective, consuming alcohol in the week prior to interview, receiving services at a site with a large patient volume and at one with a peer educator program increased the likelihood of non-adherence; while increasing age, receiving services in a hospital and at a site which routinely conducts supportive home visits for patients reduced the odds of non-adherence.

Table 14: Bivariate association of patient-level predictors and self-reported 30-day non-adherence (<100% adherent) by time since ART initiation												
	6 months N=577 (40%)			12 months N=495 (35%)			18 months N=355 (25%)			Total N=1427 (100%)		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Time since ART initiation(ref=6 months)												
12 months										1.05	0.79 - 1.40	0.748
18 months										1.08	0.79 - 1.48	0.616
Sociodemographic Factors												
Age (ref=18-30 yrs)												
31-36 yrs	0.64	0.38 - 1.09	0.098	0.51	0.28 - 0.92	0.025	1.04	0.54 - 1.99	0.916	0.68	0.48 - 0.94	0.022
37-43 yrs	0.63	0.37 - 1.08	0.090	0.83	0.49 - 1.42	0.498	0.66	0.33 - 1.32	0.240	0.70	0.51 - 0.98	0.038
≥ 44 yrs	0.39	0.22 - 0.69	0.001	0.26	0.14 - 0.51	<0.001	0.71	0.35 - 1.46	0.354	0.40	0.27 - 0.57	<0.001
Sex (ref=female)												
Male	1.18	0.78 - 1.80	0.432	2.10	1.29 - 3.41	0.003	1.01	0.60 - 1.68	0.986	1.37	1.05 - 1.78	0.022
Education (ref=no education)												
Some education	1.54	0.92 - 2.56	0.098	1.57	0.92 - 2.68	0.101	2.47	1.21 - 5.05	0.013	1.72	1.24 - 2.39	0.001
Current marital status (ref=married/living together)												
Other	0.87	0.59 - 1.29	0.489	1.19	0.78 - 1.81	0.420	0.81	0.50 - 1.34	0.416	0.95	0.74 - 1.22	0.709
Number of household members (ref= ≤4)												
5-6	0.95	0.6 - 1.51	0.835	0.72	0.44 - 1.19	0.200	0.91	0.51 - 1.63	0.750	0.86	0.64 - 1.15	0.298
≥7	1.16	0.70 - 1.90	0.570	0.98	0.58 - 1.65	0.928	1.29	0.7 - 2.36	0.417	1.12	0.82 - 1.53	0.464
Percent of household members on ART (ref= ≤25%)												
26-40%	1.48	0.90 - 2.44	0.123	0.70	0.38 - 1.27	0.238	0.45	0.23 - 0.91	0.026	0.86	0.62 - 1.20	0.380
41-100%	0.89	0.54 - 1.44	0.624	1.00	0.62 - 1.62	0.997	0.60	0.33 - 1.09	0.096	0.84	0.63 - 1.14	0.261
Poverty index (ref=most poor)												
Middle	1.86	1.12 - 3.11	0.017	1.13	0.66 - 1.94	0.659	1.94	1.04 - 3.62	0.038	1.59	1.16 - 2.19	0.004
Least poor	2.16	1.31 - 3.57	0.003	1.82	1.10 - 3.01	0.020	1.43	0.76 - 2.72	0.268	1.83	1.34 - 2.49	<0.001
Treatment-related Factors												
Side effects in past 30 days (ref=none/few)												
Moderate	1.45	0.86 - 2.45	0.161	2.42	1.27 - 4.63	0.007	1.11	0.61 - 2.01	0.730	1.54	1.11 - 2.14	0.011
Severe	2.48	1.41 - 4.36	0.002	3.88	1.95 - 7.69	<0.001	1.39	0.71 - 2.72	0.339	2.39	1.67 - 3.42	<0.001
CD4 count at ART initiation (ref= <200)												
≥ 200	1.16	0.72 - 1.86	0.537	0.85	0.54 - 1.33	0.478	1.49	0.87 - 2.55	0.146	1.07	0.82 - 1.41	0.610
Missing	1.68	0.93 - 3.02	0.086	1.12	0.58 - 2.17	0.744	1.82	0.88 - 3.77	0.108	1.46	1.02 - 2.11	0.042
Time to reach clinic (ref= ≤30 min)												
> 30 min	0.52	0.35 - 0.78	0.001	0.64	0.41 - 0.99	0.047	0.82	0.49 - 1.37	0.449	0.63	0.49 - 0.81	<0.001
Uses any reminder tool to take ART (ref=no)												
Yes	1.48	0.98 - 2.24	0.065	1.14	0.75 - 1.74	0.548	1.19	0.72 - 1.96	0.509	1.27	0.98 - 1.64	0.067

Table 14: Bivariate association of patient-level predictors and self-reported 30-day non-adherence (cont'd)												
	6 months N=577 (40%)			12 months N=495 (35%)			18 months N=355 (25%)			Total N=1427 (100%)		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Psychosocial and behavioral factors												
Stigma experienced (ref=none)												
Some or a lot	0.75	0.48 - 1.15	0.186	1.49	0.96 - 2.31	0.074	1.16	0.7 - 1.92	0.565	1.08	0.83 - 1.40	0.586
Missing	0.73	0.32 - 1.63	0.437	1.10	0.43 - 2.85	0.844	1.28	0.33 - 5.02	0.723	0.92	0.53 - 1.61	0.767
Perception of ART effectiveness (ref=effective)												
Not effective	1.97	1.00 - 3.89	0.052	2.92	1.23 - 6.94	0.016	2.25	0.89 - 5.69	0.088	2.26	1.42 - 3.58	0.001
Alcohol use in past 7 days (ref=none)												
Some or a lot	1.86	1.21 - 2.85	0.004	1.33	0.84 - 2.12	0.222	2.17	1.25 - 3.75	0.006	1.71	1.31 - 2.25	<0.001
Disclosed HIV status to ≥1 family-member (ref=no)												
Yes	0.86	0.53 - 1.39	0.543	0.68	0.42 - 1.10	0.116	1.28	0.64 - 2.54	0.487	0.86	0.63 - 1.16	0.309
Participates in PLWHA association (ref=no)												
Yes	0.66	0.44 - 0.99	0.045	0.65	0.42 - 0.99	0.046	0.67	0.41 - 1.09	0.109	0.66	0.52 - 0.85	0.001

Table 15: Bivariate association of site-level predictors and self-reported 30-day non-adherence (<100% adherent) by time since ART initiation												
	6 months N=577 (40%)			12 months N=495 (35%)			18 months N=355 (25%)			Total N=1427 (100%)		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Site ownership (ref=public)												
Faith-based	1.41	0.94 - 2.12	0.094	1.38	0.89 - 2.13	0.154	1.42	0.85 - 2.37	0.179	1.40	1.08 - 1.81	0.010
Year ART services initiated (ref=2003-2004)												
2005	0.80	0.51 - 1.26	0.341	0.73	0.43 - 1.23	0.238	1.25	0.70 - 2.23	0.444	0.87	0.65 - 1.17	0.348
2006-2007	0.52	0.26 - 1.03	0.061	0.56	0.30 - 1.06	0.075	0.94	0.49 - 1.79	0.846	0.65	0.45 - 0.94	0.022
Site location (ref=rural)												
Urban	2.95	1.81 - 4.81	<0.001	1.68	1.08 - 2.61	0.023	1.83	1.08 - 3.10	0.025	2.07	1.57 - 2.73	<0.001
Site type (ref=health centre)												
Hospital	0.82	0.55 - 1.23	0.338	0.85	0.55 - 1.30	0.443	0.77	0.46 - 1.27	0.302	0.82	0.63 - 1.05	0.112
Site ART enrollment (ref= <600)												
≥600 patients	2.12	1.38 - 3.25	0.001	2.03	1.29 - 3.19	0.002	1.28	0.78 - 2.09	0.335	1.81	1.39 - 2.34	<0.001
Peer educator program (ref=no)												
Yes	1.15	0.73 - 1.80	0.546	1.38	0.84 - 2.26	0.210	0.99	0.58 - 1.67	0.956	1.16	0.88 - 1.54	0.287
Routinely conducts supportive home visits (ref=no)												
Yes	0.74	0.5 - 1.09	0.128	0.93	0.61 - 1.42	0.750	0.61	0.37 - 1.00	0.051	0.77	0.60 - 0.98	0.034

Table 16. Multivariate association (stepwise selection) of patient-level predictors and self-reported 30-day non-adherence (<100% adherent) by time since ART initiation

	6 months N=562 20 sites			12 months N=478 20 sites			18 months N=346 20 sites			Total N=1385 20 sites		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
PATIENT LEVEL FACTORS												
Time since ART initiation (ref=6 months)												
12 months										1.13	0.83-1.54	0.448
18 months										1.22	0.86-1.71	0.266
Sociodemographic Factors												
Age (ref=18-30 yrs)												
31-36 yrs	0.54	0.30-0.97	0.041	0.59	0.31-1.11	0.100	0.98	0.49-1.97	0.950	0.69	0.48-0.99	0.044
37-43 yrs	0.56	0.31-1.02	0.058	1.11	0.62-1.98	0.725	0.48	0.22-1.03	0.060	0.77	0.53-1.10	0.149
44 yrs	0.34	0.18-0.67	0.002	0.30	0.15-0.62	0.001	0.65	0.29-1.47	0.301	0.40	0.27-0.61	<0.001
Sex (ref=female)												
Male	1.02	0.63-1.65	0.936	1.80	1.06-3.05	0.030	1.01	0.57-1.79	0.975	1.26	0.93-1.70	0.130
Education (ref=no education)												
Some education							2.56	1.18-5.57	0.018			
Number of household members (ref= ≤4)												
5-6	1.30	0.78-2.18	0.315							0.96	0.70-1.32	0.809
≥7	2.05	1.16-3.63	0.014							1.49	1.06-2.09	0.022
Percent of household members on ART (ref= ≤25%)												
26-40%							0.39	0.19-0.82	0.012			
41-100%							0.45	0.23-0.86	0.016			
Poverty index (ref=most poor)												
Middle							2.03	1.02-4.05	0.044			
Least poor							1.68	0.80-3.51	0.171			
Treatment-related Factors												
Side effects in past 30 days (ref=none/few)												
Moderate	1.30	0.74-2.29	0.357	2.24	1.15-4.38	0.018				1.43	1.01-2.03	0.046
Severe	2.41	1.30-4.46	0.005	3.33	1.63-6.81	0.001				2.07	1.40-3.05	<0.001
CD4 count at ART initiation (ref= <200)												
≥200	1.08	0.65-1.81	0.765	0.85	0.52-1.40	0.524	1.73	0.96-3.11	0.067	1.14	0.84-1.54	0.403
Missing	2.02	1.05-3.88	0.034	1.16	0.55-2.45	0.706	1.79	0.82-3.94	0.147	1.58	1.06-2.36	0.026
Psychosocial and Behavioral												
Perception of ART effectiveness (ref=effective)												
Not effective				3.60	1.38-9.44	0.009				1.87	1.11-3.15	0.018
Alcohol use in past 7 days (ref=none)												
Some or a lot	2.16	1.33-3.49	0.002							1.69	1.26-2.27	0.001
SITE LEVEL FACTORS												
Site location (ref=rural)												
Urban	3.16	1.83-5.45	<0.001									
Site type (ref=health centre)												
Hospital										0.66	0.49-0.90	0.007
Site ART enrollment (ref= <600)												
≥600 patients				1.76	1.08-2.87	0.023				1.95	1.43-2.64	<0.001
Peer educator program (ref=no)												
Yes										1.68	1.18-2.38	0.004
Routinely conducts supportive home visits (ref=no)												
Yes							0.46	0.26-0.80	0.006	0.63	0.47-0.84	0.002

Note: Estimations obtained after logistic regression using a stepwise approach (with a 5% probability of removal). Time since ART initiation, CD4 cell count at ART initiation, sex and age were forced in the model.

3.12 Bivariate and multivariate associations of patient- and site-level predictors of detectable viral load

Tables 17, 18 and 19 show the bivariate and multi-level associations of patient- and site-level factors and having a detectable viral load for the 842 patients with viral load. Time since ART initiation was not significantly associated with detectable viral load in either the bivariate or multivariate models.

In bivariate analyses, patient-level risk factors (Table 17) for having a detectable viral load at the 0.10 level included: having some education (12-month group only), higher socio-economic status (12-month group only and total), experiencing some stigma (12-month group only), and alcohol use (12-month group only). Patient-level risk factors associated with decreased odds of having a detectable viral load at the bivariate level included: older age (total only), male sex (total only), having a CD4 count ≥200 (vs. <200) cells/µl at ART initiation (total only), taking >30 minutes to reach the clinic (12-month group and total), disclosure of one's HIV status to family members (18-month group only), and participating regularly in PLWHA meetings (6- and 12-month groups and total). At the site level (Table 18), receiving services in a hospital (total only), sites with a high patient volume (18-month group and total), at sites with a peer educator program (12-month group and total) , and at sites which regularly conduct supportive home visits for patients (total only) significantly increased the odds of having a detectable viral load at the bivariate level, while enrolling in a site that initiated ART services more recently (18-month group and total) significantly decreased the odds of having a detectable viral load.

At the multivariate level (Table 19), after controlling for time since ART initiation, and other patient and site-level differences, patients who were ≥44 (vs. <44) years old, male and participated regularly in a PLWHA support group had decreased odds of having a detectable viral load, while those receiving services at sites with a peer educator program had increased risk of virologic failure.

Table 17: Bivariate association of patient-level predictors and detectable viral load (>40 copies/mL) by time since ART initiation												
	6 months N=335 (40%)			12 months N=286 (34%)			18 months N=221 (26%)			Total N=842 (100%)		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Time since ART initiation (ref=6 months)												
12 months										1.11	0.73 - 1.68	0.631
18 months										0.97	0.61 - 1.53	0.895
Sociodemographic factors												
Age (ref=18-30 yrs)												
31-36 yrs	0.73	0.34 - 1.57	0.414	0.58	0.23 - 1.44	0.239	0.63	0.23 - 1.70	0.359	0.65	0.39 - 1.07	0.089
37-43 yrs	0.85	0.38 - 1.87	0.677	0.76	0.35 - 1.64	0.481	0.76	0.29 - 2.00	0.572	0.79	0.49 - 1.27	0.331
≥44 yrs	0.50	0.22 - 1.17	0.110	0.63	0.28 - 1.45	0.279	0.56	0.20 - 1.62	0.287	0.56	0.34 - 0.94	0.028
Sex (ref=female)												
Male	0.63	0.35 - 1.13	0.123	0.63	0.34 - 1.17	0.142	0.65	0.31 - 1.33	0.236	0.64	0.44 - 0.92	0.015
Education (ref=no education)												
Some education	1.18	0.59 - 2.37	0.637	2.12	0.91 - 4.96	0.083	1.29	0.50 - 3.33	0.595	1.46	0.92 - 2.33	0.110
Current marital status (ref=married/living together)												
Other	0.97	0.55 - 1.73	0.924	1.31	0.72 - 2.39	0.383	0.89	0.44 - 1.83	0.755	1.05	0.73 - 1.51	0.781
Number of household members (ref= ≤4)												
5-6	0.61	0.31 - 1.20	0.149	1.64	0.82 - 3.29	0.164	0.90	0.39 - 2.11	0.813	0.96	0.63 - 1.45	0.840
≥7	0.56	0.25 - 1.24	0.152	1.34	0.61 - 2.94	0.463	1.24	0.51 - 3.03	0.637	0.94	0.59 - 1.49	0.778
Percent of household members on ART (ref= ≤25%)												
26-40%	0.67	0.28 - 1.62	0.376	0.60	0.25 - 1.46	0.261	1.96	0.82 - 4.71	0.130	0.89	0.55 - 1.46	0.655
41-100%	1.60	0.84 - 3.03	0.150	0.58	0.28 - 1.19	0.137	1.46	0.62 - 3.46	0.385	1.08	0.72 - 1.64	0.702
Poverty index (ref=most poor)												
Middle	1.10	0.54 - 2.23	0.801	0.95	0.43 - 2.09	0.891	0.67	0.27 - 1.67	0.393	0.93	0.59 - 1.46	0.737
Least poor	1.41	0.70 - 2.85	0.333	2.10	1.03 - 4.29	0.042	0.98	0.42 - 2.31	0.971	1.48	0.97 - 2.28	0.072
Treatment-related Factors												
Side effects in past 30 days (ref=none/few)												
Moderate	0.69	0.35 - 1.35	0.277	0.79	0.38 - 1.63	0.516	0.63	0.28 - 1.4	0.255	0.70	0.46 - 1.07	0.101
Severe	0.82	0.38 - 1.78	0.621	0.89	0.38 - 2.10	0.789	0.45	0.16 - 1.26	0.128	0.73	0.44 - 1.20	0.213
CD4 count at ART initiation (ref= <200)												
≥200	0.64	0.34 - 1.21	0.167	0.70	0.36 - 1.35	0.289	0.67	0.29 - 1.52	0.338	0.69	0.47 - 1.02	0.061
Missing	0.59	0.24 - 1.44	0.245	1.01	0.42 - 2.46	0.978	1.05	0.38 - 2.89	0.925	0.83	0.49 - 1.42	0.502
Time to reach clinic (ref= ≤30 min)												
> 30 min	0.66	0.36 - 1.20	0.172	0.47	0.25 - 0.87	0.016	0.83	0.40 - 1.73	0.622	0.62	0.43 - 0.90	0.011
Uses any reminder tool to take ART (ref=1)												
Yes	0.92	0.51 - 1.65	0.780	0.79	0.43 - 1.44	0.433	0.76	0.37 - 1.56	0.458	0.83	0.58 - 1.18	0.297

Table 17: Bivariate association of patient-level predictors and detectable viral load (cont'd)												
	6 months N=577 (40%)			12 months N=495 (35%)			18 months N=355 (25%)			Total N=1427 (100%)		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Psychosocial and behavioral factors												
Stigma experienced (ref=none)												
Some or a lot	0.98	0.52 - 1.83	0.938	0.95	0.49 - 1.83	0.872	1.34	0.64 - 2.79	0.441	1.05	0.72 - 1.55	0.800
Missing	0.74	0.24 - 2.26	0.600	3.20	1.06 - 9.67	0.040	0.81	0.10 - 0.98	0.851	1.32	0.65 - 2.66	0.445
Perception of ART effectiveness (ref=effective)												
Not effective	0.66	0.19 - 2.28	0.510	2.08	0.62 - 7.05	0.238	1.50	0.30 - 7.51	0.625	1.16	0.55 - 2.45	0.704
Alcohol use in past 7 days (ref=none)												
Some or a lot	0.78	0.39 - 1.55	0.474	2.42	1.28 - 4.58	0.006	1.24	0.54 - 2.85	0.614	1.35	0.91 - 2.02	0.140
Disclosed HIV status to ≥1 family-member (ref=no)												
Yes	1.76	0.79 - 3.91	0.167	0.76	0.38 - 1.50	0.426	0.46	0.20 - 1.07	0.071	0.90	0.58 - 1.38	0.618
Participates in PLWHA association (ref=no)												
Yes	0.53	0.28 - 0.97	0.041	0.43	0.23 - 0.83	0.011	0.55	0.27 - 1.15	0.111	0.50	0.34 - 0.73	<0.001

Table 18: Bivariate association of site-level predictors and detectable viral load (>40 copies/mL) by time since ART initiation												
	6 months N=577 (40%)			12 months N=495 (35%)			18 months N=355 (25%)			Total N=1427 (100%)		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Site ownership (ref=public)												
Faith-based	0.95	0.51 - 1.75	0.863	0.72	0.37 - 1.41	0.342	0.66	0.29 - 1.49	0.319	0.79	0.53 - 1.17	0.240
Year ART services initiated (ref=2003-2004)												
2005	0.90	0.46 - 1.76	0.765	0.56	0.25 - 1.30	0.177	0.22	0.07 - 0.66	0.007	0.56	0.35 - 0.89	0.014
2006-2007	1.06	0.45 - 2.47	0.902	1.10	0.51 - 2.36	0.812	0.41	0.15 - 1.15	0.091	0.85	0.52 - 1.39	0.503
Site location (ref=rural)												
Urban	1.35	0.72 - 2.54	0.346	1.17	0.63 - 2.17	0.628	1.22	0.57 - 2.59	0.609	1.24	0.85 - 1.81	0.268
Site type (ref=health centre)												
Hospital	1.51	0.85 - 2.68	0.161	1.43	0.78 - 2.61	0.247	1.47	0.72 - 3.00	0.295	1.47	1.02 - 2.10	0.037
Site ART enrollment (ref= <600)												
≥ 600 patients	1.02	0.57 - 1.83	0.944	1.19	0.64 - 2.21	0.589	2.69	1.23 - 5.88	0.014	1.37	0.95 - 1.99	0.094
Peer educator program (ref=no)												
Yes	1.66	0.89 - 3.11	0.115	2.79	1.45 - 5.40	0.002	1.07	0.49 - 2.32	0.869	1.74	1.18 - 2.57	0.005
Routinely conducts supportive home visits (ref=no)												
Yes	1.56	0.87 - 2.80	0.138	1.45	0.79 - 2.67	0.232	1.30	0.63 - 2.67	0.479	1.45	1.01 - 2.09	0.046

Table 19. Multivariate association (stepwise selection) of patient-level predictors and detectable viral load (>40 copies/mL)			
	Total N=823 20 sites		
	OR	95% CI	p-value
PATIENT LEVEL FACTORS			
Duration on ART (ref=6 months)			
12 months	1.07	0.69 - 1.66	0.755
18 months	0.94	0.58 - 1.52	0.791
Age (ref=18-30 yrs)			
31-36 yrs	0.68	0.41 - 1.15	0.154
37-43 yrs	0.78	0.47 - 1.30	0.335
≥ 44 yrs	0.55	0.32 - 0.96	0.034
Sex (ref=female)			
Male	0.62	0.42 - 0.92	0.017
CD4 count at ART initiation (ref= <200)			
≥ 200	0.70	0.46 - 1.07	0.100
Missing	0.87	0.50 - 1.51	0.613
Participates in PLWHA association (ref=no)			
Yes	0.60	0.41 - 0.90	0.012
SITE LEVEL FACTORS			
Peer educator program (ref=no)			
Yes	1.67	1.11 - 2.50	0.013

Note : Estimations obtained after logistic regression using a stepwise approach (with a 5% probability of removal). Time since ART initiation, CD4 cell count at ART initiation, sex and age were forced in the model.

3.13 Validation of 3-day and 30-day patient recall using viral load

Using data from the 842 patients included in the viral load sub-sample, viral load was used as the referent measure to assess the validity of self-reported perfect adherence over the three preceding the interview, collected using a modified ACTG questionnaire, and over the 30 days preceding the interview, collected using a VAS. This validation was based on the assumption that adherent patients would have undetectable viral loads (≤40 copies/mL or ≤500 copies/mL depending on threshold used) if they took all of their prescribed pills.

3.13.1 Sensitivity, specificity, positive predictive value and negative predictive value

Measurements are typically validated using four statistics: sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Sensitivity, for this study, is the percentage of participants with undetectable viral load who reported perfect adherence (i.e. took 100% of pills in the specified recall period). Conversely, specificity is the percentage of participants with detectable viral load who reported sub-optimal adherence (i.e. took <100% of pills in the specified recall period). The PPV is the percentage of participants reporting perfect adherence who had undetectable viral loads and the NPV is the percentage of participants reporting sub-optimal non-adherence who had detectable viral loads. The PPV and NPV are dependent on the prevalence of an undetectable viral load in the study population which was 83% when using a threshold of ≤40 copies/mL and 92% when using a threshold of ≤500 copies/mL with no difference by duration on ART (see Section 3.4). A valid measure will have high percentages for all four statistics.

As shown in Table 19 below, when a threshold of ≤40 copies/mL was used to classify patients as having undetectable viral loads, the sensitivity, specificity, PPV and NPV of the three-day recall measure were 93%, 13%, 84% and 29%, respectively. The corresponding values for the 30-day recall measure were 77%, 25%, 84% and 19%. When a threshold of ≤500 copies/mL was used to classify patients as having undetectable viral loads, the sensitivity of the 3-day recall measure remained steady at 93%, the specificity and PPV of the 3-day recall measure increased to 17% and 93%, respectively, while the NPV decreased to 17%. A similar pattern was seen with the 30-day recall measure: Sensitivity was virtually

unchanged at 78%, specificity increased to 33% and the PPV increased to 94% while the NPV decreased to 11%.

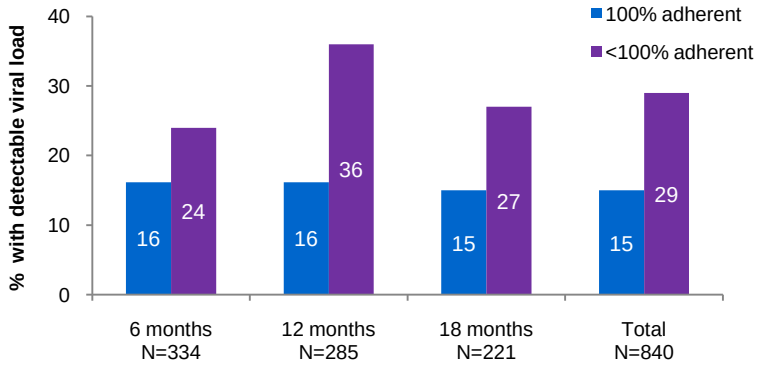
Table 20. Validity of 3- and 30-day patient recall using viral load as the referent measure

	VL ≤40 copies/mL		VL ≤500 copies/mL	
	3-day recall	30-day recall	3-day recall	30-day recall
Sensitivity	93.4%	77.1%	93.0%	77.5%
Specificity	13.3%	25.4%	17.2%	33.3%
PPV	84.0%	83.5%	93.2%	93.5%
NPV	29.2%	18.5%	16.9%	10.8%

3.13.2 Association between self-reported adherence and viral load

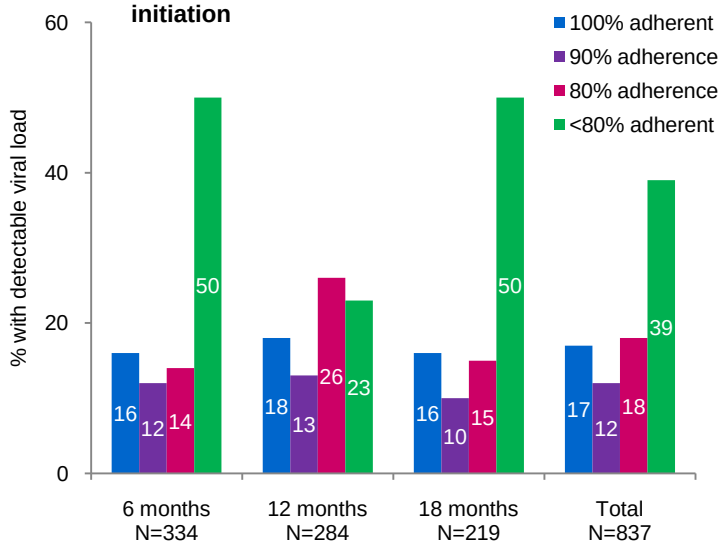
The relationship between self-reported adherence and viral load was examined further by calculating the proportion of participants with undetectable viral load (i.e. ≤40 copies/mL) for various thresholds of self-reported adherence using both three-day and 30-day recall. In all duration on ART groups, a greater proportion of those reporting <100% three-day adherence had detectable viral loads than those reporting 100% adherence (Figure 23). This difference, however, was only significant for patients on ART for 12 months, where 36% of those reporting sub-optimal three-day adherence had detectable viral loads compared to 16% of those reporting 100% adherence (p=.0.01). As shown in Figure 24, while no clear dose response emerges for 30-day self-reported adherence, participants on ART for 6 months who reported taking <80% of their pills in the 30 days prior to interview were significantly more likely to have detectable viral loads than those who reported taking a greater proportion (p=0.003). A similar but not statistically significant was observed among patients on ART for 12 and 18 months.

Figure 23. Association between self-reported 3-day adherence and viral load by time since ART initiation



Differences in association significant in 12-months on ART group (p=0.01).

Figure 24. Association between self-reported 30-day adherence and viral load by time since ART initiation



Differences in association significant in 6-month since ART initiation group (p=0.003).

4.0 Discussion

This study successfully estimated adherence using multiple indirect and direct measures among a nationally representative sample of 1,427 adult patients remaining on ART 6, 12 and 18 months after initiation at 14 public and six faith-based sites in the Rwandan national program. The study also identified patient- and site-level predictors of sub-optimal adherence and virological failure which can be used to guide program and policy decisions. Finally, for approximately half of the study participants, self-reported measures of adherence were compared against viral load, providing insights into potential low-cost measures of adherence which can be incorporated into routine service delivery.

4.1 ART adherence rates and viral suppression

Overall, self-reported adherence was very high: 93% of participants reported perfect adherence to ART in the three days preceding the interview and 77% reported taking 100% of their pills in the 30 days prior to interview. These figures are comparable to the 77% (95% CI: 68-85%) pooled estimate of perfect adherence from the African studies included in a 2006 meta-analysis of adherence to ART (Mills et al., 2006a) and recent studies from more typical HIV program settings in East Africa (Abaasa et al., 2008; Unge et al., 2009). The rates are also similar to those found in the single-site adherence study conducted in Kigali where 95% and 87% of patients reported perfect adherence in the previous 3 and 30 days (Demeester et al., 2005; Omes et al., 2005). Our study found perfect adherence rates varied by site and ranged from 85% to 100% in the previous 3 days and from 50% to 98% in the previous 30 days.

Given the high rates of self-reported perfect adherence in our study, not surprisingly, the majority (83%) of participants had viral suppression (≤40 copies/mL). The proportion of patients with undetectable viral loads was considerably higher than that observed in a large sample (n=7,000) from a South African program setting where 62% of adult patients had viral load ≤400 copies/mL at 12 months (Nachega et al., 2009) but slightly lower than that observed in Botswana where 90% of patients on ART for 1-5 years had ≤400 copies/mL (Bussman et al., 2008).

In this study, self-reported perfect adherence rates and virological response did not vary by time on ART, as was observed in the South African study mentioned above. This may be an artifact of our cross-sectional study design, as only patients who were alive and remained on ART 6, 12, and 18 months after treatment initiation were enrolled, potentially resulting in respondents with characteristics that made them similarly adherent and responsive to ART. Future analyses will compare baseline demographic and clinical characteristics of study participants with those who died, were lost to follow-up, stopped ART or transferred to another site to better understand the role survivor bias played in our adherence estimates. In Botswana, however, a sustained response to ART was observed over time as noted above (Bussman et al., 2008).

4.2 Patient-level predictors of non-adherence with 30-day recall

In multivariate models, being younger, being male, having some education, residing in large households, being in the middle to upper socioeconomic class, thinking ART was not effective, experiencing moderate to severe side effects and alcohol use were statistically significant risk factors for reporting <100% adherence in the 30 days preceding the interview.

The consistent trend of better adherence with older age (particularly above 44 years) indicates that adherence support programs should target younger adults. In a country with more than 48,000 patients initiating ART at a median age of 37 years (Lowrance et al, 2009), this translates into a significant patient population and our study provides important evidence of where adherence resources would be best utilized. Men were more likely to report non-

adherence as has been observed by other studies (Abaasa et al, 2008, Muyingo et al, 2008). While this gender differential was expected, surprisingly, men had decreased odds of having a detectable viral load (see section 4.3 below)

The implication of better adherence rates among individuals with no education and the poorest participants is encouraging as ART services in sub-Saharan Africa scale-up to grass root communities where patients are likely to have these characteristics. It is difficult to make comparisons with previous studies due to differences in study designs and analytical techniques but more educated Ugandan and Nigerian patients also exhibited poorer adherence in other studies (Abaasa et al., 2008, Uzochukwu et al., 2009). Additionally, in this study, we found that positive attitudes about ART encouraged adherence. This suggests that further counseling to engender positive personal beliefs about ART could be an important strategy in improving adherence.

The study also demonstrated positive effects of routine participation in a PLWHA support group, where patients likely receive additional support and encouragement from others infected with HIV or on ART. Similarly, patients living in households where there was a greater proportion of individuals on ART were more adherent, likely due to family support and encouragement, as well as the normalization of HIV. This provides further rationale for family-focused care in which patients are routinely asked about the HIV status of family members and encouraged to have family members of unknown HIV status tested for HIV. Living in a large household per se was a associated with lower adherence rates possibly due to the lack of privacy in taking medication, and the lack of support where there is no disclosure. Although not statistically significant, there was a tendency in the bivariate results towards better adherence where patients had disclosed HIV status to family members.

In our study, alcohol was a significant predictor of non-adherence, as has been found in a recent meta-analysis (Hendershot et al., 2009). The deleterious effect of alcohol use on adherence appears to be particularly acute among those who recently initiated ART. Since one in four participants reported consuming alcohol in the week preceding interview in our study, this finding suggests that alcohol counseling should be an integral component of pre-ART and post ART counseling, particularly early on in treatment.

4.3 Patient-level predictors of detectable viral load

The odds of having a detectable viral load were lower among the oldest patients (44 years and above), male patients and those who participated regularly in PLWHA meetings. It is unclear why male study participants were less likely to have a detectable viral load than female participants, and at the same time were more likely to report non adherence than women. In some developed-country studies, no significant association between gender and gender virological response has been observed (Purkayastha et al., 2005), while others have reported a better virological response among women (Nicastri et al., 2005; Perez et al., 2007; Moore et al., 2001). Possible explanations include underreporting of non-adherence by women due to increased social desirability bias, use of SD-NVP by a large proportion of women included in the study which led to an increased prevalence of drug resistance, or potentially genetic, nutritional or other factors unique to Rwandan women that prevent them from effectively suppressing viral HIV.

4.4 The impact of site characteristics on self-reported adherence and virological outcomes

As site-level factors may be more modifiable than patient-level factors, we examined the relationship between a range of contextual and programmatic variables on self-reported adherence and virological outcomes. The most significant site-level predictor of higher odds of non-adherence was urban location, followed by high patient volume. These findings suggest that more adherence support programs are needed in urban overcrowded sites

where patients can easily miss out on adherence counseling. Receiving services at a site which routinely conducts supportive home visits had a positive impact on self-reported adherence, but was not significantly associated with viral load suppression, as has been observed by others (Simoni et al, 2009; Pearson et al, 2007).

In direct contrast to reports from other settings (Simoni et al 2009), patients who received services at sites with peer educators were more likely to report non-adherence in our multivariate model. Our divergent finding could reflect reverse causality arising from use of a cross-sectional study design. Indeed, we cannot rule out that sites faced with non-adherent patients had recently instituted peer educator programs to address this problem,

4.5 Reasons for non-adherence

Forgetfulness was the most commonly reported reason for missing ART. This has been observed in several other African studies (Amberbir et al., 2008; Mills et al., 2006b), as well as in studies conducted in resource-rich settings (Mills et al., 2006b). This should be deconstructed in future studies, and by providers and clients during clinic encounters to devise a tailored action plan. Being away from home was also commonly reported as a reason for missing ART, and seemed to have greater significance in our study population than observed in others (Amberbir et al., 2008; Uzochukwu et al., 2009). Being away from home may reflect the inconvenience of taking one's medicine whenever one leaves home, or perhaps discomfort in taking medicine outside the home, possibly related to perceived or actual HIV/AIDS related stigma. Future beneficial interventions might include targeted reminders to bring sufficient medication and/or use of a pillbox to disguise ART for patients planning to be away from home. Lacking confidence in ART effectiveness was the least common reason for missing ART, further reflecting the positive attitude among ART patients in the study. In contrast to the 2006 study (Au et al.) on adherence at a research clinic in Kigali where 76% of the 71 patients interviewed reported not taking ART because they feared it would increase their appetite (and they lacked access to food), only 8% of the 576 non-adherent patients in our study reported not taking ART because it made them hungry.

4.6 Side effects

The most common side effects experienced by about a third of the patients were fairly non-specific (e.g. headache, fatigue and insomnia), making it hard to attribute them to ART without information on the prevalence of such complaints in the general population and among pre-ART HIV patients. Moreover, the two most commonly cited side effects, headaches and fatigue, did not appear to bother patients. Indeed, patients were most disturbed by sexual dysfunction and insomnia, suggesting the need to incorporate specific interventions to help patients manage these side effects, particularly as experiencing increasingly severe side effects was significantly associated with increased odds of non-adherence./

4.7 Validation of self-reported adherence measures using viral load

Self-reported adherence with the 3-day recall measure showed 93% sensitivity and a positive predictive value of 93% with viral load of 500 copies/mL or less. Sensitivity was much lower (78%) with 30-day recall for the same viral load threshold, but the positive predictive value remained high at 94%. 30-day recall adherence assessment measures have been shown to correlate well with viral load responses in other studies as observed in our study (Walsh et al., 2002; Simoni et al., 2006). The validation indicators were poorer when correlated with viral load of 40 copies/mL but clinically, there is likely little difference between patients with viral load <500 copies/mL and those with <40 copies/mL. Overall, adherence reported from 3-day recall questions appear to be a useful indicator of patient viral load below 500 copies/mL where no such assessments are easily accessible or affordable. Interpretation could be combined with patient physical status and concurrent illnesses to make a more clinically appropriate judgment. Unfortunately, the visual analogue scale (VAS)

was not used for 3-day recall in this study, but further studies could examine how well VAS assessments about adherence in the previous 3 days (not 30 days) correlates with viral load.

4.8 Programmatic implications

Several programmatic implications result from this study including:

- Most patients who missed ART tended to do so in the morning. As most patients reported forgetfulness as the main reason for missing ART, specific counseling is needed to support patients to take their morning doses of ART. It may be that particular morning activities (e.g. getting ready for the day, rushing to work) interfere with ART ingestion. Strategies for increasing adherence to ART in the mornings could be explored (e.g. taking ART as soon as the patient wakes up or keeping some medication with them at their place of work to ensure the availability of medication in case the patient forgets to take it before leaving home).
- Younger adults appear to have greater likelihood of non-adherence than older patients. This implies that where resources are limited, younger patients should be prioritized in adherence counseling
- Alcohol consumption was one of the strongest predictors of self-reported non-adherence. There is a recent move to incorporate prevention activities in HIV care and treatment services and one of the primary prevention activities is appropriate counseling about alcohol consumption.
- Although self-reported adherence and viral suppression did not vary by time since ART initiation, there was some temporal variation in patient- and site-level predictors of adherence. This implies that targeted adherence messages and intervention that evolve with time are needed in program implementation, rather than a standard approach for all patients.
- Adherence counseling to encourage positive perception of ART effectiveness appears to be a crucial component of ART programs in order to ensure continued adherence.
- Moderate and severe side effects were a significant predictor of non-adherence. This indicates a need for additional clinical and/or psychosocial support to help patients manage their side effects so that they are able to continue taking their prescribed medications Results indicate that some side effects are particularly bothersome to patients (e.g. sexual dysfunction and insomnia).
- Less than one-third of all participants had CD4 assessments at ART initiation and again at 6 or 12 or 18 months. Similarly the 2006 national evaluation of ART outcomes found significant missing CD4 follow up data- only 49% and 35% of patients had CD4 information at 6 and 12 months after ART initiation (TRAC, 2008). The lack of CD4 data limited our ability to assess immunological changes as a measure of adherence and pointing to an important area for intervention. In a setting where viral load assessment is not routinely available for patient monitoring, it would be important to more optimally utilize repeat CD4 assessments in patient monitoring, particularly since CD4 testing is freely available at most sites.
- The positive predictive value of viral load below 500 copies per mL was above 90% for both the 3-day and 30-day recall adherence measures. Use of simple adherence measures like the 3-day recall table or the VAS used in this study offer a low-cost, low-technology proxy to routine viral load assessments for tracking patient progress

4.9 Strengths and limitations of the study

To our knowledge, this is the first nationally representative ART adherence study in Africa and possibly worldwide. The study was based on local and international multi-institutional collaborations and produced rapid estimates of ART adherence among patients remaining on ART after 6, 12, and 18 months. There were very high response rates among eligible participants (96%) and complete data on nearly all study participants (99%). The study used multiple direct and indirect ART adherence measures that produced rapid and robust

adherence data. Important local capacity building activities were conducted as part of the study implementation, including training on good clinical practice (Appendix B) and data analysis (Appendix C). Significant data were collected on a range of patient-level predictors of adherence including socio-demographic, clinical, knowledge and attitudinal and psycho-social factors, as well as possible site-level predictors of adherence. The resulting dataset and blood specimen bank retained at NRL present an important resource for data analysis beyond what is presented in this report, and will facilitate continued capacity building of local and international researchers.

A few limitations should be noted. First, the study was limited to adults aged 18 years or older, as the determinants of sub-optimal adherence among pediatric patients likely vary significantly from that of those included in the study. The cross-sectional nature of the study and implicit exclusion of patients who were not retained in the program resulted in a survivor bias and the inability to examine adherence as a predictor of program discontinuations, including mortality and losses to follow-up. Similarly, the cross-sectional nature of the study limits our ability to definitively rule out reverse causality in some of our findings. For example, patients who attended sites with peer educator programs had a greater tendency to report non-adherence and have detectable viral loads. Due to the cross-sectional nature of our study we cannot determine whether sites faced with patients with poor adherence were the ones which instituted peer educator programs in order to address this problem, or whether the presence of peer educator programs resulted in poor adherence. Additionally, due to financial constraints, we were unable to perform viral load assessments for all study participants which limited our power to detect significant associations when modeling predictors of detectable viral load. Finally, lack of variation in some site-level variables precluded their inclusion in multivariate models.

5.0 Conclusion

Very high levels of self-reported adherence and virological suppression were observed among a nationally representative sample of patients remaining on ART for 6, 12 and 18 months in Rwanda. When combined with the positive results from the 2006 evaluation of outcomes of the Rwandan national program that showed 92% and 93% of patients were retained on ART 6 and 12 months after ART initiation (TRAC, 2008), our results provide further evidence of a successful national HIV treatment program. Risk factors of poor self-reported adherence observed in multivariate models were being younger, being male, having some education, residing in large households, being in the middle to upper socioeconomic class, thinking ART is ineffective, experiencing moderate to severe side effects, alcohol use, urban site location and high volume sites. The odds of detectable viral loads decreased with age, male sex and participation in PLWHA meetings and increased with presence of peer educators at the site. While time on ART was not significantly associated with self-reported adherence, there was some variability in the relationship between patient- and site-level determinants of adherence by time on ART. Use of simple self-reported adherence measures had a high positive predictive value for detectable viral load, but there was significant lack of specificity, indicating further field testing and refinement of short adherence recall questions may be needed.

6.0 Recommendations

- Further field test short adherence recall questions and integrate them into routine follow-up to identify patients in need of additional adherence support;
- Investigate systematic barriers to follow-up CD4 testing; implement strategies to optimally conduct and utilize repeated CD4 measures in routine patient monitoring;
- Where resources are limited, provide targeted counseling on adherence particularly focusing on patients who are younger, from large households, experiencing side effects, taking alcohol and those who have a negative perception of ART effectiveness. Provide clinical and psychosocial support to patients regarding the management of side effects, in particular those highlighted by this study as being bothersome to patients;
- Systematically address alcohol use in counseling sessions particularly soon after patients start ART;
- Utilize group and individual sessions to disseminate clear and accurate messages about HIV and ART (e.g. that HIV continues to be a serious disease regardless of the effectiveness and availability of ART, and that ART does not cure HIV); and
- Ensure that patients enrolled in HIV care are asked about the HIV status of their household members and strongly encouraged to bring them to the clinic for testing, care, and/or other appropriate services; also continue to encourage and support all patients to disclose their ART status to family members and others.

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Appendix A: Study interviewers and data entry clerks

Interviewers

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Vereranda Bajinya

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Marie Claire Iribagiza

Chantal Kayitesi

Alice Kwizera

Noelline Mbabazi

Billy Muhinyuza

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Solange Kibitenga

Henriette Uwineza

Jacqueline Uwitonze

Scovia Umulisa

Appendix B: Report for the training workshop on Good Clinical Practice (GCP), Good Laboratory Clinical Practice (GCLP), & Standard Operating Procedures (SOPs)

See attached report.

Appendix C: Rwanda Adherence Public Health Evaluation (PHE) Data Analysis Workshop Report

See attached report.