

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

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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 and 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. At the time this study was initiated, nearly 49,000 adults and children were 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 on ART (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 on ART 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, 1,472 (82%) were confirmed to be eligible, and of those, 1,417 (96%) agreed to participate and had complete data, including 571 (40%), 491 (35%) and 355 (25%) who started ART 6, 12 and 18 months prior to data collection, respectively, and 837 (59%), who received viral load assessments among the 6 (40%) 12 (34%) and 18 (26%) months on ART groups. After applying the sampling weights, the total population was 6,996: with 2,724 (39%); 2,353 (34%) and 1,921 (27%) in the 6, 12, and 18 months on ART groups, respectively. The weighted viral load population was 4,184 (60%): 1,598 (38%) 1,336 (32%) 1,250 (30%) in the 6, 12, and 18 months on ART groups, respectively.

Levels of adherence

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

- a. *3-day recall:* 94% (95% CI: 92-97%) of the population reported perfect 3-day adherence with no statistically significant differences by time on ART. Perfect three-day adherence ranged significantly across sites from 84% to 100%.
- b. *30-day recall:* 76% (95% CI: 75-79%) of the population reported perfect adherence in the 30 days preceding the interview. An additional 11% took 90% of all pills, 7% took 80%, and 4% took less than 80%. No statistically significant differences were observed by time on ART at any of the adherence cut-off levels. Perfect 30-day adherence varied by site from 50% to 98%.
- c. *Treatment interruption:* The population reported very infrequent treatment interruptions, defined as missing all pills for 3 or more consecutive days, with a rate of 1.1 per person-year on ART for both the 6- and 12- months on ART study groups and 0.8 in the 18-month group.

Immunological: Completeness of baseline and follow-up CD4 counts was very low, which limited our ability to examine immunological outcomes. In the weighted patient population, only 607 (22%), 528(22%) and 246(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 +121cells/ μ l at 6 months, +158 cells/ μ l at 12 months; and +143 cells/ μ l at 18 months.

Virological: Across the 4,184 population with viral load assessments, 83% (95% CI: 80-85%) had undetectable (<40 copies/mL) viral loads and an additional 9% had viral loads between 40-500 copies/mL. The proportion of patients with undetectable viral load varied significantly by site and ranged from 70% to 95%.

Reasons for non-adherence and side effects to ART

Among the 2,640 (38%) patients who ever missed ART, the most commonly cited reasons for missing a dose across all three study groups were forgetfulness (57%), being away from home (49%), and not having food (25%). Feeling well and therefore thinking the medication was unnecessary (2%), 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 (2%) were the least commonly reported reasons for missing ART(cited by less than 5% of the population).

Headache (37%), fatigue (34%), insomnia (33%) nervousness/anxiety (32%) and muscle pain/joint aches (32%) were the most commonly reported side effects in the 30 days prior to interview. However, in most cases, patients did not consider the side effects to be "severe": on average across all study groups and side effects, 59% of the population that experienced a given side effect were either "not bothered" by it or "bothered a little". Patients who reported sexual dysfunction and insomnia experienced these side effects more "severely", with 56% and 51% of them, respectively reporting being "very bothered."

ART attitudes and beliefs

Patients 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 the population, however, felt that HIV/AIDS is not a serious illness because of the availability of ART (59%), that ART can cure HIV (57%) and that people taking ART need to hide it (84%). Nearly all patients believed that ART was very (94%) or somewhat (5.6%) effective in keeping them healthy.

Patient- and site-level determinants of adherence

Reporting <100% adherence in the 30 days preceding interview: In multivariable models controlling for time on ART and other patient- and site-level differences, patients who were younger, experiencing severe side effects, using alcohol, and receiving services at health centers, or at 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.

Detectable viral load:

In multivariable analyses, the overall odds of having a detectable viral load were significantly lower for older patients, males, patients participating regularly in PLWHA associations, and patients who used reminder tools. The odds of having a detectable viral load were higher among patients enrolled at sites with peer educator programs.

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, the population that 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 population, 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 in multivariable analysis, 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. Additionally, several modifiable patient- and site-level variables were associated with adherence, suggesting areas for potential intervention. While peer educator programs negatively associated with adherence and viral suppression, we cannot rule out selective implementation at sites with poorer adherence. 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 prior to or 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 predictors 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 $\geq 95\%$ 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, Potchoo et al. 2010). A recent meta-analysis has also suggested that adherence is better to once-a-day than to twice-a-day regimens (Parietti et al., 2010).

1.5 Study justification

By the time of this study, an estimated 150,000 adults and children were living with HIV, including 49,000 who are receiving ART at approximately 165 facilities in Rwanda (UNAIDS, 2008). The current numbers are an estimated 169,200 adults and children living with HIV, and 76,726 receiving ART (Republic of Rwanda 2010; UNAIDS 2010). This reflects an ongoing epidemic and ongoing HIV care and treatment scale-up efforts and yet to-date, 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 the population 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

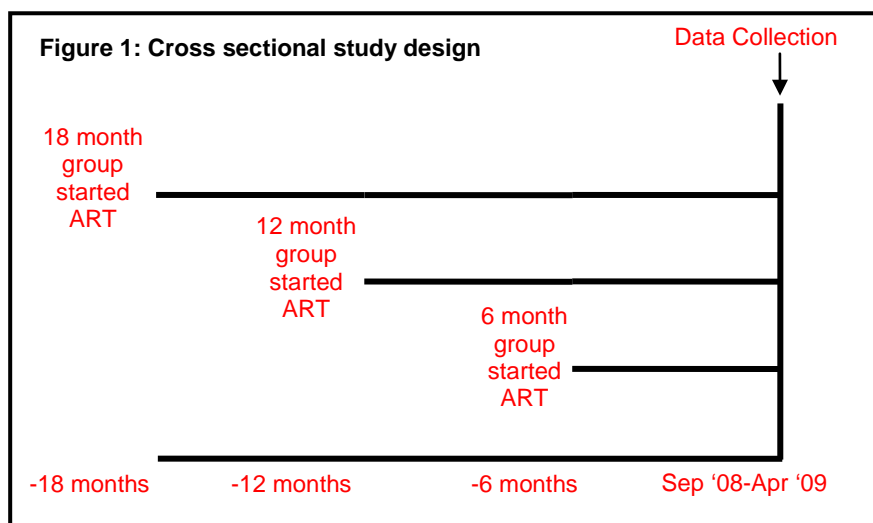
2.1 Objectives

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.



2.3 Sampling

Multistage sampling methods with stratification by time on ART (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 on ART 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 Mills et al., 2006a), a precision of $\pm 5\%$, a design effect of 1.5 and a non-response rate of 25%, we required a sample size of 2,204 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 with- replacement, we applied a finite population correction factor to the total estimated sample size, resulting in a revised total sample size of 1,796 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 and found a total of 1,798 patients eligible for the study at the selected sites. This resulted in the target sample size per stratum shown in Table 1. 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 on ART (+/- 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

The study sample was obtained by stratified two-stage cluster sampling where the sites were the clusters. There were two levels stratification: (1) by time on ART: 6, 12, and 18 months on ART; (2) and by site ownership: public and faith based sites giving a total of 6 strata. The first stage of sampling involved selecting sites in each stratum using probability proportional to size, where the measure of size was the total number of adult patients on ART at each site. The site sampling frame had a total of 113¹ sites that had initiated ART services at least 18 months prior to the survey in all 30 districts of Rwanda; and 14 public (70%) and 6 faith-based (30%) sites were selected to represent the relative contribution of those sectors to the adult ART population.

2.3.3 Patient inclusion criteria and selection

In the second stage of sampling, patient registers and charts were used to create site-specific sampling frames of all eligible patients by time on ART. The total number of eligible patients was entered into Epi Info 6.04 software and a random sample of patients generated per site. The sample of patients per site was determined by the proportion of eligible patients the site contributed to the sampling frame. For each site, the remaining patients after the random selection were kept as replacements in case the selected patient could not be contacted or was later found to be ineligible. Every alternate patient was selected for inclusion in the viral load sub-sample. 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

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.

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.

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

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 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 design weights accounting for the probability of selection and inclusion in the study at the site- and patient-levels were calculated and used together with survey design procedures and finite population correction factors in all analyses to obtain nationally representative figures. Thus, all tables and figures presented in this report reflect population estimates. Given the tendency of design weights to over-estimate significant associations, p-values <0.04 rather than <0.05 should be considered statistically significant. With the exception of CD4 count, ≤ 10 (<1%) patients were missing data per variable and patients with missing data were dropped from the analyses. In the case of CD4 count where $\geq 78\%$ of respondents were missing CD4 data at either ART initiation or at the time of interview, a category for missing data was created (Table 7). This limited our ability to examine immunological outcomes in the current report but future analyses will utilize multiple imputation using Chain Equations (MICE or ICE) in STATA to allow inclusion of missing observations. 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 on ART. 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 multivariable models. Backward stepwise selection based on a 5% level of significance was used to determine the multivariable models presented in this report, after forcing time on ART, 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 the entire population together, controlling for time on ART. Due to limited statistical power for the viral load outcome, the model was not stratified by time on ART. Bivariate and multivariable 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 the population 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 25th and 75th percentile cut-offs of this index representing whether the population 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.

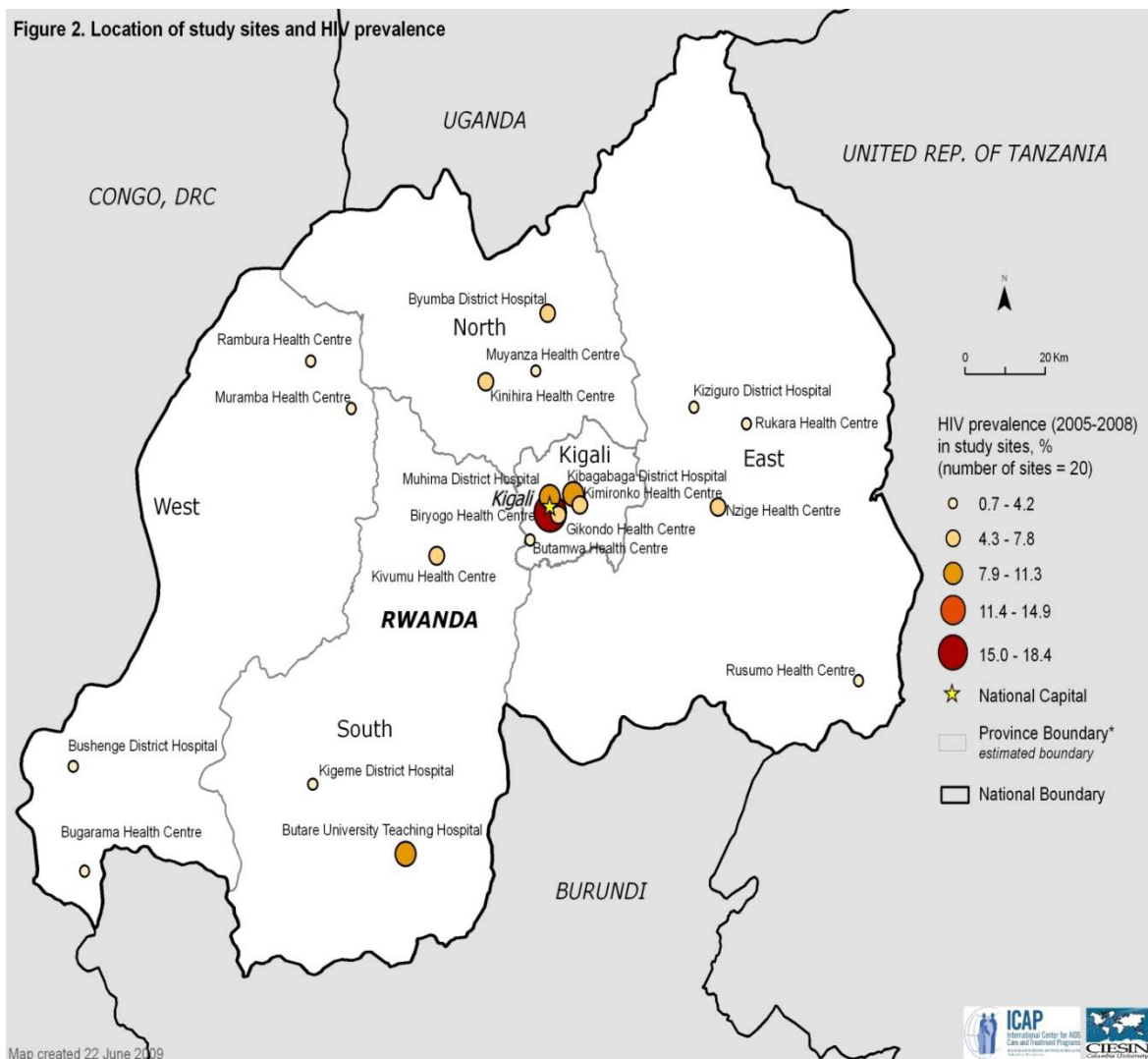


Table 4 shows the ART adherence support services, nutritional services and other services available at the 20 study sites. All sites routinely used at least one tool or approach to support ART adherence, including providing patients with appointment cards (n=17), pill boxes (n=9), paper tools such as 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, 1,472 (82%) of whom were confirmed to be eligible to participate in the study. The 326 (18%) ineligible patients included 50 who died prior to study start; 70 who were lost to follow-up; 113 who transferred to another site; 14 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 group; and 78 patients where reason for eligibility was not recorded. Of the 1,472 patients who were eligible for the study, 18 (1%) declined to participate and 37 (2%) could not be located by the study team resulting in a total of 1,417 (96%) patients enrolled into the study and included in the analyses in this report, including 571 (40%), 491 (35%) and 355 (25%) who started ART 6, 12 and 18 months prior to data collection, respectively. These 1,417 patients represent 96% of all patients confirmed to be eligible for the study. As per the study design, 837 (59%)³ had viral load assessments done, including 331 (40%), 284 (34%) and 222 (26%) in the 6, 12 and 18 months on ART study groups, respectively.

The total population after applying the patient design weight was 6,996: with 2,724 (39%); 2,353(34%) and 1,921(27%) in the 6, 12, and 18 months on ART groups respectively. The viral load population was 4,184 (60%): 1,598 (38%) 1,336 (32%) 1,250 (30%) in the 6, 12, and 18 months on ART groups respectively. No statistically significant differences in ineligibility, non-participation or incomplete information were observed by time on ART (data not shown).

3.3 Geographic and socio-demographic characteristics of sample

As per the sampling design, 74% and 26%, respectively of the 1,417 study participants were receiving services at public-sector and faith-based sites, with no difference by time on ART (Table 5). Overall, about a third (35%) of the population was from sites in Kigali city; while approximately 20%, 19% 13% and 12% were from the East, West, North and South respectively. Individual sites contributed 1-12% to the patient population.

Table 6 shows the socio-demographic characteristics of the population by time on ART. There were no statistically significant differences across the three study groups in age, sex, education, marital status, employment, number of children, household size, religious affiliation and poverty levels. The majority of the population was female (65%). On average,

³ While we aimed to obtain viral loads for 50% of study participants, we ultimately obtained them for 59%. This resulted from the greater number of available replacements for VL sub-sample non-participants compared to replacements for overall sample non-participants. The replacements for the VL sub-sample were drawn from overall number of participating patients, while the replacements for the overall sample were drawn from the total number of eligible patients at the site. Whereas every ineligible VL sub-sample patient could be replaced, there were fewer replacements in the overall sample due to the limited and finite number of eligible patients at the sites.

the population was 38.1 years old and had completed 5.0 years of school. Nearly one-third of the population was working for cash or other payment at the time of interview. The population had an average of 3.8 children ever born, an average of 3.1 living children, and were on average living in a household of 4.9 members. As described in Section 2.6.3, the population were divided into poverty tertiles. Most of the patients were Catholics (45%) and Protestants (47%) and few were Adventists (6%) or reported no religious affiliation (3%).

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	9
Bushenge DH**	Nyamasheke	Public	Rural	PEPFAR	2004	2006	2010	594	58	40	17
Butamwa HC	Nyarugenge	Public	Urban	PEPFAR	2005	2007	383	156	16	8	7
CHUB***	Huye	Public	Urban	GF	2004	2006	1059	914	7	8	12
Byumba DH	Gicumbi	Public	Urban	PEPFAR	2005	2007	1142	1106	65	43	22
Gikondo HC	Kicukiro	Faith-based	Urban	PEPFAR	2004	2007	2168	1234	82	51	38
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	35	51	27
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	13
Kiziguro DH	Gatsibo	Public	Rural	PEPFAR	2005	2006	1100	293	13	8	6
Muhima DH	Nyarugenge	Public	Urban	PEPFAR	2004	2006	2968	1669	65	41	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	11	24	6

*HC: Health Centre

**DH: District Hospital

***CHUB: Centre Hospitalier Universitaire de Butare (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

Site name	ART adherence services available					Nutritional services available					Other services available			
	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	
CHUB***	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

***CHUB: Centre hospitalier universitaire de Butare (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

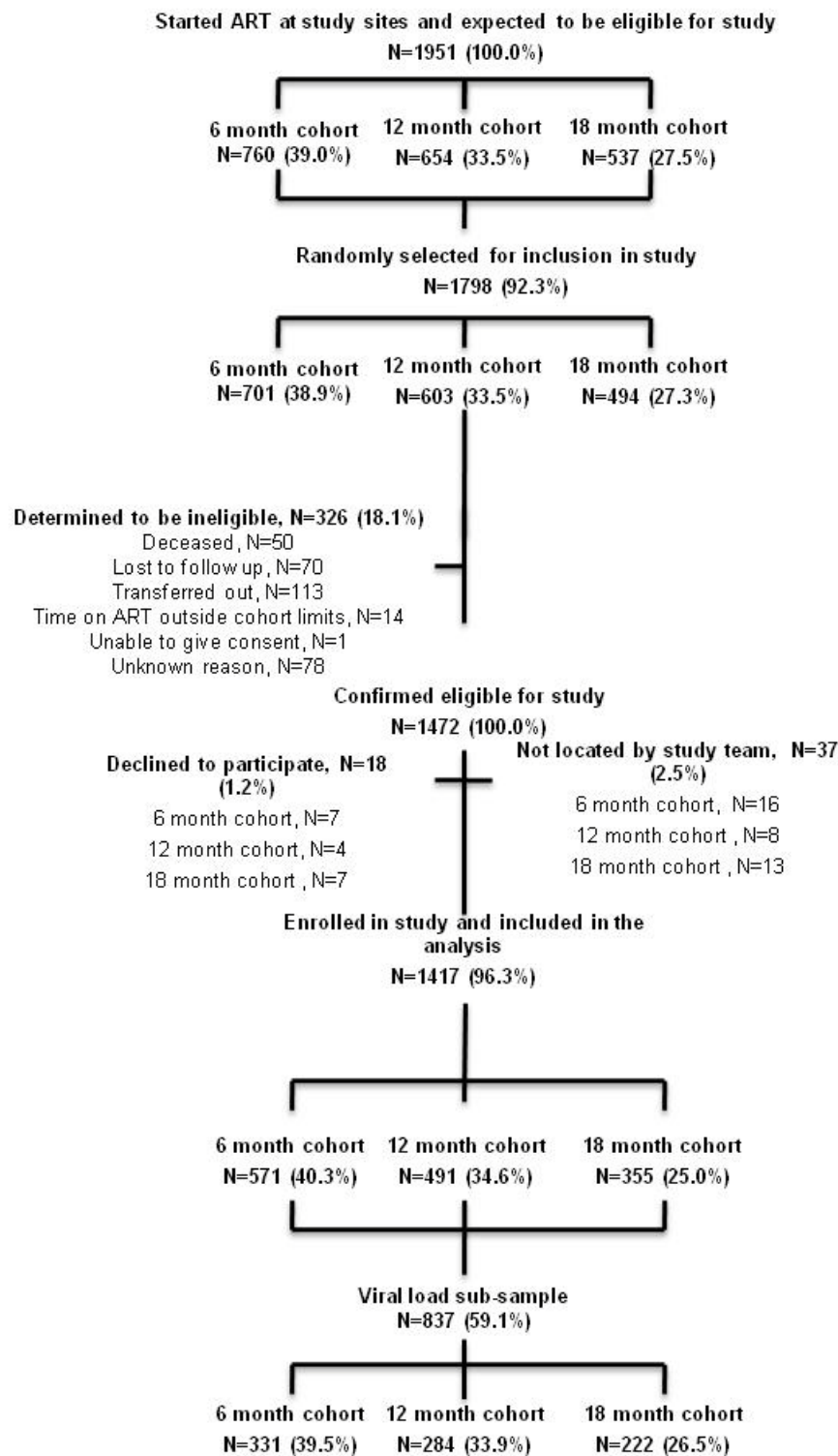


Table 5: Site characteristics of the patients by time on ART (population estimate)

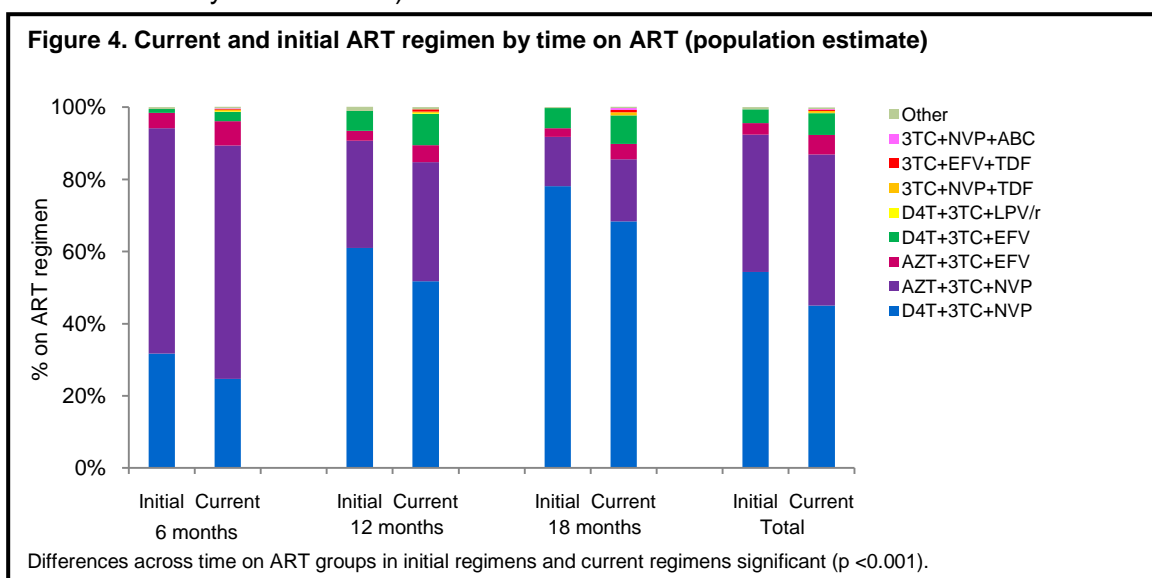
	6 months		12 months		18 months		Total		df	p-value
	N	%	N	%	N	%	N	%		
	2724	39	2353	34	1921	27	6996	100		
Facility ownership										
Public	2066	75.9	1740	74.0	1369	71.3	5175	74.0	2	0.611
Faith-based	657	24.1	612	26.0	552	28.7	1821	26.0		
Location										
Urban	1313	48.2	1302	55.3	999	48.0	3614	51.7	2	0.915
Rural	1411	51.8	1050	44.7	921	52.0	3382	48.3		
Province										
East	510	18.7	530	22.5	376	19.6	1416	20.2	8	1.000
Kigali City	1038	38.1	746	31.7	675	35.2	2459	35.1		
North	385	14.1	286	12.2	274	14.3	944	13.5		
South	253	9.3	305	13.0	264	13.7	822	11.8		
West	538	19.8	485	20.6	332	17.3	1355	19.4		
Administrative district										
Gasabo	311	11.4	319	13.6	322	16.8	952	13.6	30	1.000
Gatsibo	176	6.5	106	4.5	82	4.3	364	5.2		
Gicumbi	193	7.1	130	5.5	64	3.3	387	5.5		
Huye	60	2.2	60	2.6	121	6.3	241	3.4		
Kayanza	86	3.2	106	4.5	144	7.5	336	4.8		
Kicukiro	159	5.8	97	4.1	75	3.9	331	4.7		
Kirehe	115	4.2	240	10.2	58	3.0	413	5.9		
Muhanga	119	4.4	115	4.9	62	3.2	296	4.2		
Ngororero	125	4.6	170	7.2	72	3.7	367	5.2		
Nyamagabe	74	2.7	130	5.5	82	4.2	286	4.1		
Nyamasheke	240	8.8	162	8.9	71	3.7	473	6.8		
Nyarugenge	568	20.9	329	14.0	278	14.5	1175	16.8		
Nyabihu	87	3.2	94	4.0	123	6.4	304	4.3		
Rulindo	191	7.0	156	6.6	210	10.9	558	8.0		
Rusizi	86	3.1	59	2.5	70	3.4	211	3.0		
Rwamagana	132	4.9	79	3.4	92	4.8	304	4.3		
Health facilities										
Biryogo Health Centre	166	6.1	120	5.1	58	3.0	343	4.9	38	<0.001
Bugarama Health Centre	86	3.1	59	2.5	66	3.4	211	3.0		
Bushenge District Hospital	240	8.8	162	6.9	71	3.7	473	6.8		
Butamwa Health Centre	325	11.9	162	6.9	162	8.5	650	9.3		
Butare University Teaching Hospital	60	2.2	60	2.6	121	6.3	241	3.4		
Byumba District Hospital	193	7.1	130	5.5	63	3.3	387	5.5		
Gikondo Health Centre	159	5.8	97	4.1	75	3.9	331	4.7		
Kibagabaga District Hospital	176	6.5	115	4.9	199	10.4	490	7.0		
Kigeme District Hospital	74	2.7	130	5.5	82	4.2	286	4.1		
Kimironko Health Centre	135	5.0	204	8.7	123	6.4	462	6.6		
Kinihira Health Centre	151	5.5	75	3.2	119	6.2	346	4.9		
Kivumu Health Centre	119	4.4	115	4.9	62	3.2	296	4.2		
Kiziguro District Hospital	176	6.5	106	4.5	82	4.3	364	5.2		
Muhima District Hospital	78	2.9	47	2.0	58	3.0	183	2.6		
Muramba Health Centre	125	4.6	170	7.2	72	3.7	367	5.2		
Muyanza Health Centre	40	1.5	81	3.4	91	4.7	212	3.0		
Nzige Health Centre	132	4.8	79	3.4	92	4.8	304	4.3		
Rambura Health Centre	87	3.2	94	4.0	123	6.4	304	4.3		
Rukara Health Centre	86	3.2	106	4.5	144	7.5	336	4.8		
Rusumo Health Centre	115	4.2	240	10.2	58	3.0	413	5.9		

Table 6: Socio-demographic characteristics of the population by time on ART (population estimate)

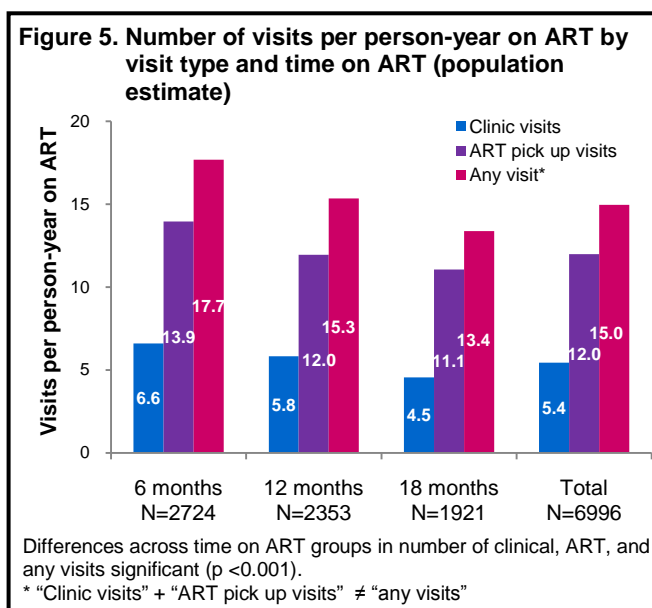
	6 months		12 months		18 months		Total		df	p-value
	N	%	N	%	N	%	N	%		
	2724	40	2353	35	1921	25	6996	100		
Sex										
Male	953	35.1	825	35.2	658	34.5	2436	35.0	2	0.982
Female	1762	64.9	1521	64.8	1248	65.5	4531	65.0		
Missing	9		6		15		30			
Age										
Mean years, SE	38	0.4	38	0.4	37	0.6	38	0.3	2	0.522
Age groups										
18-25 years	192	7.0	199	8.5	174	9.0	564	8.1	2	0.750
26-35 years	951	34.9	727	30.9	727	37.8	2404	34.4	2	0.324
36-45 years	914	33.6	883	37.6	701	36.5	2499	35.7	2	0.667
46-55 years	580	21.3	408	17.4	243	12.7	1231	17.6	2	0.090
56 years+	87	3.2	134	5.7	76	4.0	297	4.2	2	0.233
Missing	0	0.0	0	0.0	0	0.0	0	0.0		
Education										
Mean years, SE	4.9	0.4	4.7	0.3	5.5	0.3	5.0	0.2	2	0.291
Education levels										
None	688	25.3	694	29.5	463	24.1	1845	3.1	8	0.470
Primary	1578	57.9	1308	55.6	1026	53.4	3912	2.5		
Secondary	350	12.8	259	11.0	329	17.1	938	2.6		
Tertiary	22	0.8	14	0.6	46	2.4	82	0.5		
Other	86	3.2	78	3.3	57	2.9	220	0.6		
Religion										
No religion	66	2.4	112	4.8	29	1.5	206	3.0	6	0.212
Catholic	1196	44.0	926	39.5	975	51.2	3097	44.5		
Protestant	1293	47.6	1153	49.1	815	42.8	3261	46.8		
Adventist	160	5.9	157	6.7	86	4.5	403	5.8		
Missing	9		4		17		29			
Marital status										
Married/living with partner	1425	52.5	1285	54.7	1011	53.7	3721	53.5	6	0.824
Separated/divorced	430	15.8	275	11.7	307	16.2	1011	14.5		
Widowed/not living with partner	635	23.4	615	26.2	399	21.1	1649	23.7		
Never married	226	8.3	174	7.4	175	9.2	574	8.3		
Missing	9		4		28		41			
Working for cash or other payment										
Missing	15		4		17		35		2	0.700
Number of children ever born										
Mean number, SE	3.8	0.2	3.8	0.1	3.7	0.2	3.8	0.1	2	0.853
Missing	9		4		21		33			
Number of living children										
Mean number, SE	3.1	0.1	3.1	0.1	3.1	0.2	3.1	0.1	2	0.946
Missing	208		176		209		593			0.861
Number of household members										
Mean number, SE	5.0	0.1	5.0	0.1	4.9	0.1	4.9	0.0	2	0.841
Missing	16		4		17		36			
Household poverty index										
Poorest	1116	41.0	1108	47.1	756	39.3	2980	42.6	4	0.880
Less poor	969	35.6	710	30.2	655	34.1	2334	33.4		
Least poor	638	23.4	534	22.7	510	26.6	1682	24.0		
Missing	0	0.0	0	0.0	0	0.0	0	0.0		

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

The majority of the population entered care and treatment from VCT (70%) and PMTCT (15%) clinics with no statistically significant differences by time on ART (Table 7). Time since HIV diagnosis varied significantly between study groups and, as expected, increased from a median of 17 months for patients on ART for 6 months to a median of 23 months for patients on ART for 18 months. WHO stage at enrolment into care and at ART initiation varied by time on ART, and indicated that patients on ART for a longer period of time entered care and started ART in a more advanced disease stage: 26% of patients on ART for 6 months had WHO stage III/IV at enrolment into care compared to 37% of patients on ART for 12 months and 40% of those on ART for 18 months ($p=0.059$). Among patients on ART for 6, 12, and 18-months, respectively, 34%, 38%, and 46% had WHO stage III/IV at ART initiation. The median CD4 counts at enrolment into care and at ART initiation varied by time on ART, and were higher for patients who started ART more recently: 285 cells/ μ l at enrolment into care and 258 cells/ μ l at ART initiation in the 6 months on ART group, 246 cells/ μ l at enrolment into care and 209 cells/ μ l at ART initiation in the 12 months on ART group and 205 cells/ μ l at enrolment into care and 192 cells/ μ l at ART initiation in the 18 months on ART group ($p<0.0001$ for the difference in CD4 at enrolment into care and for the difference in CD4 at ART initiation by time on ART).



Most of the population on ART for 6 months started with an initial regimen of AZT+3TC+NVP (63%) while most of those who began ART earlier started with D4T+3TC+NVP: 61% in the 12 months on ART group and 78% 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 who were on at the time of the interview across the three study groups (Figure 4): 63% of patients on ART for 6 months were still on AZT+3TC+NVP, while 51% of those on ART for 12 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 time on ART ($p < 0.001$), with 0.115, 0.165 and 0.070 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 0.001 per person-year on ART with no difference by time on ART. 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 6.6, 5.8 and 4.5 clinic visits per person-year on ART ($p < 0.001$), respectively, and 13.9, 12.0 and 11.1 ART pick-up visits per person-year on ART ($p < 0.001$).

Table 7: ART-related characteristics of the patients by time on ART initiation (population estimate)

	6 months		12 months		18 months		Total		df	p-value
	N	%	N	%	N	%	N	%		
Patient admission mode	2724	39	2353	34	1921	27	6996	100		
Voluntary counseling and testing	1917	71.2	1615	69.0	1305	68.5	4836	69.7	12	0.927
PMTCT	407	15.1	317	13.5	323	17.0	1047	15.1		
Hospitalisation	81	3.0	77	3.3	83	4.3	241	3.5		
Out-patient consultation	134	5.0	100	4.3	74	3.9	309	4.4		
Tuberculosis consultation	12	0.5	11	0.5	11	0.6	35	0.5		
Transferred in ≤ 30 days of starting ART	25	0.9	77	3.3	18	1.0	121	1.7		
Other	117	4.3	143	6.1	91	4.8	351	5.0		
Missing	30		4		15		48			
Time (months) since HIV diagnosis										
Mean, SE	28.0	1.4	29.2	1.41	37.0	1.5	31.0	0.8	2	<0.001
Median, IQR	16.5	8.9-35.6	17.8	13.4-34.7	23.0	19.2-41.6	20.4	13.3-37.2	2	<0.001
Missing	218		187		114		519			
WHO stage at enrolment										
WHO stage I	1201	45.4	708	31.7	536	29.6	2445	36.5	6	0.056
WHO stage II	768	29.0	690	30.9	552	30.5	2010	30.0		
WHO stage III	612	23.1	755	33.8	643	35.5	2010	30.0		
WHO stage IV	67	2.5	81	3.6	79	4.4	227	3.4		
Missing	76		118		111		305			
WHO stage at ART initiation										
WHO stage I	549	40.5	437	27.5	372	25.4	1358	30.8	6	0.331
WHO stage II	345	25.5	541	34.1	420	28.7	1306	29.7		
WHO stage III	398	29.3	522	32.9	576	39.3	1496	34.0		
WHO stage IV	63	4.6	86	5.4	96	6.6	245	5.6		
Missing	1369		766		456		2591			
CD4 count (cells/μL) at enrolment into care										
Mean, SE	292.8	8.3	255.1	7.9	227.8	9.8	261.9	5.3	2	<0.001
Median, IQR	285.4	193.3-360.7	245.6	153.5-322.0	205.3	130.2-291.5	254.0	157.3-331.7	2	<0.001
Missing	541		370		353		1264			
CD4 count (cells/μL) at ART initiation										
Mean, SE	243.0	5.5	211.5	5.9	199.9	5.2	220.4	3.5	2	0.005
Median, IQR	258.0	184.1-309.8	209.2	139.6-287.8	191.8	130.8-270.3	221.9	149.9-293.7	2	<0.001
Missing	467		319		324		1110			

Table 7: ART-related characteristics of the patients by time on ART initiation (population estimate) (cont'd)

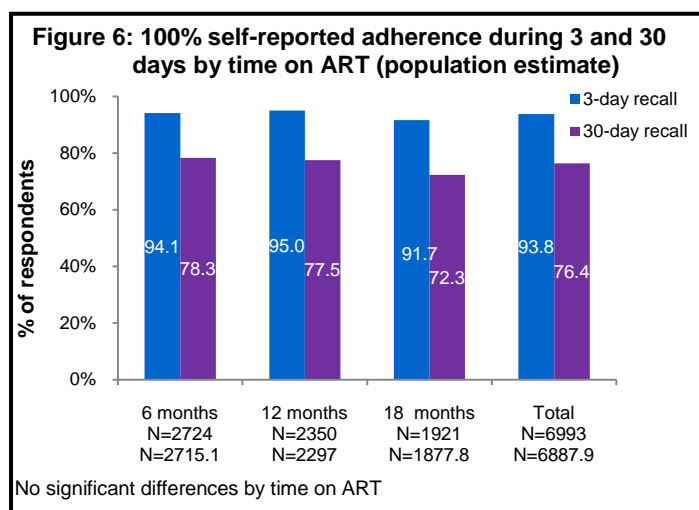
	6 months		12 months		18 months		Total		df	p-value
	N	%	N	%	N	%	N	%		
Initial ART regimen	2724	39	2353	34	1921	27	6996	100		
D4T+3TC+NVP	859	31.7	1427	61.0	1488	78.1	3774	54.3	8	<0.001
AZT+3TC+NVP	1692	62.5	694	29.7	262	13.7	2648	38.1		
AZT+3TC+EFV	113	4.2	65	2.8	46	2.4	223	3.2		
D4T+3TC+EFV	29	1.1	128	5.5	107	5.6	264	3.8		
Other	13	0.5	26	1.1	4	0.2	43	0.6		
Missing	17		4		15		35			
Current ART regimen									12	<0.001
D4t+3TC+NVP	758	28.1	1173	50.6	1378	72.3	3309	47.8		
AZT+3TC+NVP	1709	63.4	801	34.7	323	16.9	2832	41.0		
AZT+3TC+EFV	137	5.1	109	4.7	71	3.7	317	4.6		
D4T+3TC+EFV	46	1.7	192	8.3	116	6.1	354	5.1		
3TC+NVP+TDF	20	0.8	15	0.6	6	0.3	41	0.6		
3TC+EFV+TDF	3	0.1	7	0.3	4	0.2	14	0.2		
3TC+NVP+ABC	2	0.1	0	0.0	7	0.4	9	0.1		
D4T+3TC+LPV/r	3	0.1	2	0.1	0	0.0	5	0.1		
Other	18	0.7	17	0.7	1	0.1	36	0.5		
Missing	28		29		15		72			
Number of daily pills										
Mean, SE	2.1	0.009	2.2	0.022	2.1	0.026	2.2	0.011	2	<0.0001
Median, IQR	1.5	1.3-1.8	2.0	2-2	1.6	1.3-1.8	1.6	1.3-1.8	2	0.043
Missing	34		32		32		98			
Drug substitutions per person-year on ART										
Rate, SE	0.115	0.019	0.165	0.040	0.070	0.020	0.020	0.017	2	0.004
Missing	17		12		15		43			
Regimen switches per person-year on ART										
Rate, SE	0.004	0.004	0.001	0.001	0.000	0.000	0.002	0.017	2	0.012
Missing	17		4		15		36			

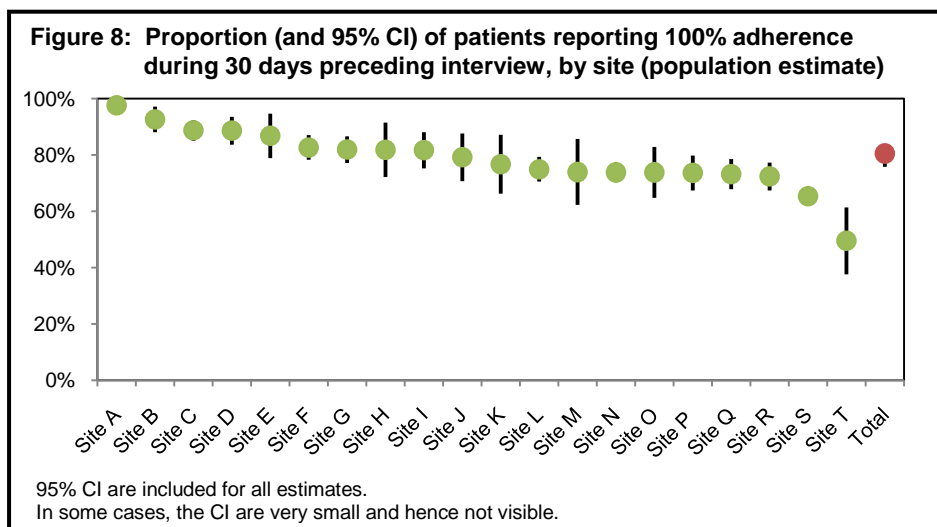
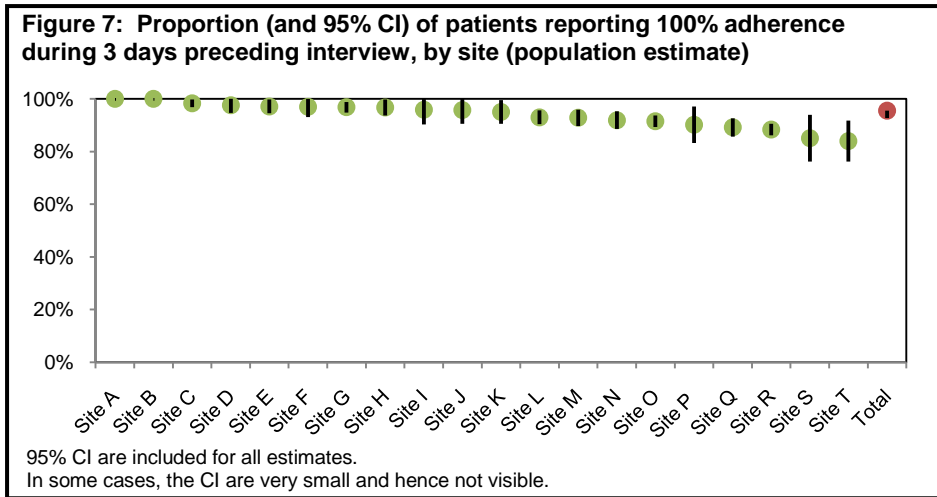
3.5 Levels of adherence

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 patients were asked whether they had missed any ART doses in the preceding three days, 94% (95% CI: 92-97%) reported 100% adherence, with no statistically significant differences by time on ART (Figure 6). However, perfect three-day adherence ranged across sites from 84% (95% CI: 76%-92%) to 100% (95% CI: 100%-100%), with a small but significant difference across sites (Figure 7).





30-day recall: Perfect (100%) adherence in the 30 days preceding the interview was reported by 76% (95% CI: 75-79%) of the population, with no statistically significant differences by time on ART (Figure 6). An additional 11% took 90% of all pills, 7% took 80%, and 4% took less than 80% (Table 8). No statistically significant differences were observed by time on ART 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: 38 - 61%) to 98% (95% CI: 95-100%).

Treatment interruption: The rate of treatment interruption (i.e. missing all pills for 3 or more consecutive days) was 1.1 per person-year on ART for both the 6 and 12 months on ART groups and 0.8 in the 18 months on ART group, but this difference was not statistically significant (Figure 9).

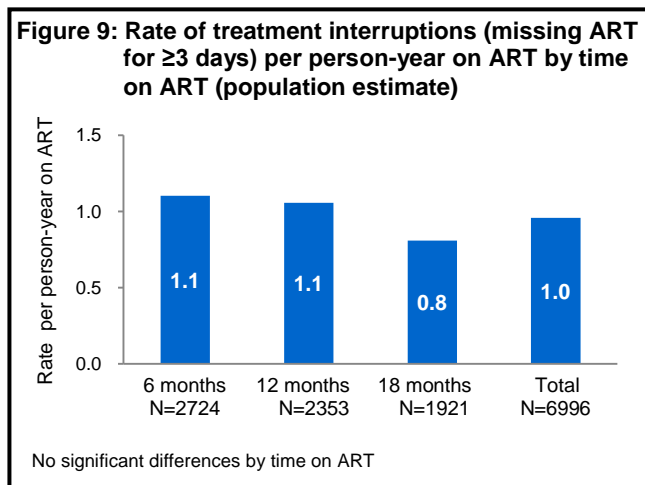
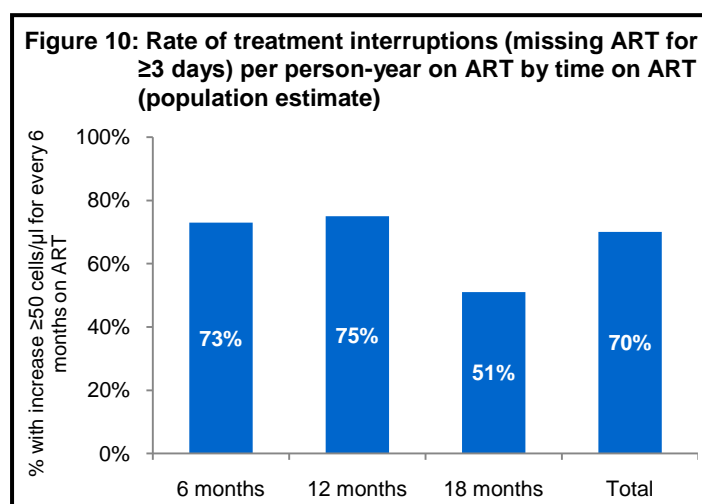


Table 8: Adherence by time on ART (population estimate)

	6 months		12 months		18 months		Total		df	p-value
	N	%	N	%	N	%	N	%		
Primary outcomes	2724	39	2353	34	1921	27	6996	100		
Patient 3-day recall										
100% adherent	2563	94.1	2235	95.0	1761	91.7	6559	93.8	2	0.238
90-99% adherent	62	2.3	75	3.2	80	4.2	218	3.1	2	0.533
80-89% adherent	17	0.6	31	1.3	41	2.1	88	1.3	2	0.139
<80% adherent	82	3.0	11	0.5	38	2.0	131	1.9	2	0.083
Mean, SE	98.0	0.4	99.2	0.1	97.9	0.5	98.4	0.2	2	0.001
Median, IQR	94.7	92.0-97.3	94.7	92.1-97.4	94.5	91.8-97.3	94.7	92.0-97.3	2	0.265
Missing	0		3		0		3			
Patient 30-day recall										
100% adherent	2131	78.3	1823	77.5	1390	72.3	5344	76.4	2	0.808
90% adherent	293	10.8	217	9.2	281	14.6	791	11.3	2	0.265
80% adherent	167	6.1	178	7.6	123	6.4	469	6.7	2	0.854
<80% adherent	123	4.5	78	3.3	84	4.4	284	4.1	2	0.859
Mean, SE	94.7	0.6	95.8	0.5	94.7	1.1	95.1	0.4	2	0.355
Median, IQR	93.6	90.4-96.8	93.7	90.6-96.9	93.2	89.3-96.6	93.6	90.3-96.8	2	0.938
Missing	9		56		43		108			
CD4 count (cells/μL) at interview										
Median, IQR	385.8	268.2-462.7	344.3	250.8-527.4	336.9	201.0-486.3	NA	NA	2	0.808
Missing	1858		1657		1560					
CD4 change between ART initiation and interview										
Number with CD4 data at ART initiation and interview	607	22.3	528	22.4	246	12.8	1381	19.7	NA	NA
Change ≥50 cells/μl for every 6 months on ART	445	73.2	394	74.7	124	50.5	963	69.7	2	0.003
Median change, IQR	120.9	49.8-195.0	157.6	86.7-249.2	143.0	102.0-322.2	NA	NA	2	<0.001
Missing	2025		1753		1627					
Viral load (copies/mL)										
Number with viral load	1598	58.7	1336	56.8	1250	65.1	4183	59.8		
Undetectable/≤40	1316	82.4	1093	81.8	1077	86.2	3486	83.3	2	0.548
41 - 500	172	10.8	125	9.4	76	6.1	374	8.9	2	0.558
>500	110	6.9	118	8.8	96	7.7	324	7.7	2	0.558
Mean, SE	4715.9	1465.7	3252.3	854.9	24606.0	14569.0	10190.0	4567.6	2	0.255
Median, IQR	40.0	40-40	40.0	40-40	40.0	40-40	40.0	40-40	2	0.803

3.5.2 Immunological

Only 607 (22%), 528 (22%) and 246 (13%) of the population 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: 73% of patients on ART for 6 months



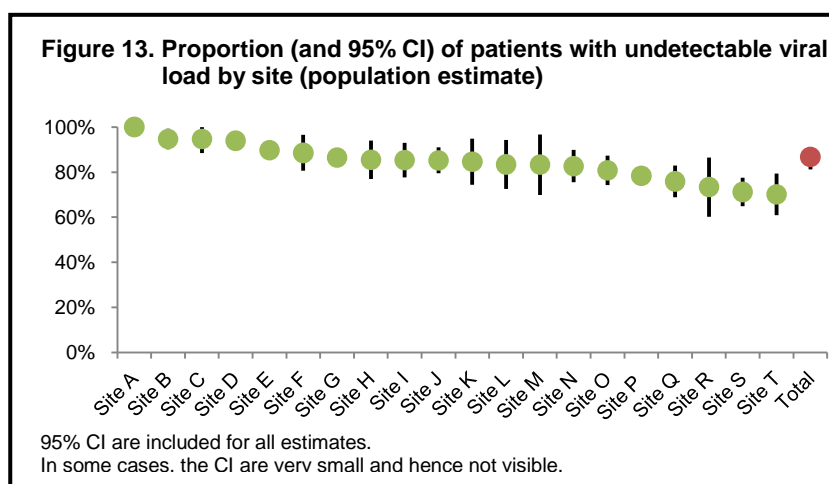
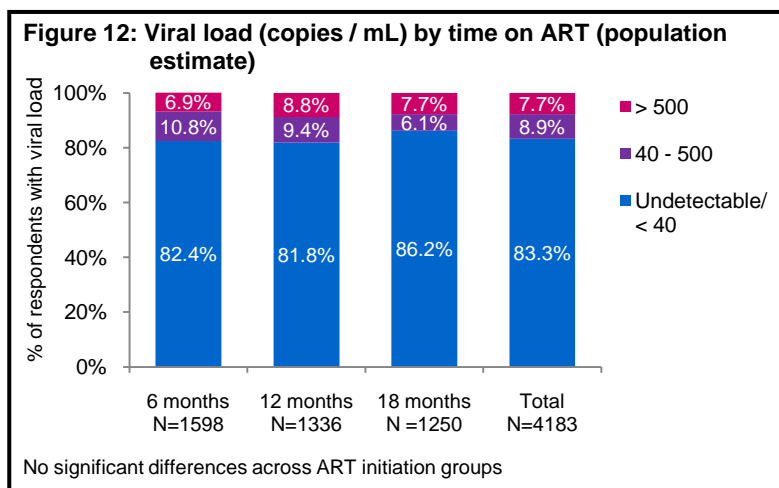
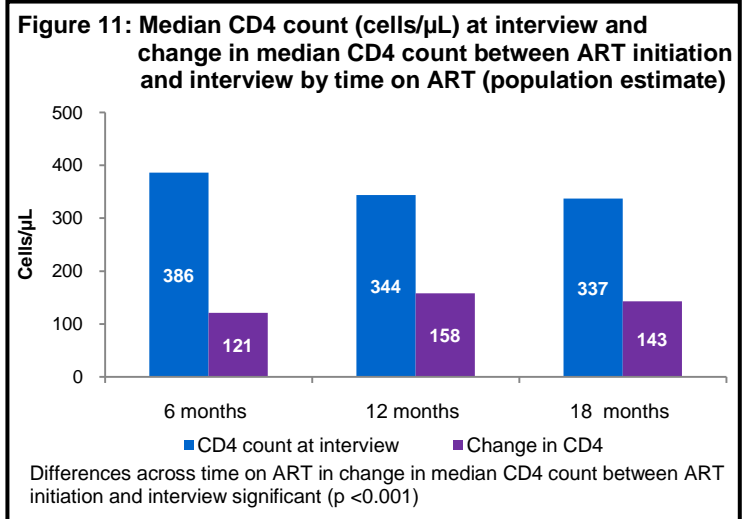
had an increase of at least 50 cells/μl; 75% of patients on ART for 12 months had an increase of at least 100 cells/μl; and 51% of patients on ART for 18 months had an increase of at least 150 cells/μl (Figure 10).

The median change in CD4 count increased with time on ART between 6 and 12 months but plateaued at 18 month: on average the change in CD4 count was +121 cells/μl at 6

months, +158 cells/μl at 12 months and +143 cells/μl at 18 months on ART (Figure 11).

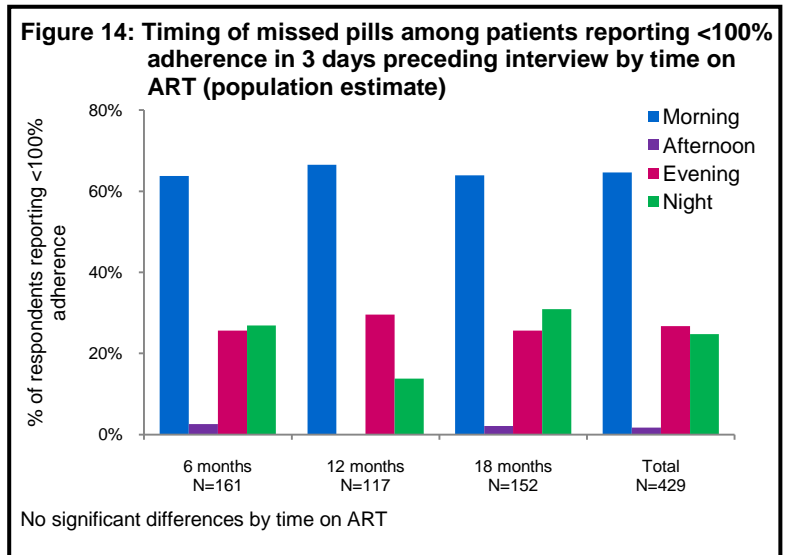
3.5.3 Virological

Among the population selected for viral load assessments (weighted n=4183), the majority, 83% (95% CI: 80-85%) had undetectable (<40 copies/mL) viral loads, with no statistically significant differences by time on ART (Figure 12). An additional 9% 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 load varied significantly by site and ranged from 70% (95% CI: 61-79%) to 100% (95% CI: 100%-100%) as shown in Figure 13.

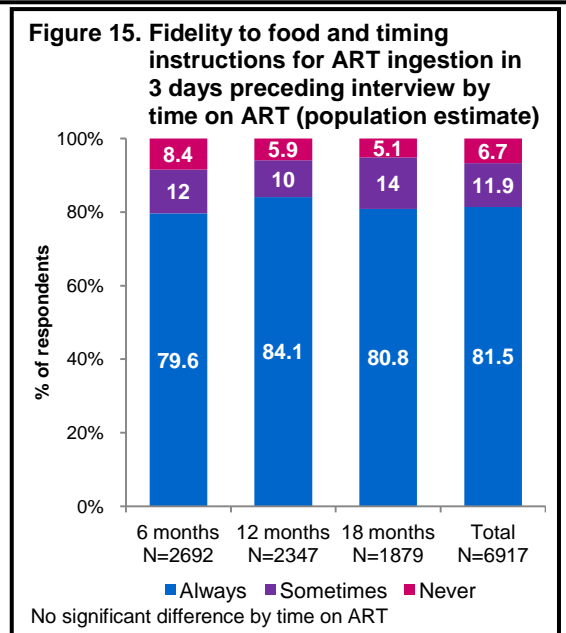


3.6 Time of ART ingestion

The population of 437 patients 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 (65%) reported missing a morning dose, with no difference by time on ART. About one-quarter (25-27%) also reported missing pills in the early evening and at night. As most patients were on regimens requiring morning and evening ingestion, very few patients noted problems with afternoon dosing.

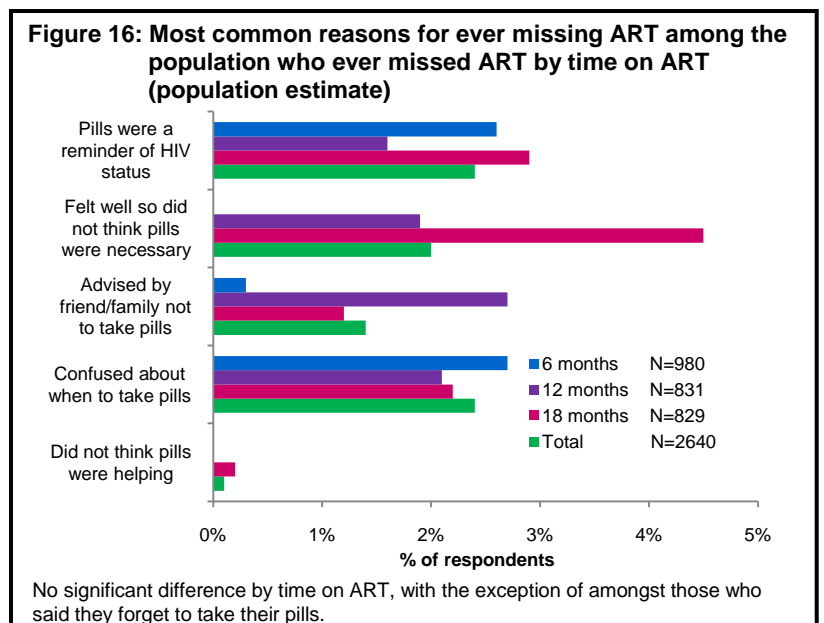


As shown in Figure 15, nearly 82% of the population, regardless of time on ART, reported “always” following the instructions they had received about when and how (e.g., food-related instructions) to take their medication in the three days preceding the interview. Between 5% and 8% reported “never” following the instructions in the three days before the interview.



The population of 2640 (38%) 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-related beliefs, logistical issues, psychosocial issues, and other reasons (Table 9). This population was 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 the population, were forgetfulness (57%), being away from home (49%), not having correct food (25%) and being too busy (16%), with no statistical difference by time on ART. Feeling well and therefore thinking the medication was unnecessary (2%), 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 (2%) were the least commonly reported reasons for missing ART (all cited by less than 5% of the population) (Figure 17). A statistically significant difference by time on ART was observed in three of the 21 potential reasons read to patients: timing inconveniences, forgetfulness and hunger resulting from ART ingestion.

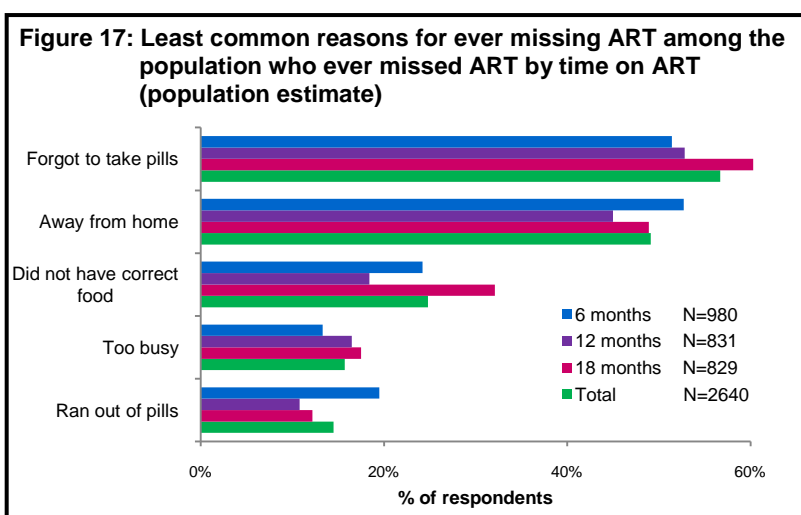
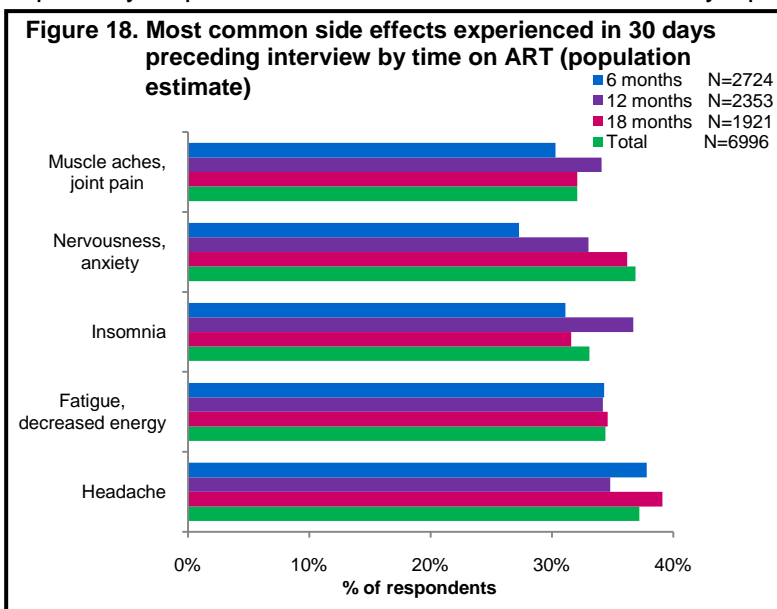


Table 9: Reasons for missing ART among patients who ever missed ART by time on ART (population estimate)

	6 months			12 months			18 months			Total			p-value
	N	%	Missing	N	%	Missing	N	%	Missing	N	%	Missing	
Health or health-belief related reasons	980	39	Missing	831	34	Missing	829	27	Missing	2640	100	Missing	
Scared pills were harmful	83	8.6	14	73	8.7	0	108	13.0	0	264	10.0	14	0.346
Too sick to take pills	72	7.4	14	76	9.2	0	129	15.6	0	277	10.5	14	0.265
Felt sick when took pills	113	11.7	14	50	6.0	0	88	10.7	0	252	9.6	14	0.320
Felt well so did not think they were necessary	0	0.0	17	16	1.9	4	37	4.5	0	53	2.0	21	0.258
Did not think pills were helping	0	0.0	14	0	0.0	0	2	0.2	0	2	0.1	14	NA
Logistical reasons													
Away from home	510	52.7	14	374	45.0	0	405	48.9	0	1289	49.1	14	0.447
Did not have correct food	233	24.2	18	153	18.4	0	266	32.1	0	651	24.8	18	0.314
Too busy	129	13.3	14	137	16.5	0	145	17.5	0	412	15.7	14	0.691
Ran out of pills	189	19.5	14	90	10.8	0	101	12.2	0	380	14.5	14	0.139
Timing was inconvenient	51	5.3	14	35	4.3	0	159	19.2	0	246	9.4	14	<0.001
Too many pills to take	19	1.9	14	32	3.9	28	42	5.1	0	92	3.6	41	0.422
Did not have water	38	4.0	14	8	0.9	0	28	3.4	0	74	2.8	14	0.231
Psychosocial reasons													
Did not want others to see	54	5.6	14	47	5.6	0	59	7.1	0	160	6.1	14	0.877
Could not afford to come to clinic to pick up pills	49	5.1	14	31	3.8	0	9	1.0	0	89	3.4	14	0.202
Had too much alcohol / was drunk	33	3.4	14	37	4.5	0	23	2.7	0	93	3.5	14	0.811
Pills were reminder of HIV status	25	2.6	14	13	1.6	0	24	2.9	0	62	2.4	14	0.771
Other reasons													
Forgot to take pills	497	51.4	14	438	52.8	0	555	66.9	0	1490	56.7	14	0.034
Pills made patient hungry	52	5.4	17	62	7.4	0	118	14.3	0	232	8.8	17	0.017
Fell asleep	44	4.5	14	34	4.1	0	84	10.2	0	161	6.1	14	0.128
Confused about when to take pills	26	2.7	14	18	2.1	0	19	2.2	0	62	2.4	14	0.967
Advised by friend/family not to take pills	3	0.3	14	22	2.7	0	10	1.2	0	36	1.4	14	0.335

3.8 Side effects to ART

Patients 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 (34%), insomnia (33%) nervousness/anxiety (32%) and muscle pain/joint aches (32%) 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 (22%), bloating/stomach pain/gas (21%), diarrhea (14%), lipodystrophy (8%), and alopecia/changes in hair texture (5%). There was no significant difference in reports of any side effect by time on ART.

The severity of the side effects experienced is shown in Figure 20. In most cases, patients did not consider the side effects to be “severe”: on average across all study groups and side effects, 59% of the population that experienced a given side effect were either “not bothered” by it or “bothered a little”. Patients who reported sexual dysfunction and insomnia experienced these side effects more “severely”, with 56% and 51% 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 patients, with 38% and 25%, respectively, of those who experienced those side effects reporting that they were “not bothered” by them.

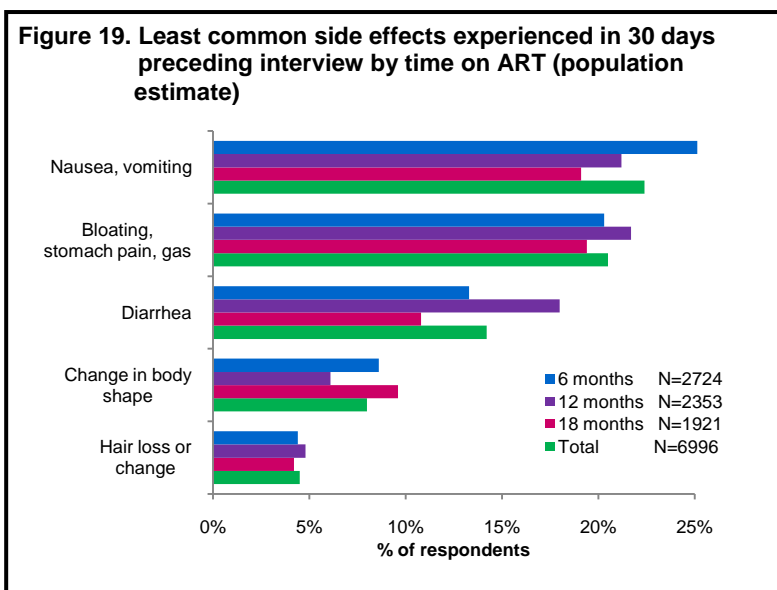


Figure 20. Severity of side effects for all participants (population estimate)

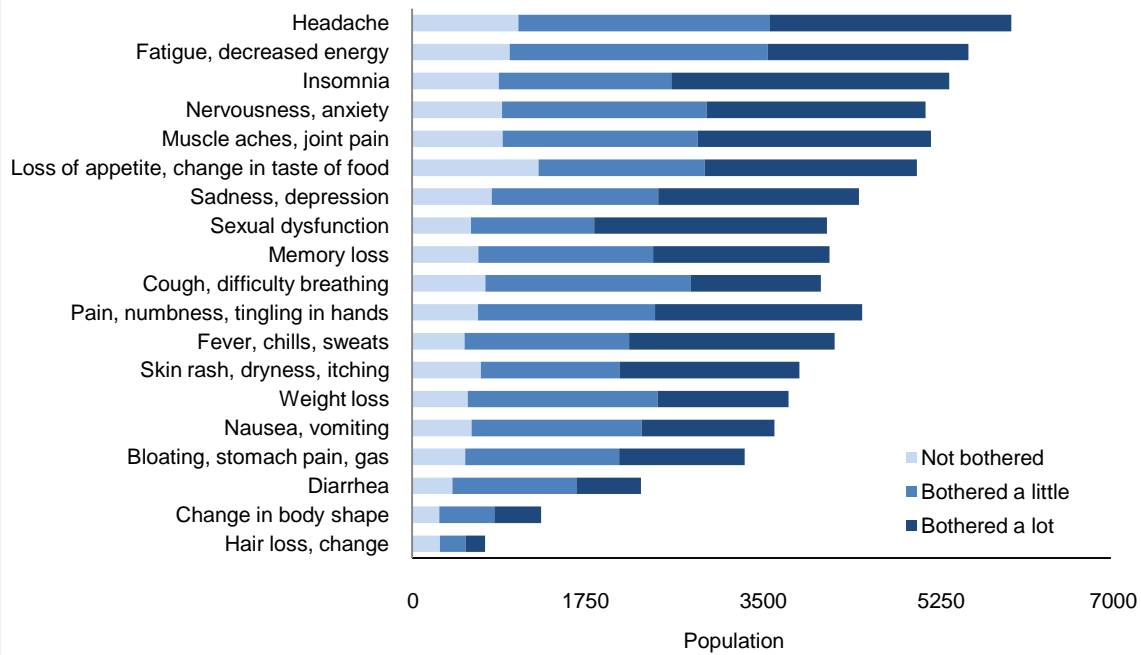


Table 10: Side effects experienced in the 30 days preceding interview by time on ART (population estimate)

	6 months			12 months			18 months			Total			df	p-value
	N	%	Missing	N	%	Missing	N	%	Missing	N	%	Missing		
Whole body, musculoskeletal, skin/connective tissue	2724	39	Missing	2353	34	Missing	1921	27	Missing	6996	100	Missing		
Headache	1006	37.8	64	816	34.8	9	750	39.1	2	2572	37.2	75	2	0.629
Fatigue, decreased energy	925	34.3	27	799	34.2	17	665	34.6	2	2389	34.4	46	2	0.997
Muscle aches, joint pain	815	30.3	29	796	34.1	18	615	32.1	2	2227	32.1	49	2	0.620
Fever, chills, sweats	742	27.6	31	597	25.7	31	475	24.8	2	1814	26.2	64	2	0.701
Skin rash, dryness, itching	611	22.7	27	636	27.2	10	415	21.6	2	1663	23.9	39	2	0.187
Hair loss, change in way hair looks, feels	120	4.4	33	113	4.8	17	81	4.2	7	313	4.5	57	2	0.926
Nervous system														
Insomnia	839	31.1	27	861	36.7	8	606	31.6	2	2306	33.1	37	2	0.373
Nervousness, anxiety	735	27.3	27	774	33.0	8	695	36.2	2	2204	31.7	37	2	0.131
Sadness, depression	635	23.7	40	692	29.5	8	591	30.8	2	1919	27.6	50	2	0.183
Sexual dysfunction	673	25.1	41	624	27.0	40	485	25.4	14	1782	25.8	94	2	0.894
Memory loss	680	25.2	29	571	24.4	11	541	28.3	7	1792	25.8	46	2	0.727
Gastrointestinal														
Loss of appetite, change in taste of food	929	34.5	27	713	30.4	8	525	27.4	2	2168	31.1	37	2	0.436
Nausea, vomiting	693	25.7	30	497	21.2	10	367	19.1	2	1556	22.4	42	2	0.102
Bloating, stomach pain, gas	548	20.3	27	508	21.7	8	373	19.4	2	1428	20.5	37	2	0.783
Diarrhea	356	13.3	39	419	18.0	28	208	10.8	2	983	14.2	69	2	0.202
Metabolic														
Weight loss	631	24.0	95	567	25.1	91	419	22.1	27	1616	23.8	213	2	0.714
Change in body shape	230	8.6	46	142	6.1	41	183	9.6	19	555	8.0	107	2	0.390
Respiratory														
Pain, numbness, tingling in hands and feet	763	28.3	27	658	28.0	8	512	26.8	7	1932	27.8	42	2	0.916
Cough, difficulty breathing	600	22.3	31	644	27.5	8	512	26.7	2	1756	25.2	41	2	0.321

Table 11: Weighted index of side effects experienced in 30 days preceding interview by time on ART (population estimate)

	6 months N=2724		12 months N=2353		18 months N=1921		Total N=6996		df	p-value
Side effect index continuous										
Mean, SE	10.8	0.5	10.7	0.4	10.4	0.5	10.7	0.3	2	0.873
Median, IQR	7.4	1.7-16.8	7.8	2.2-15.8	6.8	1.7-16.0	7.4	1.8-16.3	2	0.183
Missing	27		8		2		37			
	N	%	N	%	N	%	N	%	df	p-value
Side effect index categorized										
No or few side effects	731	27.1	563	24.0	525	27.4	1819	26.1	4	0.789
Moderate side effects	1231	45.7	1205	51.4	914	47.6	3350	48.1		
Severe side effects	735	27.2	576	24.6	480	25.0	1790	25.7		
Missing	27		8		2		37			

3.9 ART attitudes and beliefs

All patients 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 the population 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 on ART in the overall score or agreement/disagreement with any individual statement (Table 12). Nearly all patients 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 (97%); and disagreed that ART is not worth taking due to side effects (97%); and ART does not work as well as doctors and nurses say it will (96%). A substantial proportion of the population, however, felt that HIV/AIDS is not a serious illness because people living with HIV/AIDS (PLWHA) can take ART (59%), that ART can cure HIV (57%) and that people taking ART need to hide it (84%). Patients were also asked how effective they felt ART had been in keeping them healthy. Nearly all (94%) believed it was “very effective”, 6% said it was “somewhat effective” and <1% indicated it was “ineffective”, with no significant difference by duration on ART.

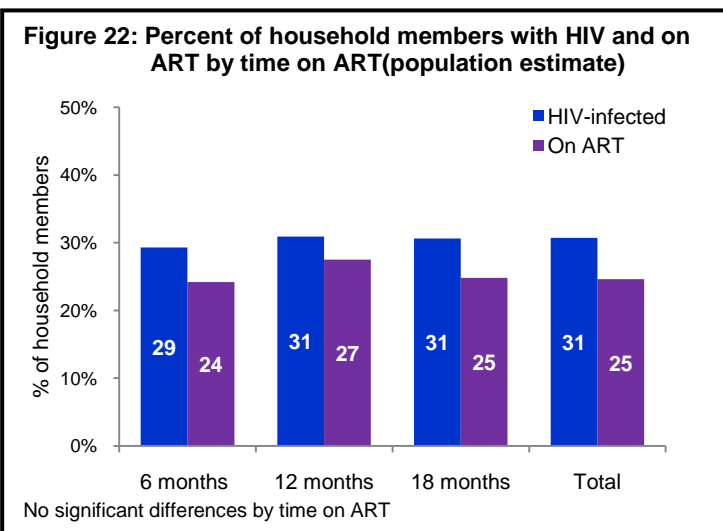
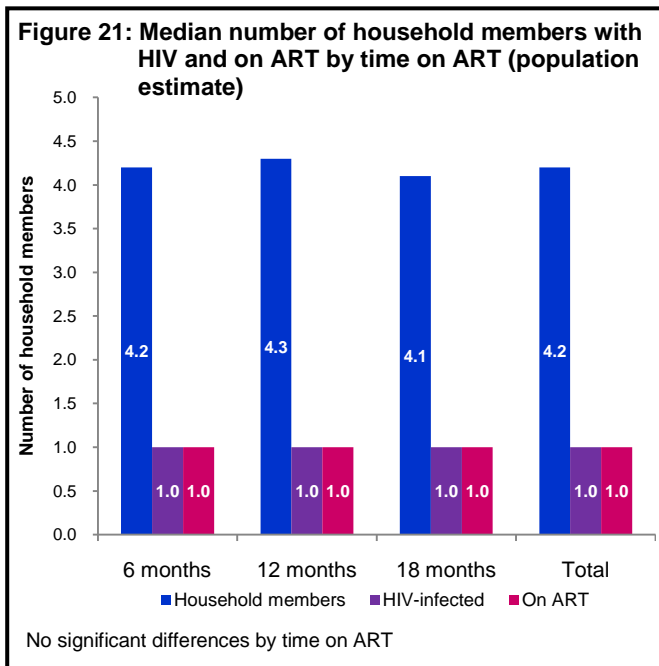
Table 12: ART knowledge and attitudes by time on ART (population estimate)

	6 months			12 months			18 months			Total			p-value
	N	%	Missing	N	%	Missing	N	%	Missing	N	%	Missing	
Proportion agreeing with statement	2724	39	Missing	2353	34	Missing	1921	27	Missing	6996	100	Missing	
ART can help people live longer	2657	98.8	35	2336	99.8	12	1903	99.1	0	6896	99.2	47	0.219
If people follow instructions about how to take ART, they will be healthier	2671	98.3	6	2348	100.0	4	1888	98.5	4	6907	98.9	14	0.854
If people stop taking ART, their illness will worsen	2587	97.1	59	2198	97.0	86	1869	98.4	22	1357	97.4	167	0.611
Proportion disagreeing with statement													
ART is not worth taking because it has a lot of side effects	2632	96.8	4	2273	97.5	20	1861	97.0	2	1379	97.1	27	0.935
ART does not work as well as doctors and nurses say it will	2568	95.7	41	2222	96.0	37	1870	97.9	11	6660	96.4	88	0.525
People taking ART need to hide it from others	2314	85.3	12	1981	85.8	45	1547	80.9	8	5842	84.3	65	0.365
HIV/AIDS is not a serious illness because PLWHA can take ART	1467	54.1	14	1389	59.4	14	1253	65.2	0	4109	59.0	28	0.042
ART can cure HIV	1418	56.9	232	1176	54.0	172	1058	59.1	131	3652	56.5	536	0.670
Index of correct* knowledge and attitudes about ART (0-100%)													
Mean score (%), SE	84.2	0.7	13.2	84.8	0.5	9.2	86.2	0.6	16.9	84.9	0.4	37.3	0.068
Scored 100%	637	26.7	335	600	28.6	257	483	27.7	176	1721	27.6	767	0.881
Perception of ART effectiveness in keeping respondent healthy													
Very effective	2489	91.4	1	2271	96.6	5	1818	94.6	4	6577	94.0	10	0.190
Somewhat effective	216	7.9		75.9	3.2		97.1	5.0		389.3	5.6		
Not effective at all	17	0.6		0	0.0		3.9	0.2		19.4	0.3		

*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

As shown in Figures 21 and 22, 31% of the population's household members were HIV-infected and 25% were on ART. Not surprisingly, then, fully 79% of the population reported having disclosed their HIV status to at least one family member (Table 13) and many (43%) 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 so the longer one was on ART with 47%, 53% and 61% of patients on ART for 6, 12 and 18 months, respectively, participating in such support groups (p=0.181). The majority (78%) of the patients had ever experienced stigma related to their HIV status in their community with 61% reporting that they experienced "a lot" of stigma and small but significant differences by time on ART (p=0.032). Use of traditional medications while on ART was extremely rare and reported by only 0.5% of the population. Use of alcohol and drunkenness in the seven days prior to the interview was far more common, reported by 24% and 13% of the population, respectively, with no difference by time on ART.



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The majority of the population (56%) used at least one tool to remember to take their ART, namely alarm clocks (22%) and cell phones (13%), 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 majority (72%) reported being "very happy" with no difference by duration on ART (Table 13).

Table 13: Disclosure, stigma, use of traditional medicine and reminder tools, alcohol and satisfaction with services at the clinic by time on ART (population estimate)

	6 months		12 months		18 months		Total		df	p-value
	N	%	N	%	N	%	N	%		
Disclosed HIV status to ≥1 family member	2125	78.3	1815	77.3	1560	81.9	5499	78.9	2	0.45
Missing	9		4		17		29			
Disclosed HIV status to ≥1 non-family member	1118	41.2	1106	47.1	797	41.8	3020	43.4	2	0.557
Missing	9		4		17		29			
Participates regularly in PLWHA meeting	1268	46.7	1230	52.7	1154	60.6	3652	52.5	2	0.181
Missing	0		0		0		0			
Experienced stigma in community										
Never	676	26.8	440	19.6	334	17.7	1450	21.8	4	0.028
Some	306	12.1	434	19.3	426	22.6	1165	17.5		
A lot	1541	61.1	1376	61.2	1123	59.6	4039	60.7		
Missing	201		102		38		341			
Took herbal medicine since starting ART	23	0.9	9	0.4	5	0.2	37	0.5	2	0.353
Missing	11		8		0		19			
Drank alcohol in the past seven days										
A lot (4-7 days)	72	2.7	60	2.6	77	4.0	209	3.0	4	0.515
Some (1-3 days)	621	22.9	509	21.7	335	17.5	1465	21.0		
Never	2017	74.4	1772	75.7	5293	78.5	5293	76.0		
Missing	14		11		4		28			
Was drunk in the past seven days, among those who consumed alcohol										
A lot (4-7 days)	7	1.0	1	0.2	13	3.2	21	1.3	4	0.115
Some (1-3 days)	54	7.9	90	16.3	48	12.0	192	11.7		
Never	628	91.1	460	83.5	341	84.8	1429	87.0		
Missing	2034		1518		1518		5353			
Reminder tools to take ART										
No tools	1205	44.2	994	42.4	778	40.5	2978	42.6	2	0.846
Cell phone	364	13.4	301	12.8	250	13.0	915	13.1	2	0.991
Alarm clock	615	22.6	507	21.6	412	21.4	1533	21.9	2	0.962
Paper diary	46	1.7	39	1.6	57	2.9	141	2.0	2	0.606
Radio	497	18.2	378	16.1	368	19.2	1243	17.8	2	0.761
Other	119	4.4	147	6.2	113	5.9	378	5.4	2	0.675
Use any tool	1496	54.93	1291	55.0	1119	58.3	3906	55.9	2	0.86
How happy with services at the clinic										
Very happy	864	71.0	720	70.8	559	74.5	2143	71.8	4	0.102
Somewhat happy	278	22.8	188	18.5	89	11.8	554	18.6		
Not happy	75	6.2	110	10.8	102	13.6	287	9.6		
Missing	1507		1335		1171		4012			

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

Bivariate (Tables 14-15) and multivariable (Table 16) analysis of patient- and site-level predictors of the population reporting <100% adherence during the 30 days preceding the interview on the VAS was conducted separately for each ART duration group and for all the population together. Time on ART was not significantly associated with self-reported non-adherence in either the bivariate or multivariable 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-month groups 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 multivariable 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 on ART. For this reason, we summarize below the results for the entire population, controlling for time on ART. 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 multivariable analysis, after controlling for time on ART, 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 the population. 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)

	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										0.95	0.57 - 1.57	0.823
18 months										1.28	0.75 - 2.20	0.336
<i>Sociodemographic Factors</i>												
Age (ref=18-30 yrs)												
31-36 yrs	1.20	0.47 - 3.03	0.670	0.62	0.23 - 1.65	0.295	1.23	0.45 - 3.36	0.649	1.01	0.59 - 1.73	0.968
37-43 yrs	1.00	0.43 - 2.36	0.995	1.07	0.51 - 2.23	0.838	0.60	0.21 - 1.69	0.293	0.88	0.54 - 1.44	0.600
≥ 44 yrs	0.45	0.21 - 0.97	0.034	0.29	0.13 - 0.66	0.004	0.56	0.19 - 1.62	0.242	0.41	0.25 - 0.67	<0.001
Sex (ref=female)												
Male	0.85	0.46 - 1.58	0.568	1.56	0.67 - 3.65	0.261	0.91	0.43 - 1.90	0.778	1.04	0.696 - 1.560	0.833
Education (ref=no education)												
Some education	0.84	0.28 - 2.49	0.724	2.06	1.05 - 4.02	0.038	2.63	1.01 - 6.83	0.038	1.52	0.85 - 2.74	0.137
Current marital status (ref=married/living together)												
Other	0.56	0.26 - 1.21	0.112	0.87	0.47 - 1.59	0.614	0.94	0.45 - 1.93	0.843	0.75	0.50 - 1.13	0.145
Number of household members (ref= ≤4)												
5-6	1.14	0.56 - 2.31	0.681	0.67	0.31 - 1.41	0.247	0.53	0.23 - 1.19	0.100	0.76	0.49 - 1.18	0.196
≥7	1.35	0.67 - 2.73	0.358	1.12	0.42 - 2.99	0.797	0.73	0.28 - 1.95	0.492	1.05	0.64 - 1.72	0.826
Percent of household members on ART (ref= ≤25%)												
26-40%	1.24	0.59 - 2.60	0.529	0.81	0.34 - 1.94	0.607	0.46	0.18 - 1.18	0.085	0.83	0.52 - 1.32	0.396
41-100%	0.81	0.41 - 1.59	0.496	0.83	0.44 - 1.59	0.543	0.94	0.38 - 2.35	0.884	0.87	0.56 - 1.35	0.514
Poverty index (ref=most poor)												
Middle	1.74	0.78 - 3.88	0.146	0.95	0.39 - 2.31	0.901	1.64	0.74 - 3.62	0.182	1.42	0.89 - 2,28	0.119
Least poor	2.59	1.28 - 5.22	0.008	1.38	0.65 - 2.96	0.358	1.08	0.48 - 2.45	0.829	1.63	1.07 - 2.50	0.018
<i>Treatment-related Factors</i>												
Side effects in past 30 days (ref=none/few)												
Moderate	1.30	0.61 - 2.77	0.455	2.54	0.99 - 6.53	0.042	0.87	0.33 - 2.31	0.764	1.36	0.82 - 2.26	0.200
Severe	2.77	1.21 - 6.36	0.014	2.74	1.03 - 7.31	0.036	1.11	0.43 - 2.84	0.815	2.01	1.21 - 3.33	0.006
CD4 count at ART initiation (ref= <200)												
≥ 200	1.48	0.65 - 3.35	0.303	0.68	0.36 - 1.26	0.183	1.38	0.56 - 3.44	0.443	1.05	0.66 - 1.67	0.838
Missing	2.03	0.97 - 4.25	0.049	0.87	0.33 - 2.27	0.748	1.04	0.36 - 3.06	0.930	1.22	0.73 - 2.05	0.425
Time to reach clinic (ref= ≤30 min)												
> 30 min	0.57	0.32 - 1.03	0.051	0.80	0.41 - 1.57	0.474	0.78	0.34 - 1.77	0.512	0.69	0.47 - 1.01	0.045
Uses any reminder tool to take ART (ref=no)												
Yes	0.86	0.49 - 1.52	0.568	1.06	0.59 - 1.87	0.837	1.16	0.60 - 2.23	0.631	1.01	0.72 - 1.42	0.937

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
<i>Psychosocial and behavioral factors</i>												
Stigma experienced (ref=none)												
Some or a lot	0.88	0.49 - 1.59	0.644	1.51	0.83 - 2.74	0.142	1.20	0.57 - 2.56	0.592	1.16	0.82 - 1.66	0.369
Missing	1.38	0.44 - 4.35	0.545	1.78	0.46 - 6.91	0.361	1.53	0.27 - 8.63	0.590	1.48	0.68 - 3.23	0.297
Perception of ART effectiveness (ref=effective)												
Not effective	2.16	0.75 - 6.25	0.126	1.89	0.60 - 5.94	0.235	2.37	0.55 - 10.23	0.207	2.13	1.05 - 4.37	0.029
Alcohol use in past 7 days (ref=none)												
Some or a lot	2.35	1.19 - 4.65	0.013	0.84	0.40 - 1.76	0.612	2.10	0.91 - 4.87	0.065	1.65	1.08 - 2.54	0.017
Disclosed HIV status to ≥1 family-member (ref=no)												
Yes	0.98	0.47 - 2.05	0.947	0.87	0.39 - 1.95	0.709	0.62	0.23 - 1.69	0.303	0.84	0.53 - 1.33	0.428
Participates in PLWHA association (ref=no)												
Yes	0.46	0.25 - 0.83	0.009	0.79	0.44 - 1.45	0.408	0.59	0.31 - 1.14	0.093	0.61	0.44 - 0.86	0.003

Table 15: Bivariate association of site-level predictors and self-reported 30-day non-adherence (<100% adherent)

	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	0.48 - 1.87	0.870	1.10	0.54 - 2.25	0.772	1.07	0.52 - 2.22	0.839	1.05	0.71 - 1.55	0.812
Year ART services initiated (ref=2003-2004)												
2005	1.08	0.51 - 2.27	0.829	1.00	0.45 - 2.23	0.992	1.79	0.740 - 4.35	0.161	1.21	0.78 - 1.89	0.366
2006-2007	0.57	0.26 - 1.29	0.147	0.60	0.26 - 1.40	0.198	1.09	0.518 - 2.27	0.807	0.72	0.46 - 1.12	0.124
Site location (ref=rural)												
Urban	2.81	1.40 - 5.65	0.004	1.83	0.90 - 3.74	0.076	1.73	0.79 - 3.80	0.138	2.10	1.40 - 3.14	0.000
Site type (ref=health centre)												
Hospital	0.93	0.47 - 1.85	0.812	0.68	0.33 - 1.39	0.244	0.78	0.37 - 1.65	0.476	0.80	0.54 - 1.19	0.238
Site ART enrollment (ref= <600)												
≥600 patients	1.62	0.86 - 3.05	0.111	1.64	0.88 - 3.07	0.096	1.01	0.52 - 1.98	0.967	1.40	0.99 - 1.99	0.046
Peer educator program (ref=no)												
Yes	1.71	0.80 - 3.65	0.133	2.06	0.95 - 4.48	0.054	1.58	0.66 - 3.81	0.265	1.79	1.14 - 2.80	0.008
Home support visits to PLWHA (ref=no)												
Yes	0.51	0.26 - 0.98	0.034	0.85	0.41 - 1.74	0.623	0.51	0.24 - 1.10	0.067	0.60	0.41 - 0.90	0.010

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

	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										1.20	0.79-1.83	0.352
18 months										1.54	0.98-2.43	0.051
<i>Socio-demographic Factors</i>												
Age (ref=18-30 yrs)												
31-36 yrs	1.12	0.39-3.21	0.811	0.63	0.25-1.60	0.290	1.20	0.41-3.49	0.712	1.02	0.60-1.74	0.937
37-43 yrs	0.93	0.38-2.25	0.858	1.21	0.57-2.53	0.583	0.42	0.14-1.30	0.106	0.95	0.57-1.58	0.840
44 yrs	0.40	0.17-0.92	0.025	0.34	0.14-0.81	0.013	0.43	0.14-1.37	0.124	0.41	0.24-0.72	0.001
Sex (ref=female)												
Male	0.68	0.35-1.32	0.215	1.47	0.61-3.57	0.345	0.88	0.40-1.96	0.734	0.94	0.60-1.48	0.774
Education (ref=no education)												
Some education				1.90	0.89-4.09	0.079	3.86	1.60-9.29	0.003			
Number of household members (ref= ≤4)												
5-6	1.35	0.64-2.88	0.386							0.83	0.54-1.26	0.349
≥7	2.06	0.99-4.28	0.042							1.22	0.74-2.02	0.405
Percent of household members on ART (ref= ≤25%)												
26-40%							0.35	0.12-0.99	0.039			
41-100%							0.58	0.26-1.29	0.147			
<i>Treatment-related Factors</i>												
Side effects in past 30 days (ref=none/few)												
Moderate	1.33	0.62-2.86	0.425	2.36	0.90-6.21	0.065				1.42	0.87-2.33	0.141
Severe	2.77	1.28-6.02	0.009	2.69	1.06-6.88	0.031				1.99	1.21-3.29	0.005
CD4 count at ART initiation (ref= <200)												
≥200	1.41	0.67-3.00	0.321	0.76	0.41-1.41	0.342	1.59	0.70-3.63	0.230	1.22	0.78-1.89	0.356
Missing	2.83	1.15-6.97	0.020	1.05	0.39-2.81	0.915	1.01	0.28-3.59	0.985	1.47	0.83-2.59	0.164
<i>Behavioral Factors</i>												
Alcohol use in past 7 days (ref=none)												
Some or a lot	2.80	1.38-5.67	0.005				2.61	1.05-6.52	0.032	1.56	0.99-2.47	0.044
SITE LEVEL FACTORS												
Site location (ref=rural)												
Urban	3.96	1.96-7.99	<0.001									
Site type (ref=health centre)												
Hospital										0.63	0.41-0.95	0.022
Site ART enrolment (ref= <600)												
≥600 patients				1.28	0.66-2.48	0.411				2.15	1.45-3.20	<0.001
Peer educator program (ref=no)												
Yes										2.43	1.53-3.86	<0.001
Routinely conducts supportive home visits (ref=no)												
Yes							0.43	0.19-0.94	0.029	0.54	0.37-0.79	0.001

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 multivariable 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 on ART was not significantly associated with detectable viral load in either the bivariate or multivariable 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 socioeconomic 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/ μ l 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 multivariable level (Table 19), after controlling for time on ART, 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)

	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										1.04	0.60 - 1.80	0.884
18 months										0.75	0.38 - 1.48	0.381
<i>Sociodemographic factors</i>												
Age (ref=18-30 yrs)												
31-36 yrs	0.88	0.30 - 2.55	0.786	0.45	0.13 - 1.52	0.162	0.32	0.07 - 1.49	0.119	0.54	0.26 - 1.11	0.075
37-43 yrs	0.54	0.19 - 1.51	0.201	0.57	0.17 - 1.87	0.308	0.38	0.09 - 1.62	0.156	0.52	0.26 - 1.01	0.044
≥44 yrs	0.90	0.26 - 3.04	0.845	0.31	0.07 - 1.31	0.089	0.38	0.08 - 1.87	0.194	0.51	0.23 - 1.13	0.082
Sex (ref=female)												
Male	0.53	0.22 - 1.28	0.130	0.87	0.31 - 2.39	0.759	0.74	0.23 - 2.31	0.558	0.68	0.40 - 1.18	0.148
Education (ref=no education)												
Some education	1.56	0.58 - 4.22	0.328	1.59	0.55 - 4.62	0.342	1.71	0.41 - 7.13	0.412	1.56	0.84 - 2.91	0.136
Current marital status (ref=married/living together)												
Other	1.00	0.30 - 2.54	0.991	1.35	0.61 - 2.97	0.417	0.87	0.29 - 2.57	0.771	1.07	0.64 - 1.80	0.782
Number of household members (ref= ≤4)												
5-6	0.55	0.19 - 1.55	0.216	1.46	0.51 - 4.15	0.434	1.36	0.38 - 4.86	0.596	0.99	0.54 - 1.81	0.962
≥7	0.44	0.14 - 1.41	0.136	0.98	0.31 - 3.13	0.977	0.77	0.26 - 2.27	0.596	0.68	0.36 - 1.29	0.209
Percent of household members on ART (ref= ≤25%)												
26-40%	0.41	0.13 - 1.33	0.111	1.40	0.36 - 5.47	0.589	1.48	0.43 - 5.10	0.486	0.93	0.45 - 1.94	0.855
41-100%	1.38	0.55 - 3.46	0.448	0.61	0.22 - 1.67	0.289	1.57	0.45 - 5.43	0.429	1.07	0.60 - 1.90	0.812
Poverty index (ref=most poor)												
Middle	1.02	0.36 - 2.91	0.965	0.93	0.31 - 2.76	0.880	0.52	0.15 - 1.79	0.254	0.84	0.46 - 0.75	0.560
Least poor	1.38	0.50 - 3.78	0.490	1.64	0.66 - 4.09	0.247	1.07	0.32 - 3.60	0.909	1.31	0.75 - 2.32	0.309
<i>Treatment-related Factors</i>												
Side effects in past 30 days (ref=none/few)												
Moderate	0.64	0.27 - 1.55	0.281	1.60	0.58 - 4.40	0.320	0.64	0.18 - 2.24	0.442	0.86	0.49 - 1.52	0.579
Severe	0.47	0.15 - 1.51	0.168	1.46	0.42 - 5.07	0.506	0.47	0.11 - 2.13	0.285	0.65	0.32 - 1.33	0.213
CD4 count at ART initiation (ref= <200)												
≥200	0.63	0.27 - 1.49	0.253	0.95	0.36 - 2.48	0.898	0.99	0.28 - 3.56	0.986	0.87	0.51 - 1.49	0.598
Missing	0.79	0.24 - 2.64	0.671	0.84	0.28 - 2.50	0.728	2.16	0.51 - 9.07	0.250	1.15	0.57 - 2.31	0.682
Time to reach clinic (ref= ≤30 min)												
> 30 min	0.92	0.41 - 2.06	0.826	0.60	0.26 - 1.35	0.178	1.26	0.40 - 4.02	0.663	0.89	0.54 - 1.44	0.588
Uses any reminder tool to take ART (ref=no)												
Yes	0.58	0.25 - 1.34	0.171	0.42	0.17 - 1.05	0.050	0.92	0.33 - 2.60	0.865	0.59	0.36 - 0.98	0.033

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
<i>Psychosocial and behavioral factors</i>												
Stigma experienced (ref=none)												
Some or a lot	0.98	0.43 - 2.28	0.968	1.20	0.50 - 3.88	0.650	0.79	0.25 - 2.47	0.645	1.01	0.60 - 1.69	0.981
Missing	0.36	0.81 - 1.60	0.146	3.80	0.70 - 20.81	0.098	0.55	0.04 - 7.05	0.607	1.07	0.36 - 3.13	0.903
Perception of ART effectiveness (ref=effective)												
Not effective	0.60	0.13 - 2.82	0.472	0.69	0.13 - 3.63	0.632	6.14	0.58 - 65.01	0.105	1.26	0.36 - 4.40	0.693
Alcohol use in past 7 days (ref=none)												
Some or a lot	0.85	0.30 - 2.42	0.733	1.55	0.63 - 3.84	0.300	1.20	0.35 - 4.13	0.751	1.15	0.64 - 2.05	0.613
Disclosed HIV status to ≥1 family-member (ref=no)												
Yes	1.46	0.47 - 4.57	0.470	0.62	0.23 - 1.63	0.286	0.65	0.19 - 2.17	0.434	0.85	0.47 - 1.55	0.577
Participates in PLWHA association (ref=no)												
Yes	0.46	0.18 - 1.17	0.083	0.40	0.15 - 1.04	0.048	0.32	0.092 - 1.11	0.057	0.39	0.22 - 0.69	0.001

Table 18: Bivariate association of site-level predictors and detectable viral load (>40 copies/mL)

	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	1.11	0.51 - 2.43	0.774	0.65	0.26 - 1.61	0.308	0.42	0.13 - 1.38	0.122	0.72	0.43 - 1.21	0.193
Year ART services initiated (ref=2003-2004)												
2005	1.16	0.53 - 2.55	0.685	0.95	0.35 - 2.57	0.912	0.49	0.10 - 2.48	0.338	0.86	0.49 - 1.50	0.570
2006-2007	1.16	0.40 - 3.39	0.763	1.25	0.51 - 3.09	0.591	0.52	0.18 - 1.56	0.206	0.97	0.55 - 1.72	0.921
Site location (ref=rural)												
Urban	1.44	0.66 - 3.17	0.313	1.14	0.50 - 2.63	0.728	2.31	0.74 - 7.26	0.121	1.46	0.89 - 2.39	0.110
Site type (ref=health centre)												
Hospital	1.50	0.67 - 3.35	0.275	1.40	0.59 - 3.33	0.403	1.27	0.44 - 3.63	0.626	1.41	0.86 - 2.30	0.146
Site ART enrollment (ref= <600)												
≥ 600 patients	0.86	0.43 - 1.71	0.629	0.93	0.45 - 1.93	0.832	2.41	0.84 - 6.94	0.082	1.17	0.76 - 1.80	0.440
Peer educator program (ref=no)												
Yes	1.29	0.52 - 3.24	0.542	2.32	0.99 - 5.48	0.042	2.10	0.68 - 6.48	0.161	1.76	1.06 - 2.96	0.024
Home support visits to PLWHA (ref=no)												
Yes	1.14	0.52 - 2.54	0.713	1.06	0.45 - 2.49	0.877	1.11	0.33 - 3.71	0.849	1.11	0.67 - 1.83	0.673

Table 19. Multivariable 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	1.04	0.61 - 1.78	0.870
18 months	0.78	0.41 - 1.50	0.427
Age (ref=18-30 yrs)			
31-36 yrs	0.60	0.29 - 1.22	0.134
37-43 yrs	0.50	0.25 - 0.99	0.037
≥ 44 yrs	0.45	0.20 - 0.98	0.034
Sex (ref=female)			
Male	0.51	0.28 - 0.93	0.021
CD4 count at ART initiation (ref= <200)			
≥ 200	0.83	0.47 - 1.46	0.496
Missing	1.12	0.31 - 0.76	0.755
Participates in PLWHA association (ref=no)			
Yes	0.40	0.23 - 0.70	0.001
Uses a reminder tool			
Yes	0.44	0.26 - 0.75	0.002
SITE LEVEL FACTORS			
Peer educator program (ref=no)			
Yes	1.98	1.20 - 3.26	0.006

Note : Estimations obtained after logistic regression using a stepwise approach (with a 5% probability of removal). The variables cohort, CD4 at initiation, sex and age have been forced to remain in the model.

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

Using data from the sub-population that had viral load assessments (n=4,184), viral load was used as the referent measure to assess the validity of self-reported perfect adherence over the three days 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 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 the population 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 the population 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 the population reporting perfect adherence who had undetectable viral loads and the NPV is the percentage of the population 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 3-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 the population 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, patients 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.

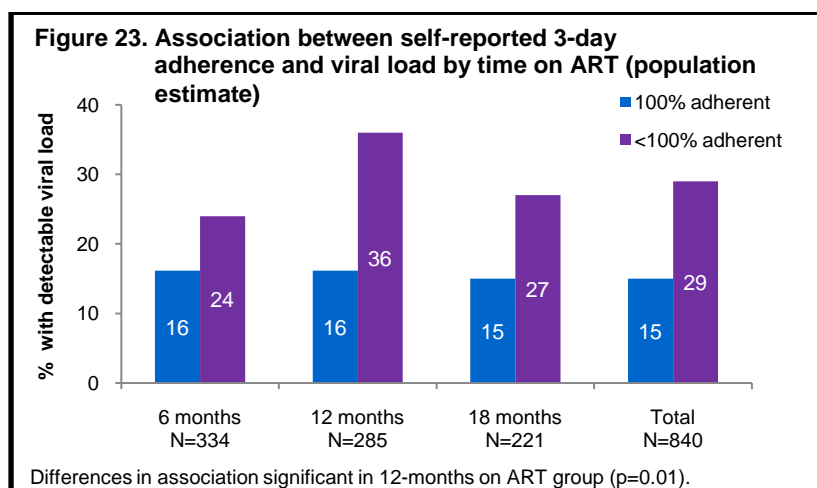
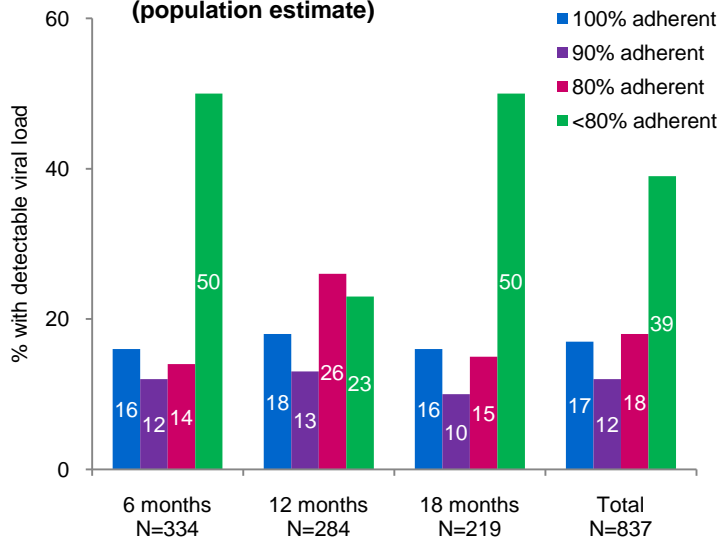


Figure 24. Association between self-reported 30-day adherence and viral load by time on ART (population estimate)



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 1,417 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 population, 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: 94% of the population reported perfect adherence to ART in the three days preceding the interview and 76% 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 84% 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 the population had viral suppression (≤ 40 copies/mL). The percentage of the population 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). The latter difference may be a reflection of our using a more stringent definition of viral suppression

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 a population with characteristics that made them similarly adherent and responsive to ART. Future analyses will compare baseline demographic and clinical characteristics of the interviewed population 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

For at least one ART duration groups, multivariable models showed that being younger, having some education, residing in large households or households where a small proportion of residents are on ART, 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.

The implication of better adherence rates among individuals with no education is encouraging as ART services in sub-Saharan Africa scale-up to rural communities where patients are likely to have had less access to education. 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)

The study also found that 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 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). Since one in four patients 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.

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.

Developed-country studies have shown no significant association between gender and virological response has been observed (Purkayastha et al., 2005), or a better virological response among women (Nicastri et al., 2005; Perez et al., 2007; Moore et al., 2001). Possible explanations for the different finding in Rwanda include 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.

Participation in PLWHA meetings exerted a positive effect on viral suppression, further providing evidence of the important of peer support and encouragement.

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 and have a

detectable viral load in our multivariable models. Our divergent findings 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 population 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 on ART, 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-quarter of the population had CD4 assessments at ART initiation and again at 6, 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 patients (96%). 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 patients 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 multivariable 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 multivariable models were being younger, having some education, residing in large households or households where a small proportion of residents were on ART, experiencing moderate to severe side effects, alcohol use, receiving care in an urban site, in a lower-level facility, a high volume site, a site with a peer educator program, or those that do not regularly conduct supportive home visits. 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 prior to or 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

Denise M. Butera

Vereranda Bajinya

Beatus Cyubahiro

Marie Claire Iribagiza

Chantal Kayitesi

Alice Kwizera

Noelline Mbabazi

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Jean de Dieu Mutankana

Déo Maxime Ndamukunda

Jules Emmanuel Nzabahimana

Janvier Twagirumukiza

Ange Umutoni

Lydie Uwamahoro

Data entry clerks

Solange Kibitenga

Henriette Uwineza

Jacqueline Uwitonze

Scovia Umulisa

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

See attached report.



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

See attached report.