Open Forum Infectious Diseases Advance Access published July 16, 2014

Time-Dependent Predictors of Loss to Follow-up in a Large HIV Treatment Cohort in Nigeria

Seema Thakore Meloni[1], Charlotte Chang[1], Beth Chaplin[1], Holly Rawizza[1,2], Oluwatoyin Jolayemi[3], Bolanle Banigbe[3], Prosper Okonkwo[3], Phyllis Kanki[1]

[1]Harvard School of Public Health, Boston, Massachusetts, USA

[2]Brigham & Women's Hospital, Boston, Massachusetts, USA

[3]AIDS Prevention Initiative Nigeria, Ltd./Gte., Abuja, Nigeria

Address for correspondence: Phyllis Kanki, DVM, DSc, Harvard School of Public Health, Department of Immunology and Infectious Diseases, 651 Huntington Avenue, FXB 405, Boston, MA 02115; e-mail: pkanki@hsph.harvard.edu

Summary: Evaluation of time-dependent predictors of loss to follow-up in a large HIV treatment program revealed that early adherence patterns, in addition to CD4 count and viral load, predicted loss to follow-up and should be used as measures in devising targeted interventions to increase program retention.

ABSTRACT

Background: Most evaluations of loss to follow-up (LTFU) in HIV treatment programs focus on baseline predictors, prior to antiretroviral therapy (ART) initiation. As risk of LTFU is a continuous issue, the aim of this evaluation was to augment existing information with further examination of time-dependent predictors of loss. **Methods:** This was a retrospective evaluation of data collected between 2004-2012 by the Harvard School of Public Health and the AIDS Prevention Initiative in Nigeria as part of PEPFAR-funded program in Nigeria. We used multivariate modeling methods to examine associations between CD4+ cell counts, viral load and early adherence patterns with LTFU, defined as no refills collected for at least two months since the last scheduled appointment. **Results:** Of 51,953 patients initiated on ART between 2004-2011, 14,626 (28%) were LTFU by 2012. Factors associated with increased risk for LTFU were young age, having non-income-generating occupations or no education, being unmarried, WHO stage, having a detectable viral load, and lower CD4+ cell counts. In a subset analysis, adherence patterns during the first 3 months of ART were associated with risk of LTFU by month 12. **Conclusions:** In settings with limited resources, early adherence patterns, as well as CD4+ cell counts and unsuppressed viral load, at any time point in treatment are predictive of loss and serve as effective markers for developing targeted interventions to reduce rates of attrition.

BACKGROUND

The successful global scale-up of antiretroviral therapy (ART) programs has vastly changed outcomes for HIV-infected patients throughout sub-Saharan Africa (SSA), shifting the disease from one that was once uniformly fatal to a chronic disease with lifelong ART. An integral factor in redefining the infection from an acute to manageable condition is the commitment from patients that once they are initiated on an ART regimen, they will remain adherent. Once a patient initiates a treatment regimen, they must return for clinical visits, laboratory tests, prescription refills and counseling services. Oftentimes, these requirements become burdensome and patients discontinue services, creating a major challenge for most HIV treatment programs.

With approximately 168 million inhabitants, Nigeria is the most populous country in SSA and has maintained an HIV prevalence of ~4% for the past 6 years [1-3]. The Government of Nigeria initiated its National ART Program in 2001 and later gained support from the President's Emergency Plan For AIDS Relief (PEPFAR) and other international donor agencies in mid-2000s. From 2004-2012, the Harvard School of Public Health partnered with the AIDS Prevention Initiative in Nigeria (APIN) to utilize PEPFAR funding provided through the U.S. Health Resources and Service Administration (HRSA) to scale-up HIV prevention, care, and treatment activities across Nigeria. The scale-up of HIV care has been a major success; however, the need to initiate over a million additional patients on ART, while retaining those already on therapy despite tightening budgets, represents a significant challenge; thus, cost-effective markers for developing and monitoring targeted interventions are needed.

Rates and predictors of LTFU have been evaluated in numerous HIV programs and rates range from 0.3% to 50% [4-18]. While the studies differ on identified predictors of LTFU, the majority focus on demographic and baseline measures taken prior to ART initiation, and do not evaluate predictors in a time-dependent fashion [17, 18]. The goal of this evaluation was to use data from the Harvard/APIN PEPFAR program, along with statistical methods that incorporate time-dependent factors, thus building upon existing information on baseline predictors of LTFU already in the literature; the hypothesis was that adherence patterns, CD4+ cell counts and viral loads (VLs) would be strong indicators of risk of LTFU in a time-dependent manner. The ultimate goal in addressing this hypothesis was to identify an easy and inexpensive method for health care workers working with limited resources and high patient volumes to identify candidates for targeted interventions to improve retention.

METHODS

Patients

Upon entry into the Harvard/APIN PEPFAR HIV care program and following informed consent, all patients were assessed for ART eligibility according to Nigerian National Guidelines, which followed the WHO guidelines [19, 20]. All consent forms were approved by the institutional review boards at Harvard, APIN and all the corresponding Harvard/APIN PEPFAR HIV care and treatment sites. All ART-eligible patients were placed on ART following a clinical examination and a set of baseline laboratory tests, which included hematology, clinical chemistries, CD4+ cell count, and VL enumeration. Patients were generally given a 30-day supply of ARV medications. Following the first prescription pick-up, refills were obtained on a monthly basis. Following the initiation of ART, laboratory tests were repeated every 6 months

unless an earlier evaluation was medically necessary. All patient data were maintained in electronic databases.

For the analyses, we included patients who were enrolled on ART between June 2004-February 2011 to ensure at least one year of follow-up time for the evaluation. All patients were at least 15 years of age at enrollment. Patients who had previous antiretroviral (ARV) experience prior to enrolling in the Harvard/APIN program were excluded.

Definition of Loss to Follow-Up

Patients were classified as LTFU if, at the time of interest, at least two months had elapsed since the patient's last scheduled pick-up date and they did not later return. Patients who died, withdrew, or transferred to non-Harvard/APIN sites during the period of evaluation were not considered LTFU.

Factors Associated with LTFU

We evaluated baseline demographic (age, sex, education, occupation type, enrollment site, enrollment year, and HIV transmission category) and clinical (HBV and/or HCV co-infection at enrollment, WHO clinical stage, ART regimen, CD4+ cell count and VL) factors, where baseline is defined as at the time of ART initiation. For analyses, age was converted to a categorical variable based on quartiles and the occupation category was collapsed into non-income-generating (i.e., unemployed, students, job applicants, housewives/homemakers, and retirees) and income-generating (laborer vs. professional) categories. Additionally, we incorporated time-dependent factors into the analyses, including adherence patterns during the first three months of treatment, CD4+ cell count and VL.

Measurement of Adherence

To evaluate the time-specific association between adherence and LTFU, we focused on adherence patterns during the first 3 months of ART to determine whether the pattern was predictive of LTFU by month 12. For these subset evaluations, we excluded patients that discontinued during the first 3 months of treatment in order to avoid biasing values with those who had poor adherence during early treatment.

We used prescription refill timeliness as the measurement of adherence, which has been previously shown in multiple studies to be a strong surrogate [21-26]. To compute pill coverage for the first 90 days of treatment, we divided the total number of pills supplied for the time period by 90 and then multiplied by 100 for an average percent adherence during the time period. Average percent adherence values were collapsed into categories for analyses.

Statistical Analyses

Univariate comparisons categorical variables were performed using the chi-squared or Fisher's exact test; Student's t-test was used for normally distributed continuous variables and the Wilcoxon rank sum test for non-normally distributed continuous variables. Statistical significance was defined at an α-level of 0.05. Categorical variables were collapsed based on results of univariate analyses.

Kaplan-Meier analyses were used to examine the probability of follow-up for patients that initiated ART between June 2004-February 2011. Patients were considered at risk of LTFU from the time they initiated ART to the date of their last pick-up, transfer, withdrawal or death. Patients who withdrew or transferred were censored at the date of their last pick-up and patients

who died were censored at the time of their death. Cox proportional hazards models were used to evaluate baseline and demographic factors associated with LTFU. Unmeasured heterogeneity between sites was controlled in the models by using random effects methods. Additionally, clinically relevant interaction terms were tested as potentially explanatory of significant findings. To address potential bias due to patients who were excluded because of missing data, multiple imputation of missing values were performed using chained equations assuming missing at random and 10 imputed data sets.

To further evaluate the time-dependent association between CD4+ cell counts and risk of LTFU, we examined LTFU in yearly increments following ART initiation, starting with the second pick-up for the CD4+ cell count. For the first time point (i.e., "after visit 1), we compared median baseline CD4+ cell counts of those who were lost following the first visit to those who were retained beyond the first visit. For each subsequent time point (i.e., months 12, 24, 36 and 48), we compared median CD4+ cell counts from the visit 6 months prior to determine if it was predictive of LTFU or retention by the noted time point. To examine the time-dependent association between VL and LTFU, we similarly analyzed retention at months 12, 24, 36, and 48 and compared VL suppression rates at the visit 6 months prior to determine if suppression was predictive of LTFU. For both the CD4+ cell count and VL evaluations, each time point contained data from those patients retained in the prior time point; patients who transferred, withdrew or died in the prior time period were removed from subsequent cohorts.

To determine whether the relationships between CD4+ cell counts and viral loads with LTFU rates remained after adjusting for other predictors of LTFU, we generated random effects Cox proportional hazard models including CD4+ cell counts and viral load suppression as time-varying covariates, while controlling for all other significant baseline and demographic

predictors of LTFU. Values for the Cox models were generated using both complete cases and multiply imputed data. Multiple imputations for time-dependent data were generated using a two-fold fully conditional specification algorithm for imputation of missing longitudinal data. All statistical analyses were conducted using Stata version 13 (College Station, TX).

For the sub-analysis on the association between adherence patterns during the first three months of treatment and subsequent risk of LTFU by month 12, we generated a random effects logistic regression model to examine predictors of loss, controlling for site variability. Significant predictors of LTFU from the Kaplan-Meier analyses were retained in the model regardless of statistical significance as they were shown to be significant predictors of LTFU when all patients were evaluated.

RESULTS

Between June 2004-February 2012, 88,983 adult patients initiated standard first-line (1L) ART at one of 32 hospitals (10 tertiary and 22 secondary) spread across nine states supported by the Harvard/APIN PEPAR program. Of those patients, 88,665 (99%) were HIV-1 mono-infected. In order to concentrate our analyses on patients with at least 1 year of since ART initiation, we focused on the 72,770 patients enrolled as of February 2011. Of those patients, we excluded 15,394 who were ARV-experienced at enrollment (Figure 1).

Of the total 57,376 ARV-naïve patients enrolled by February 2011, 4,980 (8.7%) were LTFU, 350 died (0.6%) and 93 (0.2%) transferred or withdrew following the first drug pick-up. After comparing patients who did not return after filling their first prescription to those who returned for at least one refill, and finding these groups to be very different, we also excluded patients who did not return after filling their first prescription (Table 1).

Of the 51,953 patients enrolled by February 2011, 14,626 (28%) were LTFU, 816 (2%) died, and 1,515 (3%) were reported as transferred or withdrawn following the second drug pick-up as of March 2012. The majority of the lost patients generally discontinued within the first 12-18 months following initiation of ART. When combining data across enrollment years, the retention rates were 91% following the first pick-up, 79% by month 6, 74% by month 12 and 70% by month 18. In evaluating the total percentage lost by time on treatment and year of ART initiation, these rates varied by enrollment year, where loss by month 12 appeared greater for the cohorts enrolled after 2006 as compared to those enrolled between 2004-2006.

Overall, of the ARV-naïve patients with at least 1 prescription refill, 65% were female, 57% had a secondary or tertiary level education, 58% were married, and 75% had income-generating occupations. The median age for the cohort was 35 years (IQR: 29-41). At baseline, the majority (67%) of patients had a CD4+ cell count of >100 cells/mL. In addition, 78% of patients had a baseline viral load of >10,000 copies/mL, and 22% had tuberculosis (TB) co-infection, 16% were HBsAg positive and 6% HCV antibody positive.

Baseline Predictors of LTFU

In preliminary adjusted random effects Cox proportional hazard modeling of baseline predictors, controlling for site differences, the factors associated with increased risk for LTFU in the 51,953 patients that made at least one refill pick-up were: lower age; being male; initiating ART during or after 2006; having non-income-generating occupations or no education; being single, divorced or separated; higher baseline WHO clinical stage and viral load; and, lower baseline CD4+ cell counts (data not shown). Additionally, we found that patients who started on tenofovir (TDF) + emtricitabine (FTC) or lamivudine (3TC) + efavirenz (EFV) were more likely

to be LTFU than those on the zidovudine (AZT)-containing regimens (<0.001). We tested interactions between sex and regimen as well as ART initiation year and regimen and found that neither was significant in explaining model outcomes.

CD4+ Cell Counts and Viral Suppression Rates Predict LTFU in Time-Dependent Manner

After finding that baseline CD4+ cell count was a significant predictor of LTFU, we wanted to determine whether CD4+ cell count remained a continuous predictor of loss. The median CD4+ cell counts (Figure 2a) continually increased over the 4 years for both the patients who were retained as well as those who were not retained in the evaluated time period. For patients that were lost, the median of the last CD4+ cell count prior to loss, regardless of time of loss, was 183 cells/mL (IQR: 86-316 cells/mL). At each of the assessed time points, the median CD4+ cell count from the prior 6 months was higher in those subsequently retained as compared to those LTFU (Figure 2a). Similarly, we found that retained patients were more likely to be virally suppressed at their prior six-month visit as compared to those who were LTFU (Figure 2b; $p<0.05$); the median VL prior to loss in LTFU patients was 15,457 cp/mL (IQR: 200-143,386), where nearly 71% of patients had detectable viral load within the six months preceding loss regardless of time of loss.

When we adjusted for age, sex, year of ART initiation, occupation type, marital status, education status, heterosexual sex as a risk factor, WHO stage, TB at entry, and viral load using a random effects Cox proportional hazards model that controlled for site variability, we found that the associations between CD4+ cell count and LTFU as well as VL and LTFU, in a time-dependent manner, remained statistically significant (Table 2; $p<0.001$). Interestingly, the associations between sex and LTFU as well as regimen and LTFU did not remain following

addition of CD4+ count and VL as time-dependent variables. Further, while the statistical significance of the associations between ART initiation year and WHO stage, respectively, with LTFU changed upon imputation of missing data, the associations between CD4+ count with LTFU and VL with LTFU, respectively, were not affected.

Early Adherence Patterns Predict LTFU by Month 12 Post-Initiation of ART

Of the patients with at least three months on treatment, over half were 100% adherent during the first three months. As the largest percentage of loss typically occurred during the first 12 months of treatment, we conducted a subset analysis on the 47,656 patients with at least three months on ART to examine the association between adherence patterns during the first three months of ART and LTFU by month 12. In adjusted multivariate logistic regression analyses, controlling for site variability, age, sex, year of ART initiation, occupation, marital status, education, baseline WHO stage, baseline CD4+ cell count, baseline VL, and initial ART regimen, the association between adherence and LTFU remained, with a trend of reduced risk of LTFU with better adherence during the first 3 months of treatment. Specifically, patients with 50%-94% adherence were at 32% lower risk (95%CI: 0.61-0.76), those with 94%-99% adherence were at 46% lower risk (95%CI: 0.48-0.61), and those with 100% adherence were at 64% lower risk (95%CI: 0.32-0.40) of being LTFU by month 12, as compared to those patients with <50% adherence during the first 3 months of treatment (Figure 3).

DISCUSSION

To our knowledge, this evaluation is the first to examine multiple time-dependent predictors of LTFU using nearly 7.5 years of electronically maintained patient-level data on nearly 52,000 patients. The data were captured starting at the initiation of a rapidly scaled-up HIV treatment program. Over the course of 7 years, the activities were decentralized, moving outwards from tertiary to secondary level centers. Because data were collected from program initiation, we were able to compare LTFU rates from patients enrolled as early as 2004 to those entering in 2011.

Overall retention rates in the Harvard/APIN PEPFAR program were comparable to those reported in other studies [4, 27, 28]. Similar to other studies, we also found that the majority of loss occurs within the first 12-18 months of treatment [27-31]. Interestingly, in complete case analyses, we found that LTFU rates were generally lower for those enrolled prior to 2006 than after 2006. We hypothesize that LTFU might have increased with calendar time due to the expanding nature of the scale-up program and decentralization of care, with the provision of services being shifted from tertiary-level sites down to secondary and primary sites (i.e., scale-up effect). In addition, with other programs also offering care and opening additional sites, it is possible that patients moved to sites closer to their homes. Because there was no existing mechanism to independently track movements of patients between sites in Nigeria, we were unable to track transfers to sites outside the Harvard/APIN PEPFAR network. Thus, part of the decreased risk of loss associated with calendar time might be due to undocumented transfers. It is noteworthy, however, that the association between calendar time and LTFU did not remain following imputation to time-dependent CD4+ count and VL data.

This study identified some important predictors of LTFU, particularly those that remain continuous predictors of outcomes over time through 4 years of observation. Since the program included such a large study population, we were over-powered to find statistical significance in the smallest difference. However, we found that some of the differences were of notable magnitude. Other studies have also identified lower age, marital status, and lower baseline CD4+ cell count as predictors of LTFU [7, 8, 27, 30, 32-37]. But, to our knowledge, this is the first study to show that CD4+ cell count and VL suppression rates remain predictors of LTFU in a time-dependent fashion. A few prior studies have found a correlation with adherence patterns and overall survival [11, 22]. Our analysis was unique in that we focused on early adherence pattern as a predictor of future outcomes to show time-dependent effects.

This study has several strengths based on its evaluation of a large HIV treatment program. First, the study had a large sample size with nearly 52,000 patients. Second, the evaluation used electronically stored patient-level data collected at 32 hospitals and clinics across Nigeria, thus making the results of the evaluation more generalizable. The data were collected starting in 2004 through February 2012, allowing for monitoring of temporal trends in LTFU and predictors over a significant period. Additionally, with over 7.5 years of data, we were able to examine rates and predictors of long-term retention. Furthermore, since laboratory data were electronically collected on a patient level at 6-month intervals, we were able to look at time-dependent variables as predictors of LTFU on an individual patient level.

The study was limited because the program did not actively trace all patients that were lost, which is not atypical from other ART programs. Our study is also limited in that we did not conduct retrospective analyses on data regarding reasons for discontinuation. If we were able to trace and administer surveys that solicited additional data from LTFU patients, we would have

more robust information for our clinics to improve their patient retention rates; we anticipate that having better information on reasons for loss would subsequently lower our LTFU rates and potentially affect the magnitudes of associations regarding predictors of loss. Finally, because this analysis focused only on ART patients and we were looking only at information from ART initiation through time on ART, we were not looking at additional predictors from the pre-ART phase that also might have explained retention patterns.

Studies that traced lost patients found that up to 50% of those cumulatively lost had actually died [5, 13, 38, 39] and that most deaths occurred within 30 days of the last clinical encounter with the patient [5]. Other studies that tracked lost patients found that some simply moved to other health facilities or chose to take a break from treatment due to insufficient funds to attend clinic, food insecurity, difficulty procuring childcare, fear of stigma, or issues with side effects [4, 39, 40]. As such, but utilizing the LTFU composite outcome and due to the fact that the program only passively collects death and transfer information, we are underestimating those that have died or left the program.

Various researchers have shown that developing interventions to address specific barriers can readily address the problems and encourage some patients to return [4]. It is our belief that using factors predictive of loss for targeted interventions before a patient is LTFU will be particularly helpful, specifically for those patients that are lost due to reasons other than death. For example, understanding that early adherence patterns strongly correlate with future LTFU could serve as an easy trigger for targeted adherence counseling. Furthermore, knowing that reduced increases in CD4+ cell counts or unsuppressed VL, at any time point in treatment, is predictive of loss, can also serve as a powerful and simple tool for targeted interventions.

In summary, between 2004-2012, we found that a significant proportion of patients enrolled in the Harvard/APIN PEPFAR treatment program were eventually LTFU. Understanding that CD4+ cell counts, VLs and early adherence patterns are strong predictors of future loss will aid ART programs in identifying patients for targeted interventions to improve retention rates.

Funding: This work was funded, in part, by the U.S. Department of Health and Human Services, Health Resources and Services Administration (U51HA02522) and the Centers for Disease Control and Prevention (CDC) through a cooperative agreement with APIN (PS 001058). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Disclosures: None

Acknowledgements: The authors gratefully acknowledge the patients and the incredible work and dedication of the clinical, data, and laboratory staff at all of the Harvard/APIN PEPFAR ART sites. We also want to thank Dr. Eric Tchetgen Tchetgen of the Harvard School of Public Health, Department of Biostatistics, and Dr. Geoffrey Eisen, of the Northwestern School of Medicine, for their feedback on the statistical methods utilized in these evaluations.

REFERENCES

1. Federal Ministry of Health Nigeria. 2010 National HIV sero-prevalence sentinel survey. Abuja, Nigeria, **2010**.
2. Federal Republic of Nigeria National Agency for the Control of AIDS. Global AIDS response: Country progress report, Nigeria, **2012**.
3. The World Bank. Nigeria: Country at a glance. Washington, D.C.: The World Bank, **2012**.
4. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-Saharan Africa: a systematic review. PLoS Med **2007**; 4(10): e298.
5. Dalal RP, Macphail C, Mqhayi M, et al. Characteristics and outcomes of adult patients lost to follow-up at an antiretroviral treatment clinic in johannesburg, South Africa. J Acquir Immune Defic Syndr **2008**; 47(1): 101-7.
6. Ahonkhai AA, Noubary F, Munro A, et al. Not all are lost: interrupted laboratory monitoring, early death, and loss to follow-up (LTFU) in a large South African treatment program. PLoS One **2012**; 7(3): e32993.
7. Somi G, Keogh SC, Todd J, et al. Low mortality risk but high loss to follow-up among patients in the Tanzanian national HIV care and treatment programme. Trop Med Int Health **2012**; 17(4): 497-506.
8. Zhou J, Tanuma J, Chaiwarith R, et al. Loss to followup in HIV-infected patients from Asia-Pacific Region: Results from TAHOD. AIDS Res Treat **2012**; 2012: 375217.
9. Alvarez-Uria G, Naik PK, Pakam R, Midde M. Factors associated with attrition, mortality, and loss to follow up after antiretroviral therapy initiation: data from an HIV cohort study in India. Glob Health Action **2013**; 6: 21682.

10. Clouse K, Pettifor AE, Maskew M, et al. Patient retention from HIV diagnosis through one year on antiretroviral therapy at a primary health care clinic in Johannesburg, South Africa. J Acquir Immune Defic Syndr **2013**; 62(2): e39-46.
11. Karcher H, Omondi A, Odera J, Kunz A, Harms G. Risk factors for treatment denial and loss to follow-up in an antiretroviral treatment cohort in Kenya. Trop Med Int Health **2007**; 12(5): 687-94.
12. Brinkhof MW, Dabis F, Myer L, et al. Early loss of HIV-infected patients on potent antiretroviral therapy programmes in lower-income countries. Bull World Health Organ **2008**; 86(7): 559-67.
13. Geng EH, Glidden DV, Emenyonu N, et al. Tracking a sample of patients lost to follow-up has a major impact on understanding determinants of survival in HIV-infected patients on antiretroviral therapy in Africa. Trop Med Int Health **2010**; 15 Suppl 1: 63-9.
14. Krishnan S, Wu K, Smurzynski M, et al. Incidence rate of and factors associated with loss to follow-up in a longitudinal cohort of antiretroviral-treated HIV-infected persons: an AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) analysis. HIV Clin Trials **2011**; 12(4): 190-200.
15. Mosoko JJ, Akam W, Weidle PJ, et al. Retention in an antiretroviral therapy programme during an era of decreasing drug cost in Limbe, Cameroon. J Int AIDS Soc **2011**; 14: 32.
16. Wang B, Losina E, Stark R, et al. Loss to follow-up in a community clinic in South Africa--roles of gender, pregnancy and CD4 count. S Afr Med J **2011**; 101(4): 253-7.
17. Charurat M, Oyegunle M, Benjamin R, et al. Patient retention and adherence to antiretrovirals in a large antiretroviral therapy program in Nigeria: a longitudinal analysis for risk factors. PLoS One **2010**; 5(5): e10584.

18. Odafe S, Torpey K, Khamofu H, et al. The pattern of attrition from an antiretroviral treatment program in Nigeria. PLoS One **2012**; 7(12): e51254.

19. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach - 2006 rev. Geneva: World Health Organization, **2006**.

20. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach - 2010 rev. Geneva: WHO, **2010**.

21. Grossberg R, Zhang Y, Gross R. A time-to-prescription-refill measure of antiretroviral adherence predicted changes in viral load in HIV. J Clin Epidemiol **2004**; 57(10): 1107-10.

22. Nachega JB, Hislop M, Dowdy DW, et al. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. J Acquir Immune Defic Syndr **2006**; 43(1): 78-84.

23. Grossberg R, Gross R. Use of pharmacy refill data as a measure of antiretroviral adherence. Curr HIV/AIDS Rep **2007**; 4(4): 187-91.

24. Seguy N, Diaz T, Campos DP, et al. Evaluation of the consistency of refills for antiretroviral medications in two hospitals in the state of Rio de Janeiro, Brazil. AIDS Care **2007**; 19(5): 617-25.

25. Bisson GP, Gross R, Bellamy S, et al. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. PLoS Med **2008**; 5(5): e109.

26. El-Khatib Z, Katzenstein D, Marrone G, et al. Adherence to drug-refill is a useful early warning indicator of virologic and immunologic failure among HIV patients on first-line ART in South Africa. PLoS One **2011**; 6(3): e17518.

27. Ochieng-Ooko V, Ochieng D, Sidle JE, et al. Influence of gender on loss to follow-up in a large HIV treatment programme in western Kenya. Bull World Health Organ **2010**; 88(9): 681-8.

28. Ekouevi DK, Balestre E, Ba-Gomis FO, et al. Low retention of HIV-infected patients on antiretroviral therapy in 11 clinical centres in West Africa. Trop Med Int Health **2010**; 15 Suppl 1: 34-42.

29. Rasschaert F, Koole O, Zachariah R, Lynen L, Manzi M, Van Damme W. Short and long term retention in antiretroviral care in health facilities in rural Malawi and Zimbabwe. BMC Health Serv Res **2012**; 12: 444.

30. Maru DS, Khakha DC, Tahir M, Basu S, Sharma SK. Poor follow-up rates at a self-pay northern Indian tertiary AIDS clinic. Int J Equity Health **2007**; 6: 14.

31. Cicconi P, Cozzi-Lepri A, Castagna A, et al. Insights into reasons for discontinuation according to year of starting first regimen of highly active antiretroviral therapy in a cohort of antiretroviral-naive patients. HIV Med **2010**; 11(2): 104-13.

32. Mocroft A, Kirk O, Aldins P, et al. Loss to follow-up in an international, multicentre observational study. HIV Med **2008**; 9(5): 261-9.

33. Bekolo CE, Webster J, Batenganya M, Sume GE, Kollo B. Trends in mortality and loss to follow-up in HIV care at the Nkongsamba Regional hospital, Cameroon. BMC Res Notes **2013**; 6(1): 512.

34. Guy R, Wand H, McManus H, et al. Antiretroviral treatment interruption and loss to follow-up in two HIV cohorts in Australia and Asia: implications for 'test and treat' prevention strategy. AIDS Patient Care STDS **2013**; 27(12): 681-91.

35. Honge BL, Jespersen S, Nordentoft PB, et al. Loss to follow-up occurs at all stages in the diagnostic and follow-up period among HIV-infected patients in Guinea-Bissau: a 7-year retrospective cohort study. BMJ Open **2013**; 3(10): e003499.

36. Rich ML, Miller AC, Niyigena P, et al. Excellent clinical outcomes and high retention in care among adults in a community-based HIV treatment program in rural Rwanda. J Acquir Immune Defic Syndr **2012**; 59(3): e35-42.

37. Mutasa-Apollo T, Shiraishi RW, Takarinda KC, et al. Patient Retention, Clinical Outcomes and Attrition-Associated Factors of HIV-Infected Patients Enrolled in Zimbabwe's National Antiretroviral Therapy Programme, 2007-2010. PLoS One **2014**; 9(1): e86305.

38. Geng EH, Emenyonu N, Bwana MB, Glidden DV, Martin JN. Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa. JAMA **2008**; 300(5): 506-7.

39. Geng EH, Bangsberg DR, Musinguzi N, et al. Understanding reasons for and outcomes of patients lost to follow-up in antiretroviral therapy programs in Africa through a sampling-based approach. J Acquir Immune Defic Syndr **2010**; 53(3): 405-11.

40. Tuller DM, Bangsberg DR, Senkungu J, Ware NC, Emenyonu N, Weiser SD. Transportation costs impede sustained adherence and access to HAART in a clinic population in southwestern Uganda: a qualitative study. AIDS Behav **2010**; 14(4): 778-84.

FIGURE LEGENDS

Figure 1. Flow diagram for patients included in this evaluation

Figure 2. CD4+ cell counts and viral loads predict LTFU in time-dependent manner

Figure 3. Results from random effects logistic regression model with multiple imputations examining association between early adherence patterns and LTFU by M12 post-initiation of ART

Figure 1. Flow diagram for patients included in the evaluation

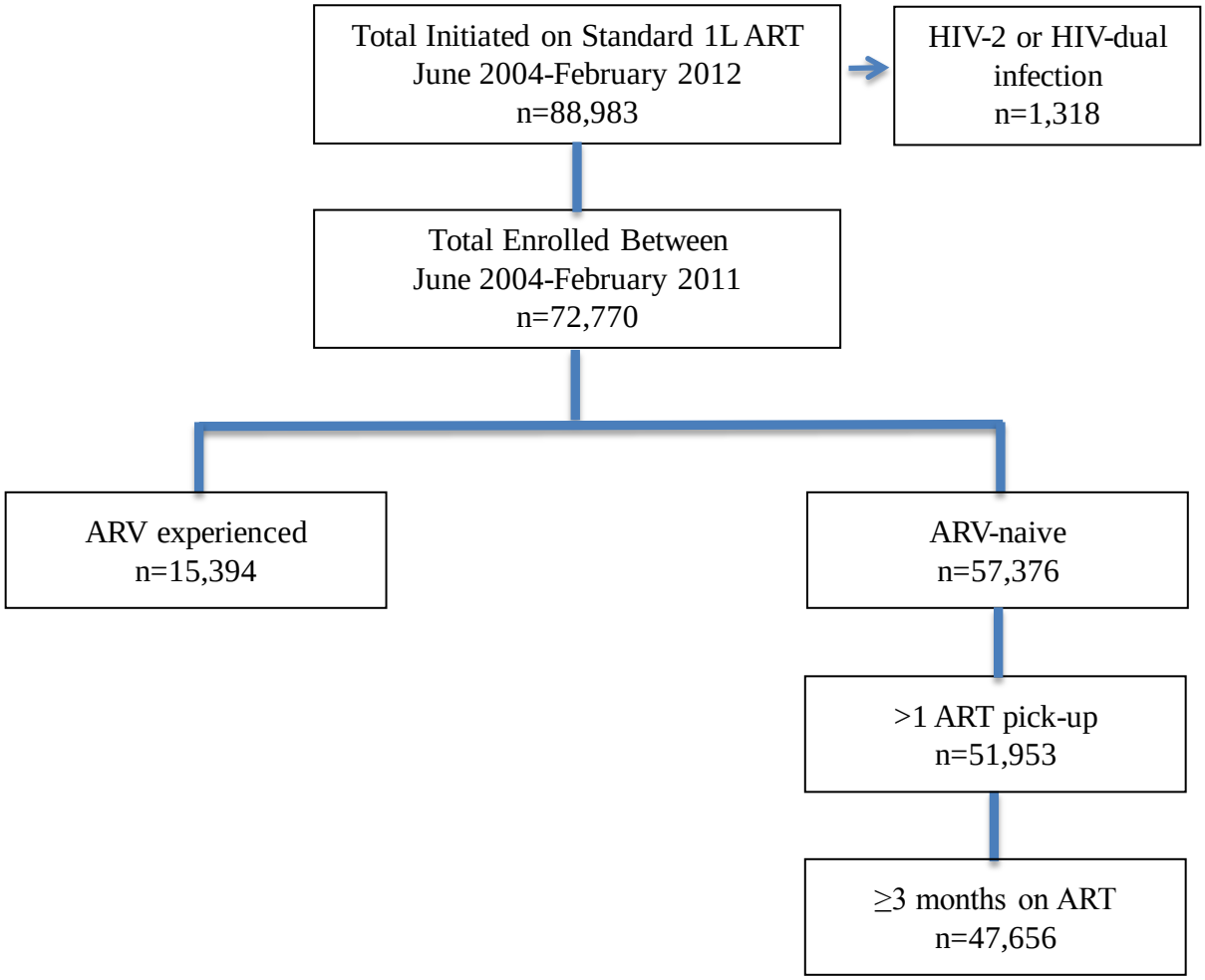
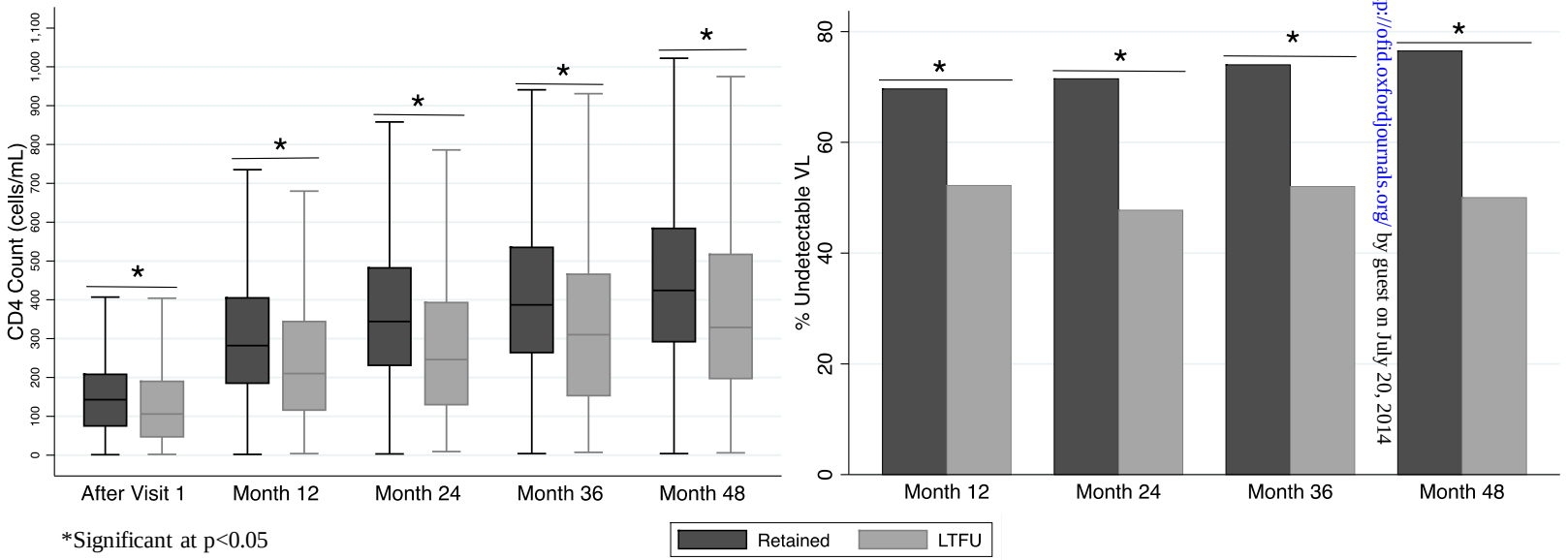


Figure 2. CD4+ cell counts and viral loads predict LTFU in time-dependent manner (N=51,953)

a) Median CD4 counts by retention status and time since starting ART

b) Percent with suppressed VL by retention status and time since starting ART



*Significant at p<0.05

Figure 3. Results from random effects logistic regression model with multiple imputations examining association predictors of LTFU by M12 post-initiation of ART (n=47,656)

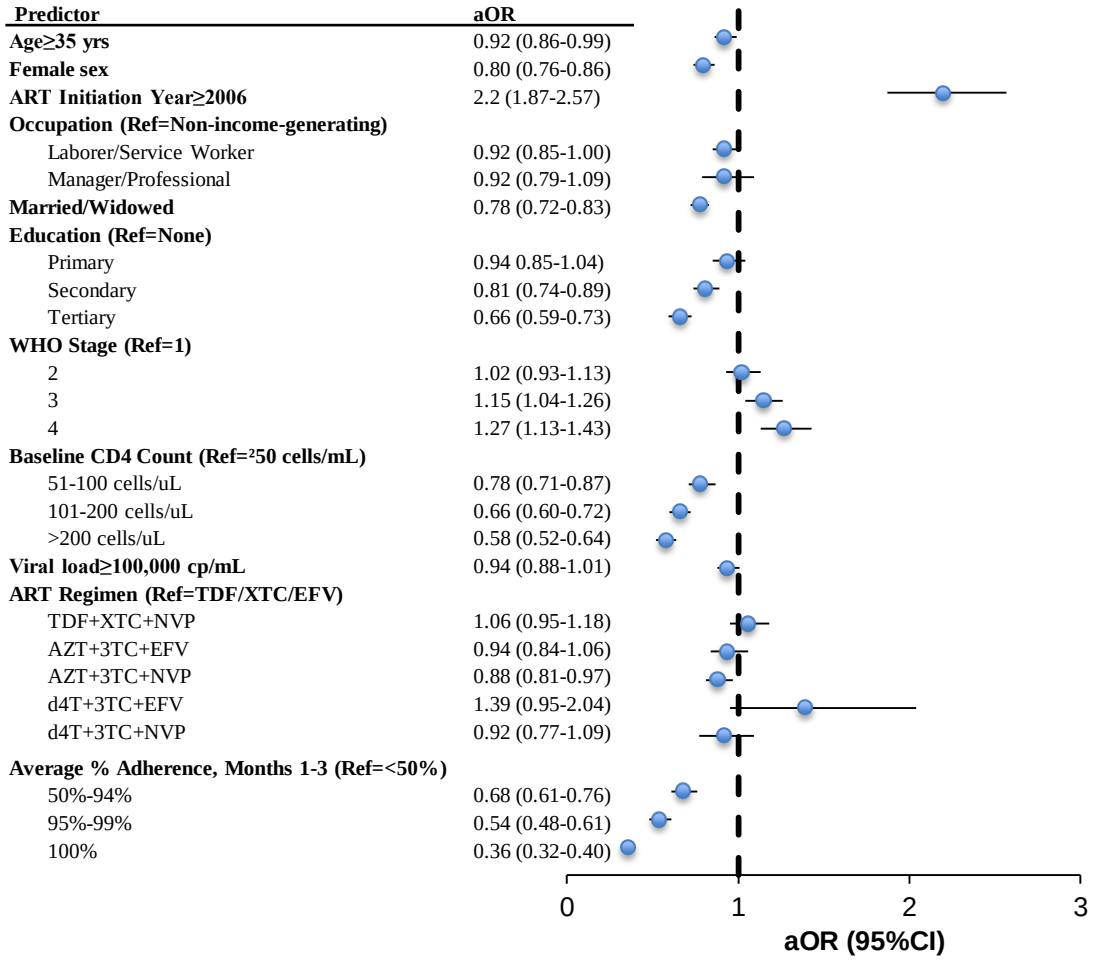


Table 1. Demographics and baseline clinical characteristics of ARV-naive treatment cohort

Characteristic	(a) All Patients	(b) Patients Discontinued after only 1 pick-up	(c) Patients Retained after 1st pick-up	(d) p-value for b vs. c	(e) Patients LTFU after 2nd pick-up	(f) Patients Retained after 2nd pick-up	(g) p-value for e vs. f
N	57,376	5,423	51,953	-	14,626	34,996	-
Median time on ART, months (IQR)	25.7 (10.8-43.1)	0	28.6 (14.8-44.9)	<0.0001	9.3 (2.9-21.0)	36.6 (23.9-51.2)	0.0001
Median age, in years (IQR)	35 (29-41)	35 (29-41)	35 (29-41)	0.49	34 (28-41)	35 (29-41)	<0.0001
Sex, n (%)							
Female	36,806 (64.1)	3,130 (57.7)	33,676 (64.8)	<0.001	8,861 (60.6)	23,307 (66.6)	<0.001
Male	20,570 (35.9)	2,293 (42.3)	18,277 (35.2)		5,765 (39.4)	11,689 (33.4)	
Site Type							
Secondary	5,732 (10.0)	549 (10.1)	5,183 (10.0)	0.73	1,108 (7.6)	3,705 (10.6)	>0.001
Tertiary	51,644 (90.0)	4,874 (89.9)	46,770 (90.0)		13,518 (92.4)	31,291 (89.4)	
ART Initiation Year							
Jun 2004 – Dec 2005	4,814 (8.4)	386 (7.1)	4,428 (8.5)	<0.001	1,333 (9.1)	2,837 (8.1)	<0.001
2006	5,145 (9.0)	431 (7.9)	4,714 (9.1)		1,756 (12.0)	2,630 (7.5)	
2007	7,972 (13.9)	1,027 (18.9)	6,945 (13.4)		2,424 (16.6)	4,130 (11.8)	
2008	13,051 (22.7)	1,297 (23.9)	11,754 (22.6)		3,545 (24.2)	7,706 (22.0)	
2009	12,838 (22.4)	1,124 (20.7)	11,714 (22.5)		3,034 (20.7)	8,183 (23.4)	
2010-Feb 2011	13,556 (23.6)	1,158 (21.4)	12,398 (23.9)		2,534 (17.3)	9,510 (27.2)	
Education, n (%)							
None	10,576 (18.8)	1,155 (22.5)	9,421 (18.5)	<0.001	3,160 (22.1)	5,811 (16.9)	<0.001
Primary	12,373 (22.0)	1,179 (23.0)	11,194 (21.9)		3,292 (23.0)	7,422 (21.5)	
Secondary	19,855 (35.3)	1,830 (35.6)	18,025 (32.3)		4,910 (34.3)	12,344 (35.8)	
Tertiary	13,406 (23.9)	970 (18.9)	12,436 (24.3)		2,966 (20.7)	8,896 (25.8)	
Marital Status, n (%)							
Single	11,211 (19.8)	1,127 (21.7)	10,084 (19.6)	<0.001	3,219 (22.3)	6,398 (18.4)	<0.001
Married	32,569 (57.5)	2,872 (55.4)	29,697 (57.7)		7,814 (54.2)	20,584 (59.2)	
Divorced/Separated	1,446 (10.0)	558 (10.8)	4,559 (8.9)		1,445 (10.0)	2,902 (8.4)	

Characteristic	(a) All Patients	(b) Patients Discontinued after only 1 pick-up	(c) Patients Retained after 1st pick-up	(d) p-value for b vs. c	(e) Patients LTFU after 2nd pick-up	(f) Patients Retained after 2nd pick-up	(g) p-value for e vs. f
Widowed	1,946 (13.5)	630 (12.2)	7,142 (13.9)		1,945 (13.5)	4,868 (14.0)	
Occupation							
Non-income-generating	13,891 (24.6)	1.279 (24.7)	12,612 (24.6)	0.002	3,890 (27.0)	8,108 (23.4)	<0.001
Laborer/Service Worker	39,086 (69.1)	3,628 (70.1)	35,458 (69.0)		9,747 (67.7)	24,178 (69.8)	
Manager/Professional	3,560 (6.3)	268 (5.2)	3,292 (6.4)		757 (5.3)	2,377 (6.9)	
HIV Risk Factor							
Heterosexual Sex	50,869 (95.4)	4,596 (94.9)	46,273 (95.5)	0.063	13,031 (95.8)	31,152 (95.3)	0.028
Other/multiple	2,435 (4.6)	247 (5.1)	2,188 (4.5)		574 (4.2)	1,532 (4.7)	
Baseline CD4 count, cells/mL							
≤50	8,938 (16.5)	1,223 (26.5)	7,715 (15.6)	<0.001	2,718 (19.6)	4,544 (13.6)	<0.001
51-100	9,743 (18.0)	977 (21.2)	8,766 (17.7)		2,685 (19.4)	5,586 (16.7)	
101-200	20,440 (37.7)	1,386 (30.1)	19,054 (38.5)		5,084 (36.7)	13,193 (39.4)	
>200	15,038 (27.8)	1,026 (22.2)	14,012 (28.3)		3,359 (24.3)	10,143 (30.3)	
Baseline viral load, copies/mL							
0-999	4,219 (8.6)	340 (8.2)	3,879 (8.6)	<0.001	1,083 (8.6)	2,633 (8.7)	<0.001
1,000-9,999	6,750 (13.7)	489 (11.8)	6,261 (13.9)		1,653 (13.1)	4,343 (14.3)	
10,000-99,999	16,942 (34.5)	1,267 (30.7)	15,675 (34.8)		4,229 (33.5)	10,761 (35.4)	
≥100,000	21,254 (43.2)	2,033 (49.2)	19,221 (42.7)		5,671 (44.9)	12,645 (41.6)	
WHO Stage, n (%)							
1	11,533 (23.7)	614 (16.5)	10,919 (24.3)	<0.001	2,412 (19.8)	8,046 (26.3)	<0.001
2	13,740 (28.3)	882 (23.7)	12,858 (26.7)		3,150 (25.9)	9,108 (29.7)	
3	16,390 (33.8)	1,362 (36.7)	15,028 (33.5)		4,321 (35.5)	10,018 (32.7)	
4	6,887 (14.2)	856 (23.1)	6,031 (13.5)		2,300 (18.9)	3,452 (11.3)	
TB at Entry							
Yes	12,529 (21.8)	1,037 (19.1)	11,492 (22.1)	<0.001	3,484 (23.8)	27,595 (78.9)	<0.001
No	44,847 (78.2)	4,386 (80.9)	40,461 (77.9)		11,142 (76.2)	7,401 (21.1)	
HBV Status at Baseline							

Characteristic	(a) All Patients	(b) Patients Discontinued after only 1 pick-up	(c) Patients Retained after 1st pick-up	(d) p-value for b vs. c	(e) Patients LTFU after 2nd pick-up	(f) Patients Retained after 2nd pick-up	(g) p-value for e vs. f
Positive	6,183 (16.0)	608 (17.3)	5,575 (15.8)	0.025	1,828 (17.5)	3,497 (15.2)	<0.001
Negative	32,536 (84.0)	2,912 (982.7)	29,624 (84.2)		8,644 (82.5)	19,592 (84.8)	
HCV Status at Baseline							
Positive	2,143 (5.6)	163 (4.7)	1,980 (5.7)	0.015	577 (5.6)	1,247 (5.5)	0.54
Negative	36,238 (94.4)	3,317 (95.3)	32,921 (94.3)		9,805 (94.4)	21,647 (94.5)	
First-line drug regimen							
TDF+XTC+EFV	10,342 (18.0)	1,245 (23.0)	9,097 (17.5)	<0.001	2,683 (18.3)	6,045 (17.3)	<0.001
TDF+XTC+NVP	11,389 (19.9)	1,124 (20.7)	10,265 (19.8)		2,977 (20.4)	6,758 (19.3)	
AZT+3TC+EFV	5,319 (9.3)	536 (9.9)	4,783 (9.2)		1,570 (10.7)	2,989 (8.5)	
AZT+3TC+NVP	26,182 (45.6)	2,035 (37.5)	24,147 (46.5)		6,230 (42.6)	16,894 (48.3)	
d4T+3TC+EFV	302 (0.5)	54 (1.0)	248 (0.5)		93 (0.6)	141 (0.4)	
d4T+3TC+NPV	3,842 (6.7)	429 (7.9)	3,413 (6.6)		1,073 (7.3)	2,169 (6.2)	

Table 2. Cox Proportional Hazards model of time-independent and time–dependent predictors of LTFU among ART-naïve adult patients that made at least 2 ART pick-ups (n=51,953)

	Unadjusted Cox Values			Adjusted Cox Values Complete Cases*			Adjusted Cox Values Multiple Imputations*		
Variable	**HR**	**95% CI**	**p**	**aHR**	**95% CI**	**p**	**aHR**	**95% CI**	**p**
Age, years									
<30	Ref	-	-	Ref	-	-	Ref	-	-
30-34	0.86	0.82-0.90	<0.001	0.81	0.66-0.98	0.036	0.80	0.70-0.91	0.001
35-40	0.83	0.79-0.87	<0.001	0.75	0.59-0.95	0.015	0.76	0.66-0.88	<0.001
>40	0.84	0.81-0.88	<0.001	0.66	0.50-0.86	0.003	0.67	0.55-0.82	<0.001
Sex									
Male	Ref	-	-	Ref	-	-	Ref	-	-
Female	0.82	0.79-0.85	<0.001	0.98	0.87-1.10	0.69	0.91	0.80-1.03	0.14
ART Initiation Year									
Jun 2004 – Dec 2005	Ref	-	-	Ref	-	-	Ref	-	-
2006	1.38	1.34-1.42	<0.001	1.24	1.11-1.37	<0.001	1.12	1.01-1.25	0.04
2007	1.41	1.37-1.45	<0.001	1.74	1.34-2.27	<0.001	1.24	0.96-1.60	0.11
2008	1.31	1.28-1.34	<0.001	1.52	1.20-1.93	0.001	1.03	0.73-1.45	0.87
2009	1.26	1.23-1.30	<0.001	1.89	1.60-2.23	<0.001	1.00	0.74-1.34	0.98
2010-Feb 2011	1.23	1.20-1.27	<0.001	2.12	1.58-2.86	<0.001	0.84	0.49-1.43	0.52
Site Type									
Secondary	Ref	-	-						
Tertiary	1.14	1.07-1.21	<0.001						
Occupation									
Non-income-generating	Ref	-	-	Ref	-	-	Ref	-	-
Laborer/Service Worker	0.90	0.87-0.94	<0.001	1.10	1.01-1.20	0.021	1.02	0.94-1.11	0.58
Manager/Professional	0.70	0.65-0.76	<0.001	1.23	0.97-1.57	0.093	1.22	0.99-1.51	0.07
Marital Status, n (%)									
Single/Divorced/Separated	Ref	-	-	Ref	-	-	Ref	-	-
Married/Widowed	0.80	0.77-0.83	<0.001	0.82	0.72-0.94	0.004	0.76	0.70-0.82	<0.001
Education, n (%)									
None	Ref	-	-	Ref	-	-	Ref	-	-

Primary	0.86	0.82-0.90	<0.001	0.77	0.67-0.88	<0.001	0.82	0..72-0.93	0.002
Secondary	0.78	0.75-0.82	<0.001	0.76	0.67-0.86	<0.001	0.81	0.75-0.88	<0.001
Tertiary	0.65	0.62-0.68	<0.001	0.65	0.56-0.76	<0.001	0.71	0.57-0.89	0.003
HIV Risk Factor									
Heterosexual Sex	Ref	-	-	Ref	-	-	Ref	-	-
Other/multiple	1.18	1.02-1.37	0.029	1.58	0.48-5.21	0.45	1.17	0.78-1.75	0.44
WHO Stage									
1	Ref	-	-	Ref	-	-	Ref	-	-
2	1.11	1.05-1.17	<0.001	1.24	0.99-1.55	0.06	1.14	0.94-1.37	0.20
3	1.34	1.28-1.41	<0.001	1.24	1.01-1.51	0.04	1.21	1.04-1.40	0.013
4	1.82	1.72-1.92	<0.001	1.29	0.85-1.95	0.23	1.38	1.07-1.79	0.013
TB at Entry	1.10	1.06-1.14	<0.001						
HBV at Entry	1.11	1.05-1.16	<0.001	0.97	0.81-1.16	0.77	0.95	0.83-1.08	0.39
HCV at Entry	0.94	0.86-1.02	0.15						
CD4+ Cell Count, cells/mL									
≤50	Ref	-	-	Ref	-	-	Ref	-	-
51-100	0.46	0.38-0.57	<0.001	0.56	0.47-0.68	<0.001	0.64	0.50-0.82	<0.001
101-200	0.25	0.21-0.30	<0.001	0.34	0.25-0.47	<0.001	0.46	0.32-0.66	<0.001
>200	0.13	0.11-0.15	<0.001	0.19	0.16-0.24	<0.001	0.25	0.19-0.33	<0.001
Undetectable Viral Load	0.31	0.28-0.34	<0.001	0.40	0.34-0.49	<0.001	0.40	0.35-0.46	<0.001
Starting ART Regimen									
TDF+FTC/3TC+EFV	Ref	-	-	Ref	-	-	Ref	-	-
TDF+FTC/3TC+NVP	0.92	0.87-0.97	0.002	0.86	0.63-1.17	0.34	0.88	0.69-1.13	0.31
AZT+3TC+EFV	1.00	0.94-1.06	0.95	0.98	0.77-1.25	0.86	0.97	0.79-1.20	0.81
AZT+3TC+NVP	0.79	0.76-0.83	<0.001	0.89	0.66-1.22	0.48	0.90	0.75-1.08	0.26
d4T+3TC+EFV	1.07	0.87-1.31	0.54	1.01	0.74-1.38	0.97	0.98	0.79-1.21	0.85
d4T+3TC+NVP	0.76	0.71-0.81	<0.001	0.73	0.37-1.42	0.35	0.83	0.60-1.15	0.26

*Random effects Cox proportional hazards model generated to control for site variability