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ORIGINAL RESEARCH

Failure to return pillbox is a predictor of being lost to follow-up among people living with HIV on antiretroviral therapy in rural Tanzania

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Abstract

Objectives: Pill count is used to assess drug adherence in people living with HIV (PLHIV). Carrying a pillbox is associated with fear of concealment and stigma and might indicate poor adherence and predict someone who will be lost to follow-up (LTFU). We therefore assessed the association between pillbox return and being LTFU in rural Tanzania.

Methods: This is a nested study of the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO). We included PLHIV aged ≥ 18 years enrolled in KIULARCO between January 2013 and March 2019 with follow-up through January 2020, who were on antiretroviral treatment (ART) for ≥ 6 months. Baseline was defined as the latest ART initiation or KIULARCO enrolment. We determined the association between time-dependent failed pillbox return updated at every visit and LTFU using Kaplan–Meier estimation and Cox models.

Results: Among 2552 PLHIV included in the study, 1735 (68.0%) were female, 959 (40.3%) had a WHO stage III/IV and 1487 (66.4%) had a CD4 cell count < 350 cells/μL. The median age was 38.4 years [interquartile range (IQR): 31.7–46.2]. During a median follow-up of 33.1 months (IQR: 17.5–52.4), 909 (35.6%)

*Other members of the KIULARCO Study Group are listed in the Acknowledgements section.

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participants were LTFU, 43 (1.7%) died and 194 (7.6%) had transferred to another clinic. The probability of being LTFU was higher among PLHIV with failed pillbox return than among those who returned their pillbox [30.0%, 95% confidence interval (CI): 26.8–33.2% vs. 19.4%, 95% CI: 17.4–21.6%, respectively, at 24 months (hazard ratio = 1.67, 95% CI: 1.46–1.90; $p < 0.001$)].

Conclusions: Failed pillbox return was associated with a higher risk of being LTFU and could be used as a simple tool to identify PLHIV for appropriate interventions to reduce their chance of being LTFU.

KEYWORDS

adherence, antiretroviral treatment, HIV treatment outcome, lost to follow-up, pillbox, rural, stigma, sub-Saharan Africa

INTRODUCTION

The rollout of antiretroviral treatment (ART) programmes has curbed the HIV epidemic to a major extent [1,2]. However, the UNAIDS goals of 90% of people living with HIV (PLHIV) knowing their HIV status, 90% of those diagnosed being on treatment, and 90% of those on treatment being virally suppressed were not achieved by the end of 2020 [3]. Major reasons for these failures are lack of testing and attrition from care in PLHIV [4-6]. Risk factors for attrition include living without a partner, non-disclosure of HIV status, poor drug adherence and advanced HIV disease [5,7].

Currently, there is no gold standard to measure adherence to treatment in order to predict the possibility of being lost to follow-up (LTFU) or virological failure (VF) [8,9]. The methods mostly used in the sub-Saharan African setting – namely, pill counts, electronic monitoring systems, Adults Aids Clinical Trial Group adherence questionnaire, plasma drug levels and patient self-report – all have strengths and weaknesses [10-12]. Bringing back the dispensed pharmaceutical packaged antiretroviral pill bottle (pillbox) on the next visit in order to count pills is requested in many care and treatment centres in sub-Saharan Africa [13,14] and is also recommended by the WHO [15]. However, carrying the pillbox is often associated with fear of being identified as HIV-positive [16], with stigma being one of the major factors leading to poor adherence and disclosure [17-19]. The assessment of pillbox return could serve as a possible proxy of poor adherence and potentially as a predictor of becoming LTFU. To our knowledge, this easily accessible information on a clinical visit has not yet been analysed as a predictor for being LTFU. Our study aims to determine the association between failed pillbox return and being LTFU.

MATERIALS AND METHODS

Study design and setting

This study was nested within the prospective Kilombero and Ulanga Antiretroviral Cohort (KIULARCO), which is among the first rural HIV cohorts in East Africa, established in 2005 at the Chronic Diseases Clinic of Ifakara (CDCI) – the HIV care and treatment centre of the Saint Francis Referral Hospital [20,21]. The CDCI provides HIV care and treatment services to people residing in the Kilombero and Ulanga Districts in Morogoro region, south-western Tanzania. According to the last census in 2012, these two districts had a total population of 673 083 [22]. Since its establishment, KIULARCO has enrolled over 11 000 PLHIV, with approximately 4200 on active follow-up in 2020. KIULARCO study procedures are described elsewhere [20,21]. In brief, PLHIV newly tested HIV-positive at our site or being referred from another centre are enrolled into care, started on ART and – if stable – are seen 3-monthly for drug refill and twice a year by a nurse and pharmacist or by a medical doctor. Once yearly laboratory parameters such as HIV viral load, CD4 count and safety laboratory are done. All data are directly collected in an open medical record system (openMRS) and stored on a local server.

Study population

We included PLHIV aged ≥ 18 years enrolled in KIULARCO between January 2013 and March 2019 with follow-up through January 2020, who initiated ART and had at least 6 months of follow-up. Participants were

excluded if they were < 18 years old, were in transit (visited facility for drug pick-up only), had never been initiated on ART, or had < 6 months of follow-up (to ensure participants were stable on ART). As per routine care, PLHIV starting ART were provided with drugs for 14–30 days in a pharmacy-packaged envelope. From the second visit onwards, clinically stable patients were dispensed pillboxes containing 30 tablets each for the duration of 3 months – or, if medically indicated, for shorter time periods. During the study period, the first-line ART regimen consisted of efavirenz, lamivudine and tenofivir as a once-daily single pill. The second-line regimen – atazanavir combined with zidovudine/lamivudine – is a once-daily two-pill regimen. In specific situations such as kidney failure or interaction with anti-tuberculous drugs, the treatment was individualized (e.g. abacavir instead of tenofovir, or lopinavir double dose instead of atazanavir). These alternative regimens could consist of up to five pills per day. Viral load data were available in a subset of PLHIV from 2017 onwards when routine viral load monitoring was rolled out in Tanzania.

Study objectives

The primary objective of this study was to determine the association between failed pillbox return and being LTFU. Secondary objectives were to evaluate the association between failed pillbox return and a combined end-point of LTFU/death, predictors of failed pillbox return, the association between failed pillbox return and VF, comparison between failed pillbox return and self-reported adherence to ART, and reasons for missed pills in PLHIV on ART.

Definitions and covariates

Baseline was defined as the latest of ART initiation (i.e. for those who initiated ART within KIULARCO) or enrolment in KIULARCO (i.e. for those who had initiated ART in another clinic before enrolment in KIULARCO). Patients were instructed from the first visit to bring their pillbox back to their next clinic visit for pill count. Failed pillbox return was defined as a failure to present the pillbox at a clinical visit during follow-up and was treated as a time-dependent covariate, updated at each clinic visit. Of course, pillbox return could only be assessed from the first follow-up visit onwards.

Visits were scheduled every 3 months; additionally unscheduled visits were recorded. Being LTFU was defined as not coming to the clinic for > 60 days after the last scheduled appointment [7,23]. While patients could experience multiple LTFU events after returning to care, we report on the first LTFU event only [7,24]. For those not LTFU, other possible outcomes were death, transfer to another clinic, or censored at database closure on 16 January 2020 for those active in care. We defined VF as the first elevated viral load > 1000 copies/mL. Poor self-reported adherence was defined as a report of any missed intake of medication in the 4 weeks prior to the scheduled clinical visit. Tuberculosis was recorded if within 3 months from enrolment acid-fast bacilli or a positive Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) from sputum or an extrapulmonary site were documented, or if anti-tuberculosis drugs with an *International Classification of Diseases*, 10th Revision (ICD-10) code or clinical signs suggestive of tuberculosis were present. Unlikely tuberculosis was defined as no prescription of anti-tuberculosis drugs and no diagnosis of tuberculosis by ICD-10. For other cases, an indeterminate tuberculosis status was stated and treated as missing data.

Baseline covariates were age, gender, marital status, disclosure of HIV status, partner HIV status, highest education level, distance in kilometres of residence from the clinic, body mass index (BMI), HIV WHO stage, CD4 cell count, tuberculosis status, as defined earlier, ART initiation status (initiated ART after or before enrolment in KIULARCO) and calendar year. The BMI, HIV WHO stage, CD4 cell count and tuberculosis status were measurements closest to baseline, at most 6 months before and up to 3 months afterwards.

Statistical methods

Medians, interquartile ranges (IQRs), frequencies and proportions were used to describe baseline characteristics. We estimated the probability of LTFU over time by pillbox return status using Kaplan–Meier methods. These curves differ from standard Kaplan–Meier survival curves because pillbox return is a time-dependent covariate, i.e. it can change for any given patient at subsequent clinic visits. The estimation procedure for these curves allows for time-dependent pillbox return status [25].

Cause-specific Cox models were used to determine the association between time-dependent failed pillbox return and being LTFU [26]. Participants contributed follow-up time from the first follow-up visit (when pillbox return could first be assessed) until the first LTFU event. For PLHIV who were not LTFU, their follow-up time was censored at the earliest time of death, transfer to another clinic, or the date of database closure. Models were adjusted for baseline covariates. For baseline covariates with missing values, we used missing indicators in order to include all participants in the models (i.e. participants

with missing data for a given variable where classified in a separate 'missing' category). In sensitivity analyses, we repeated the analyses: (a) incorporating an interaction between ART initiation status (initiated ART in or before KIUARLCO) and failed pillbox return; (b) restricted to participants who initiated ART within KIULARCO, and (c) restricted to participants with complete baseline covariates (those with missing values for any baseline covariate were excluded). We repeated the analysis with the composite outcome of LTFU or death, because in a previous study we found that 40% of KIULARCO participants who were LTFU and traced had died [27].

Baseline covariates (listed earlier) were evaluated as potential predictors of failed pillbox return, using generalized estimating equations for a multivariable repeated-measures logistic regression model to account for the correlation from the patient (i.e. multiple clinic visits for which pillbox return status was recorded). We used an exchangeable correlation structure.

The analysis for the association between failed pillbox return and VF was similar to that for the LTFU outcome described earlier, but restricted to the subset of patients with a viral load test done after implementation of routine viral load testing started in 2017. Patients contributed follow-up time from the first follow-up visit in 2017 to the first VF event, with delayed entry for those patients whose baseline was before 2017. For patients who had no VF, their follow-up time was censored at the earliest time of death, when they became LTFU, transfer to another clinic, or the date of database closure.

Comparison of failed pillbox return and self-reported adherence, and reasons for missing ART doses at each visit were assessed descriptively. Analyses were performed using Stata version 15 [28].

Ethical considerations

The study was nested within KIULARCO, which has attained ethical approval from the Ifakara Health Institute Review Board (IHI/IRB/No:16–2006) and the National Health Research Committee of the National Institute for Medical Research of Tanzania (NIMR/HQ/R.8a/Vol. IX/620), which are both updated annually. Only participants who consented to enrolment into KIULARCO were included in the study.

RESULTS

In total, 4520 PLHIV were enrolled in KIULARCO between January 2013 and March 2019. Of these, 1968 were excluded from the analysis for the following reasons:

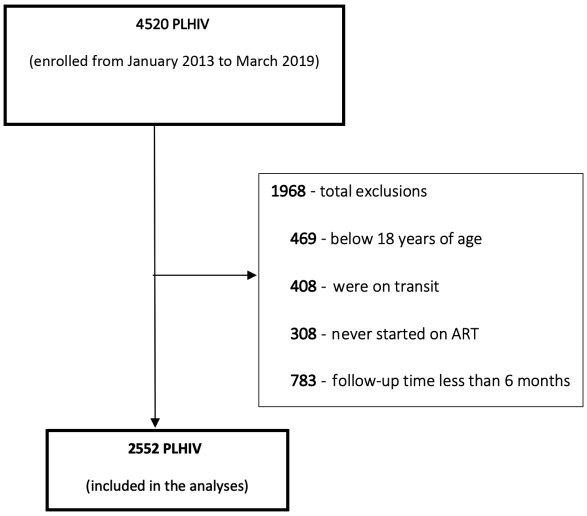

FIGURE 1 Study population flow chart. Flow chart of patients enrolled in the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) and included in this analysis. PLHIV, people living with HIV; ART, antiretroviral treatment. Transit are patients who came for drug pickup only

469 were below 18 years of age, 408 were not receiving care from our clinic (in transit), 308 had not initiated ART and 783 had a follow-up of < 6 months (Figure 1).

Patients' baseline characteristics

Among 2552 PLHIV included, at baseline, the median age of patients was 38.4 years (IQR: 31.7–46.2); the majority were female ($N = 1735$, 68.0%), had normal BMI ($N = 1577$, 62.7%), were married or cohabiting ($N = 1565$, 61.3%), and had disclosed their HIV status ($N = 1943$, 76.1%) mostly to a family member ($N = 1227$, 49.5%), %) (Table 1). Over half of patients ($N = 1417$, 59.7%) were at HIV WHO stage I/II and a third ($N = 750$, 33.5%) had a CD4 count ≥ 350 cells/μL. Most of the patients had a primary school level of education ($N = 2108$, 82.6%) and lived < 1 km from the clinic ($N = 1104$, 44.4%). Tuberculosis was diagnosed in 322 (13.0%) patients. The majority of patients were initiated on ART after enrolment in KIULARCO ($N = 2118$, 83.0%).

Follow-up visits

The total number of visits among 2552 patients was 21 420, with a median of six visits per patient (IQR: 4–12). Of these visits, patients did not bring back their pillbox in 7438 (34.7%), while the pillbox was returned every time in 431 (16.9%). Of the 7438 visits where patients did not bring back their pillbox, in 1956 (26.3%) PLHIV later became LTFU and in 5482 (73.7%) PLHIV remained in care.

TABLE 1 Patients' characteristics at baseline[a]

Patient characteristics	All patients ($n = 2552$)
Socio-demographics	
Age (years) [median (IQR)]	38.4 (31.7–46.2)
Age (years) [*n* (%)]	
18–24	197 (7.7%)
25–34	734 (28.8%)
35–44	898 (35.2%)
≥45	723 (28.3%)
Gender, female [*n* (%)]	1735 (68.0%)
Marital status [*n* (%)]	
Married/cohabiting	1565 (61.3%)
Never married	206 (8.1%)
Separated/divorced/widowed	781 (30.6%)
Disclosed HIV status [*n* (%)]	
No	535 (21.6%)
Yes	1943 (76.1%)
Missing	74 (2.9%)
Person to whom disclosed HIV status [*n* (%)][b]	
Family member	1227 (49.5%)
Partner	886 (35.8%)
Non-family member	37 (1.5%)
Partner HIV status [*n* (%)]	
Positive	543 (21.9%)
Negative	300 (12.1%)
Not tested/unknown	719 (29.0%)
No partner	916 (37.0%)
Missing	74 (2.9%)
Education [*n* (%)]	
None	236 (9.3%)
Primary	2108 (82.6%)
Secondary and above	208 (8.2%)
Distance of residence to clinic [*n* (%)]	
≤ 1 km	1104 (44.4%)
2 to < 50 km	825 (33.2%)
≥ 50 km	557 (22.4%)
Missing	66 (2.6%)
Clinical	
Body mass index[c,d] (kg/m^2) [*n* (%)]	
Underweight, < 18.5	370 (14.7%)
Normal, 18.5 to < 25	1577 (62.7%)
Overweight, ≥ 25	567 (22.6%)
Missing	38 (1.5%)
WHO stage[c] [*n* (%)]	
I	1033 (43.5%)
II	384 (16.2%)
III	709 (29.8%)
IV	250 (10.5%)
Missing	176 (6.9%)
CD4 count (cells/μL)[c] [*n* (%)]	
< 100	473 (21.1%)
100–349	1014 (45.3%)
≥ 350	750 (33.5%)
Missing	315 (12.3%)
Tuberculosis status (TB)[c] [*n* (%)]	
Unlikely	2155 (87.0%)
Yes	322 (13.0%)
Missing	75 (2.9%)
ART initiation status [*n* (%)]	
Had already initiated ART in another clinic before enrolment in KIULARCO	434 (17.0%)
Initiated ART within 1 month of enrolment in KIULARCO	1835 (71.9%)
Initiated ART more than 1 month after enrolment in KIULARCO	283 (11.1%)
Calendar year [*n* (%)]	
2013–2014	767 (30.0%)
2015–2016	926 (36.3%)
2017–2019	859 (33.7%)

Note: Results are number and column % of those with non-missing data; missing data rows are number and column %.

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range; KIULARCO, Kilombero and Ulanga Antiretroviral Cohort.

[a]Defined as the latest of ART initiation (i.e. for those who initiated ART within KIULARCO) and enrolment in KIULARCO (i.e. for those who had initiated ART in another clinic before enrolment into KIULARCO).

[b]Total numbers are more than those who disclosed their HIV status because some patients have multiple disclosures to both family member and/or partner and/or non-family member.

[c]Body mass index, WHO stage, CD4 and TB measurement closest to baseline within 6 months before and 3 months after.

[d]Excluding pregnant women.

During a median follow-up of 33.1 months (IQR: 17.5–52.4), 909 (35.6%) patients were LTFU, 43 (1.7%) died and 194 (7.6%) were transferred to another clinic.

Failed pillbox return and LTFU, and LTFU/death

At 24 months, the probability of being LTFU was higher among patients with a failed pillbox return than among

those who returned their pillbox (log-rank test, $p < 0.001$), at 30.0% (95% CI: 26.8–33.2%) versus 19.4% (95% CI: 17.4–21.6%), respectively (Figure 2). This was confirmed by an adjusted hazard ratio (HR) of 1.67 (95% CI: 1.46–1.90, $p < 0.001$). We also found an association between failed pillbox return and the combined endpoint of LTFU/death (HR = 1.73, 95% CI: 1.52–1.97, $p < 0.001$) (Table 2). The results were broadly similar in all sensitivity analyses. In particular, there was no evidence of a difference in the association between failed pillbox return and being LTFU or LTFU/death according to whether participants initiated ART in or before KIULARCO (interaction $p = 0.69$ and $p = 0.55$, respectively, with broadly similar effect estimates). Other factors associated with LTFU were younger age, living far from the clinic and advanced HIV WHO stage (Table S1).

Predictors of failed pillbox return

Factors associated with a higher probability of failed pillbox return were being male, younger age, living closer to the clinic and having a less advanced HIV WHO stage, a higher baseline CD4 count, and later baseline calendar year (Table 3).

Failed pillbox return and virological failure

After implementation of routine viral load testing in 2017, 1873 patients had 4157 viral load tests done (median of two per person, IQR: 2–3). Of these, 237 (12.7%) patients had VF during a median follow-up time of 38.0 months (IQR: 20.7–53.7). Of 1636 patients with no VF, 1398 (85.5%) were on active care, 7 (0.4%) had died, 147 (9.0%) were LTFU and 84 (5.1%) had transferred to another clinic. There was no evidence of an association between failed pillbox return and VF (HR = 1.11, 95% CI: 0.85–1.45, $p = 0.45$; Table 4). Results were robust to sensitivity analyses. The point estimates for the association between failed pillbox return and VF differed somewhat by whether patients initiated ART after or before KIULARCO enrolment (1.00 and 1.65, respectively), but the CIs were wide and the interaction p-value was relatively large ($p = 0.12$).

Failed pillbox return and self-reported adherence

Patients reported missing pills in the previous 4 weeks in 749/7438 (10.1%) visits with a failed pillbox return, compared with 805/13 982 (5.8%) visits with a pillbox return. The most common reason reported for missing any intake of medication in the previous 4 weeks was losing or running out of medication ($N = 605$, 38.9%; Table S2). Other reasons included being too ill ($N = 41$, 2.6%), feeling better ($N = 35$, 2.3%), stigma ($N = 21$, 1.4%), and depression ($N = 16$, 1.0%).

DISCUSSION

In this prospective cohort study of PLHIV in rural Tanzania, we have demonstrated for the first time that failed pillbox return is associated with being LTFU. Other

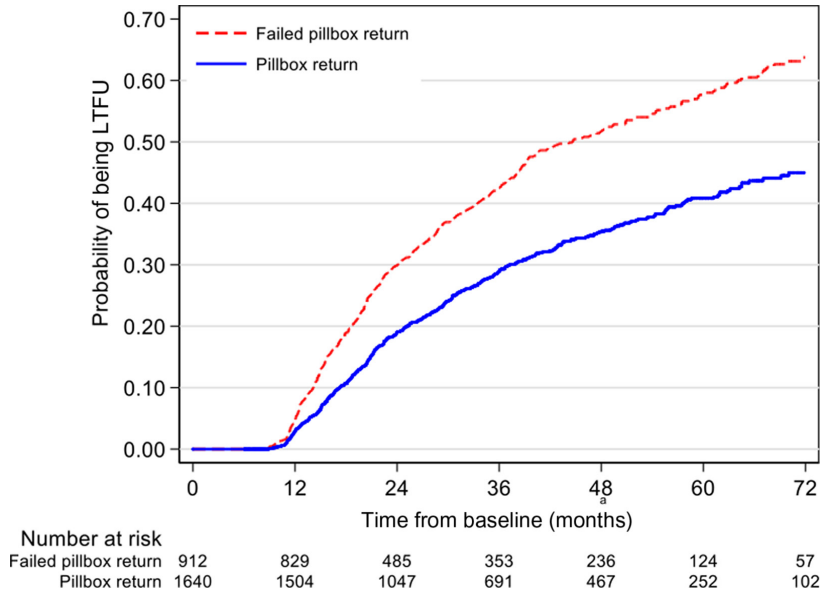

FIGURE 2 Probability of being lost to follow-up (LTFU) over time by pillbox return status. Kaplan–Meier estimation of being LTFU for patients with and without pillbox return. Patients who failed to bring back the pillbox are shown in red and those who brought it back are shown in blue

TABLE 2 Association between failed pillbox return and being lost to follow-up (LTFU), and LTFU/death

	Cox model: LTFU		Cox model: LTFU/death	
	Univariable	Multivariable	Univariable	Multivariable
Characteristics	HR (95% CI)[b]	HR (95% CI)[b,c]	HR (95% CI)[b]	HR (95% CI)[b,c]
Failed pillbox return ($N = 2552$)[c]				
No	Reference	Reference	Reference	Reference
Yes	1.64 (1.44–1.87)	1.67 (1.46–1.90)	1.69 (1.49–1.92)	1.73 (1.52–1.97)
Failed pillbox return, among those who initiated ART in KIULARCO ($N = 2118$)[c,d]				
No	Reference	Reference	Reference	Reference
Yes	1.67 (1.44–1.92)	1.69 (1.46–1.95)	1.72 (1.50–1.98)	1.76 (1.52–2.03)
Failed pillbox return among those who initiated ART before enrolment in KIULARCO ($N = 434$)[c,d]				
No	Reference	Reference	Reference	Reference
Yes	1.53 (1.12–2.10)	1.57 (1.14–2.15)	1.52 (1.13–2.09)	1.58 (1.16–2.16)
Failed pillbox return (restricted to patients who initiated ART in KIULARCO; $N = 2118$)[c]				
No	Reference	Reference	Reference	Reference
Yes	1.67 (1.45–1.93)	1.69 (1.46–1.96)	1.73 (1.50–1.98)	1.77 (1.53–2.04)
Failed pillbox return (restricted to patients with no missing baseline covariate values; $N = 2050$)				
No	Reference	Reference	Reference	Reference
Yes	1.71 (1.47–1.98)	1.77 (1.52–2.06)	1.77 (1.53–2.04)	1.84 (1.59–2.13)

[a]Hazard ratios (HR) and 95% confidence intervals (CI) obtained from Cox models. Failed pillbox return is time-dependent, updated at each clinic visit.

[b]Adjusted for baseline covariates. All baseline covariates are time-independent.

[c]Missing indicator used for missing covariates.

[d]Incorporating an interaction between failed pillbox return and whether patients initiated ART in the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO); interaction $p = 0.69$ (for LTFU outcome) and $p = 0.55$ (for LTFU/death outcome).

factors associated with being LTFU were younger age, living far from the clinic and advanced HIV WHO stage. Among the participants who were attending clinic visits, factors associated with failed pillbox return were younger age, male gender, living closer to the clinic, less advanced HIV WHO stage, higher CD4 count and later calendar year.

This is the first study assessing pillbox return as a possible predictor of being LTFU. Despite the fact that the pillbox is commonly used for pill count to measure adherence [29], the association between pill count and adherence or viral suppression is not optimal, as patients may reduce the number of pills to hide poor adherence [30-33]. The hypothesis that return of the pillbox could be a better predictor of poor adherence/being LTFU resulted from the observed association of pillbox return with stigma. For example, studies from Tanzania have shown that a significant proportion of patients re-pack the medication into other containers as a method of concealing the medication due to anticipated stigma [34,35], which in turn is associated with poor adherence to ART [19,36]. Further, a qualitative study on adherence to ART in PLHIV in Rio de Janeiro found an association between the hiding and disposal of medication and stigma [16]. Stigma has been associated with poor uptake of HIV testing [37], disengagement from care [38], poor disclosure [39] and poor adherence to ART [19,36], which together lead to poor treatment outcomes. In our study, we did not assess stigma using a standardized questionnaire, which may have resulted in under-reporting, with only a minority of patients indicating stigma as the reason for missing drug intake. However, previous studies from Tanzania found that stigmatization is prevalent in 14–58% of patients in our setting [40,41].

Although the failure to bring the pillbox to a clinical visit could provide an opportunity to identify patients with a higher risk of being LTFU at an early stage in comparable settings and thus improve retention in care and treatment outcome in the long run, the need for pillbox return could be a burden to patients fearing unplanned disclosure (e.g. during transport) and impede them from coming to the clinic. To address such aspects, counselling before initiation of ART and building a trusting relationship between patient and healthcare provider might prevent people becoming LTFU.

Factors previously reported from similar settings as associated with being LTFU and which we could confirm in our study were living further away from the clinic [7,42,43], younger age and WHO stage III/IV versus stage I/II [7,44]. The strength of association between failed

TABLE 3 Predictors of failed pillbox return

Characteristics	Multivariable OR (95% CI)[d] *N* = 2552 (Missing indicator used for missing covariates)	Multivariable OR (95% CI)[d] *N* = 2050 (No missing baseline covariate values)
Age (years)		
18–24	1.95 (1.60–2.37)	1.86 (1.49–2.31)
25–34	1.65 (1.46–1.87)	1.71 (1.49–1.97)
35–44	1.13 (1.01–1.27)	1.18 (1.04–1.35)
≥ 45	Reference	Reference
Gender		
Male	Reference	Reference
Female	0.61 (0.55–0.68)	0.62 (0.55–0.70)
Marital status		
Never married	Reference	Reference
Married/cohabiting	1.06 (0.87–1.29)	1.03 (0.83–1.28)
Separated/divorced/widowed	1.01 (0.83–1.24)	1.00 (0.81–1.25)
Disclosed HIV status		
No	Reference	Reference
Yes	1.01 (0.90–1.13)	1.02 (0.90–1.16)
Missing	0.74 (0.53–1.05)	
Partner HIV status		
Positive	Reference	Reference
Negative	1.04 (0.88–1.22)	1.12 (0.94–1.35)
Not tested/unknown	0.98 (0.86–1.11)	1.02 (0.88–1.17)
No partner	0.96 (0.83–1.11)	0.97 (0.82–1.14)
Missing	1.01 (0.85–1.26)	
Education		
None	Reference	Reference
Primary	1.09 (0.94–1.27)	1.10 (0.92–1.30)
Secondary and above	1.18 (0.94–1.47)	1.11 (0.87–1.42)
Distance from residence to clinic		
≤ 1 km	Reference	Reference
2 to < 50 km	0.86 (0.77–0.95)	0.77 (0.85–0.97)
≥ 50 km	0.75 (0.66–0.84)	0.75 (0.66–0.86)
Missing	0.78 (0.56–1.09)	
Tuberclosis status		
No	Reference	Reference
Yes	1.12 (0.96–1.30)	1.08 (0.93–1.26)
Missing	1.17 (0.95–1.1.51)	
Body mass index (kg/m^2)		
Underweight, < 18.5	0.94 (0.82–1.08)	0.92 (0.79–1.07)
Normal, 18.5 to < 25	Reference	Reference
Overweight, ≥ 25	1.08 (0.96–1.21)	1.03(0.90–1.17)
Missing	0.88 (0.61–1.27)	

TABLE 3 (Continued)

Characteristics	Multivariable OR (95% CI)[d] *N* = 2552 (Missing indicator used for missing covariates)	Multivariable OR (95% CI)[d] *N* = 2050 (No missing baseline covariate values)
WHO stage		
I	Reference	Reference
II	0.92 (0.80–1.06)	0.94 (0.81–1.09)
III	0.83 (0.73–0.94)	0.81 (0.71–0.93)
V	0.80 (0.68–0.97)	0.82 (0.67–0.99)
Missing	1.06 (0.83–1.34)	
CD4 count (cells/μL)		
< 100	Reference	Reference
100–349	1.00 (0.87–1.14)	1.04 (0.90–1.19)
≥ 350	1.25 (1.08–1.44)	1.30 (1.11–1.52)
Missing	1.16 (0.96–1.40)	
Initiated ART in KIULARCO		
No	Reference	Reference
Yes	0.95 (0.83–1.10)	0.95 (0.81–1.11)
Calendar year		
2013–2014	Reference	Reference
2015–2016	1.42 (1.28–1.59)	1.39 (1.24–1.57)
2017–2020	2.05 (1.82–2.32)	2.02 (1.76– 2.31)

[a]Odds ratios (OR) and 95% CI obtained from generalized estimating equations with the binomial distribution, logit link and exchangeable correlation structure.
[b]Adjusted for baseline covariates. All baseline covariates are time-independent except for failed pillbox return which is time-dependent, updated at each clinic visit

pillbox return and being LTFU was comparable to that for younger age. Other associations were of lower magnitude. Interventions tailored to reduce stigmatization and support young people to remain in care are urgently needed. A higher baseline HIV WHO stage in this and a previous study done in the same setting was associated with being LTFU, probably due to unreported deaths [7]. Others found a higher WHO stage to be associated with lower risk of being LTFU [45].

In our study, we did not find evidence of an association between pillbox return and VF. This could be attributed, in part, to only a subset of PLHIV with shorter follow-up being included after implementation of routine viral load testing. Further, by definition this analysis only included patients who were retained in care to have viral load measured, probably being a subset of patients with good adherence.

The main strengths of this study were the standardized data capturing system and the long-term data obtained in this cohort of PLHIV, offering a robust dataset for analysis in a representative rural sub-Saharan setting. Additionally, our results were robust to a number of sensitivity analyses. Our study has limitations. First, we were unable to know if those who were LTFU had died, been transferred to other HIV treatment centres without our knowledge, or had disengaged from care, although from previous studies in this cohort we suspect that a large proportion of these patients will have died [27]. Regardless, we observed similar associations between pillbox return and being LTFU compared with LTFU/death. Second, while we believe that our results are representative of similar rural settings, we cannot generalize results to other settings (e.g. urban environments or different socio-cultural backgrounds). Third, the association between failed pillbox return and VF could be evaluated among a relatively small number of patients remaining in care, as viral load cannot be measured in those LTFU, leading to possible overestimation of virological control. Furthermore, VF was defined as the first elevated viral load, in contrast to the WHO definition requiring two successive viral loads > 1000 copies/mL, measured at least 3 months apart while being on adherence-enhancing support [46]. This was due to the fact that routine viral load testing had only recently been implemented and adherence counselling with repeat viral load testing was not yet fully functional. Lastly, having adjusted for a number of potential confounders for

TABLE 4 Association between failed pillbox return and virological failure (VF)

	Cox model: VF	
	Univariable	**Multivariable**
Characteristics	**HR (95% CI)[a]**	**HR (95% CI)[a,b]**
Failed pillbox return ($N = 1873$)[c]		
No	Reference	Reference
Yes	1.10 (0.85–1.43)	1.11 (0.85–1.45)
Failed pillbox return among those who initiated ART in KIULARCO ($N = 1581$)[c,d]		
No	Reference	Reference
Yes	0.99 (0.73–1.33)	1.00 (0.74–1.35)
Failed pillbox return among those who initiated ART before enrolment in KIULARCO ($N = 292$)[c,d]		
No	Reference	Reference
Yes	1.64 (0.93–2.87)	1.65 (0.93–2.91)
Failed pillbox return (restricted to patients who initiated ART in KIULARCO; $N = 2118$)[c]		
No	Reference	Reference
Yes	0.99 (0.74–1.33)	0.99 (0.73–1.35)
Failed pillbox return (restricted to patients with no missing baseline covariate values; $N = 1515$)		
No	Reference	Reference
Yes	1.05 (0.77–1.44)	1.05 (0.76–1.45)

[a]Hazard ratios (HRs) and 95% confidence intervals (CIs) obtained from Cox models. Failed pillbox return is time-dependent, updated at each clinic visit.

[b]Adjusted for baseline covariates. All baseline covariates are time-independent.

[c]Missing indicator used for missing covariates.

[d]Incorporating an interaction between failed pillbox return and whether the patient initiated antiretroviral therapy (ART) in the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) (interaction $p = 0.12$).

the relationship between pillbox return and being LTFU, including demographics, clinical characteristics and measures of social support, such as disclosure of HIV status and partner's HIV status, we cannot exclude the possibility that residual confounding remains, for example socioeconomic status, which is not captured in KIULARCO.

CONCLUSIONS

To conclude, failed pillbox return was strongly associated with becoming LTFU from care. We recommend that failed pillbox return should be used to identify patients at higher risk of becoming LTFU and hence who require additional support to improve retention in care. We hypothesize that failed pillbox return is a proxy for stigmatization, which warrants further study.

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CONFLICT OF INTEREST

None of the authors reports any conflict of interest.

AUTHOR CONTRIBUTIONS

RCN designed the study and analytical plan and wrote the manuscript; JO carried out the statistical analysis and helped with the writing; AVK and JM performed data cleaning and reviewed the manuscript; ES enrolled participants into KIULARCO and contributed to manuscript writing; GF supported study development and evaluation of pillbox return; LS and HM contributed to the study planning and manuscript writing; SS contributed to study drafting and patient management; TRG supervised analysis and supported manuscript writing; MB and DP were involved in study design and manuscript writing; FV helped with the study design, supervised the statistical analysis and supported manuscript writing; MW designed the study and supervised the manuscript writing.

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