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ORIGINAL ARTICLE

ART EXPERIENCED PATIENTS FOR TACKLING ATTRITION FROM HIV CARE: A MULTI-SITE COHORT STUDY

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ABSTRACT

Introduction*: Retention of patients on anti-retroviral treatment in Ethiopia is a challenge. Use of anti-retroviral treatment experienced patients to prepare and re-engage them when they miss follow-ups is recommended, but evidence on its effectiveness is limited. This study evaluated its effectiveness.*

Methods*: A retrospective cohort study in 10 randomly selected health facilities was conducted to compare outcomes before and after initiation of the adherence supporters program in HIV care and treatment from September 2001 to August 2013. Data analysis involved Kaplan-Meier survival and Log-rank test analysis on STATA statistical software Version 12 to compare survival experiences.*

Results*: Of 18,835 records that were available, 938 (4.36%) records with missing values were excluded and data from the remaining 17,897 was analyzed. The incidence of first instance lost to follow-up was 22.2 per 100 person-years (95% confidence interval 21.7-22.7). The risk of missing follow-ups after initiation of the program was high (Hazard Ratio –1.22, P < 0.001). The incidence of restarting after missed follow-ups was 23 per 100 PY (95% CI 22.2-24.0). The likelihood of restarting after missed follow-ups was four times higher during the period adherence supporters were present (P<0.001). Patients who stayed longer in care before missing follow ups were more likely to restart (5.7 times the chance of restarting treatment for those whose first lost to follow-up occurred at≥12 months compared to <3 months, P< 0.001).Time to restarting treatment was shorter after the initiation of the adherence supporters program (median 37 vs. 115 days). The risk of recurrence of being lost to follow-up in the presence of adherence supporters was significantly higher than when there were no adherence supporters; 38.8 (95% CI 36.3-41.6) per 100 PY vs. 26.1 (95% CI 19.8-34.4) per 100 PY, respectively.*

Conclusion*: Adherence supporters were effective in improving re-engagement of patients in treatment and care after they were lost to follow-up. Yet, prevention of lost to follow-up cases has remained a challenge to the program.*

Key Words*: Adherence, adherence supporters, lost to follow-up, HIV, antiretroviral treatment*

INTRODUCTION

The HIV epidemic has affected millions and has left close to a million people currently living with the virus in Ethiopia (1,2). The country's response to HIV has shown remarkable results. The number of new infections has declined and mortality has gone down. Globally, the reduction in mortality goes as high as 65% in certain settings (3,4).

The success of antiretroviral therapy (ART) can be attributed to the increased access to the service by those who need it. There has been a massive increase in the number of people living with HIV/AIDS (PLHIV) who are taking ART (4). With 79% coverage of eligible patients (CD4<350 or WHO Stage III or IV), Ethiopia has put 492,649 patients on ART by the end of 2013. Of the 492,649 patients, only 344,344 are currently on ART, which shows a 30% difference. The difference was 23% four years earlier. (5,6) With increasing number of patients on ART, retention has continued to be an increasing challenge (7).

Ensuring adherence to treatment and care will be a major challenge for the health system if it continues to work exclusively. Involving PLHIV meaningfully in HIV services planning and delivery was found to be essential, and many PLHIV have been involved in the provision of support to fellow patients. A case in

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point is the involvement of ART experienced PLHIV in the provision of support to other patients in HIV care. The national program identifies these cadres as adherence supporters and they have been providing services for the previous six years before this evaluation.

Given the shortage of human resources for health (HRH) and with intention of ensuring greater and meaningful involvement of PLHIV in HIV care, the Federal HIV/AIDS Prevention and Control Office (FHAPCO) of Ethiopia approved the notion of involving ART experienced patients in the provision of adherence counseling, tracking and restarting patients who missed follow up (LTFU) and helping patients who have adherence/retention related challenges, as well as facilitating linkage of newly diagnosed HIV positive patients to HIV care (8).

The national adherence supporters program was launched in 2007 in the country. It was introduced in all regions within a few months' time in 2007. An implementation guideline with the details of the activities that are expected from the adherence supporters was issued by the Federal Ministry of Health (FMOH) (8). Supplementary documentation tools were developed including registration of patients who were LTFU and used to identify those who were LTFU and forms to track those who were LTFU. Though there have been some efforts to ascertain effectiveness of the program, this has not been fully and systematically assessed. This study has been conducted to fill this gap by collecting and analyzing data from ten randomly selected hospitals in four regions of Ethiopia.

METHODS

Study Setting: This is a retrospective, observational, longitudinal study that used existing records of patients in ten randomly selected hospitals located in four regions of Ethiopia, namely Addis Ababa, Benishangul Gumuz, Gambella, and Southern Nations Nationalities and Peoples (SNNP) Region. These regions were selected because of their use of patient monitoring electronic data management tool which was similar across these regions.

The adherence supporters program was initiated in April 2007 and is still being implemented. Adherence supporters were selected using criteria which were approved by FHAPCO and all were trained using a standard material from the same source (8). Those who managed to complete the training were labeled as "adherence supporters" and were deployed to facilities. The program was started in all hospitals providing antiretroviral therapy in 2007. The number of adherence supporters per facility varied depending on patient load; the assignment used one adherence supporter for 800 patients on HIV care as a standard.

Study Population: The study population included patients taking ART in public and non-governmental (NGO) hospitals in the selected regions. Of the 36 hospitals in these regions, ten were randomly selected using a lottery method. All patients enrolled in HIV care and treatment program started on ART from September 2001 to August 2013 were included in the study. Patients who were transferred from other facilities and enrolled in the selected hospitals for continuation of ART were excluded.

Variables and Source of Data: There were two outcome variables. The first was 'lost to follow-up' which is defined as not present for more than one month since the last appointment date for ART medication refill. The second outcome was 'restarting treatment'; this is whenever patients who missed follow-ups restart ART after having been labeled as "lost to follow-up". The presence of adherence supporters was the primary exposure variable. Other explanatory variables to potentially affect the outcome included age, gender, baseline World Health Organization (WHO) staging, baseline CD4 cell count, and time to first loss of follow-up were extracted from existing records.

Data Analysis: Epi Info statistical software Version 3.4 and MS Access 2007 were used to clean the data. Descriptive analysis and survival analysis were carried out using STATA statistical software Version 12. Log-rank test was used to compare survival experiences. Patients were uncensored at the first episode of loss to follow-up. Those who stopped treatment after medical consultation and those who were transferred to another facility were censored. Patients who were enrolled and started on ART before 2007 did so before the adherence supporters were deployed and hence formed a historical control group. These patients were censored on July 31, 2007 if they were actively on follow-up until that time.

For patients who started treatment after October 1 2007, adherence supporters were available to provide additional counseling as well as patient tracking; hence they formed the exposure group. These groups of patients were censored on the last day of follow-up at the end of 2013 if they remained in follow-up

in their respective facilities. Because of some lack of uniformity in the deployment of adherence supporters which took sometimes before they were fully functional, patients enrolled in that adjustment period between August and September 2007 were excluded from the analysis. Potential within-site correlation of patient characteristics was controlled by stratification using site unique identity (ID) numbers as cluster identifier. Records having at least one missing variable were excluded from analysis.

Ethics Consideration: Ethics approval for the study was obtained from the National Research Ethics Review Committee (NRERC) of Ethiopia. Patients' consent forms were not required since existing de-identified and de-linked data was used before acquisition and during analysis.

RESULTS

Baseline Characteristics: There were 18,835 records (excluding patients who were transferred in) out of which some had variables with missing values. After excluding all records with at least one missing variable, there were 17,897 records (95%). Overall, patients were observed for a minimum of one day, and a maximum of 6.1 years. The median time of follow-up was 1.25 years.

The median age (interquartile range (IQ)) was 34 (28, 40), and the minimum, and maximum ages 3 months and 86 years respectively. Pediatric patients below 15 years of age were 2% while the majority (90%) was between ages 15 and 49 years. Females accounted for 54%. Patients with WHO stage III or IV constituted 67%, while those with baseline CD4 cell count of less than 200 cells/mm^3 were 78%. In the period where adherence supporters were present, there were 10,265 patients accounting for 57% (Table 1).

Prevalence and Incidence of Loss to Follow-up: Thirty seven percent of patients (n=6,595) were LTFU at least once. Patients were followed for a total period of 29,696 person-years. This makes the incidence of LTFU 22 per 100 person-years of follow-up (95% CI:21.7-22.7).

Predictors of LTFU: Figure 1 shows the survival experience of patients with respect to presence or

Table 1. Baseline characteristics of patients on ART (N=17,897), 2001-2013, Ethiopia

Variable	Category	Total (Column %)	Adherence supporters	
			Present	Not present
			Number (row %)	Number (row %)
Age	<15	269 (2)	248 (92)	21 (8)
	15-49	16138 (90)	9241 (57)	6897 (43)
	>49	1490 (8)	776 (52)	714 (48)
Sex	Female	9722 (54)	5970 (61)	3752 (39)
	Male	8175 (46)	4295 (53)	3880 (47)
Baseline WHO Stage	I or II	5967 (33)	4431 (74)	1536 (26)
	III or IV	11930 (67)	5834 (49)	6096 (51)
Baseline CD4 Cell Count/mm3	<200	13907 (78)	7038 (51)	6869 (49)
	200-349	3496 (19)	2819 (81)	677 (19)
	>349	494 (3)	408 (83)	86 (17)
Ever lost to follow-up?	No	11302 (63)	6054 (54)	5249 (46)
	Yes	6595 (37)	4211 (64)	2383 (36)

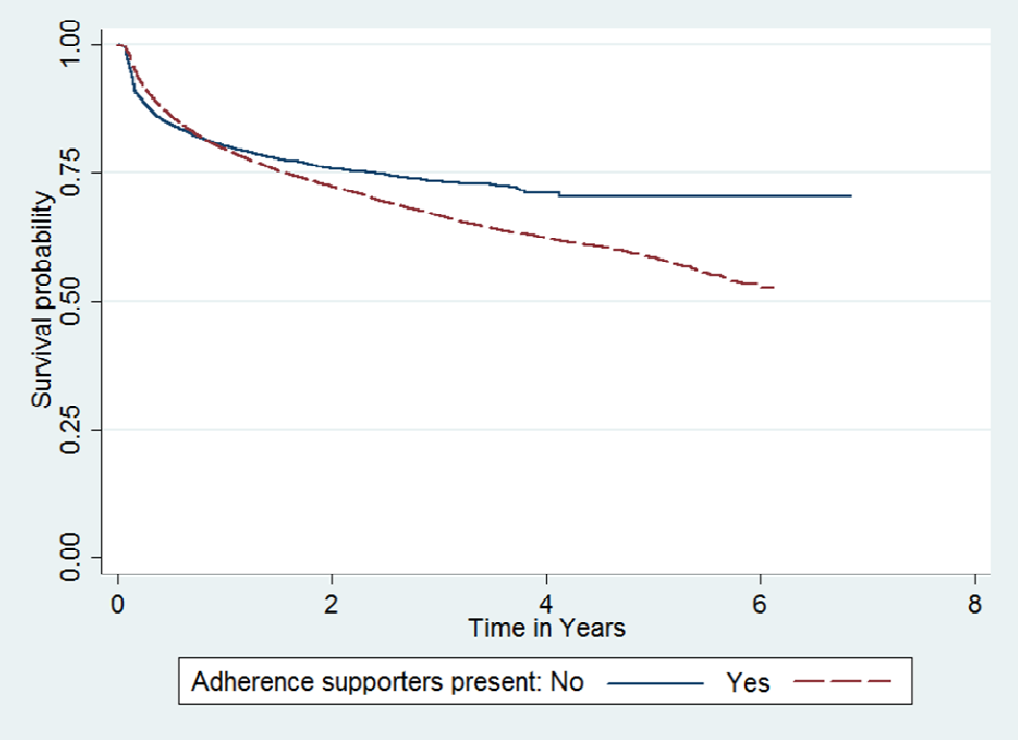

Figure 1: Kaplan Meier Survival for being lost to follow-up among patient on ART, 2001-2013, Ethiopia

It can be seen that, in general, LTFU was greater for both cases (with or without adherence supporters) in the first year of follow-up. Patients continued to be LTFU after that period, but the rate was much slower, a drop in survival of less than 10% per year as compared to 30% for the first year. The overlap between the two curves in the first year of follow-up indicates that the probability of remaining in care was comparable for the two groups during the early years of ART program initiation when adherence supporters were non-existent. After that period, patients enrolled in the presence of adherence supporters were less likely to remain in care. Table 2 below summarizes the effect of all variables on the hazard of being LTFU.

During the period that adherence supporters were present, the relative hazard of becoming LTFU increased by 22%. Being male and being in WHO stage III or IV were also associated with increased relative hazard of being lost to follow-up (p value <0.05). Age was another predictor but was significant only at the 0.1 level. Adult patients were at an increased relative hazard of being LTFU as compared to pediatric patients. No association was found between LTFU and CD4 cell count category.

Prevalence and incidence of restarting treatment after first LTFU: Among patients LTFU (n=6,595), 2,221 (34%) patients restarted treatment (Table 3).

LTFU patients were followed for a total time of 9,617 person-years until last observation. The incidence of restarting treatment was 23 per 100 person-years (95% CI: 22.2-24.0). Overall, final status was known for 3,568 (54%) of the patients LTFU. Of these, 1,347 (38%) patients had died. During the time adherence supporters were present, the proportion of patients LTFU with unknown status at the time of censoring was lower compared to the period they were not present, 37% vs 62% (p value <0.001). Time to restarting treatment was shorter after initiation of the adherence supporters program, median 37 vs 115 days (p value <0.001). The risk of recurrence of being lost to follow-up while with availability of adherence supporters was significantly higher than when there were no adherence supporters, 38.8 (95% CI 36.3-41.6) per 100 PY vs 26.1 (95% CI 19.8-34.4) per 100 PY.

Predictors of restarting treatment among those LTFU: Table 4 summarizes factors affecting the restarting of treatment among those who were LTFU.

Table 2. Predictors for being lost to follow-up of patients on ART after the first six months (n= 12,123) 2001-2013, Ethiopia

Variable	Category	Hazard ratio, Crude*	P value	Hazard ratio*, adj	P value
Age	<15	1	0.0735	1	0.059
	15-49	1.38		1.38	
	>49	1.39		1.41	
Sex	Female	1	0.0012	1	0.0001
	Male	1.13		1.16	
Baseline WHO Stage	I or II	1	<0.0001	1	<0.0001
	III or IV	1.18		1.20	
Baseline CD4 Cell Count/mm^3	<200	1	0.5532		
	200-349	1.05			
	>349	1.00			
Adherence supporters present?	No	1	<0.0001	1	<0.0001
	Yes	1.22		1.23	

* Stratified by site

Table 3. Tracing outcome of patients lost to follow-up from ART (first loss only), 2001-2013, Ethiopia

	Total First LTFU	Number Dead (%)	Number Restarted (%)	Number Still lost at the end of observation (%)
No	2383	687 (29)	215 (9)	1481 (62)
Yes	4212	660 (16)	2006 (47)	1546 (37)
Total	6595	1347 (20)	2221 (34)	3027 (46)

Table 4. Predictors for restarting treatment for patients lost to follow-up from ART, 2001-2013, Ethiopia (n=6,595)

Variable	Category	Hazard ratio, crude	P value	Hazard ratio, adj	P value
Baseline WHO Stage	I or II	1	<0.0001	1	0.0015
	III or IV	0.61		0.87	
Baseline CD4 Cell Count/mm^3	<200	1	<0.0001	1	<0.0001
	≥200	1.75		1.35	
Time to 1stLTFU	<3 months	1	<0.0001	1	<0.0001
	3-5 months	1.81		1.44	
	6-8 months	2.23		1.67	
	9-11 months	3.04		2.26	
	>=12 months	4.44		2.88	
Adherence supporters	Present	1	<0.0001	1	
	Not present	5.17		2.84	<0.0001

Those who died were excluded from the analysis. It can be seen that, all variables had an association with resumption of treatment by patients. The relative likelihood of restating treatment among those LTFU during the period adherence supporters were present was three times as high as that of patients seen when adherence supporters were not present (Figure 2).

During the time adherence supporters were present, restarting treatment was much better. Most restarted treatment in the first year after being lost to follow-up. This levels of in later years.

In addition, being in the pediatric age group (< 15 years), being female, having a WHO stage I or II disease and having a higher baseline CD4 cell count category were all associated with a higher relative chance of restarting treatment (p value <0.05). Also, restarting treatment was more likely if treatment was discontinued much later during follow-up than soon after ART initiation (Figure 3).

Those who missed follow-ups early after starting antiretroviral therapy were less likely to restart as compared to those who became lost later during follow-up. Those confirmed to have died were excluded from the analysis.

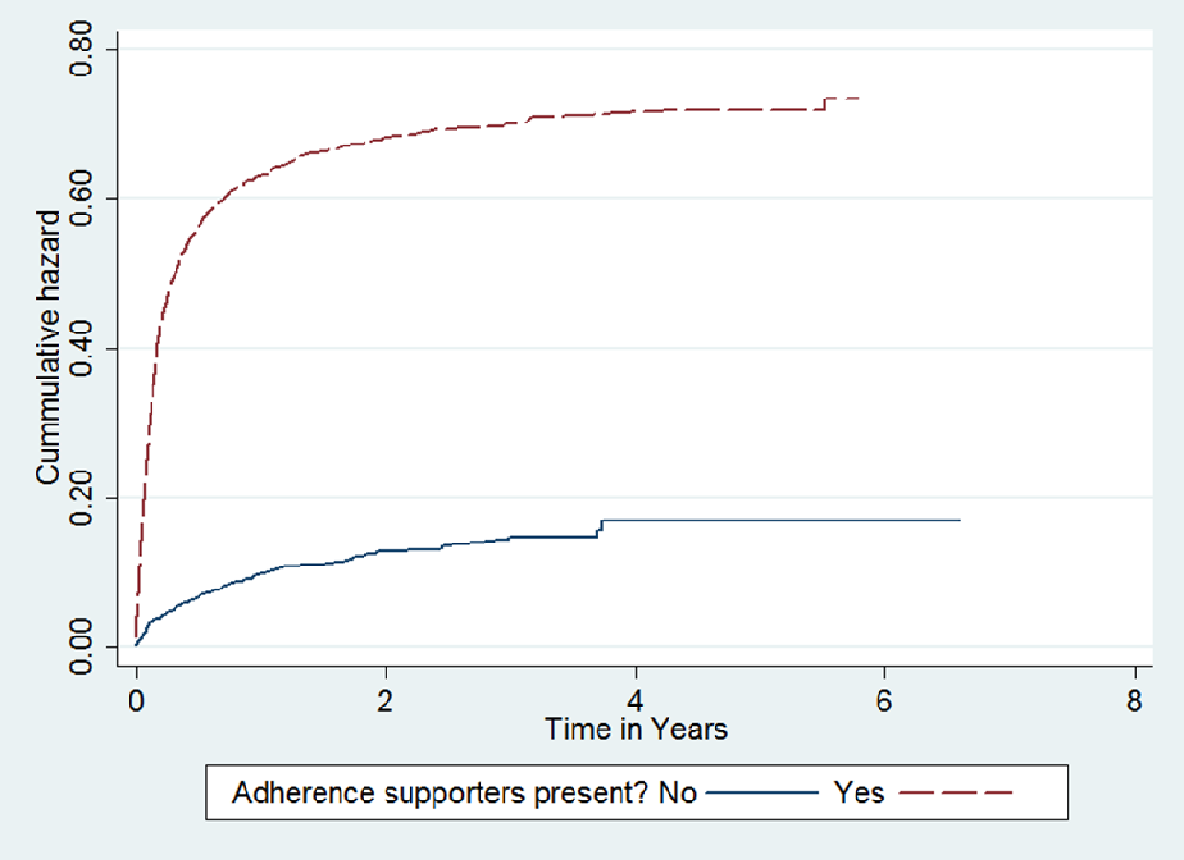

Figure 2. Cumulative hazard for restarting treatment among patients lost to Follow-up from ART by presence of adherence supporters, 2001-2013. Ethiopia.

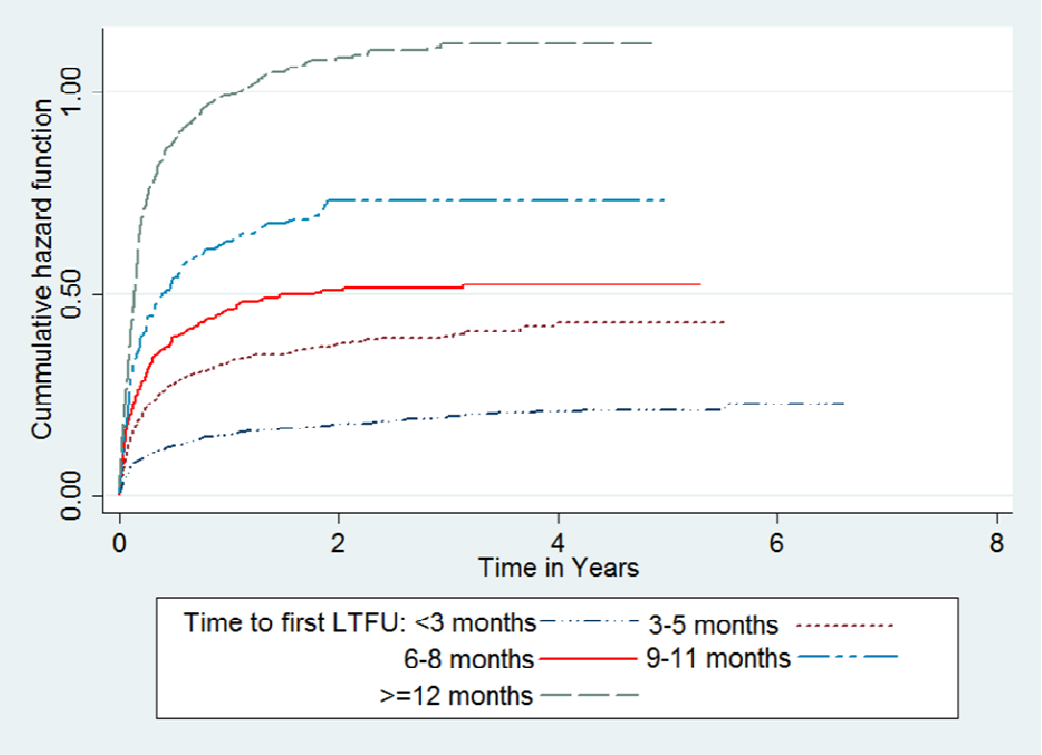

Figure 3: Cumulative hazard for restarting treatment among patients lost to follow-up by time to first LTFU, 2001-2013.

DISCUSSION

Over one-third of the patients started who were on ART were LTFU at least once during the follow-up. The peer support program was effective in improving re-engagement, but it did not reduce the magnitude of those absent for the first time. It also improved the proportion of patients whose final status was known.
A number of studies have reported on the level of treatment discontinuation ranging between 20% and 30% (9-12), which is less than what is identified in this study of 37%. The reason for the difference is that the present study assessed the proportion of those who discontinued treatment for at least one month any time during follow-up while previous studies reported on final follow-up status at the time of study.

A study in Tanzania that used a definition for LTFU similar to our study found that LTFU was 8% among 12,000 followed-up patients (13). The proportion of LTFU in the Tanzanian study was much smaller because patients were followed up for only six months. The study also revealed that peer supporters were able to re-engage 38% of those LTFU which is similar to the finding in the present study. A good number of patients could not be restarted because some had died and others were not traceable due to wrong addresses or reside far away the city where treatment is provided. In some cases patients change treatment centers without prior notice to health care providers or even started traditional treatment (9, 13).

The first year after initiation of ART was when most patients were LTFU. This is the time when most treatment related side effects occur, in addition to the occurrence of opportunistic infections and immune reconstitution inflammatory syndrome (IRIS) and a good proportion of the patients die. These factors add to existing barriers for adherence such as problems in access, lack of family or social support and stigma (14). Treatment supporters were not able to prevent LTFU in our series.

In fact, the occurrence of being LTFU was worse when adherence supporters were present. This may partly be explained by the improvement in documentation of patients' final status as the adherence sup-

porters used documentation tools and actively looked out for patients who were LTFU. This may also be due to problems in the continuum of care with respect to access for quality ART services, and use of tools to guide counseling. As with other chronic illnesses, patients may also discontinue treatment whenever they feel better. HIV/AIDS is also progressively becoming less stigmatizing and as patients learn that it is manageable they become reluctant to adhere to treatment plan (15).

The increase in the absolute number of patients LTFU could very well be a reflection of facts stated above. These facts may also make it more difficult to prevent LTFU than in the earlier period when ART was initially being rolled out. Moreover the work burden on care providers is ever increasing because of the rising number of PLHIV placed in care and treatment program. Children, female patients, patients with less advanced disease, and those being LTFU after three months of follow-up were more likely to restart treatment. This is in line with the earlier observation indicating that people are more vulnerable to illness and side effects in the early months after treatment initiation and are more likely to discontinue treatment.

This study has several implications for clinical practice and policy. With the current level of implementation despite the gains made, a significant proportion of clients remain LTFU. That implies additional early tracing options need to be sought especially for those residing far away from treatment facilities. This could be in the form of engaging health extension workers or other community agents in tracing activities, which calls for a more robust referral networking system involving health posts, the lowest health units. Continuing to reduce patient load in big treatment centers, mostly hospitals, by offloading stable patients to health centers not only decrease the burden of work on care providers, but also reduce the time required by patients to travel and better access care and treatment (9,16).

The present study also indicates that it is important to focus counseling and tracing efforts in the first few months after starting treatment when most of patients will become LTFU. Particular attention should be directed towards the most vulnerable which may include the very sick, those lacking social support, and those coming from remote areas. The adherence supporter to patient ratio may also need revision as the current ratio of 1:800 is low taking into consideration the burden of counseling needs. Healthier clients are starting treatment according to the revised ART treatment guidelines (CD4≤500) which may make it harder to convince individuals about the benefits of sustained treatment and treatment adherence, adding to existing challenges (17). A customized adherence protocol focusing on patients who start ART at higher CD4 levels is required. Strengthening the involvement of adherence supporters in multi-disciplinary teams supplemented by structured guide (cue cards) is also essential.

The fact that this was a multicenter study involving a large cohort of clients in four regions of Ethiopia spanning over a decade of follow-up, makes the findings very informative. Yet, because of lack of primary data, this is an over simplified description that does not show much of the effort put to address LTFU, including the effort by adherence supporters and the multi-disciplinary ART team in adherence preparation, and ongoing counseling for those with poor treatment adherence. The adherence counselor-patient ratio was also very low at around 1:800.

Therefore, data on which clients actually received support from the counselors would have provided further opportunity to identify their roles in preventing patient loss and re-engaging those lost to follow-up.

A separate study specifically designed to look at the detailed activities of adherence supporter program is highly needed. Lastly, the interpretations of findings must be made carefully since all limitations that apply to the use of historical controls apply in this study. Also, the fact that the study spans over a long period means that progressive changes in quality of care may influence study outcomes.

Conclusions: Adherence supporters were effective in improving re-engagement, but preventing LTFU remains a challenge.

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