Time to Attrition and Factors Associated among Adults enrolled in Pre-Anti- Retroviral Therapy Care in Tepi General Hospital, Ethiopia

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***Abstract*- Pre-antiretroviral therapy (Pre-ART) patient attrition is a growing concern in Ethiopia. Nevertheless, there is little information that assesses the magnitude and its related factors. This study assessed time to attrition and factors associated among adults enrolled in pre ART care at Tepi General Hospital in South West Ethiopia. Records of adult pre-ART patients enrolled at Tepi General Hospital from October 2010 to September 2013 were reviewed to find factors linked with time to attrition. We defined time to attrition as the period a patient was enrolled in pre-ART service till attrition. We Used Kaplan Meir curve to estimate survival time, and log-rank test to compare the time to attrition among different categories of patients. We used Cox hazard model to assess factors related with time to attrition. We followed 652 pre-ART patients for 337.6 person years of follow-up from start up to pre-ART outcomes. Of these, 179 patients were lost to follow up and 37 patients died, contributing to an overall attrition of 33.13%. During the early six months the attrition rate was 89.8%. Not starting cotrimoxazole prophylaxis (AHR=1.51, 95% CI, 1.02-2.25), being co-infected with tuberculosis (TB) (AHR=2.16, 95%CI, 1.35-3.45), living further than 10 km away from the hospital (AHR=1.44, 95%CI, 1.07-2.0), and not disclosed status of HIV(AHR=3.04) were factors significantly associated with time to attrition.**

Pre-ART patient attrition rate was high among clients not using cotrimoxazole prophylaxis, TB/HIV co-infected, living > 10 km from a health care facility and with undisclosed HIV status. Close follow-up of clients during the early months' follow-up period is greatly recommended.

Keywords: **Attrition, Death, Ethiopia, Loss to follow-ups**

I. INTRODUCTION

Globally 36.7 million mankind were living with HIV towards the end of the year 2015, of which 46% had started antiretroviral (ART) [1,2]. Greater than 60% of the worldwide cases were situated in Africa [1, 3-5]. In settings with limited resource and much disease load not entire clients who come at earlier period of their infection are qualified for antiretroviral [6,7]. Even when being qualified for ART, starting treatment early will rest on a number of factors [3, 7, 8]. Distance to healthcare facility, social stigma, being in a less advanced disease stage, feeling healthy, occupation, and level of literacy were factors that contributed to present late for ART care [4, 9-12]. It is likely in settings with limited resources and high disease burden, some patients will attrite before they are started on ART [3,4]). In sub Saharan part of Africa below one third of clients stay on care continuum between testing sero -positive for HIV and initiating ART [13].

Attrition from pre-ART in sub Saharan part of Africa has been inadequately explained leaving foremost research area, particularly concerning long lasting retention rates and socio demographic, economic, clinical and programmatic logistic determinants [6], it has only recently began to be documented in literatures [13]. Ethiopian ART hospitals are facing challenges of pre-ART attritions due to significant number in loss to follow up and death [3,7, 13,14, 16].

Significant pre-antiretroviral attrition is an alarm for inadequate uptake of interventions. Previously, strategies and resources to address attritions have focused on the ART period but, Pre-ART attrition given lesser attention [16-20].

At Tepi General Hospital, the annual HIV progress report showed that significant amount of patients who test sero-positive failed to start pre-ART and linked to pre-ART were undergoing attrition in the course of the pre-ART care continuum before ART initiation [21].

Knowing when and why attrition occurs in Ethiopia could be useful to develop pertinent intervention strategies against pre-ART patient attritions. We aimed to assess attrition times and related factors before ART initiation among adult pre-antiretroviral patients in Tepi General Hospital, South West Ethiopia.

II. METHODS

Study design, Setting and population

A retrospective cohort study was conducted among all 652 adult HIV positive clients ≥ 15 years old enrolled into Pre-ART care from October 2010 to September 2013 in Tepi General Hospital, South West Ethiopia, which is located at approximately 610 kilometers [15] from the capital, Addis Ababa. Pre- antiretroviral and ART facilities were started in the

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study area during 2006. Other services to include counseling and testing initiated by the provider (PICT), voluntarily counseling and testing (VCT), prevention of mother-to-child transmission (PMTCT), and condom advertising are delivered inherently. According to WHO and Ethiopian Health Ministry guidelines [8, 24], patients who test positive should be linked to pre ART care on the same day of testing. Linked patients are uninterruptedly followed on pre ART care till they are qualified to start HIV treatment (ART). CD4 of linked patients' is measured as early as possible, in the exact time of testing.

Operational definitions

We defined time to attrition (event) as time between enrollment and lost to follow-up or death. Lost to follow-up was defined as when patients miss their appointments 90 days after the last schedule. Death was considered as the death of patients on pre-ART during the course of follow-up period due to any cause. Clients who are on active care on pre-ART or transferred to other facilities were recorded as censored. Transfer out is considered when there is an official patient transferring to other ART center within or out of the service catchment [12].

Those patients' linked to another health facility, on active pre ART follow-up and treatments initiated were taken as censored cases when the observation period ends.

Clients who started antiretroviral, linked to another facility or active by the completion of follow-up period were considered censored.

Data Source and assessment of attrition

Tepi General Hospital patient information is recorded and kept confidentially both in hard copies and electronic formats. Except for those in medical urgency and long-lasting management, Pre-ART patients are prearranged for re-visit and follow up at every three months. Information related to patient is taken by trained adherence followers and client managers. Patient related data coding, entry and analysis is done by trained data clerks.

Sample size

Ever enrolled pre-ART patients since the start of service during 2006 were 2215 up to time of data collection. There were 652 adult sero-positive clients enrolled into pre-antiretroviral care in Tepi General Hospital from October 2010 to September 2013 and all of them were included in this study.

Variables and measurements

The major outcome variable of pre-ART care was time to attrition. Age, sex, religion and residence were among the demographic information's recorded for each patient. Baseline WHO patient staging, number of CD4 counts, Cotrimoxazole (CPT) provision, opportunistic infections, baseline functionality of the client, TB status, BMI, kind of patient linkage system and availability of ART facility within 10km distance were also measured.

Data collection

Electronic files of patients enrolled to pre ART care between October, 2010 and September, 2013 were reviewed to identify those who failed to keep scheduled appointments for more than 90 days. A list of these "LTFUs" patients was generated from medical register by observing the last appointment date.

We extracted data from both electronic data file and standard registration log books using checklist developed from WHO and national treatment guideline for pre ART care [11, 33].

Data analysis and interpretation

Data were entered to EpiData 3.1, cleaned and SPSS 20 was used for analysis. First, descriptive analysis was done, followed by bivariate analysis. Those variables in the binary cox regression analysis with P –value < 0.25 were included in the final regression model. Using back ward variable entry method the final Cox model was fitted. Attrition, mortality, and lost to follow-up rates were determined by summing-up the number of clients' who encountered the event (attrition) for the duration of a particular time divided by the overall number of years of follow up period. Attrition practices of pre ART clients separated by significant explanatory variables at linkage were compared by using Kaplan-Meier survival table. Model assumption checking was done by using log-log survival curvatures depending on Schoenfeld' s residuals. We calculated incidence density for mortality and LTFUs using person years of contribution to the cohort.

III. RESULTS

Patient characteristics

We identified an over-all of 711 clients enrolled into pre-ART care for the duration of the study period. Among these, 652 qualified for this study as per the inclusion criteria. Virtually all the remaining Pre-ART patients (n=59) were excluded from the study due to being from neighboring province (Gambella) and being children.

The mean age of participants was 30.59 (SD, 9.8) years and 59.4% were females. From the total study participants, 58.0% were married, 34.4% of the clients had dependent children below 15 years, 39.3% had primary level education, and 67.2% were orthodox Christians. More than half (50.8%)were from the rural communities and 34.4% were Amhara by their ethnicity.

From the entire of 652 study participants enrolled to pre-ART care, about two third (65.6%) were linked to care with baseline CD4 count >350 cells/ml and 59.0% were early stage presenters.

The majority (99.8%) of patients were screened for TB, of which 17% were positive.

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Among79.9% of patients with history of as a minimum of one typical opportunistic diseases during presentation to care, 55.2 % had been started with cotrimoxazole prophylaxis.
Related to participants' body-mass-index (BMI), 36.3% were underweight (BMI <=18.5), 60.1% were normal (BMI=18.5<BMI<24.9) and 0.9% were overweight.

Of all the patients, 92.6% were at working conditions and 3.8% were ambulatory and 3.2% were bedridden. With regard to distance from the hospital, 68.1% were located within 10km. With regard to HIV status disclosure, 40.8% had not disclosed at all for any one (Table1).

TABLE 1 BASELINE SELECTED SOCIO-DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF 652 ADULT PRE-ART PATIENTS ENROLLED TO PRE ART CARE AT TEPI GENERAL HOSPITAL, SHEKA ZONE, SOUTH WEST ETHIOPIA, DURING 2010-2013

Selected Variables		N (%)
Age (in years) (n=650)	15-24	161(24.5)
	25-34	296 (45.5)
	35-44	124 (19.1)
	44+	69 (10.6)
Sex	Male	265 (40.6)
	Female	387 (59.4)
Occupation (n=650)	employed	174 ((26.7)
	Unemployed	280 (43.1)
	Merchants	160 (24.5)
	Other	35 (5.4)
Educational status (n=651)	No education	112 (17.2)
	Primary	254 ((39.0)
	Secondary	149(22.9)
	Tertiary and above	136(20.9)
Religion (n=649)	Orthodox	428(67.5)
	Muslim	104(16.0)
	Protestant	88(13.6)
	Other	19(3.0)
CPT provision at enrolment	Yes	360 (55.2)
Service available within≤10km	yes	444 (68.1)
WHO clinical staging	Early stage presenters	385 (59.0%)
	Late stage presenters	267 (41.0%)
Disclosure status (n=250)	Family members	349 (53.7)
	To other relatives	36 (5.5%)
	Not at all	265 (40.8%)

*** Pre-ART; pre-Antiretroviral Therapy), CPT; Cotrimoxazole prophylaxis Therapy,*

Patient attrition during follow-up time

We followed up all of 652 clients for median period of 8.9 (IQR, 4.57-13.23) months in pre ART care from 2010 to 2013 for 337.6 Person Years of Observation (PYO) for an overall attrition rate of 33.13%. The minimum and maximum follow up time was 2 and 1080 days (36 months) respectively. From the overall attritions (31.13%), the highest attritions (89.8%) occurred within 6 months' follow-up period and increased to (93.98%) by the completion of 1year of observation period (Table 2).

Toward the end of follow up time, of the total patients who were registered to pre- ART care 22 (3.4%) were linked to other facility,282 (43.3%) had initiated treatment, 179 (27.5%) were lost to follow up, 37 (5.7%) died and 132 (20.2%) were being active on pre-ART care. Overall patient attrition was 33.13%.

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The incidence rates of attrition from pre-ART care at 1, 2and 3years of observation were 19, 24 and 21 cases per 100 PYOs respectively. The mean estimate of attrition time for patients who were put on cotrimoxazole therapy (CPT) at pre-ART care during enrolment was 25.43 (95% CI, 22.80-28.06) months.

TABLE 2 THE ESTIMATED ATTRITIONS OF ADULT PRE-ART PATIENTS AT THE END OF 3, 6, 12, 24 AND 36 MONTH'S OBSERVATION PERIODS AT TEPI GENERAL HOSPITAL, SOUTH WEST ETHIOPIA, DURING 2010-2013

Observation period in months	Attrition		Total	Cumulative attritions	Cumulative attritions in %
	LTFUs	death			
At 3	137	16	153	153	70.83
At 6	30	11	41	194	89.8
At 12	5	4	9	203	93.98
At 24	7	5	12	215	99.54
At 36	0	1	1	216	100
Total	179	37	216		

For patients who were not started on CPT it was 13.94 (95% CI, 12.06-15.83) months. The observed difference in attrition time between these two groups of patients showed statistical significant association ($P < 0.001$).

Similarly, the mean estimate of attrition time for clients who did disclose their HIV-sero status to their intimate families was27.07 (95% CI, 24.82-29.33) months whereas for patients who didn't disclose their sero status at all to any one during enrolment to care was, 10.83(95% CI, 8.94-12.72) months. The difference in attrition time between different categories of disclosure status was also found significant (P <0.001).

At enrolment, the aggregate shares of clients on retained were greater for clients who were on CPT, did disclose their sero status for their families, were negative for TB and lived with-in 10 kilo meter from the general hospital when we compared to their counter parts **(Table 3)**.

TABLE 3 COMPARISONS OF PRE ART CLIENT ATTRITIONS SEGREGATED BY CPT STATUS AND HIV DISCLOSURE STATUS AT ENROLMENT, KAPLAN MEIR TABLE

Baseline variable	Time in month	Status	Cumulative proportion surviving at time T	N of cumulative attritions	N of remaining cases
CPT provision					
Yes	at 3 month	attrition	0.90	36	324
	at 6 month	attrition	0.82	46	104
No	at 3 month	attrition	0.60	117	175
	at 6 month	attrition	0.46	148	104
Disclosure					
Family	at 3 month	attrition	0.92	28	321
	at 6 month	attrition	0.86	37	120
Not at all	at 3 month	attrition	0.56	117	148
	at 6 month	attrition	0.40	145	71

CPT, cotrimoxazole prophylaxis

Attrition predictors attributable to lost follow-up and death in pre ART

The following explanatory variables with p-values <0.25 were included into multivariate Cox Regression model depending on the bivariate Cox analysis. Baseline functionality of the client, CPT, service availability, CD4 category, TB screening result, opportunistic infections, dependent children in the home and HIV sero- status disclosure. Of these, CPT at enrolment, positive TB screening result, distance from the ART clinic and HIV status disclosure were independent predictors of time to attrition (**Table 4).**

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TABLE 3 BIVARIATE AND MULTIVARIATE COX REGRESSION FINDINGS AT TEPI GENERAL HOSPITAL, SHEKA ZONE, SOUTH WEST ETHIOPIA, DURING 2010-2013

Variables		Crude HR	95%CI	p-value	AHR	95.0%CI AHR
CPT at enrolment						
	CPT provided **				**1.0**	
CPT not provided		2.28	1.67-3.14	0.000	**1.51**	**1.02--2.25**
Baseline function						
	Working**				**1.0**	
	Ambulatory	0.69	0.33-1.47	0.337	0.73	0.33-1.62
	Bedridden	2.04	1.14-3.67	0.016	1.68	0.91-3.12
CD4 category	**<350****				**1.0**	
>=350		2.23	1.41-3.54	0.001	1.45	0.87-2.42
Disclosure status						
	To Family members**				**1.0**	
	To other relatives	2.00	1.09-3.67	0.025	1.60	0.86-3.00
	No disclosure at all	4.05	2.86-5.72	0.000	**3.04**	**2.07-4.45**
TB result	positive	1.30	0.84-2.00	0.238	**2.16**	**1.35-3.45**
	negative**				**1.0**	
Service availability	**Within <10km****				**1.0**	
>=10km		2.05	1.57-2.68	0.000	**1.44**	**1.07-2.0**
OI category						
No OI at all**					**1.0**	
	At minimum of one OI	1.60	1.19-2.16	0.002	1.13	0.75-1.71
	>=2 OI	1.19	0.82-1.74	0.354	0.83	0.59-1.17
Dependent children	Yes	1.20	0.90-1.61	0.214	1.20	0.89-1.62
No **					**1.0**	

***Reference category CPT cotrimoxazole prophylaxis, AHR, adjusted Hazard Ratio, CI Confidence Interval*

IV. DISCUSSION

Nowadays, the need to focus on attaining United Nation's target (90-90-90) on HIV/AIDS (diagnosing 90% of people who are HIV infected, putting 90% of diagnosed people on antiretroviral treatment and virally suppressing 90% of those who receive antiretroviral as of 2020), will be emphasized by retaining patients both on pre ART and antiretroviral care [5,7,19,25,24]. This study assessed attrition of pre ART clients and predicting factors in Tepi General Hospital. In this study, the rate of attrition in pre-ART care was one in every third patients. This finding is higher [19, 27, 28] compared to different settings. This could be due to differences in the choice study designs, patient follow-ups and definitions of LTFU. Unlike to this study, that defines pre ART clients as all non-repeatedly enrolled HIV/AIDS clients irrespective of their medical staging and CD4 cells count, studies done in different backgrounds [18,26,29] focused on pre ART patients with an advanced disease stage and low CD4 cell counts.

The occurrence of pre ART attrition was the uppermost in the earlier periods of the study. Approximately 94% of attrition happened during the 1st years' and overall attritions occurred by the completion of the two-year observation period. This is

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greater by 6% when we compare to finding as of Nigeria which indicated that 88% of attritions happened in the 1st year and overall deaths happened in the 1st 6 (six) months of pre ART care-continuum [13]. This difference can be explained from poor patient monitoring and tracing of default patients that occurred during the earlier times of pre-ART care-continuum [7, 13, 17]. Thus enhancing retention strategies like community based antiretroviral distribution and home based nursing interventions are highly recommended [41].

Over three-quarter of pre- ART patients (83.8%) who didn't start cotrimoxazole at linkage experienced attrition when compared to about sixteen (16%) attrition reported among those who did start cotrimoxazole at linkage point. The time to attrition for patients on CPT at pre-ART care enrolment was nearly 2-fold higher than those clients who were not on CPT. Furthermore, the patients on CPT had over 35% reduction in the possibility of attrition at six month and increased retention time when adjusting for the other predicting factors when compared to those who didn't start cotrimoxazole at linkage; and the observed difference was significant. In other investigation from Kenya, treating of ART unqualified clients with cotrimoxazole improved the 12-month retaining in care from 63% to 84%; this can suggest that clients might possibly perceive more advantage from cotrimoxazole treatment. This figures indicate that providing of free medications can increase the helpfulness insight of the clinic visits to the facility and, consequently, the retaining of clients in pre ART service [7, 13, 30, 31].

In this finding, HIV sero-status disclosure showed significant association with time till attrition across pre ART clients. Compared to those clients who did disclose their HIV sero-status to their families, those who didn't disclose it to any person had an approximately three times greater risk of attrition. In one other study, disclosure-status didn't show a significant association [37] and this can be due explained from differences in methodological variations. But, other study conducted in Ethiopia showed that HIV patients encounter both discriminatory marginalization and isolation from community, which in advance disappoints disclosing of their HIV sero status. Consequently, status disclosing and looking for health behavior could be damagingly affected. Similarly, among interviewed pre-ART clients from Ethiopian Capital, almost half didn't disclose their HIV sero-status by reason of fear of getting rejected from family members, hence they did attrite from care [37]. Another review result of 34 different studies supports the conception that HIV sero-status disclosure can develop point of entry to HIV care and, for that reason, the increased retention in pre ART care continuum [38]. Part of the underlying justification for the undisclosed HIV sero-status can be fear of stigmatization and rejection from family members and the society at large [38, 39].

Pre-ART patients who were positive for TB at enrolment to care were at more risk of attrition from care (AHR=2.16) when we compare to those TB negative at enrolment to care. This is in line with the high mortality observed in HIV/AIDS clients with tuberculosis in a study cohort from India [35]. Another perspective can be patients are dying being reluctant to take both ART and anti-tuberculosis as indicated from Soweto, South Africa [36, 42]. This may be also explained from, according to 2013 global TB report, even though Ethiopia has met TB incidence rate falling, 82% of HIV positive TB patients are on HIV/AIDS care and only 38% of patients living with HIV/AIDS and enrolled in to care were given isoniazid preventive treatment (IPT) [40]). But, in current study setting no data was found about patients' treatment status with IPT. It is vital to provide both HIV testing to tuberculosis patients and Tuberculosis diagnosis in HIV/AIDS patients. Early recognition and effective management are crucial to preventing TB-related expiries [43].

Regarding to the patient attrition in connection with service availability, patients who lived ≥10km from the center had more risk of early attrition (AHR=1.44) when compared to those who lived in less than 10km. This study is in line with finding from South Africa that, nearly half of HIV patients (45%) enrolled in to pre ART care was lost from care due to attritions and patients who lived >=10 km from the service provision area had greater risk of early attrition (ARR=1.37). But, the time to attrition is a bit late in this cohort.

Similarly a study from India indicated that, patients who lived near the service area were retained more on care when compared to individuals living abroad (ARR=1.09) [35].

The study has the following limitations; - first, the power of this study could be limited as amount of deaths might be underestimated. This may perhaps be due to defaulting patients dying at home being unreported. Using data with incomplete information might have introduced bias. Second, the outcomes of pre ART among transferred out patients is unknown. This could affect the estimated number of pre-ART outcomes.

V. CONCLUSION

More than a third of patient attrition (loss to follow up and death) from pre-ART care was observed among the study participants with the highest attrition being during the 1st year of follow up period. Predictor variables associated with these high and early patient attritions were: no cotrimoxazole uptake, being a TB patient, living ≥ 10km from the center and disclosure status.

RECOMMENDATION

Close monitoring and improved tracking of patients is recommended during the early follow up periods of pre-ART care.

Abbreviations

AIDS: Acquired Immuno-Deficiency Syndrome, ART: Anti-Retroviral Therapy, LTFU: Lost to Follow Up, PYOs: Person Years of Observations

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Ethical consideration

The study was approved by the institutional review board of Jimma University Institute of Health (JUIH), Jimma, Ethiopia and Tepi General Hospital, Tepi, Ethiopia.

Competing interests**:** none declared

Authors' contributions

TS: conceived the study, formulated the research question, and designed the study, TS: coordinated the data collection, analyzed the data, and drafted the paper. TS, HA and HA: did the analysis, reviewed the paper for intellectual content, and read and gave approval to the final version.

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