Time to Recurrence of any Opportunistic Infection after Treatment of it among People Living with HIV Infection in Debre Markos, Northwest Ethiopia: Retrospective Cohort Study

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Abstract

Introduction: Antiretroviral therapy improves time to death of people living with HIV; however, little is known about its effect on improving time of recurrence of opportunistic infections after treatment of any preceding infection. Hence, this study was aimed at assessing time to recurrence of any opportunistic infection after treatment of any preceding opportunistic infection, its magnitude and associated factors.

Methods: Retrospective cohort study was used and the required sample size was 536. Study participants were selected randomly from the list of adult people living with HIV attending the public health facilities for ART. Univariate analysis was used to describe patients' baseline and follow up characteristics. Kaplan-meier survival and log rank test were used to estimate survival and compare survival curves respectively. Cox proportional-hazard regression model was used to calculate hazard rate and to determine independent predictors of time to recurrence.

Results: During a median of 43 person weeks follow up, opportunistic infections recurred in 75.7% the participants and the proportion was not significantly different (p=0.614) in pre-ART and ART people living with HIV. The incidence rate of any opportunistic infection recurrence was 1.31 per 100 person weeks which differs by ART exposure status which was 1.57 and 1.13 per 100 person weeks in pre-ART and ART PLHIV respectively. The median time of survival was 57 weeks; however, it was different in pre-ART and ART PLHIV that was 52 and 64 weeks respectively. Marital status, occupational status, follow up CD4 count, base line hemoglobin value, ART exposure, base line ART adherence, base line and follow up prophylaxis exposure and adherence were predictors of survival.

Conclusion: The incidence rate of any opportunistic infection recurrence was 1.31 per 100 person weeks. Attention should be given for widowed, ART/prophylaxis non-adhering patients while continuing HIV care for all people living with the virus.

Keywords: HIV; Recurrence; Opportunistic infection

Introduction

According to the latest United Nation's Agency for International Development (UNAID) estimate, about 34 million people were living with human immunodeficiency virus (HIV) in 2011 [1,2]. Globally, the annual number of people dying from acquired immunodeficiency syndrome (AIDS)-related causes was 1.7 million in 2011 [3].

According to 2011 Ethiopian demographic health survey, the overall national adult (age 15-49 years) HIV prevalence was 1.5% [4].

Introduction of combination antiretroviral therapy in 1996 has led to dramatic reductions in morbidity and mortality from HIV/AIDS [1,2]. In Ethiopia, the fee based and universal free access antiretroviral (ARV) treatment was started in 2002/3 and 2004/5 respectively [5,6].

HIV infection leads to AIDS and major causes of morbidity and mortality of such patients are opportunistic infections (OIs) caused by viral, bacterial, fungal and parasitic pathogens [7]. OIs can occur in about 40% of people living with HIV (PLHIV) with a CD4 count less than 250/mm³ [8].

In Northwest Ethiopia, a study at Felegehiwot hospital in pre-ART HIV/AIDS patients showed that 88.9% of them have common OIs (chronic diarrhea (38.6%), tuberculosis (TB) (34.5%), herpes zoster (30.7%), oro-pharyngeal candidiasis (14%), pneumonia (3.5%) and other sexually transmitted infections (12.5%)) [9].

The other problems among the HIV sero-positive individuals were dual and triple OIs and other co-infections; according to studies, the most frequent dual infections were chronic diarrhea and oral candidiasis (28.92%), oral candidiasis and TB (25.49%), chronic diarrhea and TB (21.08%), HSV-2 and oral candidiasis (19.11%), HSV-2 and cytomegaly virus (14.21%), Hepatitis-B virus and HSV-2 (3.92%); the commonest triple infections were oral candidiasis, TB and chronic diarrhea (14.21%); HSV-2, CMV and oral candidiasis (10.78%); HSV-2, CMV and chronic diarrhea (8.34%); and HSV-2, CMV and TB (6.86%) [10].

Different studies showed that ART improves time to death among PLHIV [11-13] but its effect on improving time of recurrence of any OI after treatment of any preceding OI, its magnitude and associated factors are not studied in Ethiopia. Hence, this study was aimed at assessing time to recurrence of any OI after treatment of any preceding OI, its magnitude and associated factors.

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Methods and Patients

Study area, period and design

Debre Markos town has one referral hospital and one public health center, which provide ART service. The study was conducted in Debre Markos hospital and health center among 6261 adult PLHIV who were on chronic HIV care or ART follow up between 25th March 2007 and 24th March 2013. Institution-based retrospective cohort study was conducted from March 25th 2007 to March 24th using quantitative research method.

Source and study population

All 18 years old and above PLHIV infections having chronic HIV care or on ART follow up in Debre Markos town health institutions providing ART service were the source populations. All adult PLHIV infections that had developed any OI and on standard treatment in chronic HIV care or on ART follow up found in ART service providing health institutions in Debre Markos town were included in the study

Sampling and sample size determination

The sample size was calculated based on the assumption of 95% confidence interval and 80% power with ratio of one to one for ART and pre-ART PLHIV using the proportions of the commonest OI (TB) which were 6% and 14 % for ART and pre-ART PLHIV respectively [11]. Epi Info version 3.5 was used to calculate the required sample size [14].

$$n = \frac{\left[Z_\alpha \sqrt{(1+1/m)\overline{p}(1-\overline{p})} + Z_\beta \sqrt{p_o(1-p_o)/m + p_1(1-p_1)} \right]^2}{(p_o - p_1)^2}$$

$$\overline{p} = \frac{p1 + mp_o}{m+1}$$

where, n: minimum sample size required for each group

m: ratio of pre-ART and ART PLHIV

p_o: probability of event in pre-ART

p_1: probability of event in ART

α: level of significance

$Z_{\alpha/2}$: 1.96 at 95% confidence interval

Power: 1-β=80%, Z_β=1.282

Accordingly, the calculated sample size was 488 (244 for ART and pre-ART); after adding 10% contingency the sample was 536. Eligible study participants were identified by data collectors from the list of PLHIV who were on HIV care or on ART follow up from ART clinics of Debre Markos hospital and health center. Eligible PLHIV who were on pre-ART and ART history were given separate codes and then selected by simple random sampling using random number table. Moreover, in order to reduce falsely survival increment, study participants were asked by data collectors about treatment history for OIs.

Data collection instrument and procedure

Data abstraction format was developed from federal ministry of health HIV care/ART follow up form which is used in the ART clinic and also the patients' card; the format includes the following check list:

➢ socio-demographic characteristics (sex, age, residence, marital status, occupational status, educational status);

➢ ART and chemoprophylaxis information (ARV drug treatment, drug adherence, line of treatment regimen, prophylaxis treatment and its adherence);

➢ laboratory information (CD4 count, hemoglobin value);

➢ Clinical information (WHO clinical staging, weight, height, OIs (name and count treated at one time), other chronic diseases like diabetes mellitus, hypertension, cardiac disease); and

➢ Functional status of patients (working, ambulatory, bedridden).

The data were collected by reviewing HIV care/ART follow up form, laboratory requests and patients' card. If PLHIV develop any OI before completing treatment of any preceding OI while the patient is on study, the time of treatment, which is nearest to, end of the study was used as the starting time for study. If laboratory results (CD4 count, Hgb) were not found during OI treatment, the most recent laboratory results before treatment of OI were used as base line predictors. Length of follow up for each study participant was varied because of different enrollment time.

Reoccurrence of any OI was confirmed by reviewing HIV care/ART follow-up form or patient card or by asking study participant during data collection period about treatment history for OIs out of the follow up health institution. The health status was assured by asking the study participants when she or he came to ART clinic for follow up, asking using registered address on follow up form like phone number, kebele, house number, or adherence supporter groups were used to get their homes and used to trace study participants.

Individuals who change from unexposed to exposed, drop-out/loss to follow-up/transferred out/dead by any disease other than OI where cause of death not confirmed during study period or not develop any OI at the end of the study period were censored. The outcome of each subject was dichotomized into censored or recurrence of any OI.

Three data collectors and one supervisor who had direct experience and working on ART clinic were recruited for data collection and supervision respectively. Data collectors and supervisor were trained on objectives of the study, selection of exposed and unexposed, confidentiality of information, the contents of the questionnaire and data quality management by the principal investigators.

Data quality management, processing and analysis

To maintain data quality, incompletely recorded follow up formats were excluded from abstraction to check the reliability and consistency of data and accordingly correction was made. Data cleaning and editing were made before analysis.

Each abstraction format was given a code and was entered in to Epi Info version 3.35 statistical software and exported to SPSS 16 and STATA 11 statistical packages for analysis of statistical inferences.

The patient cohort characteristics including age, CD4 count, Hgb value, time to reoccurrence of any OIs and body mass index (BMI) were described in terms of mean or median value and other characteristics like sex, residence, marital status, occupational status, educational status, WHO clinical staging, ART adherence, line of ART regimen, prophylaxis treatment and its adherence, functional status, final outcome of study (censored or reoccurrence of any OIs) were described in terms percentages, tables and graphs.

Proportion and incidence of any OI were calculated at the end of the study. Incidence rate was calculated by dividing total events to person-weeks. The actuarial life table and Kaplan Meier survival was used to

estimate survival time and log rank test was used for categorical variables to compare survival curves across each strata. Before running the Cox regression model assumption of proportional-hazard was checked by Schoenfeld residual with p-value ≥ 0.1 ($\alpha=10\%$) and the assumption was not violated. Multi-colinearity was checked using Pearson correlation, tolerance or variance inflation factor and we found that base line ART regimen was highly correlated with follow up ART regimen (r=0.809 , p<0.0001) so that further analysis in the final model were not done for base line ART regimen. Similarly, follow up Hgb value were excluded in final model because of its correlation with base line Hgb value (r=0.598, p<0.0001) and it was done in only 10.8% of study participants. Exclusion of redundant variables was done to stabilize final model and to improve precision of estimation. Cox proportional-hazard model was used to calculate the univariate and multivariable adjusted hazard rate and to determine independent predictors of survival. In Multivariable cox proportional hazard model, only those variables which were associated with time to recurrence of any OI with p-value ≤ 0.2 in univariate analysis and not collinear were entered to the final model.

Study variables

Dependent variable

➤ Time to recurrence of any OIs after its treatment

Independent variables

➤ socio-demographic (age, sex, religion, residence, occupation, educational status, marital status)

➤ clinical, laboratory, ART and chemoprophylaxis information and functional status (working, ambulatory, bedridden)

Definitions

Pre-ART PLHIV: The person whose HIV positive status confirmed but not eligible for ART;

ART PLHIV: The person whose HIV positive status confirmed and started ART;

Survival: The person without any OI recurrence;

Censored: Non-recurrence of any OI in study participant during follow up on study but not sure for future recurrence;

Reoccurrence: The happening or diagnosis of any OI by health personnel working in ART health center. Confidentiality and anonymity was maintained. Informed consent was clinic after completing the preceding treatment of any OI;

Drop out: If a PLHIV on HIV care lost to follow up for more than three months as recorded by ART clinic personnel;

Lost to follow up: If PLHIV on HIV care not seen for equal to or more than one month as recorded by ART clinic personnel;

Transferred out: If PLHIV on HIV care in one health institution shift to other health institution;

Good Adherence: if adherent $\geq 95\%$; that is the percentage of missed dose is <2 doses of 30 doses or <3 dose of 60 dose) as documented by ART health personnel;

Fair Adherence: if adherent 85-94%; that is the percentage of missed dose is 3-5 doses of 30 doses or 3-9 dose of 60 dose) as documented by ART health personnel;

Poor Adherence: if adherent <85%; that is the percentage of missed dose is ≥ 3 doses of 30 doses or >9 dose of 60 dose) as documented by ART health personnel.

Ethical consideration

Ethical approval and clearance were obtained from research and ethical committee of School of Public Health of Addis Ababa University. Permission was also obtained from the concerned bodies of the hospital and obtained from study participants to get permission to extract data from their medical records. To get study participants who were not coming to the ART clinic for follow up during data collection period, in addition of using already registered address like phone number, *kebele*, house number on follow up form and ART adherence supporter groups

Recurred OI	Pre-ART (268)		ART (268)		X² p-value	PLHIV (536)	
	Frequency (%)	IR	Frequency (%)	IR		Frequency (%)	IR
Recurrent URTIs	35 (13.1)	0.27	38 (14.2)	0.21	0.91	73 (13.6)	0.24
Chronic diarrhea	30 (11.2)	0.23	22 (8.2)	0.12	0.25	52 (9.7)	0.17
Pneumonia	21 (7.8)	0.16	25 (9.3)	0.14	0.73	46 (8.5)	0.15
Oral candidacies	22 (8.2)	0.17	21 (7.8)	0.12	0.91	43 (8.0)	0.14
Herpes zoster	18 (6.7)	0.14	20 (7.5)	0.11	0.81	38 (7.1)	0.12
EPTB	15 (5.6)	0.12	16 (6.0)	0.09	0.92	31 (5.8)	0.10
Minor MC manifestations	13 (4.9)	0.10	15 (5.6)	0.08	0.92	28 (5.2)	0.09
PTB	10 (3.7)	0.08	13 (4.9)	0.07	0.72	23 (4.2)	0.07
PCP	12 (4.5)	0.09	9 (3.4)	0.05	0.61	21 (3.9)	0.07
Genital/oral ulcer	8 (3.0)	0.06	6 (2.2)	0.03	0.75	14 (2.6)	0.05
Toxoplasmosis	6 (2.2)	0.05	5 (1.9)	0.03	0.95	11 (2.1)	0.04
Encephalopathy	4 (1.5)	0.03	7 (2.6)	0.04	0.57	11 (2.1)	0.04
Wasting syndrome	8 (3.0)	0.06	3 (1.1)	0.02	0.20	11 (2.1)	0.04
Cryptococal meningitis	3 (1.1)	0.02	8 (3.0)	0.04	0.24	11 (2.1)	0.04
Persistent generalized LAP	6 (2.2)	0.05	3 (1.1)	0.02	0.33*	9 (1.7)	0.03
Others	7 (2.6)	0.06	9 (3.4)	0.05	0.78	16 (3.0)	0.05
Total #	200 (74.6)	1.57	206 (76.9)	1.13	0.61	406 (75.7)	1.31

IR: incidence rate per 100 person weeks; MC: muco-cutaneous; LAP: lymphadenopathy; URTIs: upper respiratory tract infections; PTB: pulmonary tuberculosis; EPTB: extra pulmonary tuberculosis; PCP: pneumocystis Carinii pneumonia; Row total is not sum of columns values due to occurrence of more than one OI in some study participants.

* P-value is Fisher's Exact test because of 50% of the expected cell values are less than 5.

Table 1: Proportion and incidence of recurred OIs in pre-ART and ART PLHIV in Debre Markos Hospital and Health Center, Northwest Ethiopia between 25th March 2007 and 24th March, 2013.

Figure 1: Profile of PLHIV enrolled for cohort between 25th March 2007 and 24th March 2013 in Debre Markos Hospital and Health Center, Northwest Ethiopia, 2013
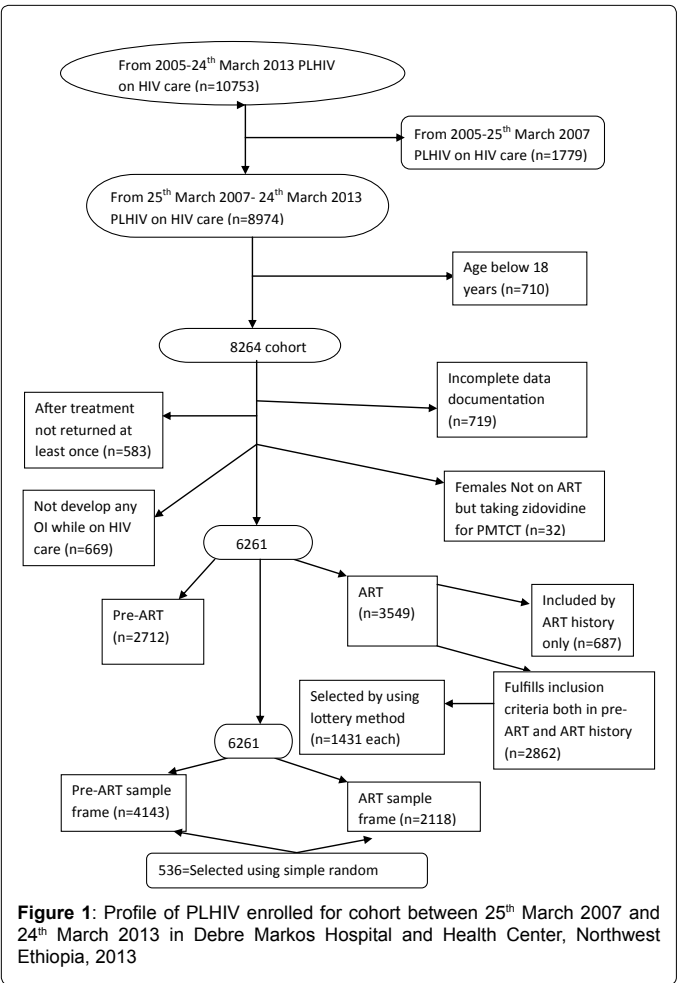
were used to trace them. For study participants who were severely ill, with coma or having hearing impairment or died before data collection period while included in the study period, the nearest relatives (family) or legal representatives were asked to give permission to extract on medical records.

Results

In this historical cohort study, between 25th March 2007 and 24th March 2013, 8,974 PLHIV aged 18 years and above were evaluated (Figure 1). Five hundred thirty six PLHIV who were on pre-ART and ART with 1:1 ratio each consisting 268 were followed for a total of 30971 person weeks and median of 43 person weeks. The minimum and maximum person week follow up was 2 and 258 respectively. The study assessed time to recurrence of any OI in pre-ART and ART PLHIV, its magnitude and baseline and follow up predictors of time to recurrence in PLHIV.

Socio demographic characteristics

In this study, 354 (66%) females and 182 (34%) males were participated. Their median age was 32 year (IQR=26-40) in which 493 (92%) were below 50 year of age. Most of the study participants were urban by residence 376 (70.1%), orthodox by religion 495 (92.4%), not educated 236 (44%), married 232 (43.3%) and employed 107 (20%) (Table 3).

Clinical, laboratory and treatment information

At base line, three quarter of the study participants (400, 74.6%) had

one episode of OI and most (214, 39.9%) of them had WHO Clinical stage III. Almost all of the study participants (394, 97.1%) had no any chronic diseases like hypertension, diabetes mellitus and others.

With regard to functional status, more than three quarters of the participants were working both at base line (418, 78%) and at follow up (471, 87.1%).

The base line and end line mean (SD) values for BMI of the participants were 19 (± 3.1) and 19.8 (± 3.1) respectively. The base line median values for CD4 count and Hgb were 280 (IQR=150-410) and 11 (IQR=9.8-13) respectively and their end line median values were 384 (IQR=237-478) and 12.5(IQR=11-13.5) respectively.

More than four-fifth of the study participants were taking prophylaxis both at base line (443, 82.6%) and at follow up (453, 84.5%) and almost all of them had good drug adherence status both at base line (415, 93.7%) and at follow up (422, 93.2%).

Almost all of the participants (423, 95.5%) were taking Cotrimoxazole prophylaxis both at base line and at follow up (439, 96.7%).

Half of the study participants (268, 50%) were taking ART both at base line and at follow up. All participants were on first line ART regimens in which about one third were taking TDF+3TC+EFV regimen both at base line (101, 37.7%) and at follow up (106, 39.6%). Almost all study participants had good antiretroviral drug adherence both at base line (252, 94%) and follow up (253, 94.4%) (Table 3).

Interval start time	Number entering interval	Number withdrawing during interval	Number of any OIs recurred	Cumulative proportion surviving at end of interval	Hazard Rate
0	536	16	38	.93	.01
10	482	12	63	.81	.01
20	407	20	41	.72	.01
30	346	17	35	.65	.01
40	294	12	38	.56	.01
50	244	16	32	.49	.01
60	196	8	33	.40	.02
70	155	4	29	.33	.02
80	122	6	21	.27	.02
90	95	2	6	.25	.01
100	87	1	14	.21	.02
110	72	2	7	.19	.01
120	63	2	6	.17	.01
130	55	0	5	.16	.01
140	50	2	4	.14	.01
150	44	1	6	.12	.01
160	37	0	7	.10	.02
170	30	3	6	.08	.02
180	21	0	4	.06	.02
190	17	0	0	.06	.00
200	17	2	4	.05	.03
210	11	2	1	.04	.01
220	8	1	3	.03	.05
230	4	0	1	.02	.03
240	3	0	1	.01	.04
250	2	1	1	.00	.10

Table 2: The actuarial life table estimation of cumulative progression to recurrence of any OI in PLHIV in Debre Markos Hospital and Health Center, Northwest Ethiopia, between 25th March 2007 and 24th March, 2013.

Characteristics	Any OI recurred		Total (%)	Log rank test p-value	CHR [95%CI]	p-value for CHR
	Yes (%)	No (%)				
Marital status						
Married	172 (42.4)	60 (46.2)	232 (43.3)		1	
Single	85 (20.9)	17 (13.0)	102 (19.0)	0.001	1.42 (1.09-1.84)	0.0088*
Divorced	103 (25.4)	37 (28.5)	140 (26.1)		1.11 (0.87-1.41)	0.4236
Widowed	46 (11.3)	16 (12.3)	62 (11.6)		1.83 (1.32-2.54)	0.0003*
Educational status						
Not educated	184 (45.3)	52 (40.0)	236 (44.4)		1	
Primary	122 (30.1)	28 (21.5)	150 (27.6)	<0.0001	0.92 (0.73-1.16)	0.461
Secondary	71 (17.5)	24 (18.5)	95 (17.7)		0.74 (0.56-0.98)	0.038*
Tertiary	29 (7.1)	26 (20.0)	55 (10.3)		0.45 (0.31-0.68)	<0.0001*
Occupational status						
Farmer	73 (18.0)	25 (19.2)	98 (18.3)		1	
Merchant	69 (17.0)	19 (14.6)	88 (16.4)		0.43 (0.31-0.60)	<0.0001*
Employed	69 (17.0)	38 (29.2)	107 (20.0)		0.35 (0.25-0.48)	<0.0001*
Daily laborer	68 (16.7)	17 (13.1)	85 (15.9)	<0.0001	0.86 (0.62-1.21)	0.390
House wife	42 (10.3)	11 (8.5)	53 (9.9)		0.66 (0.45-0.97)	0.034*
Unemployed	70 (17.3)	18 (13.9)	88 (16.4)		0.92 (0.66-1.28)	0.612
Student	15 (3.7)	2 (1.5)	17 (3.2)		0.58 (0.33-1.01)	0.055
CD4 count (cells/µl) [B.]						
<=100	25 (6.2)	10 (7.7)	35 (6.5)		1	
101-199	34 (8.4)	14 (10.8)	48 (9.0)		0.45 (0.27-0.77)	0.003*
200-350	80 (19.7)	21 (16.1)	101 (18.8)	0.04	0.68 (0.43-1.07)	0.096
351-499	124 (30.5)	35 (26.9)	159 (29.7)		0.73 (0.48-1.13)	0.158
>=500	143 (35.2)	50 (38.5)	193 (36.0)		0.57 (0.37-0.87)	0.010*
Hemoglobin (g/dl) [B.]						
<10	120 (36.4)	14 (21.9)	134 (34.0)	<0.0001	1	
>=10	210 (63.6)	50 (78.1)	260 (66.0)		0.56 (0.45-0.70)	<0.0001*
Functional status [B.]						
Working	307 (75.6)	111 (85.4)	418 (78.0)		1	
Ambulatory	88 (21.7)	19 (14.6)	107 (20.0)	0.044	1.32 (1.09-1.67)	0.0226*
Bed ridden	11(2.7)	-	11 (2.0)		1.43 (0.72-2.61)	0.2488
Prophylaxis exposure [B.]						
No	72 (17.7)	21 (16.2)	93 (17.4)	<0.0001	1	
Yes	334 (82.3)	109 (83.8)	443 (82.6)		0.54 (0.42-0.70)	<0.0001*
Prophylaxis Adherence [B.]						
Good	308 (92.2)	107 (98.2)	415 (93.7)		1	
Fair	11 (3.3)	-	11 (2.5)	0.001	1.56 (0.85-2.44)	0.1506
Poor	15 (4.5)	2 (1.8)	17 (3.8)		2.42 (1.43-4.09)	0.001*
ART [B.]						
No	200 (49.3)	68 (52.3)	268 (50.0)	<0.0001	1	
Yes	206 (50.7)	62 (47.7)	268 (50.0)		0.68 (0.56-0.83)	<0.0001*
ART regimens ¥ [B.]						
D4T+3TC+NVP	55 (26.7)	7 (11.3)	62 (23.1)		1	
D4T+3TC+EFV	19 (9.3)	2 (3.2)	21 (7.8)		1.00 (0.59-1.69)	0.9999
AZT+3TC+NVP	60 (29.1)	6 (9.7)	66 (24.6)	0.088	1.20 (0.83-1.74)	0.3311
AZT+3TC+EFV	11 (5.3)	1 (1.6)	12 (4.6)		1.89 (0.98-3.64)	0.0566
TDF+3TC+EFV	61 (29.6)	41 (66.1)	101 (37.7)		1.58 (1.08-2.32)	0.0197*
TDF+3TC+NVP	-	5 (8.1)	6 (2.2)		0.01 (0.001-1.10)	0.9881
ART adherence [B.]						
Good	194 (94.2)	61 (98.4)	255 (95.2)		1	
Fair	5 (2.4)	1 (1.6)	6 (2.2)	<0.0001	2.15 (0.88-5.25)	0.092
Poor	7 (3.4)	-	7 (2.6)		3.89 (1.81-8.36)	<0.0001*
Body mass index (kg/m^2) [F.]						
<=18.4	151 (37.2)	38 (29.2)	189 (35.3)		1	
18.5-22.9	196 (48.3)	64 (49.3)	260 (48.5)	0.008	0.87 (0.71-1.08)	0.2142
>=23	59 (14.5)	28 (21.5)	87 (16.2)		0.62 (0.46-0.84)	0.0022*
CD4 count (cells/µl) [F.]						
<=100	13 (4.8)	5 (5.7)	18 (5.0)		1	
101-199	31 (11.4)	7 (8.0)	38 (10.7)		0.58 (0.30-1.12)	0.104
200-350	93 (34.3)	33 (37.9)	126 (35.2)	0.55	0.53 (0.29-0.94)	0.031*
351-499	75 (27.7)	26 (29.9)	101 (28.2)		0.46 (0.25-0.83)	0.010*
>=500	59 (21.8)	16 (18.5)	75 (20.9)		0.43 (0.23-0.79)	0.006*
Functional status [F.]						
Working	345 (85.0)	126 (96.9)	471 (87.9)		1	
Ambulatory	51 (12.5)	3 (2.3)	54 (10.1)	0.006	1.59 (1.18-2.13)	0.0021*
Bed ridden	10 (2.5)	1 (0.8)	11 (2.0)		1.32 (0.70-2.47)	0.3909
Prophylaxis exposure [F.]						
No	63 (15.5)	20 (15.4)	83 (15.5)	0.003	1	
Yes	343 (84.5)	110 (84.6)	453 (84.5)		0.67 (0.51-0.87)	0.0032*

Prophylaxis Adherence F.						
Good	316 (92.1)	108 (98.2)	424 (93.6)	<0.0001	1	
Fair	10 (2.9)	1 (0.9)	11 (2.4)		1.49 (0.79-2.79)	0.217
Poor	17 (5.0)	1 (0.9)	18 (4)		3.48 (2.12-5.71)	<0.0001*
ART F.						
No	200 (49.3)	68 (52.3)	268 (50)	<0.0001	1	
Yes	206 (50.7)	62 (47.7)	268 (50)		0.68 (0.56-0.83)	<0.0001*

B.= at base line
F.= at Follow up
*significant at α=5%
CHR=crude hazard rate
¥ d4T: Stavudine; 3TC: Lamivudine; NVP: Nevirapine; EFV: Efavirenz; AZT:Zidouvudine; TDF: Tenofovir disoproxil fumarate

Table 3: Bivariate cox proportional hazard model of the association between base line and follow up characteristics and any OI recurrence in among PLHIV in Debre Markos Hospital and Health Center, Northwest Ethiopia, between 25 March 2007 and 24 March, 2013.
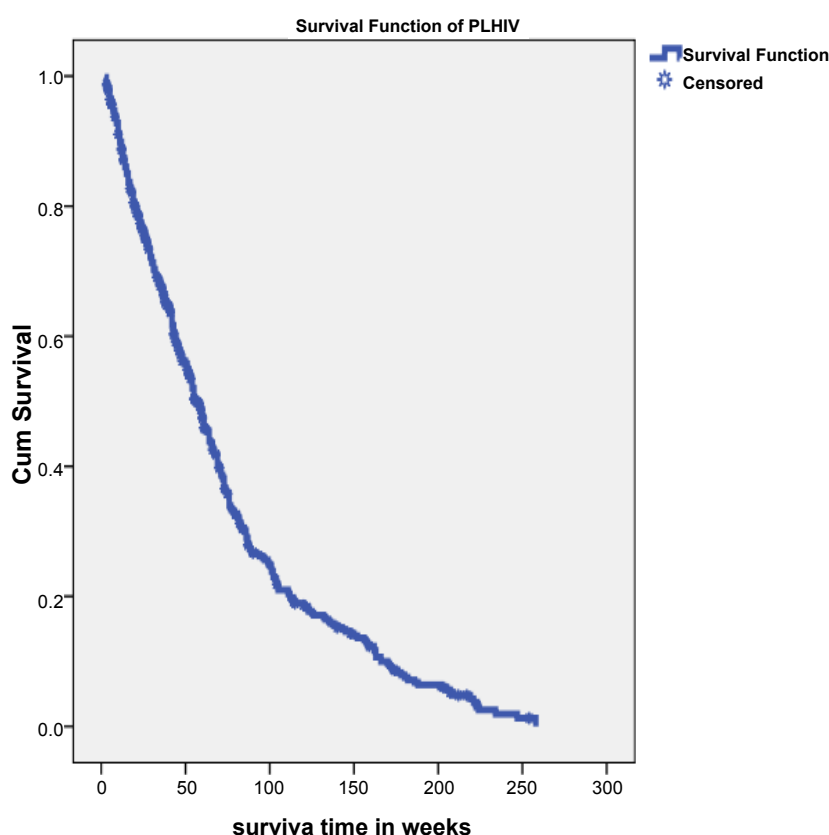

Figure 2: kaplan-meier survival estimation of time to free of any OI recurrence in PLHIV in Debre Markos Hospital and Health Center, Northwest Ethiopia, between 25th March 2007 and 24th March, 2013.

Magnitude of any OI recurrence

During follow up, OIs recurred in three quarter study participants 406 (75.7%) and the rest were censored 130 (24.3%). Proportion of recurrence was 200 (74.6%) in Pre-ART and 206 (76.9%) ART PLHIV.

In chi-square test, the proportion of recurrence was not statistically significant different in the overall or each type of OI in Pre-ART and ART PLHIV.

The overall incidence rate of any OI recurrence was 1.31 per 100 person weeks and it was 1.57 and 1.13 per 100 person weeks in pre-ART and ART PLHIV respectively. In the study area, frequently recurred OIs were recurrent upper respiratory tract infection 73 (13.6%), chronic diarrhea 52 (9.7%), pneumonia 46 (8.5%), oral candidiasis 43 (8%),

herpes zoster 38 (7.1%) though their proportions and the commonly recurred OIs were different in pre-ART and ART PLHIV (Table 1).

Survival analysis

A total of 536 PLHIV were followed for a median of 43 (IQR=20.25-75.75) person weeks. The minimum, maximum and total person weeks follow up was 2, 258 and 30971 respectively. According to the Kaplan-meier survival estimation, the median time of survival was 57 weeks (95%CI: 51.66-62.34). The actuarial life table analysis showed that most (63, 11.8%) OIs recurred from 10-20 weeks. The cumulative proportion of free from any OI recurrence up to week 20 was 81%. The cumulative proportion of free from any OI recurrence up to week 250 was 1% (Table 2).

The median time of survival was different in pre-ART and ART PLHIV, that was 52 (95%CI: 45.24-58.76) and 64 (95% CI: 54.87-73.13) weeks respectively (Figures 2 and 3).

At base line and follow up, significant difference in time to recurrence of any OI in log rank test among categorical variables strata were seen in marital status (p=0.001), educational status (p<0.0001), occupational status (p<0.0001), base line CD4 count (p=0.0084), base line Hgb value (p<0.0001), follow up Hgb value (p=0.01), follow up BMI (p=0.008), base line functional status (P=0.044), follow up functional status (p=0.006), ART exposure status (p<0.0001), base line prophylaxis exposure (p<0.0001), follow up prophylaxis exposure (p=0.003), base line ART adherence status (p<0.0001), follow up ART adherence status (p<0.0001), base line prophylaxis adherence status (p=0.001) and follow up prophylaxis adherence status (p<0.0001).

In univariate cox-regression analysis, the base line and follow up characteristics were significantly (p<0.05) associated with survival; namely marital status, educational status, occupational status, base line and follow up CD4 count, base line and follow up Hgb value, follow up BMI, base line and follow up functional status, ART exposure, base line and follow up prophylaxis exposure, base line and follow up ART adherence status, base line ART regimen, base line and follow up prophylaxis adherence status (Table 3).

In Multivariable cox proportional hazard model, only those variables which were associated with survival with p-value ≤ 0.2

and not collinear were entered to the final model. After adjustment for covariates, significant predictors reducing survival (risks for recurrence) were being widowed than married by 2.18 times, fair follow up prophylaxis adherence than good adherence by 7.27 times, fair base line ART adherence than good adherence by 14.83 times. The significant predictors that improve survival (prevent recurrence) were divorced than married by 0.57 times, compared to farmer being merchant, employed and student by 0.30, 0.22 and 0.15 times respectively, having base line Hgb value of ≥ g/dl than <10 by 0.42 times, compared ≤ 100 cells/μl CD4 count having 351-499 and ≥ 500 follow up CD4 count by 0.39 and 0.32 times respectively; moreover, taking prophylaxis at baseline, at follow up and taking ART by 0.55 and 0.49 by 0.522 times respectively. After adjusting for other variables, when follow up CD4 count increased by 50 cells/μl survival also increased by 0.91 times (p<0.0001), and when base line Hgb value increased by 5 g/dl survival also increased by 0.66 times (p=0.004) (Table 4).

Discussion

In this historical cohort study, more than three quarter of the participants had recurrence of OIs. Proportion of recurrence was not significantly different (p=0.614) between Pre-ART and ART PLHIV. The proportion of OI recurrence in pre-ART PLHIV was slightly lower than the study in Northwest Ethiopia in which 82.4% patients present with any type of OIs at start of ART [15] and in other study in Felegehiot hospital among pre-ART HIV patients, it was 88.9% at
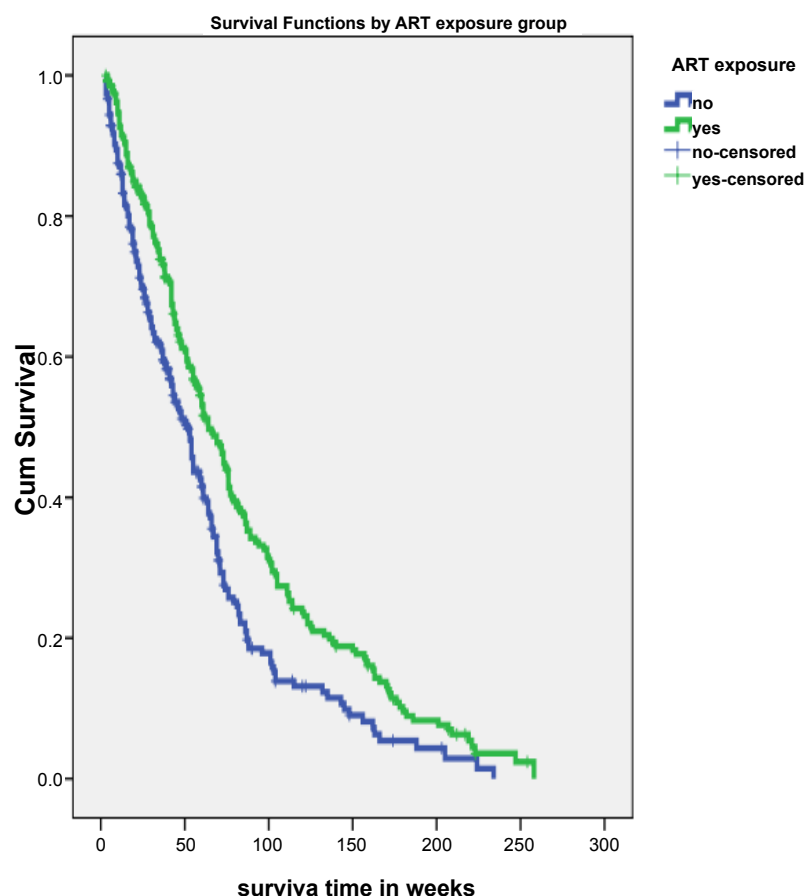

Figure 3: kaplan-meier survival estimation of time to free of any OI recurrence in pre-ART and ART PLHIV in Debre Markos Hospital and Health Center, Northwest Ethiopia, between 25th March 2007 and 24th March,

Characteristics	AHR [95%CI]	p-value		
Marital status				
Married	1			
Single	1.25 (0.83-1.87)	0.287		
Divorced	0.57 (0.38-0.84)	0.005*		
Widowed	2.18 (1.30-3.64)	0.003*		
Educational status				
Not educated	1			
Primary	1.34 (0.90-1.99)	0.151		
Secondary	1.09 (0.66-1.79)	0.747		
Tertiary	1.05 (0.49-2.21)	0.898		
Occupational status				
Farmer	1			
Merchant	0.30 (0.17-0.53)	<0.0001*		
Employed	0.22 (0.12-0.40)	<0.0001*		
Daily laborer	0.79 (0.47-1.35)	0.388		
House wife	0.55 (0.29-1.03)	0.058		
Unemployed	0.59 (0.35-1.03)	0.063		
Student	0.15 (0.06-0.38)	<0.000*		
Follow up body mass index (kg/m^2)				
<=18.4	1			
18.5-22.9	1.05 (0.74-1.48)	0.805		
>=23	0.82 (0.51-1.31)	0.400		
ART				
No	1			
Yes	0.52 (0.35-0.78)	<0.002*		
Follow up ART regimens ¥				
D4T+3TC+NVP	1			
D4T+3TC+EFV	0.45 (0.15-1.36)	0.157		
AZT+3TC+NVP	0.64 (0.32-1.29)	0.211		
AZT+3TC+EFV	1.14 (0.27-4.82)	0.861		
TDF+3TC+EFV	0.47 (0.22-1.01)	0.053		
TDF+3TC+NVP	1.33 (0.21-8.55)	0.763		
	Base line		**Follow up**	
	AHR [95%CI]	p- value	AHR [95%CI]	p-value
CD4 count (cells/µl)				
<=100	1		1	
101-199	0.46 (0.19-1.13)	0.089	0.56 (0.24-1.31)	0.182
200-350	0.59 (0.26-1.31)	0.191	0.68 (0.31-1.49)	0.338
351-499	0.60 (0.26-1.43)	0.251	0.39 (0.17-0.87)	0.022*
>=500	0.52(0.22-0.25)	0.142	0.32 (0.14-0.73)	0.007*
Functional status				
Working	1		1	
Ambulatory	1.99 (0.67-1.47)	0.961	1.12 (0.67-1.86)	0.664
Bed ridden	0.98 (0.36-2.65)	0.965	1.49 (0.57-3.93)	0.414
Prophylaxis exposure				
No	1			
Yes	0.55 (0.33-0.91)	0.021*	0.49 (0.28-0.87)	0.014*
Prophylaxis Adherence				
Good	1		1	
Fair	0.92 (0.16-5.41)	0.925	7.27 (1.31-40.45)	0.023*
Poor	2.96 (0.31-28.14)	0.346	3.59 (0.52-22.69)	0.194
ART adherence				
Good	1		1	
Fair	14.83 (1.86-12.41)	0.011*	1.91 (0.38-9.67)	0.435
Poor	6.64 (0.31-144.60)	0.229	1.81 (0.09-36.34)	0.697

*significant at α=5%

AHR=adjusted hazard rate

¥ d4T: Stavudine; 3TC: Lamivudine; NVP: Nevirapine; EFV: Efavirenz; AZT: Zidouvudine; TDF: Tenofovir disoproxil fumarate

Table 4: Multivariate cox proportional hazard model of the association between base line and follow up characteristics and any OI recurrence in study participants' in Debre Markos Hospital and Health Center, Northwest Ethiopia, between 25 March 2007 and 24 March, 2013.

ART enrolment [9]. The smaller in magnitude was due to inclusion of all Pre-ART PLHIV who were on chronic HIV care and treated for any OIs but the previous studies [9,15] assessed only Pre-ART PLHIV who were enrolled for ART which might increase the magnitude because ART enrollment was done using WHO clinical staging and CD4 count.

This study showed taking ART reduces time to any OI recurrence which is supported by different studies [12,13,16-19]. The one year follow-up study after ART initiation in Northwest Ethiopia showed ART reduces any OIs occurrence by 91.9%. HAART reduces the incidence of severe OIs by 21% during the first 6 months and 28% during subsequent follow up after adjusting for CD4 count [19].

Antiretroviral treatment adherence is one of the challenges in the

failure of HAART increasing the chance for OI progression [9,20]. This study revealed that base line fair ART adherence compared to good adherence was hazard for survival illustrating adherence is crucial to improving survival besides taking ART.

This study revealed that survival was enhanced by taking prophylaxis at baseline and at follow up similar with other studies [21-24]. A critical appraisal in 2011 showed primary prophylaxis with Trimethoprim-sulfamethoxazole is preventing life-threatening OIs like PCP, toxoplasmosis and bacterial infections [21]. Primary prophylaxis with anti-tuberculosis regimens seems more effective at reducing the incidence of active tuberculosis in PLHIV [22]. An experimental study in Ugandan adults with Cotrimoxazole prophylaxis showed its effect on prevention of OIs like diarrhea in PLHIV. Compared to those remaining on cotrimoxazole, patients who discontinued had a relative risk of diarrhea of 1.8 and at least 1 episode of diarrhea occurred in 14% among those continued versus 25% in those discontinued. Participants who discontinued cotrimoxazole were more likely to be diagnosed with a respiratory tract infection [23]. Another study also showed Cotrimoxazole is preventing PCP (RR=0.59, p=0 .03) [24].

This study revealed having higher follow up CD4 count prolongs survival, compared ≤ 100 cells/μl; this result is in conformity with previous studies [13,18,19,25,26]. Similar cohort study also showed the risk of toxoplasmic encephalitis occurrence was increased by 30% for each 50-cell decrease in CD4+ cell count, independent of antiretroviral [13].

Conclusions

Since the introduction of free ART, more patients have been presented to HIV care and support. A number of PLHIV seeking HIV care are increasing through time in health institutions of Debre Markos to get the services. During a median of 43 person weeks follow up OIs were recurred in three quarter study participants (75.7%). The overall incidence rate of any OI recurrence was 1.31 per 100 person weeks. Independent significant predictors that reduce recurrence (risk factors) and improve (preventive factors) survival were identified. Those risk factors were being widowed than married, non- adherence of ART and prophylaxis treatments; however, preventive factors were being divorced compared to married, having occupational status of merchant, employed and student compared to farmer, having ≥10 g/dl Hgb value, having CD4 count 351 cells/μl and above compared to ≤100 cells/μl, taking ART and prophylaxis treatments.

Recommendations

To hospitals and health centers with ART clinic (giving HIV care and support)

- ➤ PLHIV should be encouraged to take ART and prophylaxis drugs and counseled to adhere on them properly
- ➤ Increasing the CD4 count and Hgb value, using nutrition and drug treatments are crucial to improve survival
- ➤ Preventive efforts should focus on high risk groups such as widowed, not adhering ART or prophylaxis
- ➤ The ART care should be further enhanced to improve survival.

To Debre Markos town health office and other responsible organizations

- ➤ In-service training should be given for the healthcare provider on HIV/AIDS care and support especially on how to distinguish

and manage patients with high risk

- ➤ Health professionals should be encouraged to properly document patients' healthcare data
- ➤ Priority should be given for increasing job opportunities for PLHIV in governmental or non-governmental organizations or facilitate conditions to join other options.

To research and academic institutions

- ➤ Further studies for estimating economic losses for subsequent recurrence of OI is recommended
- ➤ Further observational studies with prospective design to ascertain the findings are recommended.

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