

## Incidence and Predictors of Tuberculosis among Adult PLWHA at Public Health Facilities of Hawassa City

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### ABSTRACT

Tuberculosis (TB) is the most frequently diagnosed opportunistic infection (OI) and disease in people living with HIV/AIDS (PLWHA), world-wide. This study aimed at determining the incidence and predictors of tuberculosis among people living with HIV. A Six year retrospective follow up study was conducted among adult PLHIV. The Cox proportional hazards model was used to identify predictors. A total of 554 patients were followed and produced 1830.3 person year of observation. One hundred sixty one new TB cases occurred during the follow up period. The overall incidence density of TB was 8.79 per 100 person-year (PY). It was high (148.71/100 PY) in the first year of enrolment. The cumulative proportion of TB free survival was 79% and 67% at the end of first and sixth years, respectively. Not having formal education (AHR=2.68, 95%CI: 1.41, 5.11), base line WHO clinical stage IV (AHR = 3.22, 95% CI=1.91-5.41), CD4 count <50 cell/ul (AHR=2.41, 95%CI=1.31, 4.42), Being bed ridden (AHR= 2.89, 95%CI=1.72, 3.78), past TB history (AHR=1.65, 95% CI = 1.06,2.39), substance use (AHR=1.46, 95% CI=1.03,2.06) and being on pre ART (AHR=1.62, 95%CI: 1.03-2.54) were independently predicted tuberculosis occurrence. Advanced WHO clinical stage, limited functional status, past TB history, addiction and low CD4 (<50cell/ul) count at enrollment were found to be the independent predictor of tuberculosis occurrence. Therefore early initiation of treatment and intensive follow up is important.

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### 1. INTRODUCTION

Human immunodeficiency virus (HIV) infection is the greatest risk factor for acquiring Mycobacterium tuberculosis infection and developing tuberculosis (TB) [1]. Tuberculosis is the most frequently diagnosed opportunistic infection (OI) and disease in people living with HIV/AIDS (PLWHA), world-wide [2]. Despite being preventable it is still a leading cause of morbidity and mortality in PLWHA. At least one in four deaths among PLWHA can be attributed to TB and many of these deaths occur in developing countries, like African countries [3]. HIV positive people with latent TB infection have a 10% annual and 50% lifetime risk of developing active TB disease, opposed to 10% of life time risk of HIV negative individuals [4]. As a result, TB becomes a major public health problem, particularly in area where HIV infection rates is higher [5]. Globally 1.2 million (12%) of 9.6 million people who developed TB (incidence) were HIV positive in 2014. Among these 74% HIV positive TB cases were in Africa. Even though the number of people dying from HIV associated TB in last decade decreases, it kills 25% (390,000) of all TB deaths and one third of the estimated 1.2 million deaths from HIV/AIDS [6]. According to World

Bank report, people who are latently infected with mycobacterium tuberculosis (about one third of inhabitants of Sub-Saharan Africa) are at greater risk of developing active TB, they are also immunologically weakened by concurrent HIV infection [7],[8].

Ethiopia is one of 22 World high burden countries of TB, ranking seventh and among top five in Africa [9]. According to WHO global TB report of 2015 the country had estimated 200,000 TB cases in 2014 with an estimated incidence rate of 207 cases per 100,000 populations [6]. In recent years, great efforts have been made to integrate TB diagnosis and treatment into HIV care which helps especially to prevent diagnosis and treat TB among people with HIV and HIV among TB patients. This has created the chance to additional research for better understanding of factors associated with incidence of TB which could help to improve service quality. Therefore the outcome of this study provide information about risk factors or the most influential covariates that have significant impact on incidence of TB and identify TB incidence rate under those significant factors at different time among HIV infected patients during ART care, which can be used to design appropriate action to reduce the occurrence of TB among HIV patients.

## **2. METHODS AND MATERIALS**

### **2.1. Study design and settings**

A six years institution based retrospective follow-up study was conducted in three health facilities (Hawassa University referral Hospital, Adare general hospital and millennium health center) which are found in Hawassa city, south Ethiopia. The city has 351,656 total populations organized in sub cities; and has one public referral hospital, one public general hospital, 10 governmental health centers, 4 private hospitals and about 36 private clinics. Hawassa university referral hospital is teaching referral hospital. The HIV care service of the hospitals was initiated at 2005 and has three clinics; adult ART, pediatric ART and VCT clinics which allowed to offered free ART services. All facilities uses national standardized monitoring and evaluation tools, and the data collection and management processes are well controlled and supported by electronic data back-up and processing. There were about a total 5,642 and 4,410 clients who ever started and currently on ART respectively in the three selected facilities.

### **2.2. Study population and sampling technique**

The Source population were Adults ( $\geq 15$  year) living with HIV who ever registered to chronic HIV care and support program in the facilities. All available 554 charts in the three hospitals that enrolled from September 1, 2009 to August 31, 2010, were included in the study. Those patients with missing chart or incomplete base line and follow up data were excluded.

### **2.3. Data collection procedures and tools**

All available information on patient records was checked and an appropriate data extraction format was prepared in English. Then, data was extracted from patients' charts by four trained nurses who had additional ART training and experience in HIV care. Two data clerk was used to support nurses by identifying the charts. Charts were retrieved using the patient's registration number which was found in data base in electronic system.

### **2.4. Data processing and analysis**

Data was checked for its consistence and completeness; then entered into a computer using EPI info version 7 and then exported to the SPSS version 20 for analysis. Data was entered by principal investigator and cleaned before analysis. Summary statistics was carried out to describe demographic, baseline and follow up data. Incidence Rate (IR) was calculated for entire study period. Life table was used to estimate cumulative survival (TB free) of PLWHIV. The Kaplan-Meier curve was used to estimate the median duration of TB occurrence. Log rank test was used to compare survival curves between the different categories of explanatory variables.

Both bivariate and multiple cox proportional hazard model were used to identify the predictors. The variables with P value  $< 0.25$  in the bivariate analysis were entered to multiple proportional hazard models. 95% confidence interval of adjusted hazard ratio was computed and variables having p value  $< 0.05$  in multiple proportional hazards model was considered as significantly and independently associated with dependent variables. The necessary assumption of cox proportional hazard model was checked using Schoenfeld residual test and graphically.

### **2.5. Ethical approval**

Ethical clearance was obtained from review board of Arba Minch University College of medicine and health science with a reference CMHS/PG/130/08. Letter of permission was obtained from the management (CEO) of the hospitals. The head of the HIV care clinics was giving the consent for extracting

data from records. Patient names and identification numbers was not extracted so as to ensure confidentiality of patient information.

### 3. RESULTS

Among, 554 patients remaining in the analysis, the mean age was 34.48 +/- 9.14 and almost half, 267 (48.2%) of them were in the age group 25-34 years. More than half 324(58.5%) of PLHIV were females and 337(6.8%) were Orthodox Christian. About 259 (46.8 %) of the participants were married and 207 (37.4%) have only primary level of education. More than half of then 315(56.7%) were have occupation in different level of work status. Majority, 499(90.1%), of the patients came from urban areas. A total of 487 (87.9%) patients had disclosed their HIV status to either their family, or other relatives. Most of the time they disclosed to their wife/husband and brother/sister which accounted 191 (34.5%) and 112(20.2%) respectively. Two hundred twenty six (40.8%) of the patients were substance users as shown in Table 1.

Table 1. Baseline Socio Demographic Characteristics of PLHIV on Chronic HIV Care at Hawassa City

Characteristics	Number/frequency	Percent
Age		
15-24	45	8.1
25-34	267	48.2
35-44	155	28.0
≥45	87	15.7
Sex		
Male	230	41.5
Female	324	58.5
Marital status		
Single	87	15.7
Married	259	46.8
Divorced	125	22.2
widowed	83	15
Religion		
Orthodox	337	60.8
Muslim	39	7
Protestant	168	30.3
Catholic	10	1.8
Level of education		
No education	105	19
Primary	207	37.4
Secondary	166	30
Tertiary	76	13.7
Occupation		
Yes	313	56.9
No	231	43.1
Address		
Urban	499	90.1
Rural	55	9.9
Disclosure		
Disclosed	484	87.8
Not disclosed	67	12.2
Substance use		
Used	226	41
Not used	324	59
Family size		
<2	296	53.8
3-4	201	36.6
>5	53	9.6

The eligibility criterion for initiation of HAART was mainly CD4 cell count in 316(57%). The predominant regimens initially prescribed were a combination of zidovudine, Lamivudine and Nevirapine (1c) 197(35.6%) followed by Stavudine, Lamivudine and Efavirenz (1d) (19.9%). One hundred forty (25.6%) patients had changed their initial regimen during the follow up period mainly to a combination of Tenofovir, Lamivudine and Efavirenz (1e) 85 (15.3%). Only 4(0.7%) patients were switched to second line HAART. The predominant reason for changing the initial regimen was drug side effect 117(21.1%) and followed by tuberculosis 6(1.1%). Half of the regimen was changed within the first two year of follow up period. About three fourth (73.6%) of them were on working functional status at baseline. Two hundred two (36.4%) and one hundred eighty eight (33.9%) of the participants were at WHO clinical stage two and three during

enrolment respectively. The median CD4 count during enrollment and end of follow up was 203 [IQR: 117-321] and 525[IQR: 368-696.5] respectively as shown in Table 2.

Table 2. Baseline Clinical and Immunological Status of PLHIV on Chronic HIV Cares at Hawassa city

Characteristics	Number	Percent
ART eligibility criteria		
CD4 count	314	57
WHO clinical stage	69	12.5
Both	168	30.5
Initial regimen		
1a(30)	100	18.1
1a(40)	89	16.1
1b(30)	6	1.1
1b(40)	43	7.8
1c	7	1.3
1d	197	35.6
1e	110	19.9
Other	2	0.4
Regimen change		
Yes	142	25.6
No	412	74.4
New regimen		
1b(40)	2	0.4
1c	3	6
1d	16	2.9
1e	85	15.3
Other	4	0.7
Reason for change		
Side effect	117	21.1
Pregnancy	4	0.7
TB	6	1.1
Not recorded	4	0.7
Other	11	2.7
Past TB history		
Yes	79	14.4
No	426	77.3
Not recorded	44	8.3
Functional status		
Working	405	73.6
Ambulatory	128	23.1
Bedridden	16	2.9
WHO clinical stage		
I	121	21.8
II	202	36.5
III	188	33.9
IV	43	7.8
CD4 count		
<50	38	6.9
51-150	140	25.3
151-250	169	30.5
251-350	82	14.8
>350	125	22.6

### 3.1. Tuberculosis incidence density

Five hundred fifty four study participants were followed for different periods for six years which gave us 1830.33 person years of observation. Within the follow up period, 161 new tuberculosis cases were observed. Hence, the overall TB incidence density rate (IDR) in the cohort was 8.79 per 100 Person Years. Study participants were followed for a minimum of 1 month and a maximum of 72 months. The mean follow up period was 39.5 months. Of the incident TB cases, 137(24.7%) were Pulmonary Tuberculosis and 24(4.3%) were Extra-Pulmonary or/and Disseminated Tuberculosis. One hundred fifteen (71.42%) of the TB cases were occurred within the first years of follow up. The highest incidence rate of TB was observed in the first year of enrolment (148.71/100 PY) and then decreased in the subsequent years of follow up (19.03 and 0.8 per 100PY in three and sixth years respectively). Similarly the number of TB incidence among ART started patients was decreased crossed the follow up period. This indirectly revealed that reductions in TB incidence rate following the stay on HAART. But the highest number of TB incident was observed on the newly ART started patients. The cumulative probability of TB survival at the end of one year, two year, three

year, four year and six year was 0.79, 0.75, 0.71 and 0.67 respectively. The median survival time from enrolment to chronic HIV care to TB occurrence is 60 months (Table 3 and Figure 1).

Table 3. Tuberculosis Incidence Density Rate Stratified by Socio-demographic Characteristics of PLHIV who were on Chronic HIV Care in Hawassa City

	Characteristics	Total	PY of Observation	TB	TB IDR/100 PY
Age	15-24	45	160.41	10	6.23
	25-34	267	872.67	79	9.04
	35-44	155	532.67	40	7.50
	≥45	87	263.58	32	12.14
Sex	Male	230	765.34	67	8.75
	Female	324	1,065	94	8.82
Marital status	Single	87	267.41	33	12.34
	Married	259	866.00	74	8.54
	Divorced	125	388.91	32	8.22
	Widowed	83	308.00	22	71.42
Religion	Orthodox	337	1070.7	106	9.90
	Muslim	39	130.08	16	12.30
	Protestant	168	598.70	37	6.18
Level of education	Catholic	10	32.52	2	6.15
	No education	105	286.50	34	11.86
	Primary	207	683.58	65	9.5
	Secondary	166	574.75	48	8.35
Occupation	Tertiary	76	285.50	14	4.9
	Yes	313	1064.08	85	7.98
	No	238	766.25	76	9.91
	Address	Urban	499	1653.91	145
Address	Rural	55	176.41	16	9.06
	Disclosure	Disclosed	484	1640.08	147
Substance use	Not disclosed	67	190.25	14	7.35
	Used*	226	1193.16	83	6.95
ART eligibility criteria	Not used	325	637.16	78	12.24
	CD4 count	314	1186.16	72	6.07
	WHO clinical stage	69	221.41	12	5.41
Initial regimen	Both	168	423.91	77	18.16
	1a(30)	100	286.33	31	10.82
	1a(40)	89	32.16	0	0.00
	1b(30)	8	103.16	23	22.29
	1b(40)	43	27.91	3	10.74
	1c	7	707.58	38	5.37
	1d	197	344.41	34	9.87
Past TB history	1e	110	325.41	32	9.83
	Yes	79	190.00	46	24.21
	No	426	1317.82	102	7.74
Functional status	Not recorded	44	167.91	13	7.74
	Working	405	1531.19	81	5.29
	Ambulatory	127	279.58	68	24.32
WHO clinical stage	Bedridden	16	27.5	12	55.81
	I	121	526.84	21	3.98
	II	202	709.16	47	6.62
	III	188	524.25	61	11.63
	IV	43	70.08	32	45.64
CD4 count	<50	38	107.50	18	16.74
	51-150	140	414.16	55	13.27
	151-250	169	544.75	48	8.81
	251-350	82	269.50	15	5.56
	>350	125	494.41	25	5.05
Year of follow up	≤1	161	77.33	115	148.71
	1-3	85	168.08	32	19.03
	≥3	311	1586.92	11	0.8
Enrolment status	Pre ART	422	1402.50	135	9.70
	ART	129	427.83	26	6.07

\*Substance used means those who used at least one of the following alcohol, tobacco or drugs

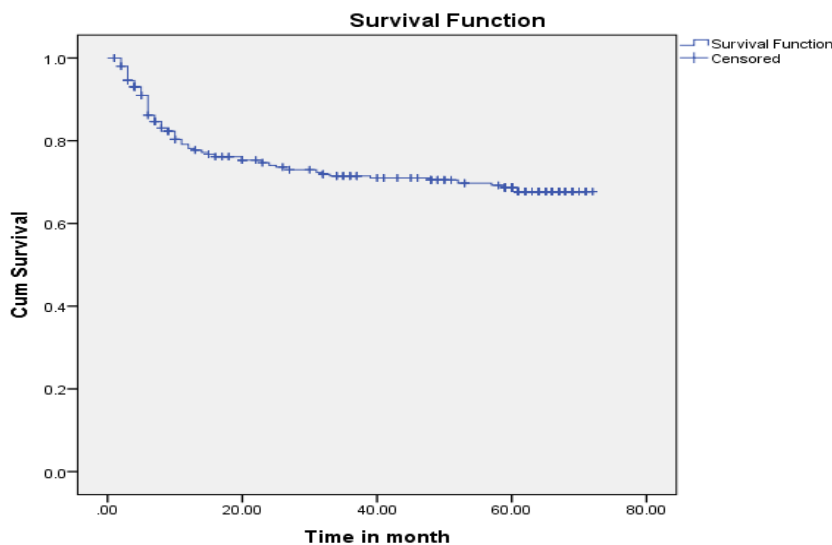


Figure 1. Kaplan-Meier curve of TB-free survival proportion for PLHIV on chronic HIV care at health facilities found in Hawassa city

### 3.2. Predictors of time to TB occurrence

In the multiple Cox-regression analysis level of education, substance use, past TB history, functional status at enrolment, CD4 cell count less than 50, WHO clinical stage IV and enrolment status (being on pre-ART or on ART) remained statistically significant predictors of TB Occurrence. Accordingly, people living with HIV who were ambulatory or bedridden at enrollment were about 3 times higher risk of Developing TB at any time as compared to those who were working (AHR=2.89, 95%CI: 1.72-3.78)). Compared with patients having tertiary level of education at enrolment, patients with no education 2.6 times tend to have higher incidence of TB (AHR= 2.68, 95%CI: 1.41-5.11). Those who were at WHO clinical stage IV had more than 3 times higher risk of acquiring TB at any time as compared to those with WHO clinical stage I or II (AHR=3.22, 95%CI: 1.91-5.41). Similarly, people living with HIV those who had past TB history were about 1.65 time higher risk of TB acquisition as compared to those who do not had (AHR=1.65, 95%CI: 1.06-2.39). In addition, people living with HIV who were substance use at enrollment were 1.46 times higher risk of Developing TB at any time as compared to those who were not addicted (AHR=1.46, 95%CI: 1.03-2.06). A patient with CD4 cell count less than 50 cell/ul was 2.41 times more likely to have TB at any time than a patient with a CD4 cell count greater than 250 cell/ul (AHR=2.41(1.31-4.42). Patients who were on pre ART at the enrolment were 1.62 times higher risk of TB acquisition as compared to those who were on ART as shown in Table 4.

## 4. DISCUSSION

The recent increase in worldwide prevalence of HIV infection has contributed to the rising global incidence of Tuberculosis [7]. In Ethiopia, infection with TB is a major public health problem with an estimated annual incidence of 207 cases per 100,000 populations for all forms of TB. HIV-positive people are 26 times at higher risk to develop TB compared to HIV-negative people in countries with a generalized HIV epidemic [6]. It is also the most common cause of death among people living with HIV [3].

In this study of HIV-infected adults who were in HIV chronic care in public health facility of Hawassa, we found that the incidence of TB was significantly higher (8.79/100PY). Patients within the first year following ART initiation had a temporary increased risk. Illiteracy, Past TB history, lower CD4 cell count, advanced WHO stage IV and enrolment status (being on pre ART) were associated with a higher risk of developing active TB. Accordingly, the overall incidence of TB was 8.79 per 100 Person-Years. It was similar with study conducted in Gonder [9], Ethiopia (7.88 per 100PY) because they use the same protocol with our study area and have the same socio-economic characteristics. But our finding was higher from study conducted in Nigeria (2.58/100PY) and Mozambique (2.32/100PY). This is because of methodological difference; they excluded patients on pre ART and the first three months after initiation of ART to minimize the effect of IRIS. Analysis that includes pre ART and the first 3 months after initiation of ART reported the highest TB incidence, as in our case [10].

The highest incidence rate of TB was observed in the first year of enrolment. TB incidence may rise during the initial months on ART (as in our case), which is largely due to ART-induced unmasking of subclinical active TB and delayed diagnosed of unspecific symptomatic patients in resource-limited settings. However, TB incidence declined with duration increment on ART, which likely reflects the concurrent CD4+ cell count increase and immune reconstitution due to ART. Because ART suppresses viral activity and promotes the restoration of the immune system, hence leading to a reduced risk of re-activating latent TB or of emerging opportunistic infections [10]-[18]. The result also showed that almost all of patients were started ART with in the first year of follow up which is responsible for IRIS. The other reason might be about 41.7 % of study participant enrolled to HIV chronic care service at their advanced WHO clinical stage (III &IV).

Table 4. Multiple Cox Regression Analysis of Predictors of Tuberculosis among PLHIV Cohorts on Chronic HIV Care at Health Facility Found in Hawassa

variables	Survival status	
	CHR(95%CI)	AHR(95%CI)
Level of education		
No educ.	1.34(0.99-1.80)	2.68(1.41-5.11)
Primary	1.12(0.88-1.45)	1.19(0.65-2.16)
Secondary	1.05(0.50-1.21)	1.5(0.81-2.78)
Tertiary	1	1
Substance use		
Used*	1.56(1.14,2.12)	1.46(1.03-2.06)
Not used	1	1
Past TB history		
Yes	2.45(1.32,4.53)	1.65(1.06-2.39)
No/not recorded	1	1
Functional status		
Working	1	1
Ambulatory/Bedridden	3.91(2.86,5.34)	2.89(1.72-3.78)
WHO clinical stage		
I/II	1	1
III	1.30(1.33,2.66)	1.17(0.79,1.75)
IV	6.26(4.10,9.57)	3.22(1.91-5.41)
CD4 count		
<50	3.05(1.78,5.33)	2.41(1.31-4.42)
51-250	1.87(1.29,2.69)	1.23(0.82,1.85)
≥251	1	1
Enrolment status		
Pre ART	1.51(0.99-2.30)	1.62(1.03-2.54)
ART	1	1

\*Substance used means those who used at least one of the following alcohol, tobacco or drugs

In the analysis, predictors that were significantly associated with increased risk of TB were past TB history, addiction, ambulatory or bedridden functional status WHO clinical stage IV and low CD4 cell count at baseline. All these predictors had already been identified in previous studies [13]-[15], [18]-[23]. In this study we found that the TB incidence was higher in patients with ambulatory or bedridden baseline functional status as compared to working functional status. This is in line with study conducted in Gonder (AHR=1.64, 95%CI: 1.13-2.38). This could be due to the fact that patients became bed reddened or ambulatory as result of affected by many infectious diseases when their CD4 cell count is low and as a result immunity became compromised the patients were eligible OIs including TB [9].

Illiteracy from the socio-demographic factors remained in the final model, by predicting the risk of developing TB. This finding was in line with study conducted in Brazil (AHR=1.95, 95%CI: 1.29-2.94). Poverty and illiteracy were closely associated; as a result those who were illiterate were expected to live unhygienic condition, unbalanced nutrition and lack of information or awareness (14, 24). WHO clinical stage IV had 3 times (AHR=2.93, 95%CI=1.72-4.98) higher risk of TB incidence than WHO clinical stage I or II, this is in line with study done in Gonder (AHR=3.82, 95%CI: 1.86-7.85) at Dare Salam, Tanzania 3.44(3.06-3.87) [18]. Another prospective study results which was also conducted in Tanzania shows similar (AHR=2.48, 95%CI: 1.88-3.26) there were many studies which was concurrent with our study [9]-[11], [15]-[18]. Even though, TB can occur at any WHO clinical stage it is more common in advanced clinical stage [8].

Baseline CD4 cell count of <50 cells/  $\mu$ l was a very strong and independent risk factor associated with a higher risk of TB in patients enrolled to chronic HIV care (AHR=2.41, 95% CI=1.31-4.42). In fact, the highest TB incidence (16.74 /100PY) in this cohort analysis was observed among patients with baseline CD4 count <50 cells/ $\mu$ l. Lower baseline CD4 count before initiation of ART has consistently been indicated

as an independent risk factor for occurrence of Tuberculosis during the course of HIV treatment and care in different settings [9],[13],[18],[22]. A study in West Africa has indicated that baseline CD4 count has no any association with the occurrence of TB during HAART [24]-[25]. This was because the study had limitations in design related to size of the study population, the number of TB cases, diagnostic criteria for tuberculosis and restricted cohort composition.

According to our results, high risk behaviors like substance use; to alcohol, tobacco or drugs were 1.46 times higher risk of developing TB than not used. These also identified as risk factors among non HIV positive peoples. These high risk behaviors might predispose HIV patients to TB infection factors [21]. According to our results, past TB history of infection was identified as risk factors. This might be because activation of latent TB on people who were immune compromised as a result of HIV infection than those who did not had history of TB infection [14], [21].

Since it was based on secondary data some of the important predictors which had a significant association with TB occurrence with other studies like body mass index were not included in the analysis due to incomplete registration of height in almost half of the charts and as well as Hemoglobin level. It is also difficult to know the exact date of tuberculosis occurrence as it is a chronic disease and not recorded the exact date of diagnosis which may over-estimate the median time of tuberculosis. Missing is another concern.

## 5. CONCLUSION

The burden of TB among pre ART enrollees was significant. Most of the cases (TB) were occurred in the first year of enrolment to chronic HIV care. Advanced WHO clinical stage (stage IV), limited functional status, past TB history, substance use, being on pre ART and low CD4 (<50cell/ul) count at enrollment were found to be the independent predictor of tuberculosis occurrence. Strengthen the importance of TB screening and early initiation of ART is very important to limit the time spent at low level of CD4 count regardless their CD4 count and WHO clinical.

## ABBREVIATIONS

**AHR:** Adjusted hazard ratio, **ART:** Anti-retroviral therapy, **HAART:** highly active antiretroviral therapy, **IDR:** incidence density rate, **OI:** opportunistic infection, **PLWHA:** people living with HIV/AIDS, **TB:** Tuberculosis, **VCT:** voluntary counseling and testing, **WHO:** world health organization.

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