

# Time to occurrence, predictors, and patterns of opportunistic infections incidence among HIV-positive patients attending Antiretroviral Therapy Clinic of Salale University Comprehensive Specialized Hospital

## A retrospective cohort study

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### Abstract

Opportunistic infections (OIs) in HIV patients are infections that are more common or more severe as a result of HIV-mediated immunosuppression. The advances in the capacity of antiretroviral therapy (ART) have diminished the incidence of OIs. However, even in the ART era, HIV-related OIs continue to be major causes of hospitalization and mortality. Therefore, this study aims to identify time to occurrence, predictors, and patterns of OIs incidence among HIV-positive patients attending ART clinic of Salale University Comprehensive Specialized Hospital, Ethiopia. A retrospective cohort study was conducted between 1<sup>st</sup> September 2016 and 1<sup>st</sup> September 2021. All 419 patients diagnosed during the study period were recruited. Data were extracted from both patient medical records and ART logbooks. Stata-16 was used for data analysis. Follow-up time was calculated from the date of HIV diagnosis to the date of OIs occurrence or censoring. Cox proportional hazards regression model was used to identify the predictors of OIs incidence. The total person-time of the follow-up was 8656 person-months of observation. During the follow-up time, 199 (47.49%) of the patients had developed OIs. The incidence rate of OIs was 23 (95%CI: 20, 26) per 1000 person-months of observation. The median OIs free survival time was 36 (95%CI: 31, 40) months. Predictors such as residence, cd4 category, baseline hemoglobin level, ART side effects, isoniazid preventive therapy, and chronic disease comorbidity were significantly predicted OIs incidence. The study area's OIs incidence remained high, requiring prompt action. To reduce the morbidity and mortality associated with OIs, HIV-positive patients with the predictors of rural residence, low CD4 category, low baseline hemoglobin level, ART side effects, not taking IPT, and baseline chronic disease comorbidity necessitate close follow-up and monitoring. Thus, we recommend focused and evidence-informed strategies to address OIs burden and improve outcomes.

**Abbreviations:** AIDS = acquired immuno-deficiency syndrome, ART = antiretroviral therapy, HAART = highly active antiretroviral therapy, HIV = human immuno-deficiency virus, LMICs = low- and middle-income countries, OIs = opportunistic infections, PICT = provider initiative counseling and testing, TB = tuberculosis, VCT = voluntary counseling test, WHO = World Health Organization.

**Keywords:** cohort, Ethiopia, HIV/AIDS, incidence, opportunistic infection, predictor

## 1. Introduction

HIV/AIDS (Human Immuno-deficiency Virus/Acquired Immuno-deficiency Syndrome) remains a major global public health concern, having claimed the lives of 36.3 million (27.2–47.8 million) people to date.<sup>[1]</sup> Opportunistic infections (OIs) continue to be the leading cause of HIV morbidity and mortality, accounting for significantly higher mortality seen in lower and middle-income countries (LMICs).<sup>[2]</sup> As a result, this is leading to a bigger financial and public burden.<sup>[3,4]</sup> Besides, OIs reduce the quality of life, increase stigma, accelerate the progression

to full-blown AIDS, reduce patients' response to antiretroviral therapy (ART) and limit one's ability to work.<sup>[4]</sup>

Globally, 1 in 3 HIV-positive people seeks health care for HIV/AIDS-related OIs.<sup>[1]</sup> OIs continue to affect HIV-positive patients in resource-limited settings due to a variety of factors including; level of literacy, WHO clinical stage, lower cd4 count, not taking OIs prophylaxis, poor treatment adherence, and low hemoglobin count.<sup>[5–8]</sup> However, reduced exposure, chemoprophylaxis (primary/secondary), immunization, and the initiation of ART are all stated as general strategies for preventing OIs.<sup>[9]</sup> Thus, interrupting OIs timely will not only benefits HIV-positive

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people who live longer lives, but it also helps to prevent transmission to others.<sup>[10]</sup>

OIs in HIV-positive people are infections that are more common or more severe as a result of HIV-mediated immunosuppression.<sup>[11]</sup> According to the Ethiopian ART guideline, the common OIs include herpes zoster, bacterial pneumonia, pulmonary tuberculosis (TB), extra-pulmonary TB, oral candidiasis, esophageal candidiasis, mouth ulcer, diarrhea, pneumocystis carinii pneumonia, central nervous system toxoplasmosis, Cryptococcal meningitis, nonHodgkin lymphoma, Kaposi sarcoma, cervical cancer, and others.<sup>[12]</sup> However, despite the incidence of OIs has decreased since the discovery of ART, the challenge of OIs in the era of ART is not well investigated in Ethiopia.<sup>[13]</sup>

Despite HIV/AIDS burden remaining high in Ethiopia, its interventions have been widely expanded over the last 2 decades by decentralizing free Highly Active Antiretroviral Therapy (HAART) in both public and private health facilities. Specifically, since 2018 general strategies like reduction of exposure, chemoprophylaxis, immunization, and starting ART are being implemented to prevent OIs. Regrettably, the high attrition rate is posing a challenge to management and resulting in the occurrence of complicated OIs.<sup>[14]</sup> As a result, OIs remain the leading cause of morbidity and mortality in HIV-infected patients in the country.<sup>[12]</sup>

Yet, empirical evidence concerning time to OIs occurrence among HIV-positive is deficient in Ethiopia. Because the frequently existing evidence generated so far are cross-sectional surveys with methodological limitations.<sup>[5,15–17]</sup> Thus, the identification of predictors and patterns of OIs using the most robust study design will help in the prevention of OIs and thus improve the lives of HIV-positive patients. Additionally, understanding the ideal time when OIs are most likely to occur helps tackle the presence of these complications. Therefore, this study aims to identify time to occurrence, predictors, and patterns of opportunistic infections incidence among HIV-positive patients attending ART clinic of Salale University Comprehensive Specialized Hospital, Ethiopia.

## 2. Methods

### 2.1. Study setting, design, and period

The study was conducted at Salale University Comprehensive Specialized Hospital. The hospital is the only Comprehensive Specialized Hospital found in the North Shewa zone of Oromia regional state and serves more than 1.6 million population in the catchment area. The ART clinic of the hospital was established independently in the year 2006 and currently, 1723 HIV-positive patients are on the active follow-up. The clinic provides care and treatment to HIV/AIDS patients including ART follow-up, voluntary counseling test (VCT), and provider initiative counseling and testing (PICT). ART will be initiated in the clinic in accordance with the national guideline of enrolling patients based on their eligibility for various regimens.<sup>[14]</sup> Furthermore, the follow-up and scheduling of the consecutive visits will be dictated by the framework for differentiated HIV service delivery in Ethiopian contexts.<sup>[12,14]</sup> A facility-based retrospective cohort study was conducted among HIV-positive adult patients (18 years old and above) who were on ART follow-ups between 1<sup>st</sup> September 2016 and 1<sup>st</sup> September 2021.

### 2.2. Sample size determination and sampling technique

The sample size was calculated by using the double population proportion formula. STAT CALC of Epi info version 7.2.2.6 software for cohort study was used to calculate the sample size with the assumptions of 95% confidence interval ( $Z_{1-\alpha/2} = 1.96$ ), 90% power ( $Z_{1-\beta} = 1.282$ ), and 1:1 ratio of unexposed to exposed. Thus, taking 53.9% of opportunistic infection

among unexposed and 36.4% of opportunistic infection among exposed by considering prophylaxis taken for opportunistic infection as a predictor variable.<sup>[8]</sup> Finally, after adding 10% contingency, the final sample size obtained was 406. However, the medical record of 494 patients that are diagnosed with HIV/AIDS since September 1<sup>st</sup>, 2016 was retrieved from HIV/AIDS logbook. Of these, 75 of them had incomplete data (outcome variable unrecorded). As a result, they were excluded from the current study. Finally, 419 patients who were on follow-up from 1<sup>st</sup> September 2016 to 1<sup>st</sup> September 2021 were study participants.

### 2.3. Measurements

The outcome variable for this study was the incidence of any form of opportunistic infection during the follow-up period. The predictors included; Socio-demographic predictors (age, sex, residence, marital status, occupation); Clinical predictors (WHO clinical stage, CD4 count, baseline hemoglobin (Hgb) level, body mass index (BMI), functional status, comorbid disease), and medication-related predictors (OI prophylaxis taken, type of baseline ART regimen, ART adherence level, ART side effects, and ART treatment failure) were measured. The data extraction tool was adapted from Ethiopian ART guidelines. The variables were extracted from the medical records of patients (ART follow-up log-book, laboratory results, and patients' cards).

### 2.4. Operational definition

**2.4.1. Time to develop opportunistic infection.** The time from HIV diagnosis to the occurrence of the event (i.e., OIs) during the follow-up period.

**2.4.2. Opportunistic infection(s).** The presence of 1 or more infections that occur among HIV-positive individuals.<sup>[9]</sup>

**2.4.3. Censored.** Adults who were lost to follow-up, transferred out to another health facility, and end of the study period before developing an opportunistic infection.

**2.4.4. Level of ART adherence.** Was classified into good, fair, or poor by the percentage of pill dosage calculated from the total monthly doses of ART drugs taken (Good > 95%, fair 85–94%, poor < 85%).<sup>[18]</sup>

**2.4.5. Low hemoglobin level (anemia).** Was defined as having a hemoglobin level < 10 mg/dl.<sup>[7]</sup>

**2.4.6. Body mass index (BMI).** As undernutrition (BMI < 18.49 kg/m<sup>2</sup>), normal (BMI 18.50–24.99 kg/m<sup>2</sup>), overweight (25.00–29.99 kg/m<sup>2</sup>), and obese (BMI ≥ 30.00 kg/m<sup>2</sup>).<sup>[18]</sup>

**2.4.7. Functional status.** Was defined in line with the definition of the national HIV care follow-up system: able to perform usual work in and out of the house (**working**), able to perform activities of daily living but not able to work (**ambulatory**); and not able to perform daily routine activities (**bedridden**).<sup>[18]</sup>

### 2.5. Data quality control

To maintain data quality, the data extraction checklist was adopted from a standardized Ethiopian ART guidelines follow-up. The checklist was also pretested on 5% of the actual sample of patients' medical records to ensure that the data was consistent and complete. Additionally, data collectors and supervisors received 2 days of training on how to review ART follow-up databases and medical records, as well as the study's aim. Furthermore, to avoid duplication and omission, the data collectors assigned a unique identifier to each patient chart.

## 2.6. Data processing and analysis

Before entry, data were checked for completeness and consistency. Epi Data Version 3.1 was used for data entry and STATA version 16 for analysis. Descriptive statistics were summarized using percentage, mean, and median, and displayed using tables and charts. The OIs free survival time was estimated using the Kaplan-Meier survival curve. Besides, the OIs free survival time between categorical explanatory variables was compared using a generalized log-rank test. Furthermore, the Cox proportional hazard model was fitted using both bivariable and multivariable to identify predictors of OIs. The variables with a  $P$ -value  $\leq 0.25$  in the bivariable analysis were a candidate for the multivariable model. In multivariable analysis, Adjusted Hazard Ratio (AHR) with 95% confidence interval (CI) was used to declare the strength of the association and variables with  $P$ -value  $< 0.05$  were considered independent predictors. The Cox regression model assumption of the proportional-hazard model was checked by Schoenfeld residuals (global test) ( $P$ -value = 0.3498) and the assumption was not violated. Multicollinearity was checked using variance inflation factor (at  $VIF \geq 10$ ) and there was no multicollinearity detected.

## 2.7. Ethical clearance

Ethical approval was obtained from Salale University's ethical review committee. Besides, a permission letter was obtained from Salale University Comprehensive Specialized Hospital. Also, names and other personal identifiers were removed to ensure the confidentiality of the subjects.

## 3. Results

### 3.1. Sociodemographic characteristics

In this retrospective cohort study, 419 HIV-positive patients were enrolled. The median (IQR) of age was 35 (42). About 224 (53.46%) of the participants were females and 241 (57.52%) were married. Slightly more than half, 219 (52.27%) were attended primary school (1–8 grade) and almost two-thirds, 280 (66.83%) were orthodox religion followers. Moreover, a third, 142 (33.89%) were urban residents (Table 1).

**Table 1**  
Sociodemographic characteristics of HIV-positive patients attending antiretroviral therapy clinic of Salale University Comprehensive Specialized Hospital, 2021 (n = 419).

Variable	Categories	Frequency (percentage)
Age category	15–24	47 (11.22)
	25–34	154 (36.75)
	35–44	152 (36.28)
	45+	66 (15.75)
Sex	Female	224 (53.46)
	Male	195 (46.54)
Educational status	No formal education	31 (7.40)
	Primary (grade 1–8)	219 (52.27)
	Secondary (grade 9–12)	106 (25.30)
	diploma and above	63 (15.04)
Residence	Urban	277 (66.11)
	Rural	142 (33.89)
Marital status	Single	110 (26.25)
	Married	241 (57.52)
	Divorced	38 (9.07)
	Widowed	30 (7.16)
Religion	Orthodox	280 (66.83)
	Muslim	67 (15.99)
	Protestant	72 (17.18)

### 3.2. Clinical and treatment-related characteristics

The median (IQR) baseline cd4 count was 384 (284). About 202 (48.21%) patients were in stage1 baseline WHO clinical stage. The median (IQR) hemoglobin was 12.5mg/dl (4.5) and more than a fourth, 114 (27.21%) had a lower hemoglobin level of  $< 10$ mg/dl. Moreover, slightly more than two-thirds, 283 (67.54%) of the patients were on the first-line ART. Also, nearly three-fourths, 310 (74%) of the patients had a good level of treatment adherence. Of the total, more than one-third, 153 (36.52%) had developed ART side effects. As well, 1 in 5, 87 (20.76%) of the patients had 1 type of baseline chronic disease. Of the patients with chronic diseases; hypertension is the most existing disease—28 (32.18%) followed by diabetes mellitus—24 (27.59%) and heart failure—16 (18.39%) (Table 2).

### 3.3. Incidence of opportunistic infections during follow-up

The patients were followed for a minimum of 2 months and a maximum of 60 months. The total person-time of the follow-up was 8656 person-months of observation. During the follow-up time, almost half, 199 (47.49%) of the patients had developed OIs. The incidence rate (IR) of OIs among the patients was 23 (95% CI: 20, 26) per 1000 person-months of observation.

### 3.4. Kaplan-Meier opportunistic infections free survival time

In this cohort, the median OIs free survival time was 36 (95% CI: 31, 40) months. The OIs free survival probability of the cohorts at the end of the follow-up period was 0.29 (95% CI: 0.36, 0.22) (Fig. 1).

### 3.5. Patterns of opportunistic infections incidence

Of the incidence of opportunistic infections, slightly more than a fourth was pulmonary Tuberculosis, 50 (25.13%) followed by oral candidiasis, 25 (12.56%), and bacterial pneumonia, 21 (10.55%) respectively (Table 3).

### 3.6. Survival function and comparison of survival experience

At any time during the follow-up, significant difference in time to occurrence of OIs in log rank test among categorical variables strata were seen in resident setting (Log rank  $\chi^2 = 19.91$ ,  $P$  value  $< 0.001$ ), baseline cd4 (Log rank  $\chi^2 = 13.96$ ,  $P$ -value  $< 0.001$ ), baseline hemoglobin (Log rank  $\chi^2 = 7.77$ ,  $P$ -value = 0.005), ART side effect (Log rank  $\chi^2 = 64.90$ ,  $P$ -value  $< 0.001$ ), isoniazid preventive therapy (Log rank  $\chi^2 = 8.49$ ,  $P$ -value = 0.003), and comorbid disease (Log rank  $\chi^2 = 63.20$ ,  $P$ -value  $< 0.001$ ).

### 3.7. Predictors of opportunistic infections incidence

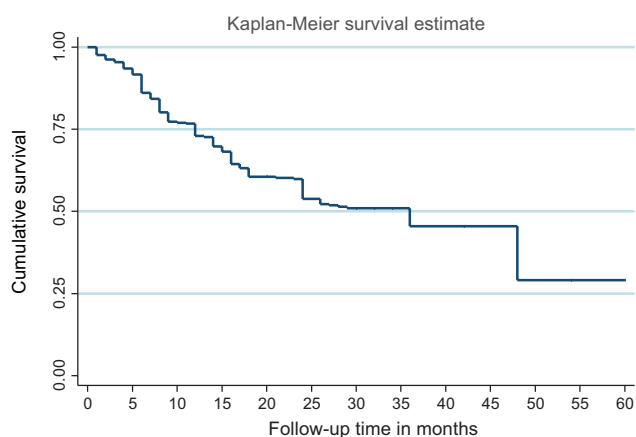
In the multivariable cox regression analysis predictors such as residence, cd4 category, baseline hemoglobin level, ART side effects, isoniazid preventive therapy, and chronic disease comorbidity were significantly predicted the occurrence of OIs incidence at any given time during the period of follow-up.

Accordingly, rural residents had nearly 2 times the higher hazard of OIs incidence than urban residents (AHR = 1.84, 95% CI: 1.39, 2.45). Similarly, patients who had low cd4 counts ( $< 200$ ) had almost 2 times the higher hazard of OIs incidence than their counterparts (AHR = 1.75, 95% CI: 1.15, 2.67). Besides, patients who had low hemoglobin levels ( $< 10$  mg/dl) had a 1.56 times higher hazard of OIs incidence than patients who had hemoglobin levels of  $\geq 10$  mg/dl (AHR = 1.56, 95% CI: 1.15, 2.12). Patients who had a history of ART side effects had more than twice hazard of OIs incidence as compared to those who

**Table 2**

**Clinical and treatment-related characteristics of HIV-positive patients attending antiretroviral therapy clinic of Salale University Comprehensive Specialized Hospital, 2021 (n = 419).**

Variable	Categories	Frequency (percentage)
Baseline cd4 count	>201	376 (89.74)
	≤200	43 (10.26)
Baseline WHO clinical stage	Stage 1	202 (48.21)
	Stage 2	133 (31.74)
	Stage 3	49 (11.69)
	Stage 4	35 (8.35)
Baseline hemoglobin (mg/dl)	<10	114 (27.21)
	≥10	305 (72.79)
ART regimen	1 <sup>st</sup> line	283 (67.54)
	2 <sup>nd</sup> line	130 (31.03)
	3 <sup>rd</sup> line	6 (1.43)
History of ART side effects	Yes	153 (36.52)
	No	266 (63.48)
ART adherence level	Good	310 (73.99)
	Fair	80 (19.09)
	Poor	29 (6.92)
History of treatment failure	Yes	68 (16.23)
	No	351 (83.77)
Functional status	Working	317 (75.66)
	Ambulatory	76 (18.14)
	Bedridden	26 (6.21)
Baseline chronic disease	Yes	87 (20.76)
	No	332 (79.24)



**Figure 1.** Kaplan-Meier of opportunistic infection-free survival time among HIV-positive patients at Salale University Comprehensive Specialized Hospital, 2021 (n = 419).

do not have a history of ART side effects (AHR = 2.42, 95%CI: 1.80, 3.25). Moreover, those patients who did not take isoniazid preventive therapy (IPT) had a 1.44 times higher hazard of OIs incidence than those patients who did take IPT (AHR = 1.44, 95%CI: 1.01, 2.07). Lastly, the risk of developing OIs incidence among patients who had chronic disease comorbidity was 2.39 times higher than their counterparts (AHR = 2.39, 95%CI: 1.77, 3.24) (Table 4).

#### 4. Discussion

Regardless of the availability and utilization of ART, OIs continue to cause wide-ranging morbidity and mortality in HIV/AIDS patients, notably in LMICs.<sup>[2]</sup> Thus, this cohort study was conducted to identify time to occurrence, predictors, and patterns of OIs incidence among HIV-positive patients attending the ART clinic of Salale University Comprehensive Specialized Hospital, Ethiopia. Accordingly, the overall incidence rate of

**Table 3**

**Patterns of opportunistic infections incidence among HIV-positive patients attending antiretroviral therapy clinic of Salale University Comprehensive Specialized Hospital, 2021.**

Types of opportunistic infections	Frequency (percentage)	95% CI for percentage
Pulmonary tuberculosis	50 (25.13)	(19.26, 31.75)
Oral candidiasis	25 (12.56)	(8.29, 17.98)
Bacterial pneumonia	21 (10.55)	(6.65, 15.68)
Skin diseases	18 (9.05)	(5.45, 13.92)
Cryptococcal meningitis	17 (8.54)	(5.05, 13.33)
CNS toxoplasmosis	15 (7.54)	(4.28, 12.13)
Chronic/acute diarrhea	12 (6.03)	(3.15, 10.29)
Extra pulmonary tuberculosis	12 (6.03)	(3.15, 10.29)
Esophageal candidiasis	11 (5.53)	(2.79, 9.67)
Pneumocystis carinii pneumonia	10 (5.03)	(2.44, 9.05)
Others*	8 (4.02)	(1.75, 7.77)

\*Herpes simplex virus, Kaposi sarcoma, bacterial sepsis.

OIs was 23 (95% CI: 20, 26) per 1000 person-months of observation. Consistent with this result other studies also stipulate the rate of OIs.<sup>[19,20]</sup> This determines that the burden of OIs continues challenging patients and health care systems<sup>[21]</sup> not only in LMICs but also in populations where access to medical care is deemed adequate.<sup>[22]</sup>

According to the patterns of OIs incidence observed in this study, pulmonary TB (25.13%) was the leading OI, followed by oral candidiasis (12.56%) and bacterial pneumonia (10.55%). This is aligned with a previous study from India that showed TB (53.4%) and oral Candidiasis (27.2%) were the leading OIs.<sup>[23]</sup> As well, Pulmonary TB was the top OI detected in both preART and On-ART groups in Addis Ababa, Ethiopia.<sup>[13]</sup> The similarity in socio-demography, study population, and settings might result in equivalent findings. Furthermore, another study from Korea reported that oral candidiasis (16.2%) was the leading OI. Similar to a current study, findings from Ethiopia revealed bacterial pneumonia (16.3%) amongst the top OI.<sup>[5]</sup> Comparability in the eligibility criteria and age of the recruited patients leads to similar results.

This study demonstrates the risk of OIs incidence among rural residents was higher than urban residents. This is because rural patients face significantly more barriers to access treatment than urban. The previous studies from the USA<sup>[24,25]</sup> confirmed this. Furthermore, rural residents were not only the risky group for the occurrence but also for the recurrence of OIs<sup>[15]</sup> due to low income, lower level of education, and limited access to health care. Additionally, patients who had low cd4 counts had a higher hazard of OIs incidence than their counterparts because a weakened cellular immunity increases the risk of OIs incidence. This is in line with studies conducted in Korea,<sup>[26]</sup> India,<sup>[27]</sup> and eastern Ethiopia.<sup>[8]</sup>

Besides, patients who had low hemoglobin levels had a higher hazard of OIs incidence than patients who had lower hemoglobin levels. Two studies from Ethiopia have reported similar findings.<sup>[5,28]</sup> Anemia has been associated with progression to AIDS and advanced complications among HIV-positive patients.<sup>[29,30]</sup> Furthermore, the history of ART side effects predicts the incidence of OIs. Because, drug side effects would result in ART discontinuation and poor treatment adherence, hastening disease progression and increasing the incidence of OIs.<sup>[31]</sup>

Moreover, those patients who did not take IPT had a higher hazard of OIs incidence than those patients who did take IPT. A comparable result was reported from a study in eastern Ethiopia.<sup>[8]</sup> This is because IPT use has a recognized impact in reducing a major OI such as TB.<sup>[32]</sup> Also, the risk of developing

**Table 4**

**Bi-variable and multivariable Cox-regression analysis of predictors of opportunistic infections incidence among HIV-positive patients attending antiretroviral therapy clinic of Salale University Comprehensive Specialized Hospital, 2021.**

Predictors	Categories	Survival status		CHR (95%CI)	AHR (95%CI)
		Events (n = 199)	Censored (n = 220)		
Sex	Male	89	106	1.34 (1.01, 1.77)	1.20 (0.89, 1.62)
	Female	110	114	1	1
Residence	Rural	87	55	1.84 (1.39, 2.44)	<b>1.84 (1.39, 2.45)*</b>
	Urban	112	165	1	1
CD4 category	< 200	28	15	2.06 (1.38, 3.08)	<b>1.75 (1.15, 2.67)*</b>
	≥ 200	171	205	1	1
Baseline WHO clinical stage	Stage 4	20	15	1.49 (0.92, 2.43)	0.98 (0.56, 1.71)
	Stage 3	30	19	1.74 (1.14, 2.64)	1.77 (0.15, 2.72)
	Stage 2	61	72	1.05 (0.76, 1.46)	1.01 (0.72, 1.43)
	Stage 1	88	114	1	1
Baseline hemoglobin	< 10 mg/dl	63	51	1.50 (1.11, 2.03)	<b>1.56 (1.15, 2.12)*</b>
	≥ 10 mg/dl	136	169	1	1
ART side effects	Yes	112	41	2.92 (2.20, 3.87)	<b>2.42 (1.80, 3.25)*</b>
	No	87	179	1	1
IPT taken	No	40	25	1.64 (1.15, 2.32)	<b>1.44 (1.01, 2.07)*</b>
	Yes	159	195	1	1
Chronic diseases comorbid	Yes	75	12	2.99 (2.24, 4.02)	<b>2.39 (1.77, 3.24)*</b>
	No	124	208	1	1
Baseline Body Mass Index	>24.5	31	25	1.80 (1.15, 2.82)	1.16 (0.71, 1.89)
	<18.5	117	99	1.73 (1.24, 2.41)	1.25 (0.89, 1.79)
	18.5–24.9	51	96	1	1

\*Significant at *P* value < 0.05.

AHR = adjusted hazard ratio, ART = antiretroviral therapy, CHR = crude hazard ratio, IPT = isoniazid preventive therapy.

OIs incidence among patients who had baseline chronic disease comorbidity was higher than their counterparts in this study. This could be because the baseline immune compromise caused by chronic disease enables the occurrence of OIs. Also, as confirmed by a previous study, chronic disease increases the likelihood of OIs recurrence.<sup>[13]</sup>

#### 4.1. Limitation of the study

This is a 5-year follow-up study, and all patients were recruited throughout that time. However, as this is a retrospective study, the interpretation of the findings should take into account the following limitations. First, other undocumented confounders such as patients' level of knowledge and access to appropriate health services could affect the findings. Second, there could have been bias in the interpretation of the medical records.

#### 5. Conclusion

The study area's OIs incidence remained high, requiring immediate action to achieve the Ethiopian Health Sector Transformation plan's goal of reducing HIV/AIDS and its complications by the end of 2025, as well as the targets of the Sustainable Development Goals.<sup>[33]</sup> To reduce the morbidity and mortality associated with OIs, HIV-positive patients with the predictors of rural residence, low CD4 category, low baseline hemoglobin level, ART side effects, not taking IPT, and baseline chronic disease comorbidity necessitate close follow-up and monitoring. Thus, we recommend focused and evidence-informed strategies to address OIs burden and improve outcomes. Furthermore, additional studies employing a prospective design to measure the undocumented predictors in this study will be beneficial.

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