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ORIGINAL RESEARCH

Prevalence Of Undernutrition And Associated Factors Among Adults Receiving First-Line Antiretroviral Treatment In Public Health Facilities Of Arba Minch Town, Southern Ethiopia

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Introduction: Access to antiretroviral drugs for all infected persons in need is a global health priority. The primary goals of initiating antiretroviral drugs are to suppress human immunodeficiency virus viral replication and to restore immune function. However, adequate nutrition is necessary to manage opportunistic infections and to maintain the immune system. Therefore, this study aimed to determine the recent prevalence of undernutrition and associated factors among HIV patients receiving first-line antiretroviral therapy in public health facilities of Arba Minch town, Gamo zone, Southern Ethiopia.

Methods: Institution-based cross-sectional study was used among 333 adult patients receiving first-line antiretroviral therapy at public health facilities of Arba Minch town. A simple random sampling technique was used to select the study subjects. Data were collected through interviewer-administered questionnaires. Binary and multivariable logistic regression analyses were used to identify factors associated with undernutrition. A p-value <0.05 with a 95% confidence level was used to declare statistical significance.

Results: The overall prevalence of undernutrition among adult patients receiving first-line antiretroviral therapy is 23.72% (95% CI: 19.13-28.27%). Current substance use (AOR=1.83, 95% CI:1.09-3.08), duration on antiretroviral therapy (AOR=1.87, 95% CI:1.06-3.30), not taking cotrimoxazole preventive therapy (AOR=2.09, 95% CI:1.15-3.82), advanced WHO clinical stages (AOR=5.1, 95% CI: 2.9-7.7), CD4 count less than 350 cell/mm³ (AOR=1.83, 95% CI: 1.09–3.05) and active tuberculosis (AOR=1.89, 95% CI: 1.02-3.53) were factors significantly associated with undernutrition among respondents who were enrolled on first-line antiretroviral therapy.

Conclusion: This study shows that the prevalence of undernutrition was high among adult patients on first-line antiretroviral therapy. Therefore, this finding shows the need to implement nutrition programs to improve the nutritional status of adults living with HIV in the study area. The interventions should emphasise those patients who use the substance, who are in advanced WHO clinical stage and have active tuberculosis. Besides, emphasis should be given for patients to undertake cotrimoxazole preventive therapy and to regularly follow their CD4 count.

Keywords: under nutrition, first-line antiretroviral therapy, adult, Ethiopia, HIV

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Plain English Summary

Globally, human immune deficiency virus remains the leading cause of morbidity and mortality. Ethiopia is one of the countries that have the highest number of people living with HIV/ AIDS. First-line antiretroviral therapy is given for all people living with HIV to improve quality of life by repairing immunologic function through suppression of viral load. However, nutritional status of the patient is one of the problems that affect the effectiveness of first-line antiretroviral therapy. Therefore, this study aims to determine the recent prevalence of undernutrition and to identify predisposing factors among adults enrolled on first-line antiretroviral therapy in public health facility of Arba Minch town, Southern Ethiopia, that may help for patient, clinical and policymaker for early intervention on factors like nutritional status of HIV/AIDS patients for better outcomes of first-line antiretroviral therapy.

Introduction

Acquired Immune Deficiency Syndrome (AIDS) is a disease caused by a retrovirus known as human immunodeficiency virus (HIV). Even though significant progress has been made in reducing the annual number of AIDS-related deaths and in preventing new HIV infections, the number of people living with HIV (PLWHA) continues to increase.¹

Globally, the human immune deficiency virus remains the leading cause of morbidity and mortality.^{2–4} Worldwide, 36.7 million people are living with HIV/AIDS, and there were 1 million AIDS-related deaths in 2016.¹ Sub-Saharan Africa was the one severely affected by HIV/AIDS.^{1,4} Ethiopia is one of the sub-Saharan countries severely affected by HIV/AIDS in which 720,000 people are living with HIV, and the total annual AIDS deaths were 33,357 in 2016.³

Combination antiretroviral therapy (ART) has demonstrated efficacy in suppressing HIV replication, improving immune function and decreasing HIV-related morbidity and mortality. Access to these antiretroviral (ARV) drugs for all HIV-infected persons in need is a global health priority; currently, 12 million individuals are receiving antiretroviral therapy (ART), and a rapid scale-up in the number of individuals receiving ART is in progress. To scale up and decentralize ART services in Ethiopia, there are increasing numbers of health facilities providing ART, and similarly, the number of patients getting ART services is increasing.

Evidence shows that people living with HIV (PLWHA) are more likely to become undernourished due to reduced food intake, poor absorption of nutrients, and changes in the way the body uses the nutrients it receives or has stored.^{5–7} In Ethiopia, prevalence of undernutrition ranged from 12.3%⁸ to 43%.⁹

Despite advocacy for nutrition services for people living with HIV, there is a clear paucity of information on the actual nutritional status of adults after being enrolled in first-line ART in developing countries.¹⁰ In Ethiopia,

routine surveillance for undernutrition among adults after being enrolled in first-line ART has not been conducted, and there are limited data on the prevalence and predisposing factors. Therefore, this study was designed to assess the prevalence of undernutrition and its associated factors among PLWHA after they enrolled in first-line ART in the public health facility of Arba Minch Town, Southern Ethiopia. Hence, this study intended to assess contextual factors of undernutrition among PLWHA who may help to understand the relationships between HIV, undernutrition, and first-line ART which are important implications for the effective integration of nutritional interventions into HIV programs. This study also expected to add to the existing knowledge about factors that affect nutrition status among adult PLHIV and thus vital in optimizing therapeutic success. Moreover, identifying such predictors provides useful information to improve care and inform treatment guidelines. Also, the outcome of this study helps the health care professional to anticipate the possible factors by early change to appropriate intervention. This study provides additional information and tools to bridge the knowledge gap and to improve the quality of patient care and treatment outcomes, which is the current challenge in many ART programs.

Methods

Study Area And Period

This study was conducted in Arba Minch town from February 15th to March 10th, 2018. Arba Minch is located about 445 km south west of Addis Ababa, the capital, and 275km from Hawassa. The town is situated 1285 meters above sea level. Arba Minch town has one general Hospital and one public health center, which provides ART service. Arba Minch hospital was among the first few public hospitals to start ART in Ethiopia in August 2003, and Arba Minch Health Center also started ART care by the end of 2007. 11 According to the Gamo zone, the health department reports the Arba Minch hospital, and Arba Minch health center provides HIV/AIDS interventions, including free diagnosis, treatment, and monitoring. There are multidisciplinary professional teams that include physicians, nurses, public health professionals, laboratory technologists, pharmacists, data clerks, and volunteer adherence supporters. ART was provided for people living with HIV regardless of CD4 count and the World Health Organization clinical stage classification.

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Study Design

A cross-sectional study is conducted to assess the prevalence of undernutrition and identify associated factors among adults receiving first-line antiretroviral treatment in Public health facilities of Arba Minch town, Southern Ethiopia.

Source And Study Populations

All adult people living with HIV (PLWHA) who were enrolled in first-line ART at the center are source population for this study. All adult PLWHA who were enrolled in first-line ART at the time of the study and who fulfill the inclusion criteria are study population for this study.

Inclusion Criteria And Exclusion Criterion

All adults living with HIV/AIDS whose age ≥18 years who started first-line ART and had a follow-up for their treatment in public health facilities of Arba-Minch town at the time of the study were included, but pregnant women, lactating mothers (6 months of postpartum), and those seriously ill were excluded from this because those groups require additional nutrients than others.

Sample Size Determination

The sample size for this study is determined using a single population proportion formula using Epi-Info Version 7. The following assumption was considered, CI of 95%, power of 80%, 5% marginal error and P=27% prevalence of undernutrition among adults with HIV/AIDS on first-line ART was taken from study conduct in East Wollega Zone. ¹⁰ and 10% of non-response rate. The final sample size was determined as 333.

Sampling Procedure And Sampling Techniques

Both Arba Minch general hospital and Arba Minch health center were included in this study. The total number of study participants were identified in each health facility. Then proportional to size allocation was applied for each health facility. A simple random sampling technique was used to select the study participants. Finally, the randomly selected the study participant was identified and interviewed at place arrange for an interview.

Operational Definition Or Measurement

To define nutritional status, standard cutoff points were used. If an individual's BMI was less than 18.5 kg/m², the individual was considered undernourished, and if the individual was considered normal if BMI was 18.5–24.9 kg/m²; when it was greater than or equal to 25.0 kg/m², the individual was considered overweight.^{5,11}

Substance use was assessed using items derived from the World health Organization (WHO) Model, Substance Use Core Questionnaire. ¹² For this study, it is defined as drinking alcohol, chewing khat, smoking cigarettes and illicit drugs for lifetime and at present (last 30 days) because those are only substances that are commonly known in Ethiopia. ^{13,14}

Disclosure Status: For this study, it is defined as the act of informing HIV-positive status to any one (sexual partner, parents, families or friends or others).^{3,15}

Data Collection Procedure And Data Quality Control

A structured interviewer-administered questionnaire was used to collect the data. Information on clinical characteristics such as CD4 cell count, WHO clinical staging, ART start date, ART treatment regimen, ART adherence, functional status and type of preventive therapy used were obtained from the individual patient care charts for the interviewed patients. Weight and height measurements for the study respondents were measured and recorded at the start of the interview. Training was given for data collectors and supervisors. Pretesting of the data collection tool was done in 17 patients receiving first-line ART in the nearby health center before actual data collection. The data collectors were regularly supervised for proper data collection as well as checked for completeness and consistency throughout the data collection period by the supervisor and the principal investigator.

Anthropometric Data

The weight and height of the study participants were measured. The height and weight of the patients were measured in light clothing and bare foots calibrated to 0.5cm and 0.5 kg, respectively. The participants' weight was measured in kilograms with 0.5 kg increments using standard beam balance, and the scale was checked at zero during measurement. The participant height was measured using a Seca vertical height scale standing upright in the middle of the board and height was recorded to the nearest 0.01 cm. BMI (weight (kg)/height² (m)) was calculated to

assess nutritional status. The standard cutoffs were used to define nutritional status.

Data Processing And Analysis

The collected data were coded, cleaned and entered by Epidata version 3.0 and exported to Statistical Package for Social Science (SPSS) version 20.0 for analysis. Descriptive statistics were described in terms of mean (SD) and median (IQR) for continuous data and frequency distribution for categorical data. Bivariable and multivariable logistic regression analyses were performed to see the association between dependent and independent variables. Variables that have a P-value of less than 0.25 in the bivariable analysis were entered in a multivariable logistic regression model. Finally, multivariable logistic regression model was used for controlling confounding factors and to identify significant factors associated with dependent variables. The results of multivariable logistic regression with the backward method after checking of model fitness test by Hosmer and Lemeshow as well as an omnibus test which had non-significant and significant test results were tested, respectively. And also, multicollinearity was checked by using the standard error of greater than 2 indicating that there was no multicollinearity. At the end AOR with 95% CI, P-value < 0.05 was considered statistically significant.

Ethics Approval And Consent To Participate

Appropriate ethical clearance is taken from the ethical review board of Arba Minch University College of Medicine and Health Science with reference number CMHS/10987/18. A support letter was obtained from Zonal Health Department as per the recommendation letter from the public health department. This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was secured from study participants after explaining the objective and purpose of the study to each study participant. Study participants' confidentiality was maintained. No personal identifiers were used in data collection forms, and the recorded data were not accessed by a third person, except the principal investigators.

Result

Socio-Demographic Characteristics Of Respondents

From 333 adult PLWHA receiving first-line ART, the majority 252 (75.68%) was from Arba Minch general

hospital. The mean age (SD) of the respondents was 33.05 (±9.09) years, and 154 (46.24%) of the study participants were in the 25- to 34-year age group. Among the study participants, 188 (56.46%) were females, 262 (78.68%) were rural resident and 179 (53.45%) were married. Regarding the occupational status of the respondents, the majority of 86 (25.83%) were merchants. Concerning the educational status of the respondents, 141 (42.34%) were attending secondary school. Among respondents, 148 (44.44%) were using a substance during the data collection period (Table 1).

Clinical And ART-Related Characteristics Of Respondents

This study reveals that a patient's median (IQR) duration of ART treatment was 10 (7–20.50) months. The median (IQR) weight was 55 (48–61) kg and median (IQR) CD4 counts of respondents were 185 (92–315) cells/µL. Concerning the WHO clinical stage, the majority of 117 (35.14%) of study participants were in clinical stage III and ninety-six (28.83%) of the study participants had active TB during the data collection period. Regarding adherence to ART, 243 (72.97%) had good adherence (>95%) (Table 2).

Nutritional Status Of Adult

The prevalence of undernutrition among adults living with HIV who were enrolled in first-line ART at public health facilities of Arba Minch town was 23.72% (95% CI: 19.13–28.27%). The prevalence of undernutrition was higher among females than males [47 (59.49%) and 32 (40.51%), respectively]. Among study participants, 61 (77.22%) undernutrition adults had a follow-up at the hospital.

Factors Associated With Nutritional Status Of The Respondents

After adjusting the effect of other variables, an adult who used substances increased the odds of developing undernutrition compared to those who did not use substances [AOR=1.84, 95% CI: 1.09 -3.08]. Similarly, this study showed that adults receiving ART who were ARV drugs less than 12 months were 1.87 times more malnourished than those who took the drug for more than 12 months [AOR=1.87, 95% CI: 1.06–3.30].

This study revealed that odds of developing malnutritionundernourishment among adults receiving ART who did not undergo cotrimoxazole preventive therapy Dovepress Oumer et al

Table I Socio-Demographic Characteristics of People Living with HIV who were Enrolled in First-Line Antiretroviral Therapy at a Public Health Facility of Arba Minch Town, Southern Ethiopia, 2018

Variables	Categories	Frequency	Percent	
Name of health facilities	Hospital	252	75.68	
	Health center	81	24.32	
Age (years)	18–24	46	13.81	
	25–34	154	46.25	
	35–44	90	27.03	
	45+	43	12.91	
Sex	Male	145	43.54	
	Female	188	56.46	
Marital status	Never married	100	30.03	
	Married	179	53.75	
	Divorced	35	10.51	
	Widowed	19	5.71	
Educational status	No education	36	10.81	
	Primary	118	35.44	
	Secondary	141	42.34	
	Tertiary	38	11.41	
Religion	Orthodox	206	61.86	
	Muslim	10	3.00	
	Protestant	92	27.63	
	Catholic	23	6.91	
	Others*	2	0.60	
Residence	Urban	262	78.68	
	Rural	71	21.32	
Ethnicity	Gamo	132	39.64	
	Gofa	61	18.32	
	Wolayita	59	17.72	
	Amhara	47	14.11	
	Oromo	23	6.91	
	Others**	Ш	3.30	
Occupational status	Housewife	79	23.72	
	Private employee	45	13.51	
	Merchant	86	25.83	
	Government	59	17.72	
	employee			
	Student	37	11.11	
	Farmer	27	8.11	
Current substance use	Yes	148	44.44	
	No	185	55.56	
Disclosure status	Disclosed	134	40.24	
	Not disclosed	199	59.76	

Notes: *Adventist, Gova; **Konso, Gurage, Slite, Tigre.

were 2.09 times greater than the odds of an adult receiving ART who underwent cotrimoxazole preventive therapy [AOR=2.09.95% CI:1.15-3.82]

Table 2 Clinical Characteristics of People Living with HIV who were Enrolled in First-Line Antiretroviral Therapy at the Public Health Facility of Arba Minch Town, Southern Ethiopia, 2018

Variables	Categories	Frequency	Percent	
Duration on ART	<12 months	213	63.96	
	≥12 months	120	36.04	
Last CD4 count	<350 cells/mm³	155	46.55	
	≥350 cells/mm³	178	53.45	
Current WHO clinical stage	Stage I	125	37.54	
	Stage II	67	20.12	
	Stage III	117	35.14	
	Stage IV	24	7.21	
Current functional status	Working	273	81.98	
	Ambulatory	40	12.01	
	Bedridden	20	6.01	
Active tuberculosis	Yes	96	28.83	
	No	237	71.17	
Cotrimoxazole preventive therapy	Yes	200	60.06	
	No	133	39.94	
Isoniazid preventive therapy	Yes	225	67.57	
	No	108	32.43	
ART adherence in the past month	<95%	90	27.03	
	≥95%	243	72.97	
Initial regimen changed	Yes	26	7.81	
	No	307	92.19	

This study found that the odds of developing malnutrition among adult PLWHIV who have a CD4 count of less than 350cell/mm³ were 1.83 times more likely to develop malnutrition than those who have CD4 count greater than 350cell/mm³ [AOR=1.83, 95% CI: 1.09–3.05]. Similarly, those who have active tuberculosis during the data collection period were 1.89 times more likely to develop malnutrition than those who have no tuberculosis during the data collection period [AOR=1.89, 95% CI: 1.02–3.53].

In this study, odds of developing undernutrition were 5.1 times higher among adults who were in advanced WHO clinical staging during data collection as compared to an adult who was in mild WHO clinical staging during the data collection period [AOR=5.10, 95% CI: 2.90–7.70] (Table 3).

Discussion

This study intended to identify the prevalence of undernutrition and associated factors among adult HIV/AIDS patients who are on first-line ART in Arba Minch town Oumer et al Dovepress

Table 3 Factors Associated with Undernutrition Among People Living with HIV who were Enrolled in First-Line Antiretroviral Therapy at the Public Health Facility of Arba Minch Town, Southern Ethiopia, 2018

Variable	Nutritional Status		COR (95% CI)	AOR (95% CI)	P-value
	Undernutrition	Normal			
Sex					
Female	47 (25%)	141 (75%)	1	1	1
Male	32 (22.07%)	113 (77.93%)	1.18 (0.71, 1.97)	1.42 (0.83, 2.42)	0.203
History of substance use					
Yes	30 (20.27%)	118 (79.73%)	1.42 (0.85, 2.38)	1.84 (1.09, 3.08)	0.022**
No	49 (26.49%)	136 (73.51%)	1	1	
Disclosure status					
Disclosed	26 (19.40%)	108 (80.59%)	1	1	
Not disclosed	53 (26.63%)	146 (73.37%)	0.66 (0.39, 1.13)	1.37 (0.81, 2.31)	0.25
Duration on ART					
<12 months	56 (26.29%)	157 (73.71%)	0.69 (0.40, 1.21)	1.87 (1.06, 3.30)	0.032**
≥I2 months	23 (19.17%)	97 (80.83%)	1	1	
WHO clinical stage					
Stage I or II	71 (36.98%)	121 (63.02%)	1	1	
Stage III or IV	8 (5.67%)	133 (94.33%)	9.76 (4.51, 21.09)	5.10 (2.90, 7.70)	0.0001**
Cotrimoxazole preventive therapy					
Yes	38 (19.00%)	162 (81.00%)	1	1	
No	41 (30.83%)	92 (69.17%)	0.53 (0.32, 0.88)	2.09 (1.15, 3.82)	0.016**
Isoniazid preventive therapy					
Yes	55 (24.44%)	170 (75.56%)	1	1	
No	24 (22.22%)	84 (77.78%)	1.13 (0.66, 1.96)	1.06 (0.56, 1.99)	0.854
Last CD4 count					
<350cells/mm ³	32 (17.98)	146 (82.02%)	1.99 (1.19, 3.32)	1.83 (1.09, 305)	0.021**
≥350 cells/mm³	47 (30.32%)	108 (69.68)	1	1	
TB incident					
Yes	18 (18.75%)	78 (81.25%)	1.53 (0.83, 2.71)	1.89 (1.02, 3.53)	0.045**
No	61 (25.74%)	176 (74.26%)	1	1	

Note: **P-value \leq 0.05 statistically significant. I = Reference category.

Abbreviation: CI, confidence interval.

public health facilities. A considerable proportion of HIV/AIDS patients, 23.7% (95% CI: 19.13–28.27%), were identified as undernourished. This finding was similar to the findings of other studies conducted in East Wollega zone, West Shewa zone and Felega Hiwot referral hospital of Ethiopia. ^{5,10,16} However, this finding was higher than the study conducted in Dill University referral hospital of Ethiopia and lower than studies done in North West Ethiopia and East Hararge zone. ^{9,17} These variations might be related to the difference in socio-economic and demographic-related characteristics of the study participants. In addition, it might be due to the difference and improvements in healthcare services.

In this study, the prevalence of undernutrition among adult HIV/AIDS patients on first-line ART was significantly associated with the use of substances like alcohol drinking, khat chewing and cigarette smoking. Substance users were approximately two times more likely to be undernourished than non-substance users. This finding was in line with the studies conducted in East Hararge zone and Northwest Ethiopia. ^{9,15} This might be due to using substances exposed individuals to loss of appetite and poor adherence to ART which in turn leads to poor immunity and under nutritionot. ¹⁶

This study depicted that having CD4 cell count below threshold level was significantly associated with having a Dovepress Oumer et al

higher probability of developing undernutrition among adult PLWHIV on ART. The odds of developing undernutrition among adult PLWHIV who have a CD4 count of less than 350cell/mm³ were 1.83 times higher than those who have CD4 count greater than 350cell/mm³. The finding was supported by the study conducted in Northwest and West Shewa zones of Ethiopia. This might be because patients with low baseline CD4 cell count have poor immunity and are more prone to opportunistic infections that might favor the probability of developing undernutrition.

The advanced WHO clinical staging of the patient was associated with undernutrition among the study participants. The odds of developing undernutrition were 5.1 times higher among adults PLWHIV who were in advanced WHO clinical staging during data collection as compared to an adult who was in mild WHO clinical staging. This finding was supported by studies conducted in Ethiopia as well as by a study conducted in Nepal.^{6,8,16} This might be because patients with advanced disease stage are more susceptible to develop comorbid opportunistic infections. Thus, additional treatment for opportunistic infections and the regular first-line ART might worsen the side effects like loss of appetite and poor nutritional status of the patients and compromise their resistance to the disease.⁴

The finding of this study revealed that infection with tuberculosis was significantly associated with the nutritional status of the patients. Those who have active tuberculosis were 1.89 times more likely to develop undernutrition than those who have no active tuberculosis. This finding was supported by studies conducted in East Wollega Zone, West Shewa Zone of Ethiopia and two public ART centers of Nepal. 6,10,16 The possible explanation for this could be patients infected with tuberculosis usually develop weight loss, appetite loss, and wasting.

The duration of PLWHIV on ART was one of the factors significantly affecting the nutritional status of the patients. In this study, those who were on ARV drugs for less than 12 months were 1.87 times more undernourished than those who took the drug for more than a year. The finding of this study was consistent with the study conducted in Felege Hiwot Referral Hospital and in East Hararge Zone of Ethiopia. This might be associated with adherence to ARV treatment contentiously and consistently throughout the life of an individual would help to improve the overall status of the patients as well as their nutritional status.

The initiation of cotrimoxazole preventive therapy at the start of ART was associated with the nutritional status of the patients. According to this study, odds of developing undernourishment among adults receiving ART who not initiated cotrimoxazole preventive therapy were 2.09 times greater than the odds of an adult receiving ART who initiated cotrimoxazole preventive therapy. The finding of this study was supported by a study conducted in a tertiary health facility of Northeastern Nigeria. ¹⁸ This might be due to the antimicrobial effect of cotrimoxazole on some bacterial diseases such as pneumonia, diarrhea, malaria, and other opportunistic infections that may help to improve the overall status of the patients. ⁴

Limitations

The limitation of this study is related to a cross-sectional study design which could not accurately show the cause and effect relationship. This study has a limitation of not considering laboratory-related variables due to the shortage of budget and time. There was also a limitation of measuring micronutrient deficiencies to assess nutritional status. However, this study shows a recent prevalence of undernutrition, especially among adult patients enrolled in first-line ART that may help for better effectiveness of HIV/AIDS interventions.

Conclusion

This study shows that the prevalence of undernutrition was high among adult patients on first-line antiretroviral therapy. Therefore, the implementation of nutrition programs to improve the nutritional status of adults living with HIV in the study area is vital. The interventions should emphasise those patients who use the substance, patients in advanced WHO clinical stage and patients who have active tuberculosis. In addition, emphasis should be given for the patients to undergo cotrimoxazole preventive therapy and for regular follow-up of their CD4 count. Moreover, effort should be taken by stakeholders in different hierarchies to improve the nutritional status of patients under first-line ART to increase treatment effectiveness.

Abbreviations

AIDS, acquired immune deficiency syndrome; AOR, adjusted odds ratio; ART, antiretroviral therapy; CI, confidence interval; COR, crude odds ratio; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; OI, opportunistic infection; OR, odds ratio; PLWHA, people living with HIV/AIDS;WHO, world health organization.

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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