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ORIGINAL RESEARCH

Magnitude of Hypertension and Associated Factors Among Human Immunodeficiency Virus Positive Adults Receiving Anti-Retroviral Therapy at Debre Markos Referral Hospital, Northwest, Ethiopia

This article was published in the following Dove Press journal: HIV/AIDS - Research and Palliative Care

Yihenew Sewale¹ Abebe Dilie Afenigus (D² Dessalegn Haile 1002 Wondimeneh Shibabaw Shiferaw (1)

¹Department of Nursing, College of Health Science, Debre Berhan University, Debre Berhan, Ethiopia; ²Department of Nursing, College of Health Science, Debre Markos University, Debre Markos, Ethiopia

Background: People living with human immunodeficiency virus are at increased risk for cardiovascular diseases such as hypertension. Current evidence on the proportion of hypertension is essential to inform policymaker to strengthen interventions and regular monitoring of hypertension, yet information is scarce concerning hypertension in this

Objective: This study aimed to assess the magnitude of hypertension and associated factors among human immunodeficiency virus-positive adults receiving antiretroviral therapy at Debre Markos Referral Hospital, Northwest Ethiopia.

Methods: A facility-based cross-sectional study was employed. Data were collected from systematically selected 412 participants using pre-tested, interviewer administered structured questionnaire. Data were entered and coded using Epi-data version 3.1 and analyzed using STATA version 14. The assumption of the logistic regression model was checked using a correlation matrix and Hosmer and Lemeshow's tests. Bivariate and multivariate logistic regression analyses were conducted.

Results: In the present study, the prevalence of hypertension among human immunodeficiency virus-positive adults who received antiretroviral therapy was found to be 41.3% (95% CI; 36.7-46.0). Age groups 35-45 years (AOR: 2.48, 95% CI: 1.17, 5.27), greater than 45 years (AOR: 5.00, 95% CI: 2.190, 11.44), no physical exercise (AOR: 2.72, 95% CI: 1.33, 5.57), body mass index greater than or equal to 25 kg/m² (AOR: 2.87 95% CI: 1.52, 5.39), and antiretroviral therapy regimens of 2 h/2f/2e/ABC+3TC+ATV/r (AOR: 3.05, 95% CI: 1.41, 6.60) were significantly associated with hypertension.

Conclusion: In the current study, the magnitude of hypertension was high among HIVpositive adults. Therefore, educating about the use of lifestyle change, counseling the use of regular physical activities, promoting weight reduction, and intervention in this situation are highly recommended.

Keywords: hypertension, HIV, ART

Introduction

Hypertension is defined as systolic blood pressure (SBP) values ≥130 mmHg and/or diastolic blood pressure (DBP) values ≥80 mmHg. It can be divided into stage I which is SBP 130-139 mmHg and/or 80-89 mmHg and Stage II SBP≥140 mmHg and/or DBP ≥90 hypertension.¹

Correspondence: Yihenew Sewale Tel +251921578419 Email yihenewsewale I 23@gmail.com



Globally, there are an estimated 1.13 billion people with hypertension, of these most are living in low-and middle-income countries.² It leads to variety of cardiovascular diseases and accounts for about 45% of deaths due to heart disease and 51% of deaths due to stroke.^{3,4}

World Health Organization (WHO) reported that approximately 34% of Ethiopian population died from non-communicable diseases (NCDs). This report also revealed that the magnitude of cardiovascular disease including hypertension was responsible approximately 15%.⁵

Human Immunodeficiency Virus/Acquired Immune Deficiency syndrome (HIV/AIDS) is a major public health problem in the world. Nearly 1 in every 20 adults living with HIV and accounting for nearly 70% of the people living with HIV worldwide. Worldwide, approximately 36.8 million people are living with HIV/AIDS in 2017.⁷ Sub-Saharan Africa is the most affected region, with 25.6 million people living with HIV and accounts for twothirds (2/3rd) of the global total of new HIV infections. A study conducted in Vietnam showed that the numbers of new HIV cases, new AIDS case and deaths from AIDS have tended to decline steadily, with annual decreases of 13.98% in people newly infected with HIV, 2.31% in new AIDS patients, and 9.65% in deaths from AIDS.⁸ The increased ART use has reduced the HIV-related mortality rate, from an estimated 2 million deaths in 2005 to 1 million in 2018. 9,10 However, in the same period, cardiovascular disease mortality rates more than doubled in people living with HIV.¹¹

Evidence showed that approximately 35% of all HIV-positive adults on ART have hypertension, compared with an estimated 30% of persons with not HIV. HIV-positive adults receiving antiretroviral therapy with hypertension also have a higher risk of cardiovascular events and mortality than persons without HIV with hypertension. A study which was conducted in American veterans on HIV-positive adults on ART and uninfected adults showed that HIV-positive adults on ART with hypertension had a 2-fold higher risk for cardiovascular events as compared to HIV-negative adults with hypertension. 16

Hypertension is responsible for cardiovascular mortality in HIV-positive adults receiving ant-retroviral therapy. The mechanisms of hypertension (HTN) in HIV-positive adults before the introduction of highly active antiretroviral therapy (HAART) were often associated with complications related to HIV. Though the origin of progressive vascular damage in HIV-positive

adults is not clear, some studies suggested that the possibility of HAART may cause hypertension after HAART initiation. ¹⁹ A study conducted in Italy confirmed higher rates of hypertension among HIV-positive adults on ART compared to uninfected adults. ²⁰ Likewise, the studies which are conducted in Sub-Sahara Africa showed that prevalence of hypertension among HIV-positive adults was high. ^{21,22} However, the study conducted in South Africa also showed that hypertension was less common among HIV-positive adults. ²³

Though factors responsible for hypertension are multifactorial, evidence showed that pro-inflammatory impact induced by HIV infection on vascular endothelium would increase the risk of hypertension.²⁴ Several studies showed that smoking,²⁵ stress,²⁶ and kidney dysfunction²⁷ were significantly associated factors for hypertension in people living with HIV.

Studies conducted in Ethiopia found that the magnitude of hypertension was ranged from 12.7%²⁸ to 29.7%.²⁹ These studies documented factors associated with hypertension such as diabetes mellitus, body mass index (BMI), drinking alcohol, CD4 count <500 cell/mL, and duration of HAART.^{28,29} In Ethiopia, the government design different strategies to achieve sustainable development goal (SDG) #3. For example, national consolidated ART care and reduced by one-third premature mortality from noncommunicable diseases, yielding marked success in reduction of HIV and hypertension patient morbidity and mortality, respectively.^{30,31}

Despite the seriousness of the problem, a few studies have been conducted to evaluate factors that responsible to hypertension among HIV-positive adults. Therefore, this study aimed to identify factors associated with hypertension and its magnitude. The results obtained from the current study will improve the quality care of clients in the study area and similar settings of Ethiopia.

Methods

Study Design and Setting

A facility-based cross-sectional study was employed at Debre Markos Referral Hospital from February to March 2020. The Hospital is located in Debre Markos Town, northwest of Ethiopia and which is 300 km away from the capital city of Addis Ababa. It was constructed in 1957 to work for approximately 25,000 people, but now it is serving more than 3.5 million people. In the hospital, about 3220 patients were HIV/AIDS-infected adults who

received antiretroviral therapy and had to undergo followup care, of these 1220 males and 2000 females.³²

Population

In this study, the source and study population were all HIV-positive adults who received anti-retroviral therapy and available during the data collection period at the Debre Markos Referral Hospital ART clinic. We excluded patients who were pregnant and developed hypertension before antiretroviral therapy.

Sample Size Determination and Sampling Procedures

We estimated the adequate sample size based on the study

objectives. For the first objective, the sample size was calculated using a single population proportion formula by considering the following statistical assumptions $z^{a/2} = 1.96 = \text{at}$ confidence level of 95%, d= margin error = 5%, p= population proportion (29.7%) of hypertension among HIV-positive adults receiving antiretroviral therapy which was taken from a study conducted in northeast Ethiopia, $z^{29} = \frac{z^{a/2} p(1-p)}{dt} = \frac{z^{20}}{dt}$

 $\frac{(1.96)^20.297(1-0.297)}{(0.05)^2}$ = 321 Finally, after adding a 10% non-response rate, the final sample size for the first objective was 353.

For the second objective, the sample size was calculated by considering age, sex and duration of HAART as the major statistical significant variables²⁹ using Epi info version 7 statistical software. This calculation provided a sample size of 412 patients (Table 1). Finally, we took the largest sample size, and a total of 412 patients attended the ART clinic of Debre Markos Referral Hospital.

Sampling Procedures

An average patient who was attending an ART clinic for the last six months (July–November 2019) was 3220 on ART care in the study facility, of which 412 participants were selected. A systematic random sampling was employed to select the participants. The sampling interval (kth) was estimated by dividing the total HIV-positive adults receiving anti-retroviral therapy hospital allocated sample size. $k = \frac{N}{n} = k = \frac{3220}{412} = 8$ The first sample was selected randomly from attending patients, and then every (kth) sample was selected for collecting information until the required sample was achieved from the study participant of daily follow-up.

Covariates of the Study

The main outcome variable for this study was hypertension. The explanatory variables were sociodemographic characteristics, including age of the participants, sex, residence, occupation educational status and family size. Clinical-related factor information included CD4 count, viral load, ART adherence, WHO stage, OI, ART duration, ART regimen, prophylactic and comorbidity diseases, and lifestyle-related factors such as smoking, alcohol consumption, physical inactivity, chat chewing, and stress.

Operational Definitions

- Hypertension: a patient having a systolic blood pressure (SBP) of ≥130 and/or a diastolic blood pressure (DBP) of ≥80 mm Hg with two measurements apart of 2 minutes.¹
- Adherence to ART: The recent adherence status of the adult to ART is recorded as poor when an adult takes less than 85% of the dose, fair when he/she takes 85–94% of the dose and good when he/she takes 95% and above of the dose.³⁰

Table I Sample Size Calculations to Assess the Magnitude of Hypertension and Associated Factors Among HIV-Positive Adults Who
Received Antiretroviral Therapy at Debre Markos Referral Hospital, 2020

Factors		%	Power	CI	Odd Ratio	Sample Size	Adding 10% Non-Responses	Total Sample Size
Age (years)	≤45year >45year	23.9 53.8	80%	95%	2.08	105	П	116
Sex	Male Female	39.3 24.9	80%	95%	1.64	374	38	412
Duration of HAART	<5 years ≥5 years	20.7 40.9	80%	95%	1.91	197	20	217

- Comorbid disease: a chronic disease with a confirmed diagnosis of the disease other than HIV infection.³⁰
- Opportunistic infections/diseases: is the list of opportunistic diseases documented on national comprehensive HIV prevention, care, and treatment.³⁰

Data Collection Procedures and Quality Control

An interviewer administered and structured questionnaire was employed to collect the data. The questionnaires were adapted and modified into the local context from previous works in the literature. 16,33-41 To measure blood pressure the patient's arm was bare and supported, use a cuff size appropriate for the patient arm (length of the bladder should be 80%, and the width of the bladder should be at least 40% of the circumference of the upper arm), the lower edge of cuff 3 cm above elbow crease, did not talk or moved before or during the measurement, legs uncrossed and feet flat on the floor. The average of at least two BP measurements spaced 2 minutes apart should be taken, and the average was used in the analysis. 42 To assure data quality, the tool was first prepared in English and then translated to Amharic and back to English. In addition, daily supervision was performed by principal investigators. Two-day training was given for data collectors concerning the data collection tool and data collection process. The tool was pretested on 10% of the total sample size at Debre Markos Health Center. Data were collected at the time of ART care follow-up by interviewing all participants who were attended to the ART clinic of Debre Markos Referral Hospital. Additionally, clinical data were obtained by reviewing the chart. Four bachelors degree nurses working in the ART clinic of Debre Markos Referral Hospital were participated as data collectors. Furthermore, collected data were checked for completeness and consistency during the data management, storage, and analysis by the research team members.

Statistical Analysis

Data were entered into EPI DATA version 3.1, and further analysis was performed using STATA version 14.1 statistical packages. Descriptive statistics, like frequency and percentage, were used depending on the nature of the variable. The assumption of the logistic regression model was checked using a correlation matrix and Hosmer and Lemeshow's tests. Binary logistic

regression analysis was computed to assess the associations of the independent variables with hypertension. In the bivariable analysis variables with a p-value of less than 0.2 were entered into the final model. Variables with a p-value of \leq 0.05 at multivariable analysis were considered as significantly associated with the outcome variable. The strength of association between independent and outcome variables was assessed using adjusted odds ratio (AOR) with 95% confidence interval (CI).

Results

Sociodemographic Characteristics of the Study Participants

A total of 412 HIV-positive adults attending the ART clinic at Debre Markos Referral Hospital were included. The response rate of this study was 100%. About 56.3% of respondents were females and the majority (82.2%) from urban areas. The mean (±SD) age of the study respondents was 43.12 (±11.29) years. Regarding marital status, approximately 43.9% were married, more than one-fifth (21.8%) were governmentally employed, less than one-third (30.6%) were unable to write and read, nearly two-thirds (61.9) had a family size of 1–3, more than two-thirds (69.9%) were nutritionally unsupported and counseled, and the majority (84.2%) had no family history of hypertension (Table 2).

Lifestyle-Related Characteristics

Most (95.1%) of the participants were non-smokers. One-fourth (26.9%) of the participants used alcohol, and the majority (87.1%) and 96.4% of the participants did not undergo physical exercise, and did not chew chat, respectively. Among all participants, one –fourth (26.5%) had symptoms of stress, of which more than half (67.9%) experienced symptoms within less than six months duration, more than one –fourth (26.5%) of participants experienced symptoms of frequency once a month, and approximately half (48%) participants were at a moderate (4–7) level of stress (Table 3).

Clinical-Related Characteristics

The majority (83%) of participants were in the world health organization stage of I&II, more than one-fourth (27.9%) had less than 350 cell/µL CD4, more than one-third (38.4) of participants had received ART for greater than or equal to 10 years, and approximately one-fifth (22.6%) had taken prophylaxis, of which the majority (80.6%) were taking CPT. Approximately fifth (5.1%) of the participants had diabetes millets, of which the majority

Table 2 Socio-Demographic Characteristics of the Study Participants at Debre Markos Referral Hospital Northwest, Ethiopia 2020

Variables	Frequency	Percent
	(Number)	(%)
Sex		
Male	180	43.7
Female	232	56.3
Age groups		
18-34 years	86	20.9
35-45 years	164	39.8
>45 years	162	39.3
Residence		
Rural	73	17.7
Urban	339	82.3
Marital status		
Married	181	43.9
Single	45	10.9
Divorced	97	23.5
Windowed	89	21.6
Occupation		
Daily laborer	65	15.8
Governmental employee	90	21.8
Private worker	81	19.7
Farmer	44	10.7
Merchants	69	16.7
Others	63	15.3
Education		
Unable to write and read	126	30.6
Able to read and write	36	8.7
Primary school	94	22.8
Secondary school	102	24.8
College/university	54	13.1

(85.3%) were type II diabetes millets. The majority (88.1%) and one-tenth (11.9%) of participants had good and fair/poor ART adherence, respectively. More than one-third (44.9%) were low literacy due to fair/poor adherence. Most (97.8%) participants did not develop comorbidities. Among participants in the study, 337 (81.80%) had a body mass index less than twenty-five, and one-third (30.6%) developed OI, of which more than one-third (34.9%) of participants developed herpes zoster and URTI. Among the participants in the study, one-third (32.5%) were taking the HAART regimen of 1e (TDF+3TC+EFV), two-fifths (38.1%) were taking 1J (TDF+3TC+DTG), and one-fifth (18%) were taking 2h (TDF+3TC+ATV/r)/2f (AZT+3TC+ATV/r)/2e (AZT+3TC+LPV/r)/(ABC+3TC+LPV/r). The

Table 3 Lifestyle-Related Characteristics of Study Participants at Debre Markos Referal Hospital Northwest, Ethiopia, 2020

Variables	Frequency	Percent (%)
Smoking		
Yes	20	4.9
No	392	95.I
Current smoker	2	10
Ex. Smoker	18	90
Alcohol use		
Yes	111	26.9
No	301	73.1
Khat		
Yes	15	3.6
No	397	96.4
Physical exercise		
Yes	53	12.9
No	359	87.I
Stress in the past month		
Yes	109	26.5
No	303	73.5

majority (92.7%) of respondents did not develop comorbidities.

Magnitude of Hypertension Among HIV-Infected Patients

In the present study, the overall magnitude of hypertension was 41.3% (95% CI: 36.7–46.0), of these 86 (20.9%) stage I and 84 (20.4%) stage II hypertension among HIV positive adults who received antiretroviral therapy.

Associated Factors of Hypertension Among HIV-Positive Adults

In bivariable logistic regression analysis, variables with (P-valve <0.2) were age, sex, marital status, occupation, educational status, household family size, nutritional support and counseling, body mass index, family history of hypertension, alcohol, physical inactivity, stress, duration of HAART, prophylaxis therapy, HAART regimen, OI, DM, drugs for comorbidities, CD4, viral load and stage of WHO. In the multivariable analysis, only four variables were identified as significantly associated factors of hypertension. Age group (35–45) and (>45) years participants were 2.48 (AOR=2.48, 95% CI: 1.17, 5.27) and 5.00 (AOR, 5.00, 95% CI: 2.19, 11.43) times more likely to develop hypertension, respectively, compared to age group (18–34) years. Participants

who did not have regular physical exercise were 2.72 times higher risk of hypertension compared with those who did physical exercise (AOR=2.72, 95% CI: 1.33, 5.57). Moreover, participants who had a body mass index greater than or equal to twenty-five (≥25 kg/m²) were 2.87 (AOR=2.87, 95% CI: 1.52, 5.39) higher odds of hypertension compared to less than twenty-five. Finally, this study found that participants who were taking the regimen of (2 h (TDF+3TC+ATV/r)/2f (AZT+3TC+ATV/r)/2e (AZT+3TC+LPV/r)/ABC+3TC+ATV/r) were 3.058 (AOR=3.058, 95% CI: 1.416, 6.605) times more likely to develop hypertension compared to participants who were taking regimens of 1e (TDF+3TC+EFV) (Table 4).

Discussion

This study aimed to evaluate the proportion and associated factors of hypertension among HIV-positive adults who received antiretroviral therapy at Debre Markos Referral Hospital, Northwest Ethiopia. In line with the study objective, it has demonstrated that a magnitude of hypertension was found to be 41.3% (95% CI: 36.7, 46.0). This finding is in line with previous studies conducted in Cameroon 36.44% (95% CI: 30.15–43.10)⁴³ and USA at the University of Florida 34.7% (95% CI: 27.4–42.8).⁴⁴

However, our finding was lower than studies conducted in Malaysians (45.60%)⁴⁵ and in South Africa (73.8%).⁴⁶ Conversely, this study finding is much higher than studies conducted in Ethiopia 12.7% (95% CI: 9.8–16.2),²⁸ northeast Ethiopia 29.7% (95% CI, 25.3–35.0%),²⁹ Cameroon 24.8% (95% CI: 20.1–30.0),⁴⁷ Malawi 23.7% (95% CI: 21.1–26.6),³⁹ and United States 22% (95% CI: 21–24).⁴⁸ The above disparity between studies could be elucidated by the study settings, cut-off point of blood pressure, ART duration and regimens, and life style related factors of the study participants.

The current study shows that older age, no physical exercise, BMI≥25 kg/m², and regimen of HAART were significant factors associated with hypertension. The current study showed that older age was significantly associated with hypertension. The finding is consistent with studies reported from Ethiopia, ²⁹ Zimbabwe, ³⁶ Malaysia, ⁴⁵ and the US. ⁴⁸ This would be explained that aging causes a loss in vessel function by stiffening of the arterial vasculature, and vascular changes include the advanced reduction in viscoelastic properties of vessels, progressive atherosclerotic arterial disease, and hypertrophy/sclerosis of muscular arteries and arterioles, which narrow the vessel wall and make resistance to blood pressure. ⁴⁹

Table 4 The Bivariable and Multivariable Logistic Regression Analysis of Associated Factors of Hypertension at Debre Markos Referral Hospital Northwest, Ethiopia, 2020

Variables	Hypertension		COR (95%)	AOR (95%)	P-value
	Yes	No			
Age groups					
18-34 years	16(3.9%)	70(17%)	1	1	
35-45 years	64(15.5%)	100(24.3%)	2.80(1.49,5.27)	2.48(1.17,5.27)	0.017
>45 years	90(21.9%)	72(17.4%)	5.46(2.92,10.22)	5.00(2.190,11.44)	0.000
Physical exercise					
Yes	30(7.3%)	23(5.6%)	1	1	
No	140(34%)	219(53.2%)	0.49(0.27,0.87)	2.72(1.33,5.56)	0.006
Body mass index					
<25 kg/m ²	122(29.6%)	215(52.2%)	1	1	
≥25 kg/m²	48(11.7%)	27(6.5%)	3.13(1.86,5.27)	2.87(1.52,5.39)	0.001
HAART regimens					
le(TDF+3TC+EFV)	43(10.4%)	91(20.1%)	1	1	
IJ(TDF+3TC+DTG)	66(16.0%)	91(20.1%)	1.53(0.94,2.48)	1.30(0.71,2.39)	0.413
2h/2f/2e/ABC+3TC+AT	39(9.5%)	35(8.50%)	2.36(1.31,4.22)	3.05(1.41,6.60)	0.004
V/r					
cand f	14(3.4%)	15(3.6%)	1.97(0.87,4.45)	1.44(0.56,3.74)	0.415
Others	8(1.9%)	10(2.4%)	1.69(0.62,4.59)	1.24(0.37,4.12)	0.893

Note: NB: Ic: AZT-3TC-NVP; If: TDF+3TC+NVP.

The present study found that physical inactivity was statistically associated with hypertension. This finding is in line with previous studies conducted in southern Ethiopia, 50 Uganda, 51 and the USA, 52 Evidence also support that physical exercise help to prevent the development of hypertension by decreasing vascular resistance, arterial stiffness, oxidative stress, decreasing body weight/mass, rennin-angiotensin system activity, decreasing stress and increasing endothelial function, and lumen diameter. 42 Additionally, a high body mass index was statistically associated with hypertension. This finding is in consistent with studies conducted in Ethiopia, 28,29 Uganda, 51 Zimbabwe, 36 Cameroon, 43 and Malaysia. 45 A possible explanation for this finding is that an increase in body mass index leads to activation of the RAAS, renal compression, increased plasma leptin and induced metabolic disorders that result in increased blood pressure.⁵³

Participants who used a combination of nucleoside reverse transcriptase inhibitors (NRTI) with protease inhibitors (PI) (2h/2f/2e/ABC+3TC+ATV/r) were at higher risk of developing hypertension compared with those who used a combination of nucleoside reverse transcriptase inhibitors with nonnucleoside reverse transcriptase inhibitors or integral transfer strand inhibitors. This finding is in line with studies conducted in southern Malawi, ³⁹ Cameroon, ⁴³ and Zimbabwe. ³⁶ The possible explanation may be that PI combinations ritonavir/lopinavir and ritonavir/atazanavir were revealed to stimulate adipokine-mediated inflammatory pathways that lead to the activation of adipose RAAS, endothelial dysfunction, arterial stiffness, lipodystrophy, and dyslipidemia.⁵⁴ However, the contradicts findings reported from a study conducted in Maryland. 41 The possible variation might be related to HIV infection has been linked to arterial stiffness and pro-inflammatory responses; hence, the virus may lead to premature vascular dysfunction causing elevated blood pressure, endothelial dysfunction, and subclinical HIV-associated kidney disease may be responsible for high rates of hypertension among HIV-positive adults. 24,45,55

The current study demonstrated that a BMI ≥ 25 kg/m² was strongly associated with hypertension among HIV-positive adults. This finding is in line with a study conducted in Brazil.⁵⁶ Therefore, obesity of individuals with HIV/AIDS may be associated with excessive weight gain during treatment with HAART and should be avoided.

Limitation of the Study

The study has a number of limitations. These are there may be measurement bias, and information on lipid profile, renal function, and other lab results were not collected.

Conclusion

In the present study, more than two-third of the study participants was developed hypertension among HIV-positive adults. No physical exercise, age group 35–45, body mass index >25kg/m², HAART regimen 1J(TDF+3TC+DTG and 2h/2f/2e/ABC+3TC+ATV/r) increased the risk of hypertension among peoples living with HIV/AIDS. Therefore, policymakers and clinicians should emphasize on educating about the use of lifestyle change, counseling the use of regular physical activities, promoting weight reduction, and intervention in this situation are highly recommended.

Abbreviations

AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; HAART, hyperactive anti-retroviral therapy; HTN, hypertension; WHO, World Health Organization.

Data Sharing Statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical Approval and Consent to Participate

Ethical clearance was obtained from the ethical review committee of Health Science Debre Markos University with institutional research ethics review committee number of HSC/R/C/SE/PG/Co/422/11/12. Permission was obtained from hospital administrators. All participants were informed about the purpose of the study prior to consenting to participate. Verbal consent was obtained from each participant prior to data collection. The Ethical Review Committee of Health Science Debre Markos University approved the informed verbal consent process. A participant name was not included in the data collection format, and the data were not disclosed to any person other than principal investigators. This study was conducted in accordance with the Declaration of Helsinki.

Consent for Publication

Not applicable.

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Acknowledgments

We would like to acknowledge Debre Markos Referral Hospital officials to allow us to conduct this project on their customers. We extend our special thanks to all data collectors and respondents.

Author Contributions

YS: Conception of the research protocol, literature review, study design, data analysis, interpretation and drafting of the manuscript. YS, ADA, WSS and DH: Data analysis, interpretation, and manuscript review. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors have declared that they have no competing interests.

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