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Prediction of Esophageal Candidiasis among Newly Diagnosed People Living with HIV at a Tertiary Hospital in Northwestern Tanzania; A Cross Sectional Study

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Abstract

Background

HIV infection causes a multisystem disease. Patients with upper gastrointestinal symptoms like dyspepsia, odynophagia, and dysphagia sometimes are usually treated empirically for esophageal candidiasis. Studies have suggested that a variety of other conditions may present with upper GIT and thus empirical treatment could potentially delay the institution of definitive treatment. This study describes endoscopic findings and prediction of esophageal candidiasis, which is an AIDS-defining illness among newly diagnosed people living with HIV at the Gastroenterology and hepatology unit at Bugando Tanzania.

Methods

A cross-section study was carried out among adult patients who presented at gastroenterology and hepatology unit for endoscopic service. All patients underwent HIV testing and counseling before the endoscope. Those who tested positive for HIV were serially enrolled in this study. Demographic, symptom profile, CD4 counts, and endoscopic findings were analyzed using STATA 13. The odds ratio (OR) with 95% Confidence Interval (CI) was calculated using univariate analysis followed by a multivariate analysis model to assess the extent of association. P value of <0.05 was considered as significant.

Results

In total 210 patients were enrolled in this study. The top three endoscopic findings were gastritis, 70 (33.3%; 95%CI: 26.9-39.7), esophageal candidiasis, 63 (30.0%; 95%CI: 23.8-36.2) and esophageal carcinoma, 28 (13.3%; 95%CI: 8.6-17.9). The presence of esophageal candidiasis was independently associated with Odynophagia, (OR: 6.1; 95%CI: 2.1-17.7; p=0.001), upper abdominal pain (OR: 2.3; 95%CI: 1.0-5.1, p=0.045) and CD4 count of less than 200cells/µL, (OR: 2.7; 95%CI: 1.3-5.3; p=0.005).

Conclusion

Esophageal candidiasis is prevalent in this study. Though Odynophagia, epigastric pains, and low CD4 counts can predict the presence of esophageal candidiasis, endoscopy is indicated for precise diagnosis of other conditions including esophageal carcinoma.

Keywords: *Endoscopy, esophageal candidiasis, HIV.*

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Background

HIV is a virus causing immunodeficiency that depletes the body's ability to recognize and control both infectious and malignant opportunistic conditions in all organ systems in the human body (1). The gastrointestinal tract (GIT) is commonly involved and accounts for the highest proportion of presenting symptoms in People Living with HIV (PLHIV) both before and after ART initiation (2). Apart from diarrheal conditions, other common AIDS defining conditions include oral and esophageal candidiasis (ECAN), Cytomegalovirus (CMV) infection, Herpes simplex virus (HSV) infection and malignant diseases including Kaposi Sarcoma (KS) and esophageal carcinoma (ESOCA) (3).

Case reports indicate that untreated ECAN may progress to its severe form (4) which may potentially complicate into a hemorrhage, esophageal stricture, and fistula among others (5-7). Among PLHIV the treatment, therefore, has long been symptom-based where antifungal drugs are initiated targeting ECAN as the commonest cause of upper GIT symptoms (8, 9). Patients with ECAN usually have typical gastrointestinal (GI) symptoms such as odynophagia, dysphagia, epigastric pain, abdominal pain, and heart burn (10-13). A combination of these symptoms has been reported in about a third of PLHIV in the course of their illness (14) however these symptoms are nonspecific and may lack the acceptable predictive ability (13).

Endoscopy is an extremely valuable diagnostic modality for ECAN since it is capable of identifying the white fungal plaque specific for candida infection, and biopsy can be performed on lesion samples (4, 14, 15-17). About 33.4% of PLHIV with upper GIT symptoms have been found to have associated organic disease following endoscopic examination (18) and literature suggests that ECAN is not the only cause of upper GIT symptoms in PLHIV and an in-depth evaluation for proper management is necessary (19). ECAN has been reported in prevalence rates of 3.0% to 53% among PLHIV with upper GIT symptoms (20).

Based on the above findings it is clear that investing in empirical treatment can potentially delay the diagnosis of other non-candida gastrointestinal causes (18-21) contributing to unfavorable outcomes of these patients. This is because most of these conditions are markers of advanced HIV disease associated with substantially high mortality (22-24). For instance, in one study where PLHIV were re-evaluated following the failure of symptoms resolution on Fluconazole for presumed esophageal candidiasis, it was subsequently found out that 77% had esophageal ulcers that were consistent with CMV infection and idiopathic ones among others (25). The literature on the prevalence and etiological patterns of

gastroesophageal symptoms among PLHIV is still scarce in our setting. This study was designed to determine the prevalence and prediction of esophageal candidiasis, and document other non-Candida etiology of upper GIT symptoms among newly diagnosed adult HIV patients attending endoscopic services at Bugando in Northwestern part of Tanzania.

Material and methods

Study area

The study was done in the gastroenterology and hepatology unit at Bugando Medical Centre (BMC) in Mwanza. BMC is a consultant and University teaching hospital for the lake and western zones of the United Republic of Tanzania serving a catchment population of nearly 16 million people in super-specialized units. Gastroenterology and hepatology unit is one of the rapidly growing units in internal medicine. One of the core activities of this unit is to provide endoscopic diagnostic and therapeutic services. All patients undergoing endoscopic examination undergo HIV counseling and testing prior procedure on routine basis. Patients testing positive for HIV are usually linked to HIV care and treatment clinic (CTC) for treatment and care services after OGD. Following endoscopic diagnosis appropriate treatment is given whenever possible.

Study design and population

This was a cross-sectional study with a serial enrollment of PLHIV from 2014 January to December 2018. This study involved all adult PLHIV who underwent oesophago gastro duodenoscopy (OGD) following upper GIT symptoms like painful swallowing, difficulty in swallowing, and abdominal pains between January 2014 and December 2018.

Sample size

A minimum sample size of 153 patients was estimated from Kish and Lisle formula (26) for cross-sectional studies, assuming 11.2% of newly diagnosed HIV individuals with upper GIT symptoms will have ECAN (18) with a tolerable error of 0.05 at 95% Confidence Interval (CI).

Data collection

All participants underwent counseling and testing as per guidelines before OGD. Informed consent was sought to participate in this study for those who tested positive for HIV and samples were taken for baseline CD4 counts. The diagnosis of ECAN was based on visualization of candida white plaques in the esophagus, detected by endoscopy that could

not be washed away as done previously (16,27). A cross-sectional record of demographic data, presenting GIT symptoms, baseline CD4 counts, and OGD results were done for analysis.

Endoscopic examination

Endoscopies were carried out by a team of gastroenterologists and experienced endoscopists in the department, by using a Pentax EPM 3500 fiber optic endoscope (Pentax Medical, Tokyo, Japan).

CD 4 counts analysis

CD4 counts were performed according to the standard operating procedures in the hospital laboratory. The blood samples were collected using ethylenediaminetetraacetic acid (EDTA) tubes and stored at room temperature (22-27^{0}C). These samples were analyzed within 24 hours using an automated FACS Calibur Flow Cytometry machine (Becton Dickinson, San Jose, USA).

Study variables

Dependent variable was the prevalence of esophageal candidiasis among people who were newly diagnosed to have HIV-AIDS. Independent variables were the demographic and clinical characteristics.

Data analysis

Data were analyzed using STATA version 13 (Stata Corp LP, college station, TX). Continuous variables were summarized as medians with Interquartile range (IQR) while categorical variables were expressed as proportions with percentages. The proportion of patients with ECAN was calculated and other endoscopic findings were also recorded. Symptomatic and CD4 prediction of ECAN was assessed. The odds ratio (OR) with 95% Confidence Interval (CI) was calculated using univariate analysis followed by a multivariate analysis model to assess the extent of association of different variables to the outcome of interest. Factors with $p<0.25$ on the univariate model were subsequently included in the final multivariate model. In the final model, all factors were considered to have a significant statistical association with the outcome of interest if the p-value < 0.05. The goodness of fit of the final model was assessed by Hosmer–Lemeshow technique and the area under the curve was determined using the receiver operating curve (ROC).

Ethical Consideration

The permission to conduct and publish the findings from the study was sought from the Catholic University of Health and Allied Sciences/ Bugando Medical Center joint ethical committee with an IRB clearance certificate number 923/2019. Informed consent was sought from all participants following an in-depth explanation of the study. Confidentiality was highly observed, the patients' information was handled by the researchers alone, and their identifiers like names and registration numbers were not included in this analysis. Patients who were found to have pathologies during endoscopies, were treated according to the hospitals protocols.

Results

Study characteristics of 210 PLHIV

In this study, a total of 210 participants were included in the analysis. Most, 117 (55.7%) were male participants with a median age of 40 [IQR: 32-49] years. The majority, 165 (78.6%) were married, with a median CD4 count of 198 [IQR: 100-360] cells/µl (Table 1). The common presenting symptoms were epigastric pain, 84(40.0%; 95%CI: 33.3-46.9), and dysphagia, 53 (25.3%; 95%CI: 19.5-.31.6) as summarized in Figure 1.

Table 1: General study characteristic among 210 study participants

Variable	Frequency	Percent or Median (IRQ)
Sex		
Female	93	44.3
Male	117	55.7
Age (years)	210	40 [32-49]
Marital status		
Married	165	78.6
Others	45	22.4
Occupation		
Formal employment	16	7.6
Self employed	65	31.0
Peasant	63	30.0
None	66	31.4
CD4 counts		198.5[100-360]

CD4: Cluster of differentiation 4, IQR: Interquartile range

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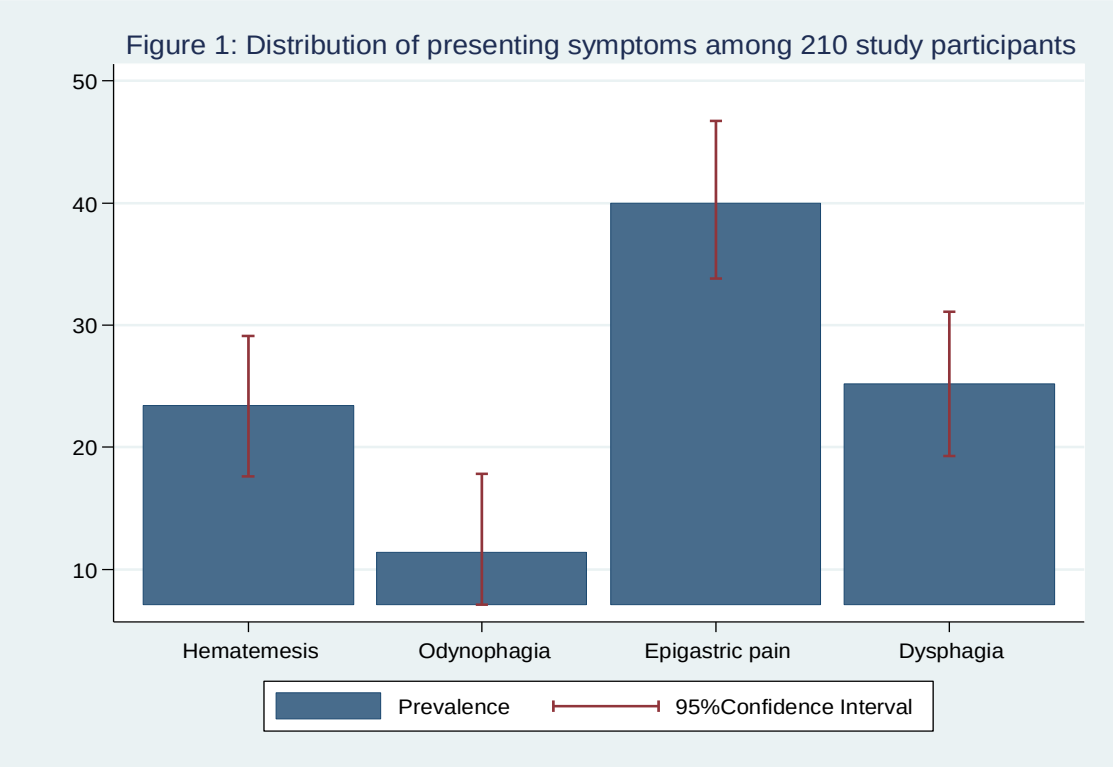

Figure 1: Distribution of presenting symptoms among 210 study participants

Prevalence of Esophageal candidiasis by endoscopy

Sixty-three participants (30%) were found to have esophageal candidiasis in this study and majority of them (58.3%) presented with dysphagia. Other presented symptoms and endoscopic diagnoses have been shown in Table 2.

Table 2: Prevalence of esophageal candidiasis and distribution of symptoms by endoscopic diagnosis among 210 participants

Symptoms	Upper Gastrointestinal tract Endoscopic findings						Total
	PUD	Gastritis	Candidiasis	Varices	Normal	Esoph Ca	
Hematemesis	8 (16.3)	18 (36.7)	5 (10.2)	8 (16.3)	3 (6.2)	7 (14.3)	49 (100)
Odynophagia	0 (0.0)	4 (16.7)	14 (58.3)	0 (0.0)	4 (16.7)	2 (8.3)	24 (100)
Epigast pain	6 (7.1)	31 (36.9)	33 (39.3)	2 (2.4)	3 (3.6)	9 (10.7)	84 (100)
Dysphagia	5 (9.4)	17 (31.1)	11 (20.8)	6 (11.3)	4 (7.5)	10 (18.9)	53 (100)
Total	**19 (9.1)**	**70 (33.3)**	**63 (30.0)**	**16 (7.6)**	**14 (6.7)**	**28 (13.3)**	**210(100)**

PUD: Peptic ulcer disease, Epigast: Epigastric, Esoph ca: Esophageal cancer

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Endoscopic findings, symptom and CD4 prediction of Esophageal Candidiasis

The commonest endoscopic finding was gastritis, 70 (33.3%; 95%CI: 26.9-39.7). Esophageal candidiasis, 63 (30.0%; 95%CI: 23.8-36.2) and esophageal carcinoma, 28 (13.3%; 95%CI: 8.6-17.9) were the second and the third most common endoscopic findings, respectively (Figure 2, Table 2). The presence of esophageal candidiasis was independently associated with Odynophagia, (OR: 6.1; 95%CI: 2.1-17.7; p=0.001), upper abdominal pain (OR: 2.3; 95%CI: 1.0-5.1, p=0.045) and CD4 count of less than 200cells/µL, (OR: 2.7; 95%CI: 1.3-5.3; p=0.005) (Table 3). Testing for the goodness of fit by Hosmer-Lemeshow proved no gross lack of fit, p= 0.6297 with the area under the ROC curve of 0.7337 (Figure 3).

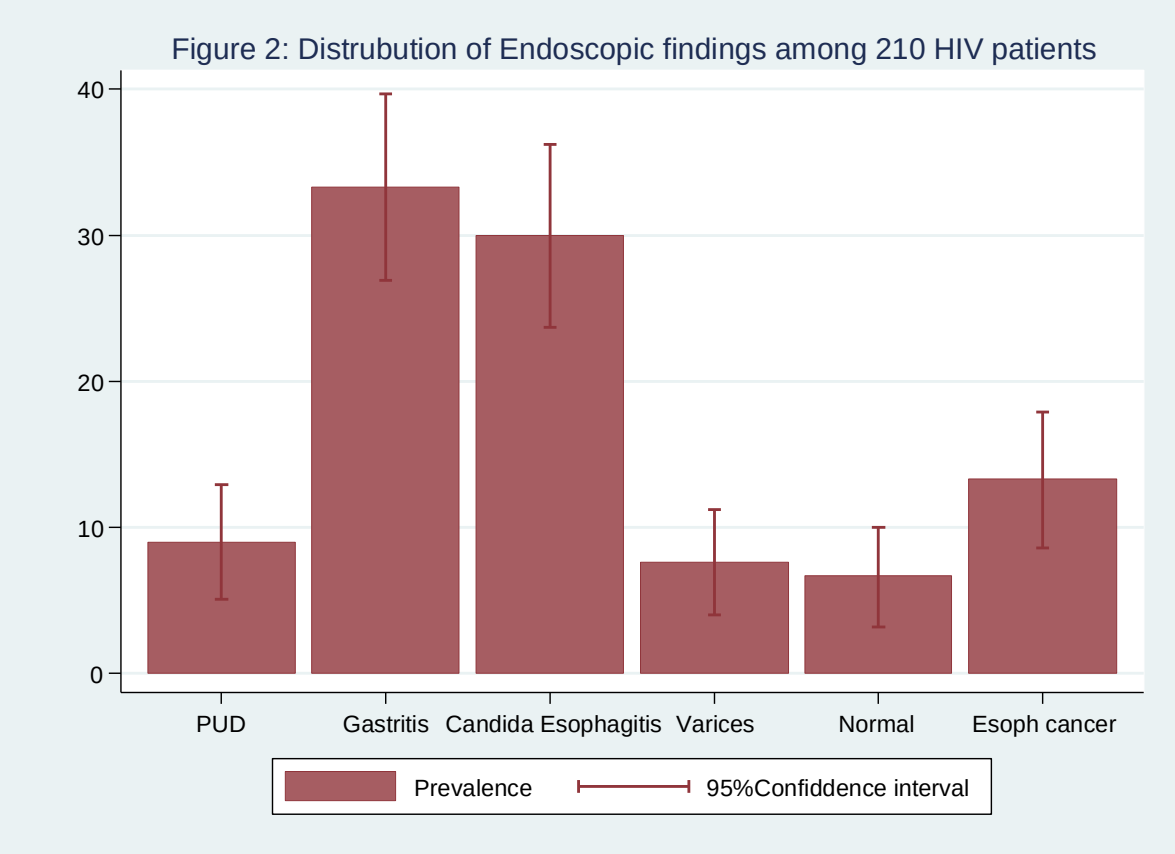

Figure 2: Distribution of Endoscopic findings among 210 HIV patients

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Table 3: Symptom and CD4 correlates of esophageal Candidiasis among 210 participants

Variables	Esophageal Candidiasis		Un adjusted		Adjusted	
	No (N=147	Yes (n=63)	OR (95%CI)	P-value	OR (95%CI)	P-value
Hematemesis			0.2(0.1-0.5)	0.001	0.4(0.1-1.2)	0.125
No	103 (70.17)	58 (92.1)				
Yes	44 (29.9)	5 (7.9)				
Odynophagia			3.9 (1.6-9.3)	0.002	6.1(2.0-17.7)	0.001
No	137 (93.2)	49(77.8)				
Yes	10 (6.8)	14 (22.2)				
Epigastric pain			2.1 1.1-3.7)	0.017	2.3 (1.0-5.1)	0.045
No	96 (65.3)	30 (47.6)				
Yes	51(34.7)	33 (52.4)				
Dysphagia			0.5 (0.2-1.1)	0.093		
No	105(71.4)	52 (82.5)				
Yes	42 (28.6)	11 (17.5)			-	-
CD4 (cell/µL)			2.3 (1.2-4.4)	0.008	2.7(1.3-5.3)	0.005
≥200	115 (78.2)	38 (60.3)				
<200	32 (21.8)	25(39.7)				

CD4: Cluster of differentiation 4, IQR: Interquartile range OR: Odds ratio

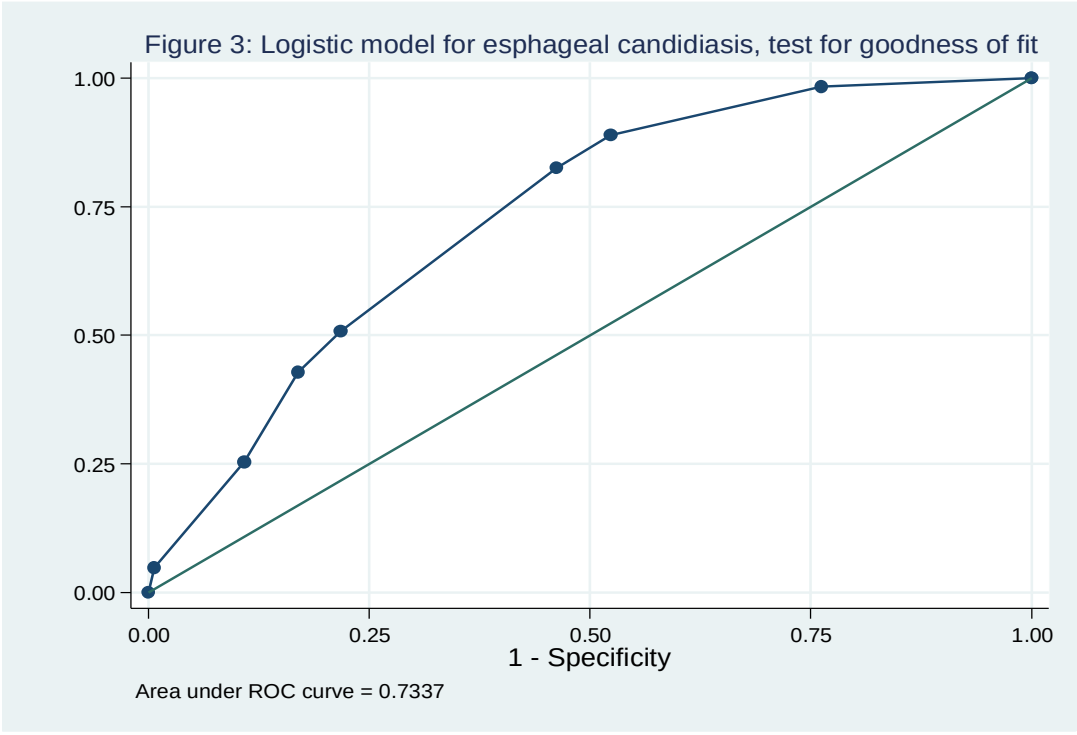

Figure 3: Logistic model for esphageal candidiasis, test for goodness of fit

Discussion

The prevalence of ECAN in this study is similar to a prevalence rate of 25.3% reported from Argentina (28) and 36% reported previously by Skwara et al. (29). However our prevalence is higher than the prevalence rate of 3% reported by Parvin et al. (20), 8.46% reported from Japan earlier in 2013 (17), and also 11.2% reported in 2015 (18). Much higher ECAN prevalence rates of 51% and 53% were reported previously from Kenya (30) and Tanzania 21), respectively. The difference could be due to the diagnostic modality used. For instance, in a previous study from Tanzania 2018, the diagnosis was mycologically based contrary to the index study where the diagnosis was made on endoscopic visual inspection of symptomatic PLHIV. Mycological diagnosis is likely to pick more cases of candidiasis even at their asymptomatic stages.

In agreement with our study, one study indicated that the presence of esophageal candidiasis was more likely among patients who had esophageal symptoms including Odynophagia 14). Similarly Asayama et al. indicated that presence Odynophagia and epigastric pains were independently associated with even more severe ECAN (27). However; a study done by Takahashi et al. found that a significant association of Odynophagia and dysphagia with ECAN on the univariate model alone (19). But also Nishimura et al. similarly indicated PLHIV who had lower CD4 counts more likely to have ECAN (18).

In our setting, this is the first study to assess endoscopic findings among HIV positive patients with upper gastrointestinal symptoms. In this study apart from candidiasis, (30.0%), nearly two thirds, (63.3%) of the participants had other organic causes of their GIT symptoms including gastritis, (33.3%), peptic ulcer diseases, esophageal carcinoma, (13.3%), (9.1%), and esophageal varices, (7.6%). These findings are very similar to previous reports indicating that Gastritis is the commonest cause of gastrointestinal symptoms among PLHIV however with a slight difference in prevalence rates depending on the study design (20, 31). These studies have also reported the presence of gastritis in 48.0% of studied participants. Other endoscopic findings among PLHIV were hiatus hernia, 42 (14%), and peptic ulcer disease, 31 (10.0%). In another study where candida esophagitis was reported among 29 (15.1%) PLHIV, other endoscopic findings in this study were gastritis in a total of 103(53.6%) participants, peptic ulcers, 23 (12.0%), duodenitis, 13 (6,8%), gastric cancer, 1 (0.5%) and Kaposi sarcoma, 1 (0.5%) among others (30). Similarly, a study done in India

among 53 PLHIV who were scoped for upper GIT symptoms indicated that 14 (35.8%) had normal endoscopic findings with 12 (22.6%) who had candida esophagitis. In this study, other endoscopic findings were antral gastritis,14 (26.4%, and esophageal varices among 1 (1.9%) participants (32).

The findings from this study are clinically important indicating that esophageal candidiasis is only one of the wide range of organic conditions that may be responsible for upper gastrointestinal symptoms. Symptom and CD4 prediction of esophageal candidiasis are significantly less sensitive and initiation of treatment reliant on symptomatic approach may potentially delay the diagnosis of other serious causes of symptoms in this subgroup of patients. Thus these results suggest that whenever possible PLHIV presenting with upper gastrointestinal symptoms should undergo endoscopic evaluation of their condition.

This study is liable to some limitations including it being a single-center cross-sectional study. However, this is one of the few studies which have endoscopically assessed newly diagnosed HIV patients presenting with upper GIT symptoms in a resource-limited setting where HIV patients are usually treated based on symptomatic evaluation. Also, viral load for HIV was not done in this study.

Conclusion and recommendation

Esophageal candidiasis was prevalent among the study population and was associated with Odynophagia, epigastric pains and low CD4+ counts. Examination of esophageal candidiasis is recommended during endoscopic examination among newly diagnosed HIV patients.

Competing interests

The authors declare that they have no competing interests and no funds received for this study. All authors read and approved the final version of the manuscript.

Authors' contributions

DCM, PMM, SEK, and SBK: participated in the conception, designing of the study and acquired the data; SBK, DWG, & HDM, did data analysis and interpretation; DCM and DWG: did manuscript drafting. All the authors critically reviewed the manuscript for its intellectual content and approved the final version.

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Abbreviations

AIDS:	Acquired immunodeficiency syndrome
BMC:	Bugando Medical Centre
CD4:	Cluster of differentiation
CI:	Confidence interval
CTC:	Care and treatment clinic
GIT:	Gastro intestinal tract
HIV:	Human immunodeficiency virus
CMV:	Cytomegalovirus
ECAN:	Esophageal candidiasis
ESOCA:	Esophageal carcinoma
OGD:	Oesophago-gastro-duodenoscopy
PLHIV:	People living with HIV
PUD:	Peptic ulcer disease
KS:	Kaposi sarcoma
ROC:	Receiver operating curve

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