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Original Article

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Upper and Lower Gastrointestinal Endoscopic Findings in HIV-Infected Patients in the Era of Highly Active Antiretroviral Therapy

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Abstract

Background: Endoscopic evaluation with biopsies are instrumental in the diagnosis and management of gastrointestinal (GI) disorders in the setting of human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS), especially in the era of highly active antiretroviral therapy (HAART).

Methods: A retrospective chart review of 304 HIV-positive and 199 HIV-negative patients who had undergone upper and/or lower endoscopy in an urban community hospital from the years 2012 - 2017 was performed. Inclusion criteria included men and women between the ages of 45 to 75 years, which had undergone colonoscopies between within 2012 - 2017 and had tested positive for HIV. They were selected from that population if they had complete charts that included information regarding symptoms, viral load, cluster of differentiation 4 (CD4) count, prescribed HAART medication, findings from the upper and lower colonoscopy both from the gastroenterologist's report and pathologist's report. Only then would they be added to the pool of final selection that we could compute data from and draw conclusions.

Results: Among HIV patients, those with less than 200 CD4 cells/µL counts had lower rates of diverticulosis and hemorrhoids, as compared with those with greater than 200 cells/µL counts. Other gross and histological findings (from either upper or lower endoscopy) were not statistically different between these two groups. In HIV-positive patients, gastritis, *Helicobacter pylori* (*HP*) infection, and esophagitis were significantly less common, while Candida esophagitis was more common. Among HIV patients taking different HAART regimens, the prevalence of peptic ulcers was significantly higher in those taking IIs than that in those who were not.

Conclusions: Physicians should consider the possibility that the GI symptoms in HIV-infected patients on HAART may be due to an opportunistic infection, even when the CD4 count is more than 200 cells/µL and the viral load is low.

Keywords: Endoscopy; Colonoscopy; HIV; HAART; AIDS

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Introduction

Gastrointestinal (GI) symptoms and pathology are very common in patients infected with human immunodeficiency virus (HIV), affecting almost half of this population [1]. GI disorders and their presentations in setting of HIV or acquired immunodeficiency syndrome (AIDS) are varied and often nonspecific, and endoscopic evaluation with biopsies are instrumental in their diagnosis and management. Possible etiologies of GI complaints in HIV disease may include the HIV itself, opportunistic and non-opportunistic infections, side-effects of medications, and disease processes unrelated to HIV. The prevalence and incidence of many GI disorders in HIV have changed dramatically in the era of highly active antiretroviral therapy (HAART), particularly with the newer generation of HIV regimens. In this retrospective chart review, we report upper and lower GI endoscopic findings in HIV-infected patients in an urban, community hospital. We have also examined patterns of GI findings in patients with low *versus* high CD4 counts, as well as those taking various regimens of HAART.

Materials and Methods

We performed a retrospective chart review of 304 HIV-positive and 199 HIV-negative patients who had undergone upper and/or lower endoscopy at our hospital over the past 5 years (2012 -2017). The patients included for data collection and analysis were randomly selected from a larger pool of patients who had met inclusion criteria. Inclusion criteria were all non-pregnant adult patients who had undergone endoscopy at our hospital. The study sample was divided into HIV-positive and HIV-negative patients. The HIV-positive group was further divided into several categories, including those with CD4 counts below 200 cells/µL *versus* those with CD4 counts of 200 cells/

Table 1. Endoscopy Indications, Gross Findings, and Histological Findings

	HIV-negative (n = 199)	HIV-positive (n = 304)	P value
Indications/presenting symptoms			
Abdominal pain/dyspepsia	90 (45%)	69 (23%)	< 0.0001
Heartburn	58 (29%)	30 (10%)	< 0.0001
Dysphagia	23 (12%)	26 (9%)	0.2676
Anemia	23 (12%)	25 (8%)	0.2112
Variceal screening	1 (0.5%)	24 (8%)	< 0.0001
Endoscopic findings			
Gastric erythema	185 (93%)	137 (45%)	< 0.0001
Hiatal hernia	45 (22%)	42 (14%)	0.0108
Peptic ulcer	26 (13%)	31 (10%)	0.3211
Erosions	0 (0%)	19 (6%)	0.0003
White plaques	0 (0%)	12 (4%)	0.0046
Histological findings			
Gastritis	172 (86%)	145 (48%)	< 0.0001
Esophagitis	29 (15%)	29 (10%)	0.0838
Helicobacter pylori	44 (22%)	12 (4%)	< 0.0001
Duodenitis	24 (12%)	18 (6%)	0.0150
Gastric polyp	14 (7%)	5 (2%)	0.0019
Candida esophagitis	0 (0%)	8 (3%)	0.0179

μL or higher, and those not taking any HIV-targeted therapy *versus* those on HAART. The patients compliant with HAART were further categorized into one of three groups, based on the specific HAART regimen they were taking at the time of endoscopy: backbone of non-nucleoside reverse transcriptase inhibitors (NNRTIs) *versus* protease inhibitors (PIs) *versus* integrase inhibitors (IIs).

Data collected included indications for endoscopy, the endoscopic findings, biopsy results, age, sex, and ethnicity, HIV status, CD4 count, medications, comorbidities, and social history such as smoking or alcohol use. The different groups of the study were compared with respect to these parameters. Statistical analyses were performed using Statistical Analysis System (SAS) version 10.1 and significant level of P = 0.05 was used.

Results

In a total eligible population of 503 patients, 304 were HIV-positive and 199 were HIV-negative patients. In this group, 376 esophagogastroduodenoscopies (EGDs) (of which 126 were for HIV-positive patients) and 378 colonoscopies (of which 231 were for HIV-positive patients) were performed and analyzed. Mean ages in the two groups were statistically equivalent (54 and 53 in the HIV and control groups, respectively; P = 0.1768). The HIV group comprised significantly more males (54% vs. 35%; P = 0.0001), more smokers (29% vs. 11%; P = 0.0001), more alcohol users (25% vs. 7%; P = 0.0001), and fewer proton pump inhibitor (PPI) users (19% vs. 29%; P = 0.0115).

Overall, the most common indications for EGD were dyspepsia (32%), heartburn (18%), dysphagia (10%), and anemia (10%). Dyspepsia and heartburn were significantly less common in HIV patients (10% vs. 29%, P < 0.0001 for heartburn). The most common gross findings on EGD were gastric mucosal erythema (64%), hiatal hernia (17%), peptic ulcer (11%), and gastric erosions (4%). In HIV patients, gastric erythema (45% vs. 93%, P < 0.0001) and hiatal hernia (14% vs. 22%, P = 0.0108) were significantly less common, and erosions (6% vs. 0%, P = 0.0003) more common. The most common histological findings from EGD were gastritis (63%), *Helicobacter pylori* infection (11%), esophagitis (11%), and duodenitis (8%). In HIV patients, gastritis (48% vs. 86%, P < 0.0001) including *Helicobacter pylori* infection (4% vs. 22%, P < 0.0001) were significantly less common, while Candida esophagitis (3% vs. 0%, P = 0.0179) was more common (Table 1).

Overall, the most common indications for colonoscopy were screening (46%), bleeding (13%), abdominal pain (7%), and anemia (7%). Anemia (6% vs. 11%, P = 0.253) and abdominal pain (5% vs. 11%, P < 0.0001) were significantly less common in HIV. The most common gross findings on colonoscopy were hemorrhoids (49%), polyps (30%), and diverticulosis (19%). The most common histological findings from colonoscopy were hyperplastic polyps (12%), adenomas (6%), and mucosal lymphoid aggregates (4%). In HIV, both hyperplastic polyps (20% vs. 9%, P = 0.0005) and mucosal lymphoid aggregates (6% vs. 0%, P = 0.0003) were more common. Adenomas (10% vs. 14%, P = 0.2008) and other histological findings were equivalently prevalent between HIV patients and controls (Table 2).

Among HIV patients, those with CD4 counts less than

Table 2. Colonoscopy Indications, Gross Findings, and Histological Findings

	HIV-negative (n = 199)	HIV-positive (n = 304)	P value
Indications/presenting symptoms			
Screening	85 (43%)	145 (48%)	0.2430
Gastrointestinal bleeding	24 (12%)	42 (14%)	0.5701
Anemia	22 (11%)	17 (6%)	0.0253
Abdominal pain	22 (11%)	14 (5%)	< 0.0001
Colonoscopy findings			
Hemorrhoids	96 (48%)	148 (49%)	0.6307
Colonic polyps	58 (29%)	93 (31%)	0.9617
Diverticulosis	45 (23%)	53 (17%)	0.1099
None/normal	4 (2%)	17 (6%)	0.0499
Colorectal cancer	3 (2%)	8 (3%)	0.3969
Histological findings			
None/normal	96 (48%)	118 (39%)	0.0366
Hyperplastic polyp	17 (9%)	61 (20%)	0.0005
Tubular adenoma	27 (14%)	30 (10%)	0.2008
Mucosal lymphoid aggregates	0 (0%)	19 (6%)	0.0003
Colitis	9 (5%)	10 (3%)	0.4792

200 cells/μL had lower rates of diverticulosis (7% vs. 21%; P = 0.0402) and hemorrhoids (31% vs. 52%; P = 0.0107), as compared with those with CD4 counts greater than 200 cells/μL. Other gross and histological findings (from either upper or lower endoscopy) were statistically equivalent between these two groups. Among HIV patients taking different HAART regimens, there were no significant differences in endoscopic findings, except that the prevalence of peptic ulcers was significantly higher in those taking IIs (15%) *versus* those taking NNRTIs (8%) or PIs (7%) (P = 0.0495).

Discussion

HIV/AIDS is a multisystemic disorder that affects virtually every organ of the body. The GI system is one of the most common organ-systems to be affected by HIV/AIDS, producing a wide variety of symptomatic complaints. Given that HIV/AIDS is an immunological disorder, infectious etiologies, both opportunistic and non-opportunistic, are among the most important factors in HIV symptomatology. With the advent of HAART, particularly the newer regimens of antiretroviral therapy, the incidence and prevalence of various GI infections in HIV have changed dramatically.

In our study, mucosal erythema of the upper GI tract and histologically defined esophagitis, gastritis, or duodenitis from various causes were among the most common findings. Candida esophagitis is the most common esophageal disorder observed in HIV patients [2], with a prevalence of 43-53% in the pre-HAART era, and 17-24% since the introduction of HAART [2]. In our study, the incidence of Candida esophagitis was higher in HIV-positive patients than that of HIV-negative patients. Our results were similar to many prior studies, where the incidence of Candida esophagitis in HIV-positive patients was significantly higher than that of HIV-negative patients [2]. Numerous studies further demonstrate that the prevalence of Candida is higher in HIV-positive patients with CD4+ count < 200 cells/μL than those with CD4+ count > 200 cells/μL, and higher in those with a greater HIV viral load [2, 3]. Our study revealed a 3.0% prevalence of Candida esophagitis, lower than previously reported since the introduction of HAART new regimens. Our results indicate that the effectiveness of the new HAART regimens.

Cytomegalovirus (CMV), herpes simplex virus (HSV), and Kaposi's sarcoma are other important etiologies of esophagitis in HIV patients. CMV esophagitis is characterized by symptoms of odynophagia, dysphagia and endoscopic findings of multiple, well-demarcated vertical/horizontal linear shallow ulcers, most commonly between the mid-third and lower-third areas of the esophagus [4]. HSV is the least common of the infectious agents that cause esophagitis in HIV-infected patients. The shallow erosive ulcers are similar to erosive reflux esophagitis and have a wider distribution pattern than CMV [5]. Kaposi's sarcoma is rarely found in the esophagus, and presents as dysphagia rather than odynophagia [5]. It appears as submucosal ulcerations or as linitis plastica in the stomach [6]. While Kaposi's sarcoma lesions in the latter parts of the upper GI tract are generally asymptomatic, it has been reported to cause acute hemorrhage [6, 7]. Our study did not document any cases of CMV/HSV infection or cases of Kaposi's sarcoma or lymphoma, likely due to a relatively small sample size and higher CD4 count than that is usually found in patients with these disease entities.

As in the general population, infection with *Helicobacter*

pylori is an important finding in HIV patients. In our study, both *Helicobacter pylori* and gastroduodenitis of any etiology were less common in HIV patients, as compared with control subjects. These findings are congruent with prior studies, where the prevalence of *Helicobacter pylori* was less in HIV-positive patients as compared with HIV-negative patients, and in those with a CD4 count of < 200 cells/μL than those with a CD4 count of > 200 cells/μL [2, 8-11]. These results could be the consequence of HIV-positive patients receiving multiple antibiotics therapeutically or prophylactically for typical or opportunistic infections, commonly having received erythromycin, amoxicillin or broad spectrum antibiotics [11]. An impairment of *Helicobacter pylori* colonization might also be due to progressive atrophic involution of the gastric mucosa with secondary hypochlorhydria, representing an unfavorable environment [8-10]. Another possibility is that for *Helicobacter pylori* to persist in a gastric environment, it requires an intact mucosal cellular immunity and inflammatory response leading to gastritis, which is a response that has been reported to be decreased in CD4+ T-cell-deficient individuals [12].

In our study, the most common findings on lower endoscopy were hemorrhoids, polyps, and diverticulosis with the relative prevalence of these findings statistically equivalent between HIV-positive and HIV-negative patients. On histology, however, hyperplastic polyps and mucosal lymphoid aggregates on biopsy samples were more common in HIV-positive patients. Kasapovic et al investigated rates of mucosal abnormalities detected by screening colonoscopy in 96 HIV-infected patients over the age of 50 in Germany, and found that the adenoma detection rate during colorectal cancer (CRC) screening colonoscopy in HIV-positive patients was higher than that seen in the general population in the country [13]. Their data showed that adenomas were detected in 26% of all screened HIV-positive patients, while published data predict adenoma detection rates of 12-20% in the general population [14]. Studies in the United States such as from Bini et al showed that, compared with control subjects, HIV-positive patients were significantly less likely to have hyperplastic polyps and were significantly more likely to have adenomas 6 - 9 mm in diameter [15]. Advanced neoplastic lesions and colorectal adenocarcinomas were more common in HIV-positive patients, although these differences did not reach statistical significance [15]. In our study, the relative prevalence of colonic polyps on endoscopy was statistically equivalent between our HIV-positive and HIV-negative patients, possibly because the statistical power may not have been strong enough to detect a difference. Alternatively, the study population in our study may be different as we included patients undergoing colonoscopy for screening (48%) as well as for other indications such as GI symptoms (52%).

One hospital-based cross-sectional study in Cameroon was undertaken in order to determine the prevalence and determinants of anorectal pathology in 390 HIV-infected patients who visited a hospital HIV treatment center [16]. The median duration since HIV diagnosis was 3 years and the median CD4 count was 411 cells/μL [16]. The prevalence of anorectal pathology was 22.8% [16]. Hemorrhoids and proctitis were the most common lesions found; each was discovered in 10% respectively [16]. In our study, hemorrhoids were the most common findings on colonoscopy in both the HIV-positive cohort and the HIV-negative cohort.

After the widespread use of HAART, several studies showed changes in the incidence of AIDS-defining and non-AIDS-defining malignancies among HIV/AIDS patients. One systematic review of 21 observational studies, involving more than 600,000 HIV-positive individuals and 10,891 new cases of malignancies, evaluated the incidence of cancers before and after the introduction of HAART [17]. After introduction of HAART, the incidence of AIDS-defining cancers (e.g., Kaposi's sarcoma and non-Hodgkin's lymphoma) decreased significantly, as HAART decreased the patient's total HIV burden, maintained immune system function, and prevented opportunistic infections that previously led to death [17]. The incidence of several non-AIDS-defining cancers increased after the early use of HAART, likely due to the increased survival made possible by the new antiretroviral drugs [17]. In our study, the rates of colorectal cancer were statistically equivalent between the HIV-positive and HIV-negative groups. Interestingly, studies that have compared pre- and post-HAART eras have demonstrated, on a consistent basis, an alarming increase in the incidence of invasive anal cancer during the HAART era [18]. The reasons for this development are likely multifactorial. There are several theories but further research is needed to explain this finding.

Our study findings yielded low rates of colitis or specific colonic infectious agents, possibly due to small sample sizes. However, lower GI infections certainly are important entities in GI disorders in the setting of HIV. Since the introduction of HAART, the incidence of opportunistic infections has decreased significantly, but has not disappeared. In fact, in large inner-city hospitals, where there are often more HIV-infected patients, who are either unaware of their HIV status or noncompliant with their HAART regimens, GI symptoms and corresponding endoscopic findings and biopsy results are not uncommon [19]. There is a broad spectrum of pathogens and opportunistic infections that affect the lower GI tract in HIV/AIDS. These include bacterial infections (*Listeria, Salmonella, Shigella, Mycobacterium avium* complex, and spirochetes), viral infections (CMV, adenovirus, and herpes simplex), fungal infections (*Candida, Cryptococcus, Histoplasma,* and microsporidia), and parasitic infections (*Giardia, Isospora,* and cryptosporidium) [19]. In our study, the etiology of colitis has not been further subclassified.

Although the frequency of opportunistic infections in HIV-positive individuals with CD4 counts greater than 200 was low, performing colonoscopy was still useful, especially to diagnose CMV infection [20]. Indeed, although the use of HAART has led to a decreased incidence of opportunistic infections, the physician should not abandon the possibility that the GI symptoms in HIV-infected patients on HAART may be due to an opportunistic infection, even when the CD4 count is high and the viral load is low [21].

Author Contributions

The above authors contributed equally and significantly to the

Abstract, Introduction, Methods, Results, and Discussion sections in the above titled paper.

Conflict Of Interest

None.

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