**Original article**

# The Prevalence of *Helicobacter Pylori* Infection and Peptic Ulcer Disease in *HIV*-Positive Patients with Gastrointestinal Symptoms Is not Related to Absolute CD4 Counts: A Case-Control Study

## *Prévalence de l'infection à Helicobacter pylori et de l'ulcère peptique chez le sujet VIH-positif en relation avec le taux de CD4: étude cas-témoin*

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**ABSTRACT**

***BACKGROUND.*** The prevalence of *Helicobacter pylori* (*H. pylori*) infection and peptic ulcer (PU) in HIV-positive subject was reported to be low in previous studies. The aim of this study was to evaluate the prevalence of *H. pylori* infection and of PU in relation to absolute CD4 T cells counts in HIV-positive subjects with gastrointestinal symptoms (GI).

***MATERIAL AND METHODS.*** One hundred and twelve age- and sex-matched subjects (56 HIV-positive patients and 56 HIV-negative patients) with GI symptoms were assessed by upper endoscopy and gastric biopsies. The prevalence rate of *H. pylori* infection was the main variable that was assessed. Patients were classified based on HIV status and CD4 count: In Group A: HIV-positive patients with a CD4 count below 200; group B: HIV-positive patients with a CD4 count from 200 to 499; Group C: HIV-positive patients with a CD4 count higher or equal to 500 and group D: HIV-negative control patients.

***RESULTS.*** The prevalence rate of *H. pylori* infection in the four groups was as follow: Group A 42.1% (8/19), group B 65.4% (17/20), group C 27.3 % (3/11) and group D 55.4% (31/56). The prevalence rate of PU was 21.05 % (4/19) in group A, 23.07 % (6/26) in group B, 36.4 % (4/11) in group C (p = 0.07), and 17.85 % (10/56) in group D. The prevalence of *H. pylori* infection in HIV-positive subjects did not differ between patients with and without PU.

Compared with HIV-negative control subjects, HIV-positive subjects with a CD4 count less than 200 had a low prevalence rate of *H. pylori* infection, this difference was not significant (p = 0.32). The prevalence of PU in HIV-positive subjects with a CD4 count less than 200 was higher compared to that found in HIV-negative control subjects, this difference was not significant (p = 0.97).

***CONCLUSION.*** Although the prevalence of *H. pylori* infection is low in HIV-positive subjects, the PU is contrarily frequent. The *H. pylori* infection and PU are not in relation to CD4 counts in HIV-positive subjects.

***KEYWORDS.*** Prevalence, *Helicobacter pylori*, peptic ulcer, HIV, CD4 count, gastrointestinal symptoms

**RÉSUMÉ**

***OBJECTIF.*:** La prévalence de l'infection à *Helicobacter pylori* (*H. pylori*) et de l'ulcère peptique (UP) chez le sujet *VIH*-positif a été rapportée comme étant basse dans des études précédentes. Le but de cette étude était d'évaluer la prévalence de *H. pylori* et de l'UP en relation avec le taux absolu de cellules T CD4 chez le sujet *VIH*-positif avec des symptômes gastro-intestinaux (GI).

***MATÉRIELS ET MÉTHODES.***: Cent douze sujets (56 patients *VIH*-positif et 56 patients *VIH*-négatif) appariés selon l'âge et le sexe, avec des symptômes GI ont été évalués par endoscopie digestive haute avec biopsies gastriques. Le taux de prévalence de l'infection à *H. pylori* était le paramètre principal étudié. Les patients ont été stratifiés sur la base du statut *VIH* et du taux de CD4: groupe A : patients *VIH*-positif avec un taux de CD4 <200, groupe B : patients *VIH*-positif avec un taux de CD4 200-499, groupe C : patients *VIH*-positif avec un taux de CD4 ≥500, et groupe D : sujets contrôles *VIH*-négatif.

***RÉSULTATS.***: Le taux de prévalence de l'infection à *H. pylori* dans les quatre groupes était de : groupe A 42,1 % (8/19), groupe B 65,4 % (17/20), groupe C 27,3% (3/11), et groupe D 55,4 % (31/56). Le taux de prévalence de l'UP était de 21,05% (4/19) dans le groupe A, 23,07 % (6/26) dans le groupe B, 36,4 % (4/11) dans le groupe C (p=0,07), et 17,85 % (10/56) dans le groupe D. La prévalence de l'infection à *H. pylori* chez les sujets *VIH*-positif n'était pas différente entre ceux avec ou sans UP. En comparaison avec les sujets contrôles *VIH*-négatif, les sujets *VIH*-positif avec un taux de CD4 <200 avaient un taux de prévalence de *H. pylori* bas, cette différence n'était pas significative (p =0,32). Le taux de prévalence de l'UP chez les sujets *VIH*-positif avec un taux de CD4 <200 était élevé comparé à celui retrouvé chez les sujets contrôles *VIH*-négatif, cette différence n'était pas significative (p=0,97).

***CONCLUSION.***: Quoique la prévalence de l'infection à *H. pylori* soit faible chez les sujets *VIH*-positif, l'UP est fréquent. L'infection à *H. pylori* et l'UP ne sont pas associés au taux de CD4 chez les sujets *VIH*-positif au Cameroun.

***MOTS CLÉS.***: Prévalence, *Helicobacter pylori*, ulcère peptique, VIH, taux de CD4, symptômes gastro-intestinaux.

## INTRODUCTION

The prevalence of the *Helicobacter pylori* (*H. pylori*) infection and of the peptic ulcer disease among HIV-positive subjects was reported to be low in previous epidemiological studies [1, 2, 3]. Indeed, the HIV infection leads to a progressive loss of CD4 T cell [4, 5, 6]. This is seen especially in the mucosa of the gastrointestinal (GI) tract, where most CD4 + T cells reside [4, 7]. Thus, the prevalence of the *H. pylori* infection in HIV-positive subjects with a CD4 count less than 200 / $mm^3$ is reported to be significantly low compared to the prevalence of the *H. pylori* in HIV-negative subjects [1]. Similarly, the number of peptic ulcers in HIV-positive subjects with a CD4 counts less than 200 / $mm^3$ would be less than that found in HIV-negative subjects [1].

Cameroon is in a highly endemic area for HIV infection. Indeed, the Joint United Nations Program on HIV-AIDS (UNAIDS) estimates that the HIV prevalence rate was 4.8% in Cameroon in 2014, about 660 000 individuals living with HIV [8].

Data on the *H. pylori* infection and of the peptic ulcer disease among HIV-positive subjects does not exist in Cameroon.
The aim of this hospital-based prospective case-control study was to evaluate the prevalence of the *H. pylori* infection and of the peptic ulcer disease in relation to absolute CD4 T cells counts in HIV-positive subject with GI symptoms.

## MATERIAL AND METHODS

### *Study Design and Study Population*

A hospital-based prospective case-control study conducted from July 2014 to July 2015, during which all patients aged 20-71 years, already diagnosed as HIV-positive cases, referred for an upper digestive endoscopy, in the assessment of GI symptoms, admitted to university hospitals in Yaounde and Douala were consecutively enrolled in this study.
Controls were subjects with negative test result for HIV, individually age- and sex-matched to cases, referred at the same period for the same reasons as cases, in the same hospitals were consecutively enrolled in this study. The search for anti-HIV1 and HIV2 antibodies was first performed by a rapid diagnostic test (Alere Determine® HIV-1/2, Alere Inc., USA), confirmed by ELISA (HIV Ag Murex® / Ab Combination, DiaSorin SpA, Saluggia, Italy). The diagnosis of the HIV infection was established when both tests were positive (rapid test and ELISA). Patients with negative ELISAs were considered HIV-negative.
A questionnaire completed by an internal physician in gastroenterology, included the demographic features (age, sex), GI symptoms, medications, including non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, antisecretory and antifungal drugs taken within six months prior to endoscopy. Among the cases, there were combined antiretroviral therapy (HAART) and the CD4 count of less than one month before the beginning of the study. Patients were classified on the basis of the HIV status and CD4 counts: In Group A: HIV-positive patients with a CD4 count less than 200; Group B: HIV-positive patients with a CD4 count between 200 and 499; Group C: HIV-positive patients with a CD4 count above or equal to 500; and Group D HIV-negative control subjects.
Endoscopy was performed in the cases and in controls in various university centers by four experienced endoscopists. All patients had not eaten since the night before the test. They underwent a standard upper endoscopy with local anesthesia of the oropharyngeal mucous membrane with lidocaïne 10 % spray or oral gel without any other sedation. The endoscopic findings were recorded using the appropriate systems of standard terminology for gastrointestinal endoscopy [9]. Gastric biopsies (five) were taken for histological examination and the rapid urease test. Samples for histology were immediately fixed in formalin 10% for research of *H. pylori* and sent to pathology laboratories of hospitals to be stained with Giemsa. Rapid urease tests were carried out following the recommendations of the various manufacturers. The *H. pylori* infection was considered positive if the rapid urease test and histological examination were both positive.
Patients aged less than 20 years and those aged over 71, patients with co morbidities, those who had received corticosteroid, antibiotics, *H. pylori* eradication therapy or anticoagulant therapy within the past 4 weeks were excluded from the study.

### *Statistical analysis*

Data were analyzed using the Statistical Package for Social Sciences (SPSS Version 20.0, IBM Inc., Chicago, USA). For quantitative variables, data were presented as mean ± standard deviation. The proportions were determined for qualitative variables. The Chi-square test was used to compare the prevalence of the *H. pylori* infection between groups. A P-value of less than 5% was considered to be statistically significant.

### *Ethical considerations*

The study was approved by the ethics committees of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde 1 and the Faculty of Medicine and Pharmaceutical Sciences of the University of Douala, informed consent was obtained from each patient before enrolment in this study.

## RESULTS

One hundred and twelve subjects were included: 56 HIV-positive patients (48 type 1 and 8 type 2, 33 under HAART, 23 untreated and 48.2 % (27/56) were male) and 56 HIV-negative control subjects, age- and sex- matched. The average age of HIV-positive patients was 42.8 ± 8.4 years in group A, 44.6 ± 11.8 years in group B, and 43.5 ± 16.7 years in group C. average age in the HIV-negative control group was 43.7 ± 11.7years.

The prevalence rate of the *H. pylori* infection in the four groups was: Group A 42.1 % (8/19), group B 65.4 % (17/20), group C 27.3 % (3/11), and group D 55.4 % (31/56). The prevalence of the peptic ulcer was 21.05 % (4/19) in group A, 23.07 % (6/26) in group B, 36.4 % (4/11) in group C, and 17.85 % (10/56) in group D. Among HIV-positive patients, the prevalence of the peptic ulcer decreased according to the drop in CD4 (p = 0.07) and gastric ulcer was more frequent than duodenal ulcer (16.1 % vs. 8.9 %, p = 0.03). The *H. pylori* infection was more frequent in the gastric ulcer (66.7 %) than in the duodenal ulcer (20.0 %). The prevalence of *H. pylori* infection in HIV-positive subjects did not differ between those with (50 %) or without (50 %) peptic ulcer. Table 1.

Table I: The prevalence of the *Helicobacter pylori* infection and of the peptic ulcer in relation to HIV status and CD4 counts in HIV-positive subjects and in HIV-negative control subjects

| Variables | Group A* N=19 | Group B* N=26 | Group C* N=11 | Group D* N=56 |
|---|---|---|---|---|
| ***H pylori* positive** | 42.1 | 65.4 | 27.3 | 55.4 |
| **Peptic ulcer** | 21.05 | 23.07 | 36.4 | 17.85 |
| **Duodenal Ulcer** | 5.3 | 3.8 % | 27.3 | 10.7 |
| **Gastric ulcer** | 15.8 | 19.2 | 9.1 | 7.1 |

* A : CD4 < 200/mm$^3$. B : CD4 200-499/mm$^3$. C: CD4 ≥500/mm$^3$. D: HIV negative subjects

Compared with HIV-negative control subjects, HIV-positive subjects with a CD4 count less than 200 had a low prevalence rate of *H. pylori*, this difference was not significant (42.1 % vs. 55.4 %, p = 0.32). The prevalence of the peptic ulcer in HIV-positive subjects with a CD4 count less than 200 was higher compared to that found in HIV-negative control subjects, this difference was not significant (21.05 % vs . 17.56 %, p = 0.97). Table 2

Table II: Comparison of HIV-positive subjects with CD4 less than 200 / mm$^3$ and HIV-negative subjects

| Variables | CD4 <200/mm$^3$ (n=19) | HIV-negative (n=56) | *P-Value* |
|---|---|---|---|
| ***H pylori* positive** | 8 (42.1 %) | 31 (55.4 %) | 0.32 |
| **Peptic ulcer** | 4 (21.05 %) | 10 (17.56 %) | 0.97 |
| **Duodenal Ulcer** | 1(5.3 %) | 6 (10.7 %) | 0.67 |
| **Gastric ulcer** | 3 (15.8 %) | 4 (7.1 %) | 0.27 |

The frequency of dysphagia (26.8 %; 15/56), anorexia (26.8 %; 15/56), weight loss (51.8 %; 29/56) and vomiting (26.8 %; 15/56) was significantly elevated in HIV-positive patients compared to HIV-negative control subjects (p = 0.0004, p = 0.001; p <0.0001, p = 0.0001, respectively). Table 3

Table III: Main reasons for endoscopy in HIV-positive subjects and in HIV-negative subjects

| Reasons for endoscopy | HIV+ (n=56) n (%) | HIV- (n=56) n (%) | Total | P value |
|---|---|---|---|---|
| **Dysphagia** | 15(26.8) | 1(1.8) | 16 | 0.0004 |
| **Anorexia** | 15(26.8) | 2(3.6) | 17 | 0.001 |
| **Weight loss** | 29(51.8) | 1(1.8) | 30 | <0.0001 |
| **Anemia** | 3(5.4) | 0(0.0) | 3 | 0.24 |
| **Epigastric pain** | 46(82.1) | 39(69.6) | 85 | 0.12 |
| **Vomiting** | 15(26.8) | 0(0.0) | 15 | 0.0001 |
| **GI bleeding** | 3(5.4) | 7(12.5) | 10 | 0.32 |

HIV+: positive. *HIV*-: negative. n: number of cases. GI: gastrointestinal

## DISCUSSION

Despite the widespread use of antiretroviral combination therapy (HAART) in HIV infection, the GI tract is still frequently affected by HIV-associated diseases process [10]. Gastric disorders, though less common than esophageal diseases, frequently involve *Cytomegalovirus* (CMV), *Mycobacterium avium intracellulare*, and neoplasia (Kaposi's sarcoma, lymphoma) [3, 10, 11]. Peptic ulcer and *H. pylori* infection are uncommon [1, 11]. In this case-control study, nearly 25 % of HIV-positive subjects had peptic ulcers, while the prevalence of peptic ulcer in HIV-negative control subjects was only 17.85 %. In HIV-positive subjects, the prevalence rate of *H. pylori* infection was low compared to that reported in the general population in Cameroon [12]; it was not possible to demonstrate a clear association between *H. pylori* infection and absolute CD4 counts. The number of

peptic ulcers decreased proportionally with the drop of CD4 cell count, without being significant. The number of gastric ulcers was paradoxically high compared with duodenal ulcer, and the *H. pylori* infection was more common in gastric ulcers than in duodenal ulcers. The prevalence of *H. pylori* infection in HIV-positive subjects did not differ between those with and without peptic ulcer.

The role of the *H. pylori* infection in the genesis of gastro duodenal lesions might be different between the general population and HIV-positive subjects [3]. At present the role of *H. pylori* infection in the GI mucosa of HIV-positive patients has not been well defined [4, 7]. The prevalence of the *H. pylori* infection has been reported to be low in HIV-positive subjects with a CD4 count less than 200 [1]. In this study, we found that the prevalence of *H. pylori* infection was independent from the CD4 count. However, compared to HIV-negative control subjects, HIV-positive subjects with a CD4 count less than 200 had a low prevalence rate, this was not significant ($p = 0.32$). We interpreted this result in light of the presence of gastric ulcer which was more associated with the *H. pylori* infection. Thus, the gastric ulcer was more common in HIV-positive subjects with a CD4 count between 200 and 499, followed by subjects with a CD4 count less than 200 and finally subjects with CD4 counts greater or equal 500. In the same way, the *H. pylori* was respectively found.

The peptic ulcer is rare among gastroduodenal lesions of HIV-positive subjects [1, 4]. The commonest endoscopic findings in the stomach include erythemous and atrophic gastritis [4, 13]. In this study, the peptic ulcer was more common in HIV-positive subjects (25 %) compared to HIV-negative control subjects (17.85 %). This result is different from the literature and above that reported by Cacciarelli et al. [1]. The poly-medication for HIV-positive subjects partly explains our results. However, and paradoxically, it is in the group of HIV-positive subjects with a CD4 count greater or equal to 500, without HAART or other treatment that we found the highest prevalence rates. The duodenal / gastric ulcer ratio was well below unity, contrary to the results in the general population. Also, contrary to our earlier results reported in the general population, the *H. pylori* infection was more common in the gastric ulcer than in the duodenal ulcer [12]. This result, like many others in the literature, suggests a different mechanism of the genesis of peptic ulcerogenesis, and different causes in HIV-positive subjects [1, 3, 10, 11, 14, 15]. The role of the *H. pylori* would be different in peptic ulcer in HIV-positive subjects. In a case-control study comparing the prevalence of the *H. pylori* infection to that of the *CMV* infection in HIV-positive subjects and in HIV-negative control subjects, Chiu et al. [3] concluded that low prevalence of the *H. pylori* infection and that of peptic ulcer in HIV-positive subjects suggests a different role of *H. pylori* infection in peptic ulcer disease, and that the *CMV* infection, rather than *H. pylori*, may be the main causative pathogen of peptic ulcers in AIDS patients. *CMV* seem to be the most frequent opportunistic infection and may be the most commonly identified cause of ulcer disease in symptomatic patients [3,10,11,14,15].

Previous studies have shown that HIV-positive patients at AIDS stage have high gastrin and pepsinogen II blood levels compared to HIV-positive subjects who are not yet at the AIDS stage [16]. The hypochlorhydria would entail a less suitable environment for *H. pylori* but favorable to the proliferation of other pathogens [5, 17]. Thus, the inhibition of *H. pylori* by competition with other opportunistic infections such as *CMV* by unknown mechanisms has been suggested [18, 19]. Biochemical analyzes were not performed in this study to test these hypotheses.

The main reason for endoscopy in HIV-positive subjects was the epigastric pain, which accounted for 82.1 % of referrals. Vomiting (26.8 %) and dysphagia (26.8 %) were the other GI symptoms we recorded. These symptoms are common to HIV-positive patients [4, 10].

## CONCLUSION

Although the prevalence of the *H. pylori* infection is lower in HIV-positive subjects, the peptic ulcer is on the contrary frequent and mainly gastric ulcer. The *H. pylori* infection and peptic ulcer disease are not in relation to absolute CD4 cell counts in HIV-positive subjects in Cameroon.

## COMPETING INTERESTS

The authors declare no competing interest.

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## CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this paper.

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