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## **Impact of HIV infection on the course of inflammatory bowel disease and drug safety profile: a multicenter GETAID study**

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LG and MS wrote the article. LG, MS and LPB conceived and supervised the study. HR and CB performed the statistical analysis. MU, CR, GD and LPB critically revised the manuscript. The manuscript was approved by all authors.

### **Conflict of interest**

L Guillo declares no conflict of interest. M Uzzan has served as a speaker and consultant for Janssen. L Beaugerie has received consulting fees from Janssen and Pfizer, lecture fees from Abbvie, Janssen, MSD, Ferring Pharmaceuticals, Mayoly-Spendler, Takeda and Tillotts, and research support from Abbott, Ferring Pharmaceuticals, Hospira-Pfizer, Janssen, MSD, Takeda and Tillotts. J-M Gornet has served as a speaker for Amgen, Janssen Cilag, Sanofi, Takeda and Tillotts Pharma. A Amiot declares counseling, boards, lecture, transports or fees from Abbvie, Hospira, Takeda, Gilead, Biocodex, Janssen, Ferring and MSD. A-L Pelletier declares no conflict of interest. R Altwegg declares counseling, boards, transports or fees from Abbvie, Biogen, Ferring, Janssen, MSD, Pfizer, Takeda, Tillotts. D Laharie declares counseling, boards, transports or fees from Abbvie, Biogaran, Biogen, Ferring, HAC-pharma, Janssen, MSD, Novartis, Pfizer, Prometheus, Roche, Takeda, Theradiag, Tillotts. V Abitbol declares counseling, boards, transports or fees from Janssen, Takeda, sandoz, Mylan, Amgen, Fresenius, Tillotts, Celltrion, Gilead, Pfizer. J Filippi declares declares

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## **Abstract**

**Background and aims:** Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), and human immunodeficiency virus (HIV) both impact innate and adaptive immunity in the intestinal mucosa. As it is a rare situation, the intersection between HIV and IBD remains unclear, especially the impact of HIV infection on the course of IBD, and the drug safety profile is unknown.

**Methods:** We conducted a multicenter retrospective cohort study between January 2019 and August 2020. All adult patients with IBD and concomitant HIV infection were included. Each IBD patient with HIV was matched to two HIV-uninfected IBD patients.

**Results:** Overall, 195 patients with IBD were included, including 65 HIV-infected patients and 130 without HIV infection. Of the 65 infected patients, 22 (33.8%) required immunosuppressants and 31 (47.7%) biologics. In the HIV-infected group, the need for immunosuppressants ( $p=0.034$  for CD and  $p=0.012$  for UC) and biologics ( $p=0.004$  for CD and  $p=0.008$  for UC) was significantly lower. The disease course, using a severity composite criterion, was not significantly different between the two groups for CD (hazard ratio (HR) = 1.3 [0.7; 2.4],  $p=0.45$ ) and UC (HR = 1.1 [0.5; 2.7],  $p=0.767$ ). The overall drug safety profile was statistically similar between the two groups.

**Conclusion:** Although HIV-infected patients receive less treatments, the course of their IBD did not differ than uninfected, suggesting that HIV infection might attenuate IBD. The drug safety profile is reassuring, allowing physician to treat these patients according to current recommendations.

**Keywords:** Inflammatory bowel diseases, HIV, disease progression, therapeutics.

## **What You Need to Know**

### **Background**

The intestinal mucosa is very permissive to HIV, leading to gastrointestinal dysfunctions during HIV infection. The clinical course of IBD in HIV-infected patients as well as the drug safety profile is unknown.

### **Findings**

HIV-infected patients receive less immunosuppressants and biologics, but the course of their disease does not differ from that of uninfected patients.

The drug safety profile is similar to that reported in uninfected IBD patients.

### **Implications for patient care**

The reassuring overall drug safety profile allows physician to treat HIV-infected patients according to current recommendations. HIV infection might attenuate the IBD course.



## **Introduction**

Human immunodeficiency virus (HIV) decreases immunity by targeting T cells, especially the cluster of differentiation 4 (CD4<sup>+</sup>)<sup>1</sup>. It has been demonstrated that more than 50% of CD4<sup>+</sup> are preferentially depleted from the gut associated lymphoid tissue (GALT) during the primary HIV-1 infection, highlighting the importance of the mucosal compartment of HIV pathogenesis<sup>2-4</sup>. On the other hand, inflammatory bowel diseases (IBD), consisting of ulcerative colitis (UC) and Crohn's disease (CD), are characterized by a chronic gut mucosal inflammation and a state of immune activation<sup>5-7</sup>. UC is defined by a Th2/natural killer T cells (NKT) immune response and CD by a Th1/Th17 T cells immune response<sup>6,7</sup>. Both diseases can be considered as ends of a spectrum, with IBD being associated to immune excess and HIV to immune paucity<sup>8</sup>. The intersection of these two diseases remains unclear and is a rare situation. Older studies suggested that the clinical course of IBD may be attenuated by concomitant HIV infection, supported on the decrease CD4 count hypothesis<sup>9-12</sup>. However, many cofounders may have mislead conclusions and contradictory data exist<sup>13</sup>. For instance, IBD onset has also been reported after HIV diagnosis<sup>13</sup>. The influence of their pathophysiology on each other may be more complicated. Indeed, they both impact innate and adaptive mucosal immunity mechanisms at the intestinal level (e.g. dendritic cells, macrophages, NKT cells or regulatory T cells)<sup>8</sup>.

To date, only a total of 58 patients with concomitant HIV and IBD were reported in the literature<sup>9-12,14-28</sup>, most of them prior to the biologics era. Whether these patients may have an attenuated course of IBD is still poorly known<sup>9-11,16,19-22</sup>. In the present multicenter

exposed/non-exposed cohort study, we therefore aimed to determine the impact of HIV infection on the course of IBD and the overall drug safety profile.

## **Methods**

### *Study design and study population*

We conducted a multicenter exposed/non-exposed cohort study in 22 GETAID (Groupe d'Etude Thérapeutique des Affections Inflammatoires du Tube Digestif) referral centers. All adult patients (older than 18 years) followed for confirmed IBD in a gastroenterology department were eligible for inclusion. HIV infection diagnosis was made using HIV-specific antibodies by enzyme-linked immunosorbent assay (ELISA), confirmed by Western blot assay. First, we identified patients with concomitant prevalent HIV infection between January 2019 and January 2020. We further matched each HIV-infected (HIV-I) patient with two HIV-uninfected (HIV-UI) patients from the Nancy IBD cohort database. Matched patients were randomly selected based on disease type (UC or CD), disease duration from diagnosis ( $\pm 2$  years) and date of birth ( $\pm 5$  years) from the HIV-UI cohort. The study was conducted according to loi Jardé and the CNIL (Commission Nationale de l'Informatique et des Libertés) number is 2210131. Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

### *Data collection and endpoints*

The following data for each patient were collected: date of birth, sex, smoking status (non-smoker, former smoker, or active smoker), date of IBD diagnosis, cumulative Montreal classification, first degree family history of IBD, associated extra-intestinal manifestation, history of IBD related complications (e.g. hospitalization, stricture, fistula or abdominal abscess), history of IBD related surgery (e.g. date, type and number), previous IBD medical

treatments and start date, adverse event or hospitalization related to treatment, history of cancer, history of serious infection and date of the last visit. Concerning patients exposed to HIV infection, the following data were also collected: date of HIV diagnosis, mode of HIV contamination, coinfection with hepatitis B or C, date of highly active antiretroviral therapy (HAART) start, nadir CD4 level and CD4 count at last visit.

We aimed to analyze the impact of HIV infection on the course of IBD and the drug safety profile. For patients with HIV diagnosed after IBD, only events from HIV diagnosis were used in the statistical analysis. Only for HIV-UI patients matched with HIV-I patients, index date was defined as date of IBD diagnosis to which was added the time elapsed between the IBD-HIV diagnosis of his paired HIV patient. Conversely, for patients with HIV diagnosed before IBD, only events from IBD onset were analyzed. The impact of HIV infection on IBD course was assessed using a severity composite criterion, including hospitalization or surgery in UC patients and hospitalization, surgery or bowel damage (stricture, intestinal fistula or intra-abdominal abscess) in CD patients. The use of immunosuppressants (thiopurines or methotrexate) and biologics (anti-tumor necrosis factor (anti-TNF), ustekinumab or vedolizumab) was also included in the analysis. Adverse events were defined as any event, infectious or not, related to the treatment. Serious infections were defined as any infectious manifestation needing hospitalization or specialist expertise.

### *Statistical analysis*

Categorical variables were described as percentage, while continuous variables were reported as mean  $\pm$  standard deviation (SD) or median [interquartile range (IQR)], depending on their distribution. The comparative analyses of patient's characteristic between HIV-infected and HIV-uninfected patients were performed using Chi2 test or exact test of Fisher for the categorical variables. Student's t test or Wilcoxon test were used for the

continuous variables. Complicated IBD course-free survival was assessed with Kaplan-Meier methods. Cox proportional hazards regression stratified on pairs was performed to assess for factors associated with a complicated IBD course. Associations were described by Hazard Ratios (HRs) with 95% confidence interval (CI). Bivariate conditional regressions analyses were performed to examine associations between HIV exposure and drug use. The threshold for statistical significance was set to  $p < 0.05$ . All statistical analyses were performed using SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA).

## **Results**

### *Patients' characteristics*

A total of 195 patients with IBD were included after matching, including 65 infected patients to HIV and 130 uninfected (*Table 1*). The distribution of HIV-I patients according to center is provided in *Supplementary Table 1*. There were 57 men (87.7%) and 36 patients with CD (55.4%) in the HIV-I group, while in the HIV-UI group 56 men (43.1%) and 72 patients with CD (55.4%) were recruited. Some differences in the disease phenotype were observed, especially for proctitis (E1), perineal disease and colitis (L2). Details according to Montreal classification are presented in *Table 1*. Median age at IBD diagnosis was 37 years [28.9; 50.2] in the HIV-I group and 37 years [27; 51] in the HIV-UI group. Median follow-up duration was 7.7 years [3; 11.5] in HIV-I patients and 8 years [3.7; 11.5] in HIV-UI patients. Extra-intestinal manifestations were documented for 11 HIV-I patients (16.9%) and for 30 HIV-UI patients (23.1%). A history of smoking, active or former at last visit, was found in 38 HIV-I patients (63.3%, 38/60), while in 58 HIV-UI patients (44.6%, 58/130). Only a few patients had a family history of IBD in the HIV-I group (4.6%) and in the HIV-UI group (8.5%).

The diagnosis of IBD was made after HIV infection in 38 patients (58.5%) (*Table 1*). The way of HIV contamination was sexual for 25 patients (38.5%), intravenous drug addiction for 8 patients (12.3%) and blood transfusion for 3 patients (4.6%). Coinfections with hepatitis B and C were reported in 10.8% and 18.5% of cases, respectively. Median nadir CD4 count was 267.5/mm<sup>3</sup> [127; 435] and median CD4 count at last visit was 705/mm<sup>3</sup> [485; 890]. Finally, median delay between HIV diagnosis and start of HAART was 0.2 years [0; 5].

#### *Impact of the HIV infection on the course of IBD*

In the survival analysis using a composite criterion including hospitalization for CD and/or bowel damage (stricture, intestinal fistula or intra-abdominal abscess) and/or intestinal surgery, the course of CD was not different between the HIV-I group and the HIV-UI group (hazard ratio (HR) = 1.3 [0.7; 2.4], p=0.45) (*Figure 1A*). Survival without a complicated course of the disease was estimated at 72.2%, 59.4% and 48.9% at 1, 3 and 5 years, respectively for HIV-I patients, and 81.7%, 68.3% and 57.2% for HIV-UI patients without significant differences between the two groups. By taking into account only bowel damage and/or intestinal surgery, the CD course in the HIV-I group was also similar (HR = 0.6 [0.3; 1.3], p=0.19) (*Figure 2A*).

As for patients with CD, in the survival analysis using a composite criterion including hospitalization for UC and/or colectomy, the course of UC was not different between groups according to the HIV infection status (HR = 1.1 [0.5; 2.7], p=0.767) (*Figure 1B*). Survival without a complicated course of the disease was estimated at 79.2%, 75.6% and 64.3% at 1, 3 and 5 years, respectively for HIV-I patients, and 82.6%, 72.2% and 65.6% for HIV-UI patients without significant differences between groups. By taking into account only colectomy, the UC course in the HIV-I group was also similar (HR = 1.6 [0.5; 5.2], p=0.462) (*Figure 2B*).

After adjusting on the significant results of the bivariate analysis of patient characteristics, the results remained unchanged.

#### *Need for immunosuppressants and biologics*

In the overall cohort, all immunosuppressants and biologics treatments were used approximately half as much in the HIV-I group, while steroids use was similar (69.2%) (*Table 1*). Data on exposure to immunosuppressants or biologics were pooled and analyzed according to the IBD type. In CD, immunosuppressants were needed for 14 HIV-I patients (38.9%) versus 44 HIV-UI patients (61.1%;  $p=0.034$ ), and biologics for 17 HIV-I patients (47.2%) versus 56 HIV-UI patients (77.8%;  $p=0.004$ ) (*Figure 3*). In UC, immunosuppressants were needed for 8 HIV-I patients (27.6%) versus 33 HIV-UI patients (56.9%;  $p=0.012$ ), and biologics for 14 HIV-I patients (48.3%) versus 46 HIV-UI patients (79.3%;  $p=0.008$ ).

#### *Safety profile of immunosuppressants and biologics*

The number of patients experienced adverse events under immunosuppressants and biologics was numerically similar between HIV-I and HIV-UI groups, with 50% (11/22) and 44.2% (34/77) for immunosuppressants, respectively. Similarly, 25.8% (8/31) and with 30.4% (31/102) patients experienced adverse events for biologics in the HIV-I group and the HIV-UI group, respectively (*Figure 4*). The overall number of adverse events for immunosuppressants was of 12 and 45 in the HIV-I and HIV-UI patients, respectively, and for biologics it was of 8 and 32. The distribution of adverse events by treatment is provided in *Supplementary Table 2*. Clinical details of the 20 adverse events in the HIV-I group are presented in *Supplementary Table 3*. The treatment was stopped in 13 cases (13/20, 65%) and hospitalization was required in 6 cases (6/20, 30%) in HIV-I patients.

Patients experienced serious infections were numerically higher in the HIV-I group (17/65, 26.2%) compared to the HIV-UI group (14/130, 10.8%) (*Table 2*). However, some serious infections were specific to HIV infection (e.g. pneumocystis pneumonia, cerebral toxoplasmosis or ecthyma gangrenosum), while other events could be related to HIV infection or IBD-related medications (e.g. herpes zoster). Results about cancer occurrence were similar with 5 cases (7.7%) in the HIV-I group and 7 cases (5.4%) in the HIV-UI group (*Table 2*). One patient of the HIV-I group experienced a Kaposi sarcoma, which is specifically associated to HIV infection.

## **Discussion**

The intersection between HIV and IBD is a challenging and rare situation. We investigated data from 195 patients with IBD from GETAID referral centers. Overall, 65 patients with concomitant prevalent HIV infection were analyzed. Our study presented the largest cohort in the biologics era, assessing the impact of HIV infection on the IBD course. Patients characteristics between the two groups were similar, excepted the proportion of men which was higher in the HIV-I group (87.7% vs 43.1%). Gender does not affect the course of IBD<sup>29</sup>. Groups were matched according to date of birth, disease follow-up and disease type in order to guarantee comparability. However, differences in disease phenotype were observed, especially for proctitis, colitis and perianal disease. We can hypothesize that physical irritation and some changes in the microbiome due to sexual behavior are related to these differences.

Several case reports and case series suggest that HIV infection can attenuate disease activity by reported stable remission of IBD symptoms<sup>9-11,16,19-22</sup>. A case control study including 20 HIV exposed patients and 40 controls demonstrated a significant reduction of relapse rate in HIV group (0.016/year vs 0.053/year)<sup>12</sup>. Although relapse rates are low and the

sample population is small, it was the first significant evidence of the effect of HIV in this setting. Our study showed that the course of IBD was similar for CD (HR = 1.3 [0.7; 2.4], p=0.45) and UC (HR = 1.1 [0.5; 2.7], p=0.767) in the survival analysis. However, in the HIV-I group the need for immunosuppressants (p=0.034 and p=0.012) and biologics (p=0.004 and p=0.008) was numerically lower for patients with CD and UC, respectively. The difference between the groups could be explained in two different ways. Either the fear of serious infection could have led physicians to avoid biologics and immunosuppressants in HIV-I patients, or HIV actually favorably influences the course of IBD leading to a decrease need of immunomodulators. Nevertheless, while HIV-I patients received less treatments than HIV-UI patients, their IBD course was similar. This suggests that HIV infection could attenuate the IBD course. However, the median CD4 count at last visit was 705/mm<sup>3</sup> [485; 890] suggesting that patients were not in an immunodeficiency state, probably due to HAART therapy, and that CD4 count could not explain this impact on IBD course. HIV infection also impact innate and adaptive mucosal immunity mechanisms at the intestinal level<sup>8</sup>. It preferentially depletes Th17 and NKT cells which express CCR5 and regulatory T cells (Treg) appear to be elevated, which may explain an attenuation of IBD course<sup>8</sup>. HIV is also associated with alterations of the gut microbiota composition and a dysfunctional mucosal barrier resulting in microbial translocation<sup>30</sup>. These modifications lead to an increase of indolamine 2,3-dioxygenase (IDO) enzyme which promote Treg expansion and may explain an attenuation of IBD course<sup>30</sup>. Finally, 27 (41.5%) of patients were HIV positive after their IBD diagnosis, introducing immortal time bias since their follow-up starts after HIV diagnosis. For this reason, no definitive conclusions can be drawn.

Our results showed similar drug-related adverse events rates in both groups. Adverse events were reported in 50% and 44.2% of patients for immunosuppressants in the HIV-I and in the HIV-UI group, respectively. Similarly, adverse events were reported in 25.8% versus



30.4% of patients for biologics in the HIV-I and in the HIV-UI group, respectively. The overall drug safety profile appears to be reassuring in this setting of concomitant HIV infection. These safety data are in line with current literature. Case reports and case series suggest that the use of anti-TNF agents is safe in IBD patients with concomitant HIV infection and no significant changes in viral load and CD4 count have been observed<sup>22,23,25-27</sup>. Moreover, it has been demonstrated that TNF-alpha is involved in the viral replication and the pathogenesis of HIV-1<sup>31-34</sup>. In a recent study, 6 IBD patients with HIV infection were treated with vedolizumab (anti integrin  $\alpha_4\text{-}\beta_7$ ) without reported adverse event<sup>28</sup>. The integrin  $\alpha_4\text{-}\beta_7$  appears to play a key role in the pathogenesis of HIV infection, especially at initial stage and for viral propagation<sup>35-37</sup>. Regarding ustekinumab, while there is no available data in IBD, 3 cases reports in patients with psoriasis showed a good safety profile and no significant changes in viral load and CD4 count<sup>38-40</sup>. Finally, a close monitoring should be required, and treatment continuation should be discussed when CD4 count fall below 250/mm<sup>3</sup><sup>22</sup>.

To the best of our knowledge, this is the first multicenter study addressing the impact of HIV infection on the course of IBD and the drug safety profile. In addition, our work presents the largest cohort on this complex topic in the literature. Other relevant strengths of the study lie in the strict matching criteria which guarantee the comparability of the two groups, and in the long median follow-up. Our study was limited by its retrospective ~~study~~ design, the lack of data regarding disease activity (such as biomarkers, endoscopic or clinical scores), the lack of data regarding cumulative exposition to drugs, the differences in disease phenotype and the relatively small sample size of the HIV-I group. We were unable to bring more findings about the impact of CD4 count on the IBD course due to missing data. To confirm the CD4 count related hypothesis a prospective study design is probably necessary.

In conclusion, our study showed that although HIV-infected patients receive less treatments, the course of their IBD was not different than uninfected patients for both CD and

UC, suggesting that HIV infection might attenuate IBD. No safety concern was raised regarding treating HIV-infected patients with current biologics used in IBD.

**Table 1: Characteristics of patients according to HIV infection**

	HIV-uninfected n (%)	HIV-infected n (%)	P-value
<b>Total</b>	<b>130 (66.7%)</b>	<b>65 (33.3%)</b>	
<b>Sex</b>			<0.0001
Male	56 (43.1%)	57 (87.7%)	
<b>Median age at IBD diagnosis, years [Q1; Q3]</b>	<b>37 [27; 51]</b>	<b>37 [28.9; 50.2]</b>	<b>0.84</b>
<b>Montreal A</b>			<b>0.97</b>
A1: <17 years	8 (6.1%)	3 (4.6%)	
A2: 17-40 years	66 (50.8%)	33 (50.8%)	
A3: >40 years	56 (43.1%)	29 (44.6%)	
<b>Crohn's disease</b>	<b>72 (55.4%)</b>	<b>36 (55.4%)</b>	<b>1.00</b>
<b>Montreal L</b>			<b>0.02</b>
L1 (ileitis)	32 (44.4%)	13 (36.1%)	
L2 (colitis)	12 (16.7%)	15 (41.7%)	
L3 (ileocolitis)	28 (38.9%)	8 (22.2%)	
<b>L4 (upper)</b>	<b>3 (4.2%)</b>	<b>1 (2.8%)</b>	<b>1.00</b>
<b>Perianal disease</b>	<b>17 (23.6%)</b>	<b>16 (44.4%)</b>	<b>0.03</b>
<b>Montreal B</b>			<b>0.16</b>
Non-stricturing and non-penetrating (B1)	30 (41.7%)	22 (61.1%)	
Stricturing (B2)	17 (23.6%)	6 (16.7%)	
Penetrating (B3)	25 (34.7%)	8 (22.2%)	
<b>Ulcerative colitis</b>	<b>58 (44.6%)</b>	<b>29 (44.6%)</b>	<b>1.00</b>
<b>Montreal E</b>			<b>0.04</b>
E1 (proctitis)	4 (6.8%)	8 (27.6%)	
E2 (left-sided colitis)	27 (46.6%)	11 (37.9%)	
E3 (pancolitis)	27 (46.6%)	10 (34.5%)	
<b>Median follow-up, years [Q1; Q3]</b>	<b>8 [3.7; 11.5]</b>	<b>7.7 [3; 11.5]</b>	<b>1.00</b>
<b>Extra-intestinal manifestations</b>	<b>30 (23.1%)</b>	<b>11 (16.9%)</b>	<b>0.32</b>
<b>Family history of IBD</b>	<b>11 (8.5%)</b>	<b>3 (4.6%)</b>	<b>0.39</b>
<b>Smoking</b>			<b>0.05</b>
Active smoker	25 (19.2%)	18 (30%)	
Former smoker	33 (25.4%)	20 (33.3%)	
Non-smoker	72 (55.4%)	22 (36.7%)	
<b>IBD treatments</b>			
5-ASA	77 (59.2%)	51 (78.5%)	0.0032
Steroids	90 (69.2%)	45 (69.2%)	1.00
<u>Immunosuppressants</u>	77 (59.2%)	22 (33.8%)	0.0011
Thiopurines	70 (53.8%)	17 (26.2%)	0.0004
Methotrexate	39 (30%)	8 (12.3%)	0.0084
<u>Biologics</u>	102 (78.5%)	31 (47.7%)	<0.0001
Anti-TNF	98 (75.4%)	30 (46.2%)	0.0002
Vedolizumab	29 (22.3%)	7 (10.8%)	0.04
Ustekinumab	15 (11.5%)	3 (4.6%)	0.15
<b>Diagnosis profile</b>			
HIV before IBD	N/A	38 (58.5%)	N/A
HIV after IBD	N/A	27 (41.5%)	N/A

<b>Mode of contamination</b>			
Sexual	N/A	25 (38.5%)	N/A
IV drug addiction	N/A	8 (12.3%)	N/A
Blood transfusion	N/A	3 (4.6%)	N/A
Unknown	N/A	29 (44.6)	N/A
<b>Coinfection</b>			
Hepatitis B	N/A	7 (10.8%)	N/A
Hepatitis C	N/A	12 (18.5%)	N/A
<b>Median nadir CD4 count, /mm<sup>3</sup> [Q1; Q3]</b>			
31/65 (47.7%)*	N/A	267.5 [127; 435]	N/A
<b>Median CD4 count at last visit news, /mm<sup>3</sup> [Q1; Q3]</b>			
49/65 (75.4%)*	N/A	705 [485; 890]	N/A
<b>Median delay start-up of HAART, years [Q1; Q3]</b>			
55/65 (84.6%)*	N/A	0.2 [0; 5]	N/A

HIV, human immunodeficiency virus; IBD: inflammatory bowel disease; IV, intravenous; n: number; N/A, not available; Q: quartile; TNF, tumor necrosis factor; 5-ASA, 5-aminosalicylic acid;

\* Patients with available data

**Table 2: Clinical details of serious infection and cancer cases**

<b>HIV-infected</b>		<b>HIV-uninfected</b>	
Patient	Type of serious infection	Patient	Type of serious infection
4	Acute pyelonephritis	1	Endocarditis
6	Cerebral toxoplasmosis*	5	CMV
10	Ecthyma gangrenosum*	7	Acute sepsis
	Herpes Zoster	22	Herpes zoster
15	Lung infection	27	Recurrent herpes infection
	Lung infection	28	Clostridium colitis
17	CMV	68	Acute sepsis
26	Pneumocystis pneumonia*	76	CMV colitis
35	Lung infection under thiopurines		Lung infection
38	Pneumocystis pneumonia*	85	CMV
41	Staphylococcal sepsis	89	CMV
47	Herpes zoster	92	Clostridium colitis
49	Anal herpes	111	Acute Pyelonephritis
51	Acute pyelonephritis		Lung infection
	Herpes zoster	118	Lung infection
58	Acute sepsis	126	Lung infection
59	Syphilitic chancre		
	Genital gonococcal infection		
60	Campylobacter jejunii infection		
61	Lung infection		
65	Lung infection		
Patient	Type of cancer	Patient	Type of cancer
13	Basal cell carcinoma	45	Bronchial carcinoma
18	Anal carcinoma	46	Colon cancer
37	Left colon cancer	54	Neuroendocrine tumor of the pancreas
51	Kaposi sarcoma**		Gut lymphoma
60	Breast cancer	68	Cholangiocarcinoma
		70	Colon cancer
		87	Colon cancer
		88	Colon cancer

CMV, cytomegalovirus; HIV, human immunodeficiency virus;

\* Infection related to HIV

\*\* Cancer related to HIV

## Figures legends

### **Figure 1: Survival analysis of the IBD course according to HIV infection**

A/ Survival curve of composite events (hospitalization, bowel damage or intestinal surgery) in CD according to HIV infection

B/ Survival curve of composite events (hospitalization or colectomy) in UC according to HIV infection

CD, Crohn's disease; HIV, human immunodeficiency virus; UC, ulcerative colitis;

### **Figure 2: Complementary survival analysis of the IBD course according to HIV infection**

A/ Survival curve of composite events (bowel damage or surgery) in UC according to HIV infection

B/ Survival curve of colectomy events in UC according to HIV infection

CD, Crohn's disease; HIV, human immunodeficiency virus; UC, ulcerative colitis;

### **Figure 3: Comparison of the need of drug according to HIV infection in CD and UC**

CD, Crohn's disease; HIV, human immunodeficiency virus; UC, ulcerative colitis;

\* Immunosuppressants: thiopurines or methotrexate

\*\* Biologics: anti-tumor necrosis factor, ustekinumab or vedolizumab

### **Figure 4: Treatment related adverse events according to HIV infection**

HIV, human immunodeficiency virus;

\* Immunosuppressants: thiopurines or methotrexate

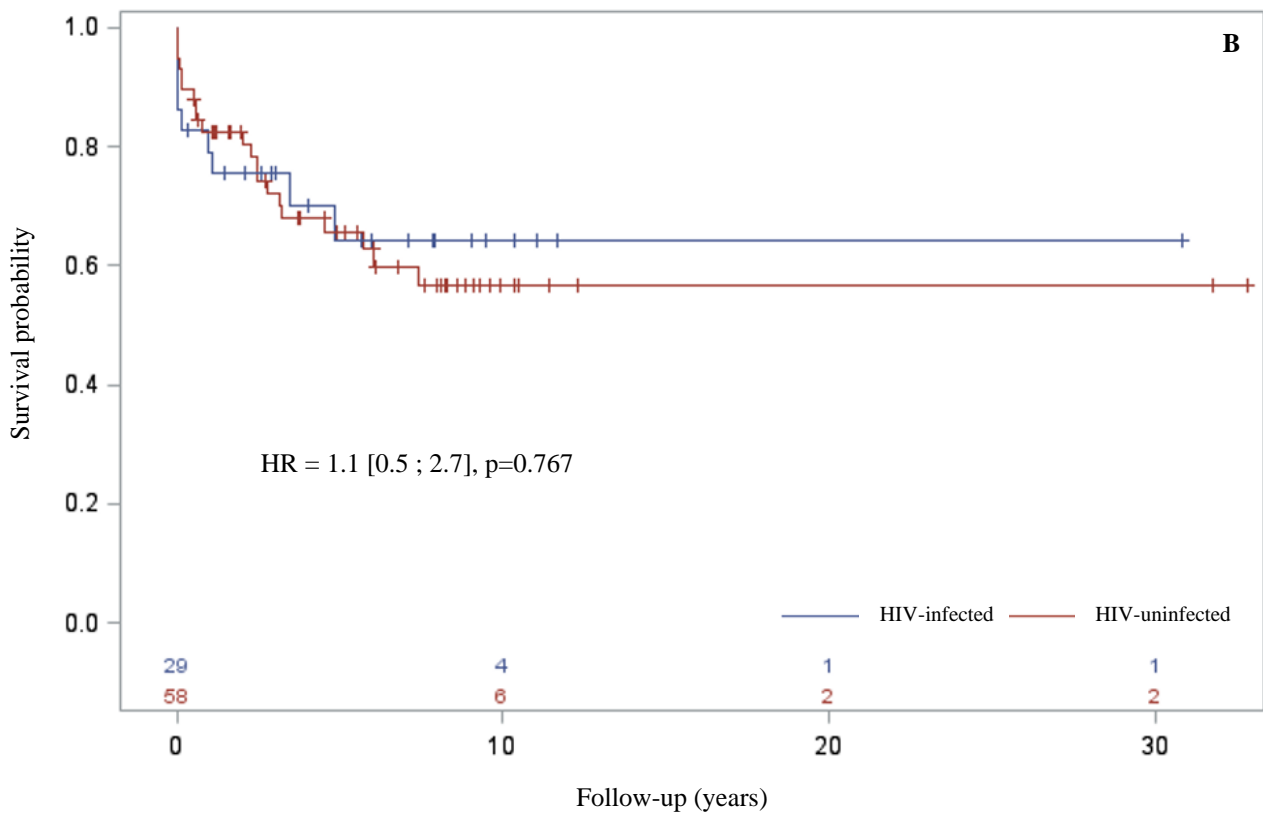
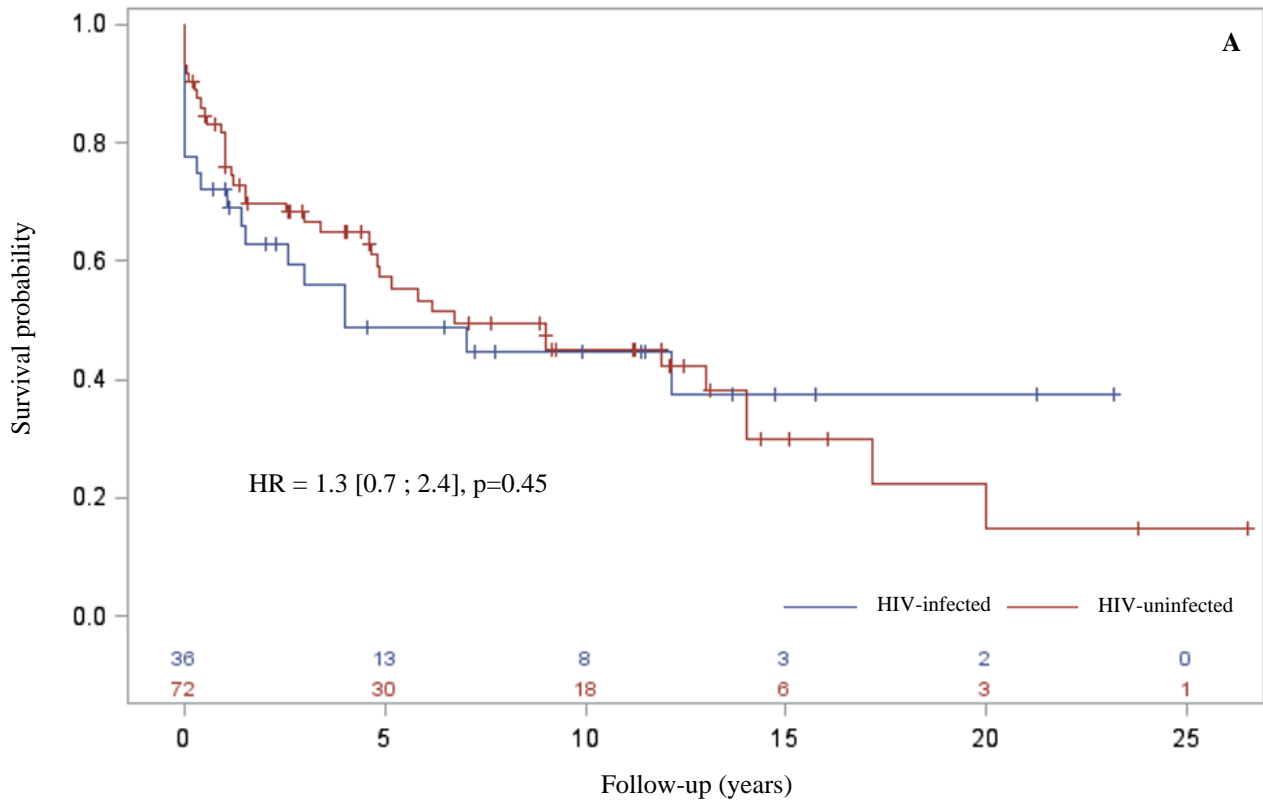
\*\* Biologics: anti-tumor necrosis factor, ustekinumab or vedolizumab

## References

1. Woodham AW, Skeate JG, Sanna AM, et al. Human Immunodeficiency Virus Immune Cell Receptors, Coreceptors, and Cofactors: Implications for Prevention and Treatment. *AIDS Patient Care STDS* 2016;30:291-306.
2. Mehandru S, Poles MA, Tenner-Racz K, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med* 2004;200:761-70.
3. Schneider T, Jahn HU, Schmidt W, et al. Loss of CD4 T lymphocytes in patients infected with human immunodeficiency virus type 1 is more pronounced in the duodenal mucosa than in the peripheral blood. Berlin Diarrhea/Wasting Syndrome Study Group. *Gut* 1995;37:524-9.
4. Veazey RS, DeMaria M, Chalifoux LV, et al. Gastrointestinal tract as a major site of CD4+ T cell depletion and viral replication in SIV infection. *Science* 1998;280:427-31.
5. Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. *Lancet* 2007;369:1627-40.
6. Ungaro R, Mehandru S, Allen PB, et al. Ulcerative colitis. *Lancet* 2017;389:1756-70.
7. Torres J, Mehandru S, Colombel J-F, Peyrin-Biroulet L. Crohn's disease. *Lancet* 2017;389:1741-55.
8. Ho TH, Cohen BL, Colombel J-F, Mehandru S. Review article: the intersection of mucosal pathophysiology in HIV and inflammatory bowel disease, and its implications for therapy. *Aliment Pharmacol Ther* 2014;40:1171-86.
9. Yoshida EM, Chan NH, Herrick RA, et al. Human immunodeficiency virus infection, the acquired immunodeficiency syndrome, and inflammatory bowel disease. *J Clin Gastroenterol* 1996;23:24-8.
10. Sharpstone DR, Duggal A, Gazzard BG. Inflammatory bowel disease in individuals seropositive for the human immunodeficiency virus. *Eur J Gastroenterol Hepatol* 1996;8:575-8.
11. Pospai D, René E, Fiasse R, et al. Crohn's disease stable remission after human immunodeficiency virus infection. *Dig Dis Sci* 1998;43:412-9.
12. Viazis N, Vlachogiannakos J, Georgiou O, et al. Course of inflammatory bowel disease in patients infected with human immunodeficiency virus. *Inflamm Bowel Dis* 2010;16:507-11.
13. Skamnelos A, Tatsioni A, Katsanos KH, et al. CD4 count remission hypothesis in patients with inflammatory bowel disease and human immunodeficiency virus infection: a systematic review of the literature. *Ann Gastroenterol* 2015;28:337-46.
14. Dhar JM, Pidgeon ND, Burton AL. AIDS in a patient with Crohn's disease. *Br Med J*. 1984;288:1802-3.

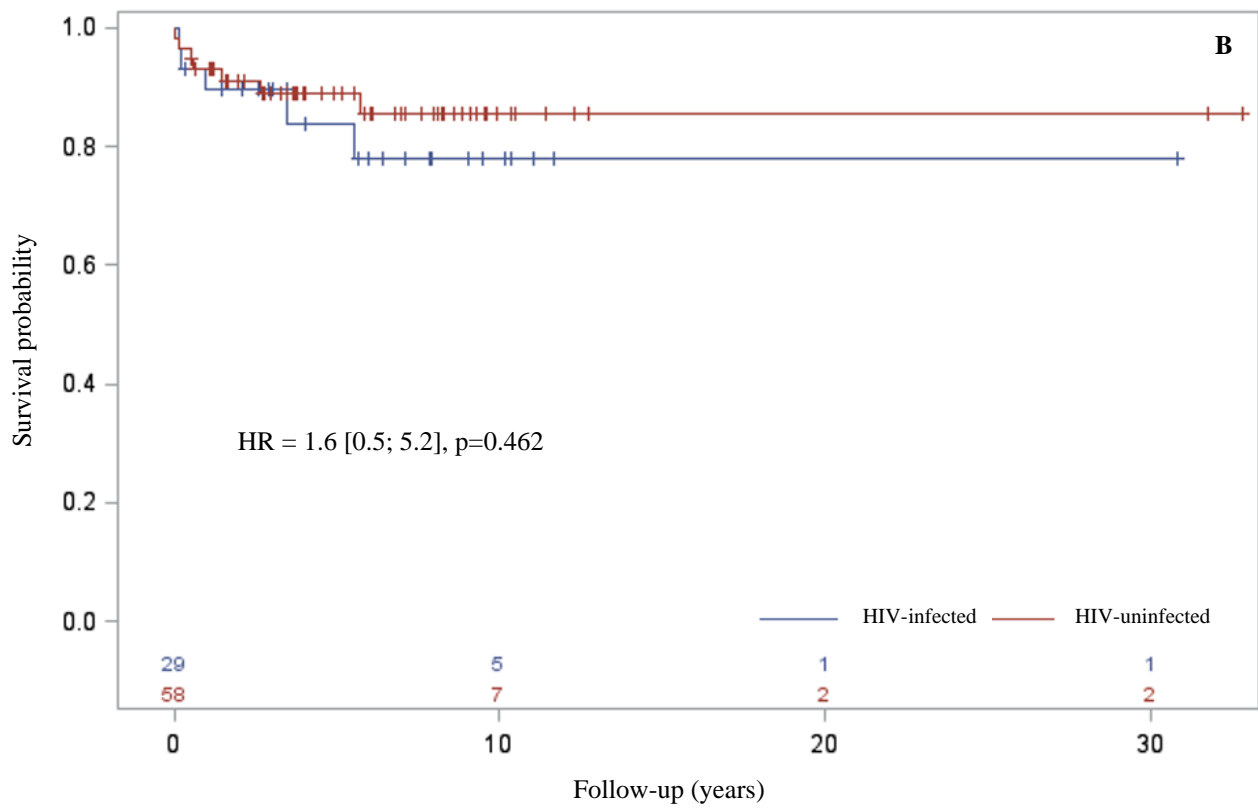
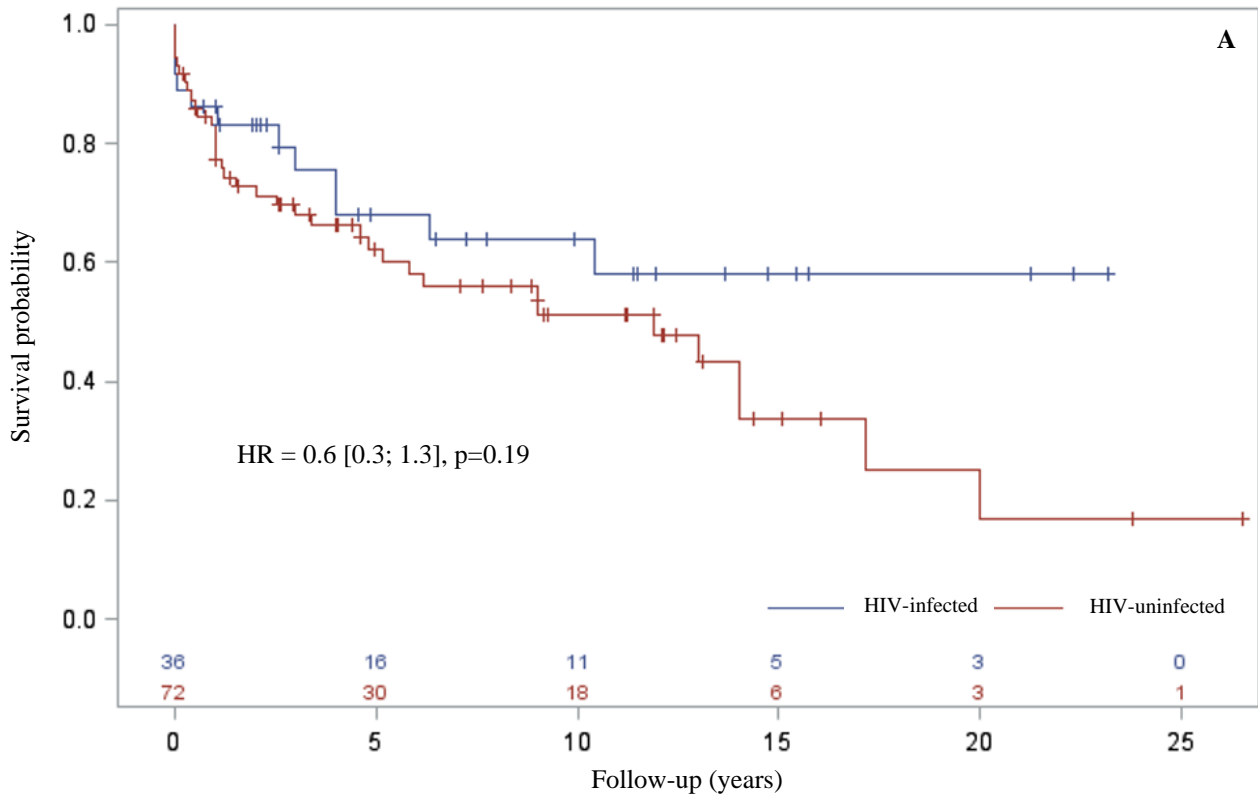
15. Liebowitz D, McShane D. Nonspecific chronic inflammatory bowel disease and AIDS. *J Clin Gastroenterol* 1986;8:66-8.
16. James SP. Remission of Crohn's disease after human immunodeficiency virus infection. *Gastroenterology* 1988;95:1667-9.
17. Bernstein CN, Snape WJ. Active idiopathic ulcerative colitis in a patient with ongoing HIV-related immunodepression. *Am J Gastroenterol* 1991;86:907-9.
18. Sturgess I, Greenfield SM, Teare J, O'Doherty MJ. Ulcerative colitis developing after amoebic dysentery in a haemophiliac patient with AIDS. *Gut* 1992;33:408-10.
19. Bernstein BB, Gelb A, Tabanda-Lichauco R. Crohn's ileitis in a patient with longstanding HIV infection. *Am J Gastroenterol* 1994;89:937-9.
20. Christ AD, Sieber CC, Cathomas G, Gyr K. Concomitant active Crohn's disease and the acquired immunodeficiency syndrome. *Scand J Gastroenterol* 1996;31:733-5.
21. Lautenbach E, Lichtenstein GR. Human immunodeficiency virus infection and Crohn's disease: the role of the CD4 cell in inflammatory bowel disease. *J Clin Gastroenterol*. 1997;25:456-9.
22. Beltrán B, Nos P, Bastida G, Iborra M, Hoyos M, Ponce J. Safe and effective application of anti-TNF-alpha in a patient infected with HIV and concomitant Crohn's disease. *Gut* 2006;55:1670-1.
23. Filippi J, Roger P-M, Schneider SM, et al. Infliximab and human immunodeficiency virus infection: Viral load reduction and CD4+ T-cell loss related to apoptosis. *Arch Intern Med* 2006;166:1783-4.
24. Bongiovanni M, Ranieri R, Ferrero S, et al. Crohn's disease onset in an HIV/hepatitis C virus co-infected woman taking pegylated interferon alpha-2b plus ribavirin. *AIDS* 2006;20:1989-90.
25. Habib SF, Hasan MZ, Salam I. Infliximab therapy for HIV positive Crohn's disease: A case report. *J Crohns Colitis* 2009;3:302-4.
26. Bernardes C, Russo P, Carvalho D, et al. Primary HIV infection in a Crohn's disease patient receiving infliximab maintenance therapy. *AIDS* 2018;32:130-1.
27. Rafael MA, Lourenço LC, Oliveira AM, et al. Successful treatment of severe perianal Crohn's disease with infliximab in an HIV-positive patient. *Clin J Gastroenterol* 2019;12:583-7.
28. Uzzan M, Tokuyama M, Rosenstein AK, et al. Anti- $\alpha 4\beta 7$  therapy targets lymphoid aggregates in the gastrointestinal tract of HIV-1-infected individuals. *Sci Transl Med*. 2018;10:eaau4711.
29. Severs M, Spekhorst LM, Mangen M-JJ, et al. Sex-Related Differences in Patients With Inflammatory Bowel Disease: Results of 2 Prospective Cohort Studies. *Inflamm Bowel Dis* 2018;24:1298-306.
30. Vyboh K, Jenabian M-A, Mehraj V, Routy J-P. HIV and the gut microbiota, partners in crime: breaking the vicious cycle to unearth new therapeutic targets. *J Immunol Res* 2015;2015:614127.
31. Osborn L, Kunkel S, Nabel GJ. Tumor necrosis factor alpha and interleukin 1 stimulate the human immunodeficiency virus enhancer by activation of the nuclear factor kappa B. *Proc Natl Acad Sci U S A* 1989;86:2336-40.
32. Herbein G, Khan KA. Is HIV infection a TNF receptor signalling-driven disease? *Trends Immunol* 2008;29:61-7.
33. Kumar A, Abbas W, Herbein G. TNF and TNF receptor superfamily members in HIV infection: new cellular targets for therapy? *Mediators Inflamm* 2013;2013:484378.
34. Vaidya SA, Korner C, Sirignano MN, et al. Tumor necrosis factor  $\alpha$  is associated with viral control and early disease progression in patients with HIV type 1 infection. *J Infect Dis* 2014;210:1042-6.

35. Arthos J, Cicala C, Nawaz F, et al. The Role of Integrin  $\alpha 4\beta 7$  in HIV Pathogenesis and Treatment. *Curr HIV/AIDS Rep* 2018;15:127-35.
36. Lertjuthaporn S, Cicala C, Van Ryk D, et al. Select gp120 V2 domain specific antibodies derived from HIV and SIV infection and vaccination inhibit gp120 binding to  $\alpha 4\beta 7$ . *PLoS Pathog* 2018;14:e1007278.
37. Girard A, Rochereau N, Roblin X, et al. Targeting and role of  $\alpha 4\beta 7$  integrin in the pathophysiology of IBD and HIV infection. *Med Sci* 2015;31:895-903.
38. Pappas V, Rallis E, Kirsten L, Kyriakis K. Ustekinumab for the treatment of HIV psoriasis. *J Dermatolog Treat* 2012;23:398-9.
39. Saeki H, Ito T, Hayashi M, et al. Successful treatment of ustekinumab in a severe psoriasis patient with human immunodeficiency virus infection. *J Eur Acad Dermatol Venereol* 2015;29:1653-5.
40. Wang DM, Fernandez AP, Calabrese CM, Calabrese LH. Treatment of psoriasis with ustekinumab in a patient with HIV-related Kaposi sarcoma. *Clin Exp Dermatol* 2019;44:113-5.

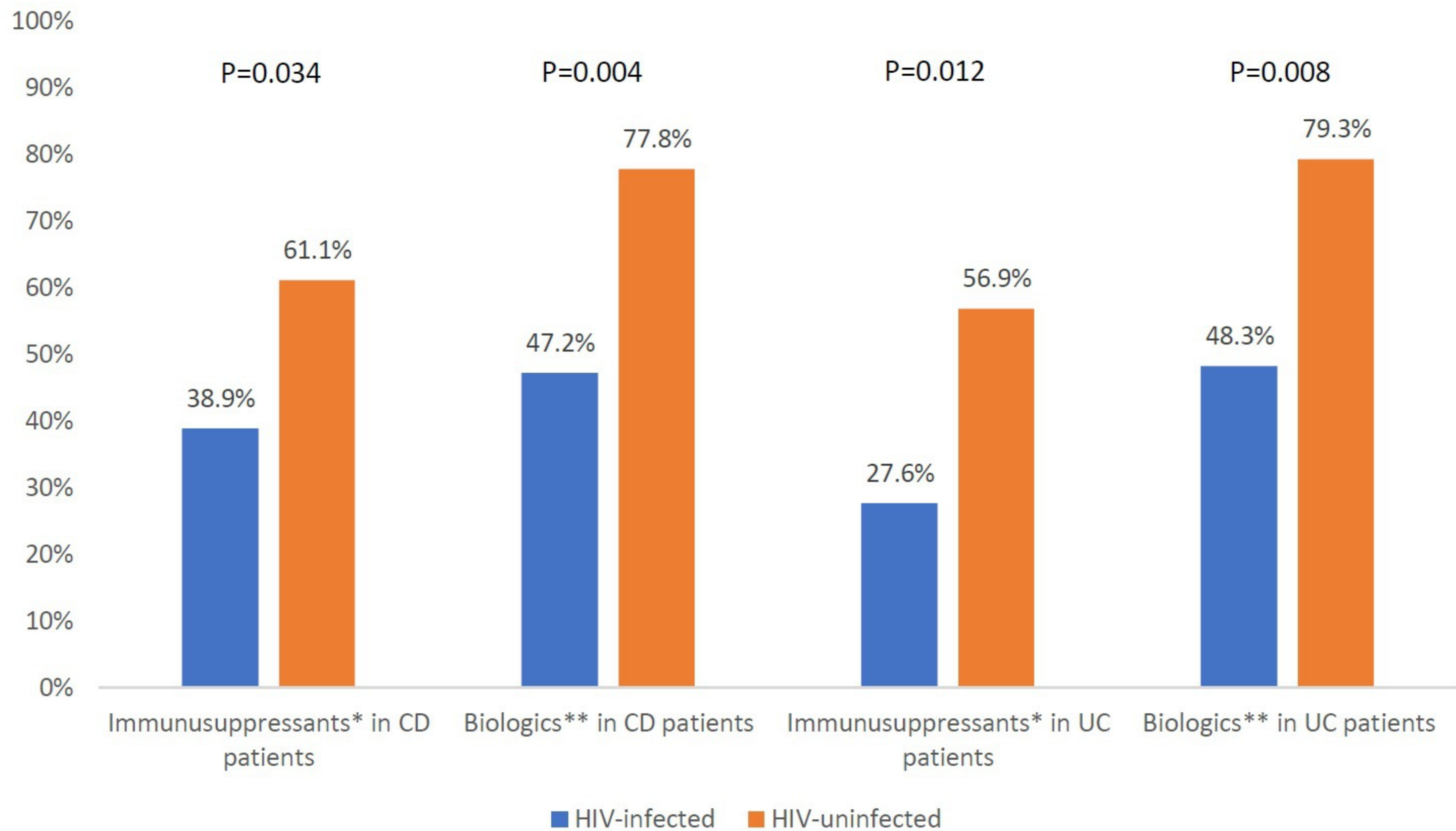


**Figure 1**

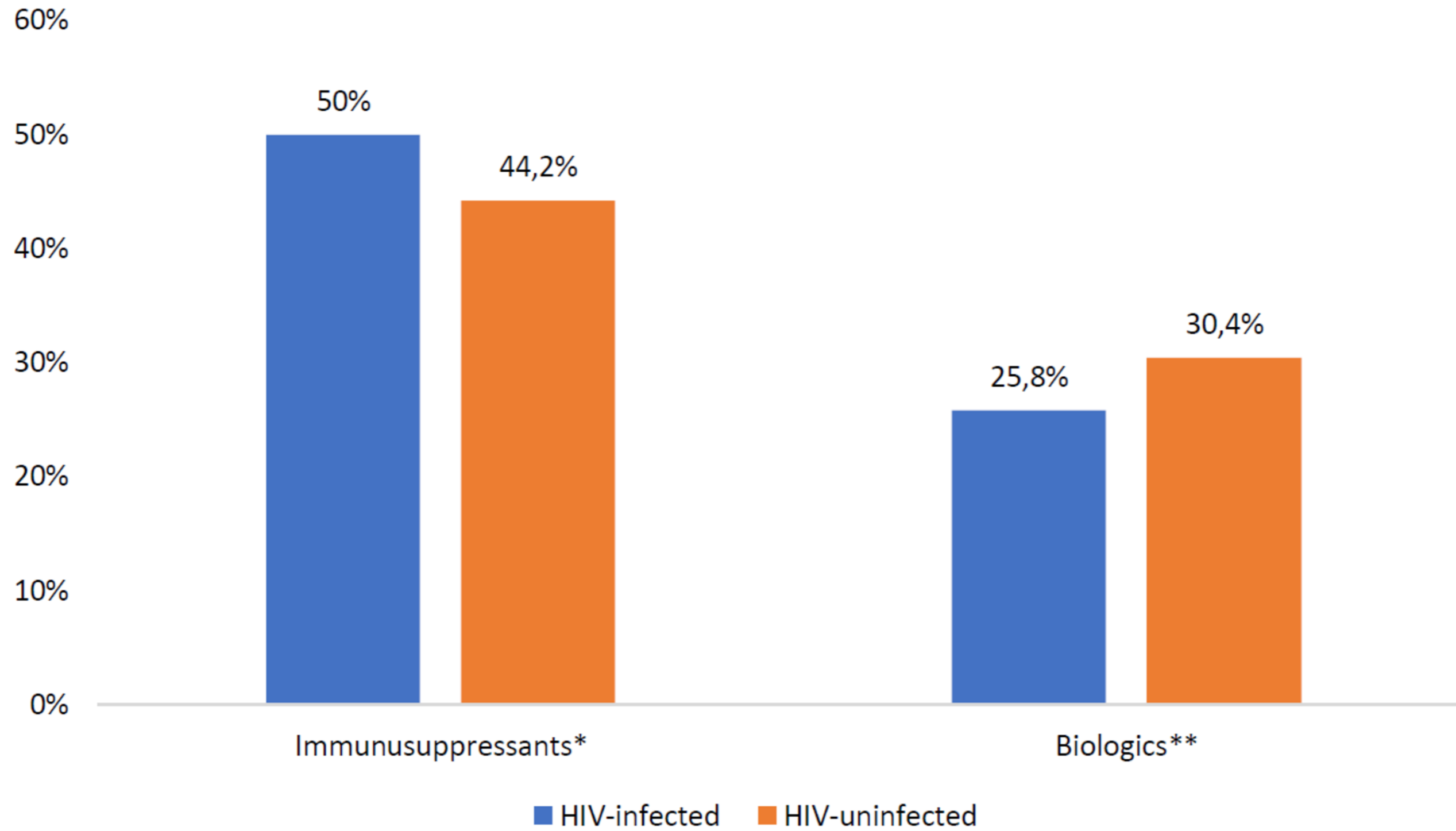




**Figure 2**



**Figure 3**



**Figure 4**