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CD4 count remission hypothesis in patients with inflammatory bowel disease and human immunodeficiency virus infection: a systematic review of the literature

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Abstract

Background Patients with inflammatory bowel disease (IBD) and human immunodeficiency virus (HIV) infection have shown controversial data concerning the remission hypothesis of IBD due to CD4 count depletion caused by HIV. The aim of our systematic review was to investigate the hypothesis whether low CD4 count due to HIV is related to IBD remission.

Methods We systematically searched PubMed for studies reporting on HIV infection in IBD patients. We extracted characteristics of IBD and HIV disease course and CD4 counts.

Results Thirteen papers (2 case-control studies, 2 case series, and 9 case reports) were eligible including 47 patients with IBD and HIV infection (43 male; 27 with Crohn's disease, 19 with ulcerative colitis, and 1 with indeterminate colitis). The IBD diagnosis criteria were heterogeneous among studies. Remission was reported for patients with IBD and HIV infection in 5 studies, including 4 case-control or case series and 1 case report. Four of 5 studies with IBD cases reported remission related to the CD4 count remission hypothesis but only 2 of them explicitly reported the CD4 count cut-off point (500 cells/μL and 200 cells/mm^3 respectively). On the contrary, 7 case reports described an active IBD course or relapse even in patients under immunosuppression.

Conclusions Current literature cannot support or reject the CD4 count remission hypothesis in IBD patients with HIV infection. Prospective studies using uniform criteria on IBD and HIV disease course and CD4 counts are needed.

Keywords HIV, IBD, CD4, remission, systematic review

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Introduction

Inflammation in inflammatory bowel disease (IBD) is currently believed to be initiated and perpetuated by an aggressive cell-mediated immune response to an unknown environmental antigen in a genetically susceptible host. Crohn's disease (CD) and ulcerative colitis (UC) are sharing common pathways, despite the fact that CD is a T-cell-mediated disease while UC is characterized as an antibody-mediated disease. Acute episodes of both CD and UC are characterized by infiltration of large numbers of inflammatory cells including monocytes, neutrophils, and lymphocytes into the intestinal epithelium and wall. This inflammatory infiltrate is accompanied by extensive mucosal and transmural injury, including edema, loss of goblet cells, decreased mucus production, abscesses, erosions, and ulcerations. Pathology specimens suggest an important role for leukocytes in the pathophysiology of IBD. Likewise, CD4+ T-lymphocytes seem to play an important role. HIV infection results in a wide range of clinical consequences from an asymptomatic stage to life-threatening opportunistic diseases [1]. The immunological changes associated with infection by HIV include a progressive loss of peripheral and mucosal CD4 lymphocyte number and function, which leads to the development of opportunistic infections. There is also a

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switch from cell-mediated Th1 response to that of an antigen-antibody-mediated Th2 response [2].

A potential pathophysiological relationship between human immunodeficiency virus (HIV) infection and IBD remains controversial. There are some case series [1-4] and a few case reports [5-13] of IBD in individuals infected with HIV. Some studies suggested that the incidence of IBD in individuals with HIV is increased, either because of the rectal inflammation, or because the changes in the immune system induced by HIV such as loss of CD4 lymphocyte number and function facilitate the development of IBD [2]. Clinical studies hypothesized that a progressive decline in CD4 count caused by HIV may reduce IBD disease activity and contribute to remission [1-4,11,13]. Other investigators claimed that IBD and HIV run an independent course [5-10,12].

In our paper, we systematically tried to retrieve all the studies that included at least one group of patients with IBD and HIV infection and investigate whether they supported that IBD and HIV infection are presented with an independent course in these patients, or whether they provided clinical data that CD4 count remission hypothesis may exist.

Materials and methods

Search strategy

We searched PubMed (from inception to September 2013) using combinations of search terms including inflammatory bowel disease (IBD), human immunodeficiency virus (HIV), and acquired human immunodeficiency syndrome (AIDS). Electronic searches were supplemented by perusal of the references of the retrieved papers.

Study selection

We included studies irrespective of study design that recruited at least one group of adults or adolescents presenting with both IBD and HIV infection regardless of which diagnosis preceded. We also included studies including patients with a simultaneous diagnosis of IBD and HIV infection. However, we excluded studies in which IBD was reported as an HIV-related opportunistic infection, and studies without primary data, i.e., commentaries, or letters to the Editor. We included only papers in English.

Data extraction

For each study, we extracted the name of first author, publication year, country, and type of research center or department where the study was conducted. We also recorded sample size, age of participants, gender, preceding diagnosis (IBD or HIV), and time interval between the two diagnoses. We further extracted the type of IBD (CD, UC, or indeterminate colitis [IC]), and what criteria for IBD diagnosis were mentioned, i.e., clinical, laboratory, radiological, endoscopic, and histological. In addition, we recorded whether IBD distribution, IBD treatment, and IBD complications or specific outcome were reported, whether a specific diagnostic score was used to support IBD relapse, and whether surgery or hospitalization were required during relapse. For HIV infection, we captured whether HIV risk factors that may have induced HIV infection were mentioned, and the potential mode of HIV transmission when data were available; the CD4 count at different times, if reported; and whether HIV treatment, and complications or specific outcome were mentioned. We also recorded any cause for hospitalization or death.

Finally, we noted whether the authors reported any hypothesis related to IBD and HIV infection course. Specifically, we recorded whether IBD remission was mentioned, whether the authors referred to the CD4 count-related IBD remission hypothesis to support patients' remission, and, if they did, whether they provided a CD4 cut-off level related to IBD remission.

All items were extracted by one investigator (AS) and were confirmed by two other investigators (AT and KHK). Discrepancies were resolved after consensus.

Results

Eligible studies

The search of PubMed yielded 604 citations. After screening titles and abstracts, 566 citations were rejected because they were irrelevant to our research questions. We retrieved in full text 38 articles. We rejected 9 of 38 papers because they were not written in English (3 were written in Spanish, 3 in German, 2 in French, and 1 in Japanese). We further excluded 12 articles because after reading the full text we concluded that they were irrelevant to our research question; and 4 articles because they did not include primary data. Thus, we finally selected 13 papers. The 13 articles included 2 case-control studies, 2 case series, and 9 case reports.

Characteristics of eligible studies

Studies were published between 1984 and 2009. Five articles were conducted in USA, 1 in Canada, and 7 in Europe. Case series studies included a small number of participants ranging from 4 to 8. There were two case-control studies that included 60 and 16 patients respectively. In total, there were 47 patients with IBD and HIV, one group of 40 patients with only IBD, and one group of 8 patients with only HIV. The majority of participants were males, 17-49 years old. Of the 47 patients with IBD and HIV, IBD predated HIV infection in 12 of them, 14 were HIV positive at the time IBD occurred, while one case report included a patient with concurrent diagnosis of IBD

and HIV. For 20 patients, there was no information on which disease was diagnosed first (Table 1).

IBD type, criteria of diagnosis, distribution, therapy, complications, and outcome were generally reported among the studies. However, IBD diagnosis criteria were heterogeneous among the studies. Two studies clearly stated that they used a definition to assess relapse for IBD. Viazis *et al* defined IBD relapse as necessity for surgery or clinical recurrence, as assessed by an experienced clinician based on clinical features of diarrhea, abdominal pain, general well-being, weight loss, and inflammatory parameters hemoglobin, erythrocyte sedimentation rate, C-reactive protein, white cell count, and platelets. The definition of IBD relapse described by Sharpstone *et al* included more than three bowel movements a day for more than 3 days in the absence of small bowel pathogens. Most of the studies also reported the need of hospitalization, or surgery when applicable (Table 2).

Almost all studies reported risk factor(s) for HIV exposure. However, only two studies described treatment for HIV. Half of the studies reported complications or outcomes for HIV infection (Table 3).

CD4 count-related IBD remission hypothesis

Remission was described for patients with IBD and HIV infection in 5 studies, including case-control studies [1,2], case series [3,4], and one case report. Seven of the 9 case reports reported no remission for the patients while one case report provided no data on remission. Four of the five studies with cases presenting with remission referred to the CD4 count-related IBD remission hypothesis. However, only two of them mentioned a CD4 count cut-off point in relation to CD4 count remission hypothesis (Table 4).

Table 1 Characteristics of patients in eligible studies

First author Publication year Country	Research center type	Sample size	Age	Gender (Male /Female)	Type of first diagnosis	Time of second diagnosis
Case controls						
Viazis [1] 2009, Greece	Gastroenterology Internal Medicine Infectious Diseases	Cases: 20 Controls: 40	Cases: Mean 38 y Controls: Mean 41 y	Cases: 18 M /2 F Controls: 36 M /4 F	No data	No data
Sharpstone [2] 1996, UK	HIV Center (Kobler Center)	Cases: 8 Controls: 8	Mean 35 y	8 M	IBD (3 patients/ HIV (5 patients)	3 y later on average
Case series						
Pospai [3] 1998, France, Belgium	Gastroenterology Internal Medicine	4	Mean 17 y	3 M /1 F	IBD	Range 4-21 y later
Yoshida [4] 1996, Canada	Medicine Pathology	6	Range 31-49 y	6 M	IBD (2 patients)/ HIV (4 patients)	No data*
Case reports						
Bongiovanni [5] 2006, Italy	Infectious Diseases Pathology	1	39 y	F	HIV	1 m later
Lautenbach [6] 1997, USA	Gastroenterology Internal Medicine	1	30 y	M	HIV	7 y later
Christ [7] 1996, Switzerland	Gastroenterology Pathology	1	41 y	M	IBD	1 y later
Bernstein [8] 1994, USA	Gastroenterology Pathology	1	48 y	M	HIV	5 y later
Sturgess [9] 1992, UK	Nuclear Medicine Hematology Pathology	1	44 y	M	HIV	5 y later
Bernstein [10] 1991, USA	Gastroenterology	1	35 y	M	IBD and HIV	Same period for both diagnoses
James [11] 1988, USA	Immunology Allergy and Infectious Diseases	1	38 y	M	IBD	18 y later
Liebowitz [12] 1986, USA	No data	1	40 y	M	IBD	14 y later
Dhar [13] 1984, UK	Medicine	1	37 y	M	HIV	1 y later

IBD, inflammatory bowel disease; HIV, human immunodeficiency virus; y, year(s); CD, Crohn's disease; UC, ulcerative colitis; M, male; F, female; IC, indeterminate colitis, *Yoshida 1996, provided time of second diagnosis for one of the patients only (4 years later)

Table 2 Characteristics of IBD and IBD course of patients in eligible studies

First author Publication year	Patients	Criteria for IBD diagnosis	IBD distribution reported	IBD treatment reported	IBD complications / outcome reported	IBD relapse definition	Surgery / hospitalization due to IBD relapse
Case controls							
Viazis [1], 2009	14 CD /6 UC Control group: 28 CD/12 UC	Symptoms Laboratory tests Radiology Endoscopy Histology	Yes	Yes	Yes	Yes	Yes
Sharpstone [2], 1996	2 CD /6 UC	Histopathology†	No	Yes	Yes	Yes	Yes
Case series							
Pospai [3], 1998	4 CD	Symptoms# Radiology# Endoscopy#	Yes	Yes	Yes	No	Yes
Yoshida [4], 1996	1 CD /4 UC /1 IC*	Endoscopy Histology	No	Yes	Yes§	No	Yes§
Case reports							
Bongiovanni [5], 2006	CD	Symptoms Laboratory tests Endoscopy	Yes	Yes	Yes	No	Yes
Lautenbach [6], 1997	CD	Symptoms Radiology Endoscopy Histology	Yes	No	Yes	No	Yes
Christ [7], 1996	CD	Symptoms Laboratory tests Endoscopy Histology	No	Yes	Yes	No	Yes
Bernstein [8], 1994	CD	Symptoms Laboratory tests Radiology	Yes	Yes	Yes	No	Yes
Sturgess [9], 1992	UC	Symptoms Laboratory tests Radiology Endoscopy Histology	Yes	Yes	Yes	No	Yes
Bernstein [10], 1991	UC	Symptoms Laboratory tests Endoscopy Histology	Yes	Yes	No	No	No
James [11], 1988	CD	Symptoms Laboratory tests Radiology Endoscopy Histology	Yes	Yes	Yes	No	Yes
Liebowitz [12], 1986	UC	Symptoms Radiology Endoscopy Histology	Yes	Yes	Yes	No	Yes
Dhar [13], 1984	CD	Symptoms Radiology Histology	Yes	Yes	Yes	No	Yes

IBD, inflammatory bowel disease; HIV, human immunodeficiency virus; y, year(s); CD, Crohn's disease; UC, ulcerative colitis; M, male; F, female; IC, indeterminate colitis, *Yoshida reported that one patient was diagnosed by IC, an idiopathic IBD that had features of both, #Reported only for certain patients, †Confirmation of IBD by a gastrointestinal histopathologist using standard diagnostic criteria, §Reported only for 1 patient, little information for 2 patients

Table 3 Characteristics of HIV infection and HIV infection course of patients in eligible studies

First author Publication year	Reported risk factor(s) for HIV exposure	HIV treatment reported	HIV complications/ outcome reported
Case controls			
Viazis [1], 2009	No	Yes	No
Sharpstone [2], 1996	Yes	No	Yes
Case series			
Pospai [3], 1998	Yes	No*	Yes
Yoshida [4], 1996	Yes	No	Yes
Case reports			
Bongiovanni [5], 2006	Yes	No treatment was administered	No
Lautenbach [6], 1997	Yes	Yes	No
Christ [7], 1996	Yes	No	Yes
Bernstein [8], 1994	Yes	No	No
Sturgess [9], 1992	Yes	Yes	No
Bernstein [10], 1991	Yes	No	Yes
James [11], 1988	Yes	No	No
Liebowitz [12], 1986	Yes	No	Yes
Dhar [13], 1984	Yes	No	Yes

*Zidovudine was reported as treatment for 1 patient *HIV, human immunodeficiency virus*

Table 4 CD4 count IBD remission hypothesis for patients in eligible studies

First author Publication year	IBD remission reported	CD4 count remission hypothesis supported	CD4 cut off
Case controls			
Viazis [1], 2009	Yes	Yes	≤500 cells/μL
Sharpstone [2], 1996	Yes	Yes	≤200 cells/mm^3
Case series			
Pospai [3], 1998	Yes	No/ unclear	No
Yoshida [4], 1996	Yes	Yes	No
Case reports			
Bongiovanni [5], 2006	No	No	NA
Lautenbach [6], 1997	No	No	NA
Christ [7], 1996	No	No	NA
Bernstein [8], 1994	No	No	NA
Sturgess [9], 1992	No	No	NA
Bernstein [10], 1991	No	No	NA
James [11], 1988	Yes	No	No
Liebowitz [12], 1986	No	NA	NA
Dhar [13], 1984	ND	ND	ND

IBD, inflammatory bowel disease; NA, non applicable; ND, no data

Viazis *et al* [1] compared IBD activity in 20 IBD patients infected with HIV with a matched group (2 controls per case) of 40 IBD patients without HIV. The relapse rate of IBD was significantly lower for IBD patients with HIV infection (0.016/ year vs. 0.053/year; P=0.032). However, these IBD relapse rates were relatively low in these patients as compared to other studies [1]. In the same study, survival curves showed that time to first relapse is longer for IBD patients infected with HIV [1]. Pospai *et al* [3] reported 4 cases of patients with long-standing relapsing CD who became infected with HIV and experienced a stable remission for the next 5, 8, 8, and 8 years respectively, a period that corticosteroid therapy was stopped. However, explicit data on immunosuppression were inadequately provided during CD remission, except for the latest period when the patients presented both with CD and HIV infection. Yoshida *et al* [4] reported that 3 patients with UC experienced active UC, with mildly depressed CD4 counts. One patient with CD had an episode with a CD4 count equal to 210 cells/mL. The rest 2 patients, who were followed until the CD4 count reached an end-stage nadir, experienced quiescence in IBD activity. Sharpstone *et al* [2] studied 8 cases with IBD-HIV coinfection. All IBD exacerbations occurred in patients with a CD4 count more than 200 cells/mm^3. Finally, James *et al* [11] reported a patient with an 18-year history of CD who became infected with HIV and had a complete remission of IBD with progressive immunodeficiency. However, the patient had been asymptomatic for 2 years before the diagnosis of HIV infection, and his initial CD4 count was 410/mm^3, a level not commonly associated with severe immune suppression and risk for opportunistic disease.

Dhar *et al* described a man with classic HIV-related illnesses (PCP, monilial esophagitis) and inactive CD. However, HIV serological testing had not been developed when the patient was presented with the symptoms, and the authors were not able to clarify which disease occurred first [12].

On the contrary, 7 of the 9 case reports argued against the CD4 count-related IBD remission hypothesis [5-10,12]. They described an active IBD or IBD relapse even when patients were in severe immunosuppression.Four case reports [5-7,9] described IBD as a new onset (event) in an HIV-infected patient. One of these presented a HIV-positive patient with a CD4 count equal to 170 cells/mm^3 at the *de novo* development of UC [9]. However, this patient was not followed long enough so that the authors could report disease activity with a CD4 count <170 cells/mm^3. One case report did not clearly state the CD4 cell count because it had been published before the absolute CD4 count became a standard clinical point of reference (Table 5) [12].

Discussion

There were few studies, mainly case reports, on a very small number of patients with IBD and HIV infection. The largest

Table 5 Analytical overview of studies, case series and case reports on HIV and IBD

First author, publication year Journal	Time interval between the two diagnoses	IBD distribution	Potential route for HIV acquisition	CD4 count	HIV therapy	IBD therapy	HIV complications / outcome	IBD complications /outcome	Cause for death / hospitalization
Case control									
Viazis [1], 2009 *Inflamm Bowel Dis*	No Data	CD: Terminal ileum (4 pts), colitis (6 pts), ileocolonic (4 pts) UC: Extensive colitis (2 pts), left-sided (2 pts), proctitis (2 pts)	No Data	Mean lowest CD4 count: 616 cells/μL	At entry: 14 pts HAART	At entry: 6 pts Azathioprine, 20 pts Mesalazine Relapse: 3 pts Steroids	No Data	3 pts relapsed (CD4 Count ≥500 cells/μL), 1 pt (CD) developed fistula	No Data
	No Data	CD: terminal ileum (8 pts), colitis (12 pts), ileocolonic (8 pts) UC: extensive colitis (4 pts), left-sided (4 pts), proctitis (4 pts)	No Data	Mean lowest CD4 count: 1218 cells/μL	NA	At entry: 12 pts Azathioprine, 40 pts Mesalazine Relapse: 18 pts Steroids, 4 CD pts Infliximab	No Data	18 pts relapsed, 1 pts developed fistula	No Data
Sharpstone [2]*, 1996 *Eur J Gastroenterol Hepatol*	3 pts: IBD/ mean time 36 months earlier 5 pts: HIV/ mean time 36 months earlier		Male-to-male sexual contact	At entry: 342±98 cells/mm^3		Colectomy	Few data (shigellosis, CMV inclusions)	Remission with a CD4 <200 cells/ mm^3	
				At entry: 323±77 cells/mm^3					
Case series									
Pospai [3], 1998 *Dig Dis Sci*	IBD (1967)/ HIV (1985)	Ileum, perianal, colon	Contaminated blood product transfusion	320/mm^3 (1986), 165/mm^3 (1990)	Zidovudine (1988)	Sulfasalazine, Corticosteroids, Ileal Resection, Right Colectomy	Death (1990)	5 y remission after HIV infection	Multifocal progressive viral leukoencephalopathy
	IBD (1975)/ HIV (1987) *contamination 1980-1983	Ileum, perianal, right/left colon	Contaminated blood product transfusion	50/mm^3 (1988)		Corticosteroids, Ileo-Right Colectomy,	Death (1991)	8 y remission after HIV infection	Multiple organ failure (opportunistic infection)
	IBD (1982)/ HIV (1985)	Terminal ileum, right colon,	IV drug user	162/mm^3 (1989), 396/mm^3 (1992)		Corticosteroids, Sulfasalazine,	Alive at the time of study publication	9 y remission after HIV infection	

Table 5 Contd...

First author, publication year Journal	Time interval between the two diagnoses	IBD distribution	Potential route for HIV acquisition	CD4 count	HIV therapy	IBD therapy	HIV complications / outcome	IBD complications /outcome	Cause for death / hospitalization
	IBD (1980)/ HIV (1990) *contamination 1980-1983	Colon, stomach, rectum, small intestine	Contaminated blood product transfusion	34/mm^3 (1990), 10/mm^3 (1992)		Corticosteroids, Total Colectomy, Partial Gastrectomy, Proctectomy	Death (1992)	8 y remission after HIV infection	Septic shock
Yoshida [4], 1996 *J Clin Gastroenterol*	ND		Male-to-male sexual contact	Before IBD: 470 cells/mL, Remission: 190 to 30 cells/mL		Active disease: 5-Aminosalicylic acid	PCP	No data	
	ND		Male-to-male sexual contact	Before IBD: 210 cells/mL, Remission: 130 cells/mL		Active disease: 5-Aminosalicylic acid, prednisone. Remission: 5-Aminosalicylic acid, prednisone		Lost to follow up, phone call revealed limited episodes of abdominal cramps and nonbloody diarrhea	
	ND	Proctitis	Male-to-male sexual contact	Before IBD: 680 cells/mL, Remission: 640 cells/mL		Active disease: 5-Aminosalicylic acid		No data	
	ND		Male-to-male sexual contact	Before IBD: 700 cells/mL Remission: 700 cells/mL		Active disease: 5-Aminosalicylic acid, prednisone		No data	
	ND		Male-to-male sexual contact	Remission: 530 to 440 cells/mL		Active disease: 5-Aminosalicylic acid, prednisone. Remission: 5-Aminosalicylic acid		Recurrence at 440 cells/mL	
	HIV 4y later		Male-to-male sexual contact	Remission: 130 to 20 cells/mL		Active disease: 5-Aminosalicylic acid, prednisone	PCP, MAC infection, cryptosporidiasis	Minimal symptoms after seroconversion	
Case reports									
Bongiovanni [5], 2006, *AIDS*	HIV (10/2004)/ IBD (1/2006)	60 cm from anus	Sexual contact	Onset at: 275 cells/μL		Mesalasine (800 mg)		New onset, 3 m follow up	
Lautenbach [6], 1997 *Jl Clin Gastroenterol*	HIV (1987)/ IBD 7y later (1994)	Terminal ileum, colon, rectum	Male-to-male sexual contact	Onset at: 100/ mm^3 (8/1994)	Dapsone			New onset / at CD4 count: 100/mm^3	

Table 5 Contd...

First author, publication year Journal	Time interval between the two diagnoses	IBD distribution	Potential route for HIV acquisition	CD4 count	HIV therapy	IBD therapy	HIV complications / outcome	IBD complications /outcome	Cause for death / hospitalization
Christ [7], 1996 *Scand J Gastroenterol*	IBD (1985)/ HIV (1986)		Sexual contact	At relapse: 84/μL (1995)		Prednisone, Mesalazine	Pneumonia (1990), Lymphadenopathy (1990), Candida stomatitis (1990), Candida Esophagitis (1993)	Relapse : (2/1992), (5/1992), (7/1993), (12/1993), (2/1994), (10/1995)	
Bernstein BB [8], 1994 *Am J Gastroenterol*	IBD 5y later	Ileum	Male-to-male sexual contact	Onset at: 480/ mm^3		Resection of terminal ileum		New onset	
Sturgess [9], 1992 *Gut*	HIV (1984)/ IBD (1989)	Rectum, colon	Hemophilia	220/mm^3 (3/1989), 170/mm^3 (12/1989)	Zidovudine	Mesalazine, Prednisolone,		At onset: toxic dilatation 2 m later colonoscopy: quiescent colitis	
Bernstein CN [10], 1991 *Am J Gastroenterol*	Concurrent diagnosis	Colon	Sexual contact or tattoo or IV drug abuse	546/mm^3 (2/1989), 260-520/mm^3 (9/1989)		Prednisone, Azulfidine, Sulfasalazine	Tongue ulcers (HSV)	Pancolitis	
James [11], 1988 *Gastroenterology*	IBD (1968)/ HIV (1986)	Ascending colon, cecum, rectum	High risk behavior	410/mm^3 (1986) 25/mm^3 (1988)		Prednisone, Sulfasalazine, Lomotil ??		After seroconversion, free of IBD symptoms for >3 y	
Liebowitz [12], 1986 *J Clin Gastroenterol*	IBD (1970)/ HIV (1984)	Colon (pancolitis, transverse colon)	Male-to-male sexual contact			Prednisone, Sulfasalazine	Kaposi's sarcoma	No data provided following the diagnosis	
Dhar [13], 1984 *Br Med J (Clin Res Ed)*	HIV (1976)/ IBD (1977)	Ascending colon	Contaminated blood product transfusion			Right Hemicolectomy, Ileal (terminal) resection	PCP (7/1982), Encephalopathy, Esophageal Candidiasis (1/1983), Death (11/1983)	Death (11/1983)	Lung squamous carcinoma

IBD, Inflammatory bowel disease; CD, Crohn's disease; pt(s), patient(s); y, year(s); IV, intravascular; HAART, Highly active antiretroviral therapy; NA, non applicable; ND, no data; PCP, Pneumocystis carinii pneumonia; MAC, Mycobacterium avium complex; HSV, herpes simplex virus; CMV, cytomegalovirus, *Time for HIV diagnosis corresponds to time when positive HIV laboratory test was found while contamination happened earlier, Different control groups between case controls: Viazis: only IBD pts, Sharpstone only HIV pts

case-control study suggested that relapse in IBD patients infected with HIV had less frequent relapses than IBD patients without HIV [1]. The small number of case series studies tended to support that CD4 depletion may be related with IBD remission [1-4]. However, the absence of a control group substantially compromises the robustness of their conclusion. Most case reports supported that IBD remission did not follow HIV infection in their patients [5-10,12]. However, in addition to their weakness for firm conclusions due to study design, there were issues related to the CD4 count, which either was not clearly reported or remained at higher levels than the CD4 count in studies that supported the IBD-HIV remission hypotheses.

Small sample sizes may be unavoidable since the reported prevalence of HIV among IBD patients is generally low. Specifically, Viazis *et al* [1], claimed that a 21-year (1988-2009) IBD database review of more than 1,600 patients revealed 20 patients with IBD and coexisting HIV. Sharpstone *et al* [2] reported a 41/100,000 mean incidence in the 6-year study period, but noticed that the prevalence of IBD in the region's HIV population in 1993 was 364/100,000. Yoshida *et al* [4] described that during a 4-year period (1989-1993) in a 2-million population area according to hospital discharges, there were 1,839 patients with HIV diagnosis, and 1,115 patients with IBD diagnosis, but only 6 patients with both diagnoses. To address this issue, an international registry of IBD patients with HIV infection might help increase the number of patients to be prospectively followed long term and improve the precision of conclusions.

Diagnosis of IBD in HIV positive patients is often difficult. Patients with HIV frequently present with diarrhea caused by opportunistic infection, and may be misdiagnosed as having chronic inflammatory bowel disease. In fact, some of these infections may mimic IBD, e.g., cytomegalovirus (CMV), *Mycobacterium avium-intracellulare*, *Treponema pallidum*, and other pathogens including *Cryptosporidium*, microsporidia, *Isospora belli*, *Giardia lamblia*, herpes simplex virus, *Entamoeba histolytica***,** and several other bacteria [3,7]. In the case reported by Wajsman *et al* [15] the pathogen (CMV) was identified only by microscopic examination of the bowel resected during a second laparotomy. The terminal ileum had profound mucosal ulcerations and transmural fibrosis without granuloma, an endoscopic presentation similar to the case described by Bernstein *et al* [3] Gastrointestinal Kaposi's sarcoma, with extensive submucosal infiltration and overlying mucosal inflammation, may also resemble UC [4]. Thus, it is substantial that diagnosis of IBD in HIV patients is confirmed by biopsy in all cases.

Absolute CD4 cell count might not be the appropriate factor to correlate with IBD course. CD was suggested that may depend more on CD4 functional ability and less on their absolute number [6]. Specifically, although no difference in absolute numbers of lamina propria CD4 cells was noted when comparing patients with CD with healthy controls, a higher proportion of lamina propria T lymphocytes secreting IL-2 (indicating T-cell activation) was observed in patients with CD compared with controls [15,16]. Additionally, peripheral T-cell counts may not accurately reflect levels at the intestinal mucosa [8], and thus a decrease in the peripheral blood CD4 count does not necessarily imply intestinal mucosal immune cell depletion. However, in patients with CD, this issue remains controversial [6].

Our review had several limitations. The type of the study design and the sample size for the eligible studies did not allow us for any robust conclusion. In addition, specific issues related to both IBD and HIV characteristics were also raised. The definition of diagnosis and relapse of IBD was heterogeneous among the studies. Despite the fact that all studies reported diagnostic criteria, the use of biopsy was not uniquely applied. Moreover, relapse definition was mentioned only in two of the studies. The CD4 count has significant diurnal variation and day-to-day fluctuations, and, therefore, investigators who design studies on patients with IBD and HIV should agree on whether the lowest CD4 count or the mean CD4 count would be more appropriate. Otherwise, the diversity of CD4 count reporting would pose an additional barrier in the interpretation of the results. Finally, eligible studies did not provide information to explore other speculations, i.e. individuals who develop IBD involving the rectum before their HIV status is known may have an increased risk of HIV transmission during unprotected anal intercourse.

In conclusion, there is a paucity of data in the literature to support or reject the hypothesis that CD4 count depletion may induce remission of bowel inflammation in IBD patients. However, if we had to pick a side on that argument, there is a trend supporting the CD4 hypothesis and most reports seem to suggest that IBD might be less aggressive in patients infected with HIV.

Due to the low prevalence of patients with IBD and HIV infection, an international registry is recommended to prospectively follow larger number of patients. In addition, certain requirements, including the performance of biopsy for IBD exacerbation diagnosis, and appropriate CD4 count reporting should be ensured to enhance robustness of conclusions.

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