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Managing IBD patients with concomitant HIV infection - a systematic review

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Abstract

Inflammatory bowel disease (IBD) is a chronic gastro-intestinal inflammatory condition resulting from dysregulated mucosal immune system activation. Many medications used may have an immunosuppressive effect, thereby increasing the risk of infection. The Human Immunodeficiency Virus (HIV) infection, on the other hand, induces an immunosuppressive state, which could affect the natural history of IBD patients, but also predisposes to infections and cancer. Therefore, managing patients with IBD and concomitant HIV infection (IBD-HIV_{pos}) may pose therapeutic challenges. The aim of this systematic review is to report data on epidemiology, disease course and treatment safety. A systematic literature search was conducted on PubMed/MEDLINE, EMBASE and CENTRAL databases, yielding 2 483 results. Overall, 32 papers were included, representing a total of 2631 IBD-HIV_{pos} patients (14 on epidemiology, 16 on disease course and 11 on treatment regimens); most papers had a fair quality, missing standardized criteria for outcome assessment and accounting for possible confounding factors.

Our qualitative synthesis showed that the prevalence of IBD-HIV_{pos} ranges from 0.1 to 2%. Regarding disease course, no significant impact caused by IBD in HIV patients was described. Some studies reported a milder IBD phenotype in HIV_{pos} patients, although disease progression was similar overall. In terms of morbidity, there was an increase in the risk of cancer (mostly colorectal cancer), however survival was similar. In terms of treatment, immunosuppressive regimens were used less frequently in IBD-HIV_{pos} patients, either due to doctor's concerns or a milder IBD phenotype. Overall, the safety of IBD treatment was reassuring, provided that close monitoring was implemented.

In summary, we found a low prevalence of IBD among HIV patients. While IBD did not seem to affect HIV course, some studies reported milder IBD phenotype and less frequent use of immunomodulatory medications. IBD therapy seems to be safe in IBD-HIV_{pos} patients, however close monitoring should be conducted.

Keywords: Inflammatory Bowel Disease; Crohn's Disease; Ulcerative Colitis; Human Immunodeficiency Virus; Acquired Immunodeficiency Syndrome

Resumo

A Doença Inflamatória Intestinal (DII) caracteriza-se por inflamação crónica, contrariamente, a infeção pelo Vírus da Imunodeficiência Humana (VIH), induz um estado de imunossupressão. Muitas teorias surgiram relativamente ao impacto que estas patologias poderiam ter uma na outra. O objetivo desta revisão sistemática foi reportar dados sobre epidemiologia, impacto no curso da doença e segurança do tratamento, na presença de ambas as patologias.

Foi realizada uma pesquisa nas bases de dados PubMed/MEDLINE, EMBASE e CENTRAL, selecionando artigos de interesse, produzindo 2 483 resultados, com 32 artigos incluídos (14 sobre epidemiologia, 16 sobre curso da doença e 11 sobre terapêutica), totalizando 2 631 doentes.

A prevalência de DII em doentes infetados por VIH é de 0.1 a 2%. Não houve alteração no curso da infeção por VIH. Não foi possível chegar a uma conclusão relativamente à hipótese de remissão dos CD4+. Alguns estudos reportaram um fenótipo mais ligeiro de DII em doentes com VIH, ainda que a progressão da doença seja semelhante. Em termos de morbilidade, existe um risco acrescido para neoplasias, nomeadamente cancro colorretal. Não se verificou um impacto na sobrevivência dos doentes. Em relação ao tratamento, os imunossupressores são utilizados com menor frequência em doentes com VIH. Podendo dever-se a receio dos médicos ou a um fenótipo de DII mais ligeiro. Em termos de segurança, não se identifica um impacto significativo provocado pela terapêutica com imunossupressores, desde que se garanta uma monitorização cuidada dos doentes.

Sumarizando, não foi possível chegar a uma conclusão sobre a hipótese de remissão dos CD4+, ainda que, existam vários estudos que reportem um fenótipo de DII menos agressivo, na presença de infeção por VIH. Mais estudos deveriam ser realizados, com critérios uniformizados. Os dados sobre tratamento, são tranquilizadores, sugerindo que a terapêutica usada na DII é segura em doentes com VIH, desde que sejam vigiados.

Palavras-chave: Doença Inflamatória Intestinal; Doença de Crohn; Colite Ulcerosa; Vírus da Imunodeficiência Humana; Síndrome de Imunodeficiência Adquirida

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Introduction

Inflammatory bowel disease (IBD) is a chronic condition, composed of two main disorders: Crohn's disease (CD) and Ulcerative colitis (UC). These diseases present with symptoms such as abdominal pain, chronic diarrhea, weight loss and fatigue, manifested in a relapsing and remitting course, with the potential to cause significant bowel damage and disability.

The prevalence of IBD has been steadily increasing worldwide. Between 1990 until 2017, the number of cases increased from 3.7 million (95% CI 3.5-3.9) to more than 6.8 million (95% CI 6.4-7.3), with an increase on the global age-standardized prevalence from 79.5 per 10^5 (95% CI 75.9-83.5) in 1990 to 84.3 per 10^5 (79.2-89.9) in 2017 (Alatab et al., 2020). We are also witnessing an increase of these diseases in developing countries, even though the total number of cases are still lower compared to developed countries (Torres *et al.*, 2017; Ungaro *et al*., 2017).

While the cause of IBD remains unknown, the current dogma is that this is a multifactorial disease, resulting from a complex interaction between genetics, environmental factors and altered microbiota, leading to a dysregulated and chronic immune response. Regarding Crohn's disease, there seems to be a role played by the microbiota, in which dysbiosis might perpetuate the underlying inflammation, as well as the activity of the intestinal immune system. It has been shown that in CD, there is a CD4+ T-helper cell response, mainly composed of Th1 and Th17 cells (which secrete IFN-γ and TNF-α, IL-17 and IL-22, respectively), and also an impairment of Treg cells. Innate lymphoid cells (ILC), particularly, ILC3 and ILC1 have been implicated in CD, potentially contributing to the inflammatory state (Torres et al., 2017). In the pathophysiology of UC, defects in the epithelial and mucous barrier are a strong predisposing factor, dysbiosis is also reported to a lesser degree than CD, ultimately resulting in a dysregulated mucosal immune response. ILC3 are also involved with an increased expression of inflammatory mediators. An important difference from CD, is that there is a predominantly T-helper-2 response with the production and release of IL-4, IL-5 and IL-13 (inducing cytotoxicity and barrier dysfunction). T-helper-9, producing IL-9 (inhibits cellular proliferation and repair and increases TNF-α) (Ungaro et al., 2017) have also been implicated in UC´s pathophysiology.

While IBD represents a plethora of dysregulated immune responses towards the epithelial barrier and gut microbiome, HIV acts on the other side of the spectrum. HIV is a viral infection leading to an immunodeficiency syndrome, increasing the risk of invasive and/or opportunistic infections and even cancer. The Human Immunodeficiency Virus (HIV) is a retrovirus, which primarily infects cells of the immune system, impairing our immune response. It has been labeled as a pandemic, infecting people worldwide and increasing the risk of infections and mortality.

According to the latest report published by the Joint United Nations Program on HIV/AIDS (UNAIDS), in 2021, there were 38.4 million people globally with an HIV infection (only 28.7 million accessing antiretroviral therapy), with a reported 1.5 million new cases worldwide and 650 000 dying from Acquired Immunodeficiency Syndrome (AIDS)-related complications. Since 2010, there seems to be a reduction in new cases per year, with new infections declining by 32%, from 2.2 million to 1.5 million in 2021; however there still remain a significant number of new infections in developing countries mainly in Eastern and Southern Africa (*Global HIV & AIDS Statistics*, 2023), demonstrating that despite the advances in antiretroviral therapy and prevention, there is still a long way to go in terms of controlling the HIV pandemic.

Regarding pathophysiology, HIV primarily infects cells that express the CD4 receptor, predominantly activated T lymphocytes, but also monocytes, macrophages and dendritic cells; it also requires a co-stimulatory receptor to enter the cell, either CCR5 or CXCR4 (Deeks et al., 2015). It has also been demonstrated that once transmission occurs, the primary site of viral replication is the mucosal tissues, including the gastro-intestinal tract and lymphoid tissues (mainly gut-associated lymphoid tissue – GALT). Once inside the cell, the virus takes control of the cell machinery to start producing more virions. In some cases, it may succeed in integrating itself into the host's DNA, making the virus eradication from the body virtually impossible (Ghosn et al., 2018). With the perpetuation of infection, the immune system starts declining, mainly CD4+ T-lymphocytes count, resulting in an increased risk of opportunistic infections and neoplasms, and if left untreated it may progress to AIDS.

It has been postulated by many authors that the concomitant presence of both diseases, HIV and IBD, might impact one another, as the increased inflammation in IBD might be

attenuated by the immune depletion induced by HIV. From this perspective, the CD4+ count remission hypothesis arose, in which authors tried to correlate the CD4+ count with disease activity or the number of flares in patients with both diseases, with conflicting results (Skamnelos et al., 2015). Apart from this hypothetical interaction, perhaps a more relevant clinical question pertains with differential diagnosis and infectious risk. Chronic diarrhea is an overlapping symptom between HIV (due to opportunistic infections or HIV-enteropathy) and IBD, which may pose diagnostic challenges (Clerinx et al., 1995), (Olariu C. & Nurciu A., 2014). Additionally, since active IBD may increase the risk of infectious complications, which may be further aggravated by the immunosuppressive properties of many of the therapeutic regimens used, it is important to understand the safety of IBD therapies in the setting of HIV, and vice-versa. Given that IBD is increasing in rapidly developing countries, which are also affected by higher numbers of HIV infection, and considering that IBD is typically diagnosed during early adulthood, it might be expected that the number of cases with concomitant HIV and IBD will increase, which can raise diagnostic and therapeutic challenges. Therefore, the aim of this systematic review was to investigate the relationship between HIV and IBD co-presence, the impact one has on the other and assess how co-occurrence of both diseases may impact therapeutic efficacy and safety.

Materials and methods

Eligibility criteria and search strategy

A study protocol was designed (Supplementary Material Annex 1), to define our search question and to allow us to devise a comprehensive literature search strategy on HIV and IBD, in line with the PRISMA checklist. During the development of our search strategy, a qualified librarian was consulted, in order to create a broad and inclusive result with both indexed terms, keywords and associated alternative terms. The databases used were PubMed/MEDLINE, EMBASE and Cochrane's CENTRAL, all consulted on 22nd of November of 2022. No language restrictions were applied in the

initial phase and animal studies were excluded. The full search strategy used can be consulted in the Supplementary Material Table 1.

Selection criteria

We included all studies that reported on concomitant inflammatory bowel diseases (Crohn's disease or Ulcerative colitis) and HIV infection. No restrictions in population age nor in date of publishing were applied.

The outcomes of interest were incidence and prevalence of both diseases, impact on IBD activity, serious infections, risk of mortality, adverse effects of treatment regimens and efficacy of treatment regimens.

Studies reporting adjustments made to the standard IBD therapeutic regimen to account for other causes rather than the HIV infection were not considered. Studies published in other languages rather than English were excluded. Review papers and case reports were excluded.

The results obtained were imported to a Zotero library, with deletion of duplicates. Two independent reviewers (H. S. and J. B.) screened tittle and abstracts for eligibility, afterwards, full-text analysis was conducted by one reviewer, using the software Rayyan. Any conflicts in study eligibility were discussed between authors, and if when needed a third person intervened (J. T.).

Data extraction and quality assessment

Data was extracted by one reviewer during the full-text eligibility assessment phase with a custom-made data extraction sheet. The data of interest included year of publication, type of study, number of participants of interest and associated characteristics and any outcome of relevance to the present systematic review. Study quality was assessed in case-control and cross-sectional studies using the Newcastle-Ottawa Quality Assessment Scale (Abesig et al., 2020; *Newcastle - Ottawa Quality Assessment Scale Case Control Studies*, n.d.).

Categorization of studies

Studies were divided into 3 categories: (1) epidemiology, (2) impact of HIV in IBD´s natural history, and vice-versa and (3) efficacy and safety of IBD medication in infected patients.

Results

Characteristics of included studies

Our search strategy yielded 2 483 results, with 1 040 from PubMed/MEDLINE, 1 225 from EMBASE and 218 from CENTRAL. After duplicate removal 2 286 results were screened for tittle and abstract, with 41 being included. Additionally, 4 papers were added posteriorly from citation searching (total of 45). After full-text analysis, 13 papers were excluded, as shown in the PRISMA diagram (Figure 1). The final number of results included in this systematic review were 32, with 1 letter, 7 case series, 9 case-control studies, 10 observational studies, 1 non-randomized clinical trial, 2 scientific reports and 2 systematic reviews. From the studies included, 14 reported on epidemiology, 16 on the impact each disease had on the other, and 11 reported on efficacy and safety of treatment regimens. Quality assessment of studies can be consulted in Supplementary Material tables 2 and 3.

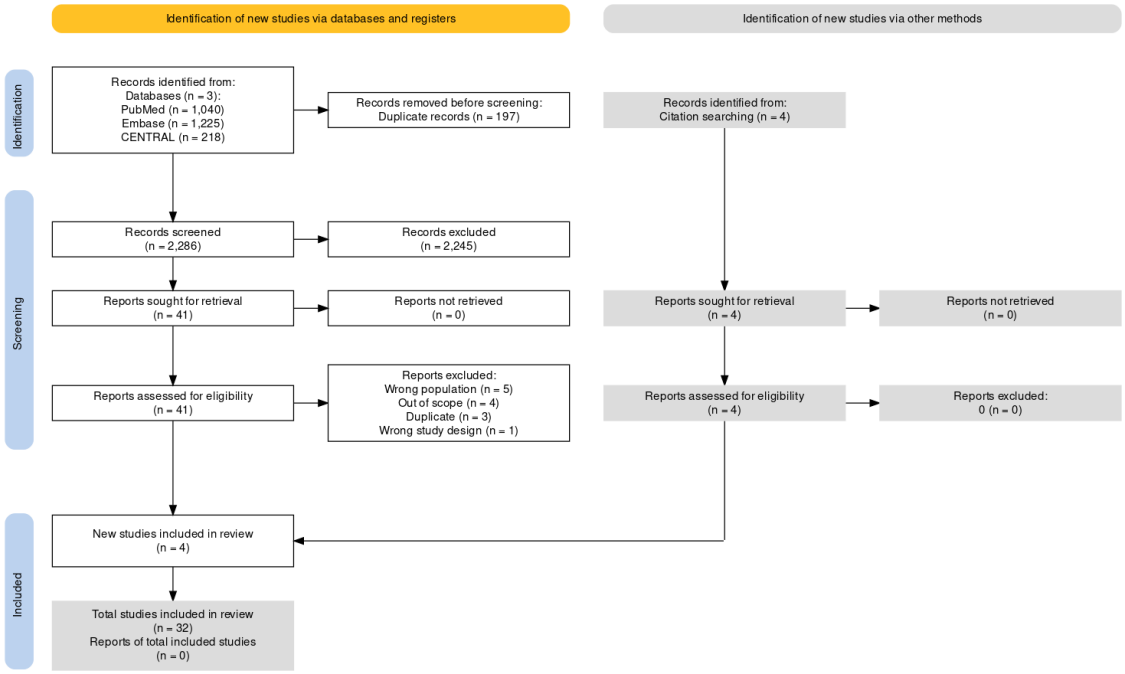

Figure 1 - PRISMA flow chart

Epidemiology

Overall, 14 studies reported on 2180 IBD-HIV$_{pos}$ patients. Most of the data was acquired from national observational and case-control studies, making it difficult to correctly determine the prevalence of IBD-HIV$_{pos}$. Epidemiology data from the included studies can be consulted in Table 1. In Switzerland, a study of 4 791 IBD patients showed that 0,4% had HIV infection (Bähler et al., 2017). In the USA, in a population of 78 835 UC patients, 0.4% of them had concomitant HIV infection (Kommuru et al., 2022).

In patients with HIV infection, the estimates of prevalence of IBD are similar. In a case-control study from the USA with 276 809 HIV$_{pos}$ patients, 0.5% had IBD (Dalsania et al., 2020), while in another study from Canada, Quebec, reported a 2.20% prevalence of IBD among 4 245 HIV$_{pos}$ patients (Damba et al., 2021). In France, in a population of 33 403 HIV patients, IBD was present in 0.60% of patients [95% CI 0.49 – 0.71] (Lebrun et al., 2017). On the whole, the prevalence observed from the included studies is low, ranging from 0.1% to 2%.

Table 1 - Prevalence of IBD and HIV infection reported in the included studies

Author	Country	Year	Population studied	Prevalence of IBD-HIV$_{pos}$
Sharpstone (1996)	London, UK	1988 - 1993	HIV patients	0.36%
Yoshida (1996)	Vancouver, Canada	1989 - 1993	HIV patients	0.11%
Landy (2008)	London, UK	1999 - 2006	HIV patients	UC – 1.9 : 10 000[1] CD – 0.2 : 10 000[1]
Michelini (2016)	Rome, Italy	Not reported	HIV patients	0.69%
Lebrun (2017)	France	2000 - 2013	HIV patients	0.60%
Dalsania (2020)	USA	2010 - 2015	HIV patients	0.50%
Damba (2021)	Québec, Canada	1996 - 2011	HIV patients	2.20%
Siwak (2022)	Warsaw, Poland	2001 - 2019	HIV patients	1.32%
Juneja (2010)	USA	Not reported	IBD patients	1.30%
Harsh (2017)	North India	2004 - 2016	IBD patients	0.10%
Bähler (2017)	Switzerland	2014	IBD patients	0.40%
Kommuru (2022)	USA	2019	IBD patients	0.40%
Clerinx (1995)	Kigali, Rwanda	1991 - 1993	Chronic diarrhea patients	2%
Olariu (2014)	Romania	Not reported	HIV patients with chronic diarrhea	12.5%

[1] - in this study only mean annual incidence was reported

Disease course

IBD usually evolves in a relapse and remitting manner, which may lead to complications, such as fistulas or stenosis in CD, or colectomy in UC for example (Torres et al., 2017; Ungaro et al., 2017). On the other hand, HIV infection, induces a deep immunosuppression, depleting various immune cells, among them CD4+ cells. This depletion was found to be predominantly on the gut-associated lymphoid tissue (GALT), indicating a possible impact of HIV pathogenesis on IBD (Guillo et al., 2022). We found 16 papers comprising 922 patients IBD-HIV_{pos} patients which described the impact of HIV in IBD´s disease course and vice-versa.

The impact of HIV in IBD´s disease course and phenotype

The CD4+ count remission hypothesis

The CD4+ count remission hypothesis theorizes that, as the HIV infection causes a progressive decline in CD4+ T cells, that this may, in turn, reduce IBD disease activity and contribute to remission, as these cells are part of the immune dysregulation observed in IBD (Skamnelos et al., 2015). Some studies have supported this hypothesis, by demonstrating a reduction in flares, as HIV-induced immunosuppression develops. A 1996 case series, followed 6 IBD-HIV_{pos} patients reporting that 3 patients with UC and mildly decreased CD4 counts, still experienced IBD symptoms, 1 patient with CD experienced symptoms with a CD4 count of 210 cells/µL, and that the remaining 2 patients experienced remission with low CD4 counts (< 200 cells/µL), suggesting that severe immunosuppression might attenuate IBD´s activity, and that in patients with normal to mildly depressed CD4 counts, IBD might remain active (Yoshida et al., 1996). In a case-control study, 8 IBD-HIV_{pos} patients (6 UC and 2 CD) were compared to a control population of HIV alone; no IBD flares were reported with a CD4+ count < 200 cells/mm^3 (Sharpstone et al., 1996). Another case series of 4 CD patients reported a stable

remission of CD after HIV infection, with patients remaining asymptomatic without need of treatment, as CD4+ counts declined (Pospai et al., 1998).

In a case-control study with a population of 20 IBD-HIV_{pos} patients and a IBD only (IBD-HIV_{neg}) control group, a lower relapse rate (0.016/year vs 0.053/year, p = 0.032), and a longer time to relapse was found for the IBD-HIV_{pos} group, implying a protective role of HIV. In the IBD-HIV_{pos} group, 70% of patients were on HAART, 14 (70%) were immunosuppressed (defined as CD4+ count < 500 cells/µL), never experiencing a relapse, whereas 3 out of 6 (50%) not immunosuppressed, relapsed (p = 0.017). On IBD-HIV_{neg} group, 18 patients (45%) relapsed, however no patient in this group had a CD4+ count below 500 cells/µL (Viazis et al., 2010). Lastly, a study of 50 IBD-HIV_{pos} patients in Warsaw, showed that around 20% patients experiencing at least one IBD related relapse had CD4+ cell counts > 200 cells/µL and HIV viral loads < 50 copies/mL. Patients experiencing multiple relapses had median CD4+ count of 440 cells/µL, and there was a linear relationship between number of relapses and progressive increase in CD4+ count (Siwak et al., 2022).

A 2015 systematic review included 9 case reports of IBD-HIV_{pos} patients: 7 of the 9 cases, reported no IBD remission with low CD4+ counts, actually having flares while the patients were severely immunosuppressed. Other studies have neither found a relationship between CD4 counts and number of flares (Arroyo-Mercado et al., 2019). Lastly, 1 study refuted the hypothesis (Abramowitz M. et al., 2013).

Overall, the CD4 count hypothesis has been shown to be difficult to be confirmed, which may be driven by lack of appropriately powered studies, low quality of the studies without adjustment for confounding factors, and without using standardized definitions of flares coupled with objective markers of inflammation. Additionally, absolute CD4+ count might not be the sole most appropriate factor to correlate with IBD course, as it might not reflect the CD4+ count in the intestinal mucosa, nor reflect the functional properties of these cells, (Skamnelos et al., 2015).

Apart from the CD4+ count hypothesis, multiple studies reported data on disease phenotype and disease course.

A multi-center study with 195 patients with IBD (65 of them IBD-HIV_{pos}) showed that there were not any significant differences in the course of CD and UC in HIV_{pos} vs HIV_{neg} patients, in terms of hospitalization, surgery or intestinal complications (strictures, fistulas, abscesses) (Guillo et al., 2022). A recent case-control study with 88 IBD-HIV_{pos} patients, showed that the coexistence of IBD and HIV were associated with a less aggressive IBD phenotype: among UC patients, HIV_{pos} had less extensive disease (24.5% vs 44.8%, p = 0.002) and a higher proportion of proctitis (38.8% vs 16.6%, p = 0.002) without differences in disease proximal progression; among CD patients, HIV_{pos} patients presented more frequently colonic involvement (40.6% vs 12.6%, p = 0.002) and lower rates of penetrating behaviour (10.7% vs 25%, p value not specified). HIV_{pos} patients also presented with lower rates of extra-intestinal manifestations (10.7% vs 25.4%, p = 0.005) (Calafat Sard et al., 2023).

A large study conducted in the USA, with 145 patients (75 UC-HIV_{pos} and 70 CD-HIV_{pos}) showed differences among the number of examinations done, when compared to IBD-HIV_{neg} patients. In terms of colonoscopy rates (surrogate marker for disease activity), there was not a statistically relevant difference among UC patients (with and without HIV), conversely, among CD patients, the colonoscopy rates were lower among HIV_{pos} patients (0% vs 17.4%, p-vale < 0.01) (Then et al., 2021).

In terms of need for surgery, in 93 patients with IBD (31 of them HIV_{pos}) the rates of surgery were similar in CD (HIV_{pos} 57% vs HIV_{neg} 50%, p = 0.7) and also in UC (HIV_{pos} 26% vs HIV_{neg} 21%, p = 0.8) (Ho T.H. et al., 2016).

Mortality and complications

Increased intestinal permeability and increased microbial translocation is a feature shared by both IBD and HIV. One study assessed this risk by measuring plasma markers of microbial translocation in 7 UC-HIV_{pos} patients and compared them to controls UC-HIV_{neg} and another population only HIV_{pos} (all HIV patients had suppressed viral loads and UC patients were treated with oral mesalazine). Soluble CD14 (sCD14) (indirect marker of microbial translocation, produced by the presence of lipopolysaccharide), intestinal fatty acid-binding protein (I-FABP) (marker of intestinal epithelium

destruction) and endotoxin core antibodies (endoCAB), and also markers of inflammation and immune activation were assessed in the 3 groups. They found lower levels of I-FABP and sCD14 UC-HIV_{pos} group when compared to the other groups, mainly the HIV_{pos} group, pointing to the fact that having both diseases does not seem to increase bacterial translocation. (Michelini et al., 2016).

In a population of 78 835 UC patients, it was found that having AIDS was associated with an increased odds ratio of developing colorectal cancer (OR 6.23, 95% CI 2.48 – 15.68), with males presenting a two-times higher risk of increased risk of mortality (Kommuru et al., 2022). Whether having colonic inflammation and concomitant HIV act synergistically to increase the risk of CRC is unknown.

Regarding hospitalization, one study found a trend towards reduced hospitalizations (25.6% vs 35.3%) and IBD complications (6.3% vs 9.2%) in IBD-HIV_{pos} patients (Calafat Sard et al., 2023). Lastly one study found that regarding length of stay, no difference was noted in the CD population, however, in the UC population, they found a shorter hospital length of stay in HIV_{pos} patients (4.1 days vs 5.9 days, p-value < 0.01), suggesting a milder course. Additionally, in terms of intra-hospital mortality they did not find a difference between the UC and CD cohort, and in each cohort no deaths were found among the HIV_{pos} group (Then et al., 2021).

In another study they found that in IBD-HIV_{neg} vs IBD-HIV_{pos} there was a similar survival in patients without complicated course of the disease (Guillo et al., 2022).

Does IBD influence HIV's disease course?

Few studies have looked into this topic. A study of 8 patients IBD-HIV_{pos}, reported that, having IBD did not impact the rate of CD4+ count decline and that IBD flares did not cause significant changes in mean CD4 count. In terms of need for surgery, 4 patients required colectomy, and the results showed that at the time of surgery the CD4+ count rose, and after surgery there was a fall in CD4+ count up to 6 months, with a subsequent average rise of 4 cells/mm^3/year, in 3 of the 4 patients, significantly different from the HIV_{pos} control group, which continued to fall ($p < 0.05$). This might be explained by the

fact that in a colectomy, a large amount of lymphoid tissue is removed (GALT), which is a known reservoir for HIV, therefore reducing viral load (Sharpstone et al., 1996).

Treatment

The grand majority of IBD treatments involve the use of immunosuppressive medication, such as, anti-TNF agents (infliximab, adalimumab, certolizumab pegol and golimumab), integrin antagonists (natalizumab, vedolizumab and etrolizumab), corticosteroids and small molecules (thiopurines, methotrexate, tofacitinib, filgotinib, upadacitinib, ozanimod). One important concern regarding these agents is whether they can be safely used in IBD patients infected with HIV. Our search included 11 papers on this matter, with information from 257 patients (Table 2).

A recent study showed that among IBD-HIV_{pos} patients, immunosuppressants (40.5% vs 58.7%; p = 0.003) and biologics (28.3% vs 42.8%, p = 0.020) were used less frequently (Calafat Sard et al., 2023). Another study published in 2022, showed that all immunosuppressants and biologics were used approximately half as much in the IBD-HIV_{pos} compared to IBD-HIV_{neg} group (Guillo et al., 2022); another study from 2016, corroborates the data previously reported, showing that in patients with CD or UC and concomitant HIV, the proportion of patients treated with biologic therapy, thiopurines and steroids is significantly lower than IBD patients without HIV: CD patients (HIV_{pos} vs HIV_{neg}) – biologic therapy (29% vs 67%, $p < 0.05$), thiopurine (21% vs 50%, $p < 0.05$) steroids 43% vs 82%, $p < 0.05$); UC patients (HIV_{pos} vs HIV_{neg}) – biologic therapy (6% vs 26%, $p < 0.05$), thiopurine (6% vs 36%, $p < 0.05$) and steroids (29% vs 76%, $p < 0.05$) (Ho T.H. et al., 2016). A small case series, with 6 IBD-HIV_{pos} patients, showed that immunosuppressive medication can be used and achieve successful management of both diseases, however this study did not report the impact on CD4+ cell counts, viral loads and overall safety with the treatment used (Hunt T.J. et al., 2021). Lastly, another reported that no significant difference was noted in UC-HIV_{pos}, in terms of use of systemic steroids and anti-TNF therapy during flares (Abramowitz M. et al., 2014). With this data, two possible explanations were brought forward, either IBD phenotype improves with HIV infection or there is a component of concern of doctors with having

IBD patients with immunosuppressive medication, however no final conclusion was achieved.

Author	Nº of patients (IBD-HIV$_{pos}$/$_{neg}$)	Treatment agent	UC-HIV$_{neg}$	CD-HIV$_{neg}$	UC-HIV$_{pos}$	CD-HIV$_{pos}$
Calafat Sard (2023)	88 / 264	Immunosuppressants	58.7%		40.35%	
		Biologics	42.8%		28.3%	
Guillo (2022)	65 / 130	Immunosuppressants	56.9%	61.1%	27.6%	38.9%
		Biologics	79.3%	77.8%	48.3%	47.2%
Ho T.H. (2016)	31 / 62	Thiopurines	36%	50%	6%	21%
		Steroids	76%	82%	29%	43%
		Biologics	26%	67%	6%	29%

Table 2 - Percentage of use of different treatment regimens among IBD-HIV$_{neg}$ and IBD-HIV$_{pos}$ patients

Safety and adverse events of IBD treatment in HIV infected patients

In terms of safety, one study showed higher rates of opportunistic infections (38.3% vs 17.8%, $p < 0.001$) and malignancies (12.5% vs 8.3%, not specified) among IBD-HIV$_{pos}$, when compared to IBD-HIV$_{neg}$ patients (Calafat Sard et al., 2023). Another study, reported that the adverse event rate is similar between IBD-HIV$_{pos}$ and IBD-HIV$_{neg}$ patients, as well as cancer occurrence. In terms of serious infections (CMV infection, *Pneumocystis* pneumonia, Herpes zoster, among others), these were particularly higher in the HIV$_{pos}$ group (26.2% vs 10.8%, not specified), however some were specific to HIV infection, while others were due to IBD medication. They also reported stopping treatment in 13 of 20 IBD-HIV$_{pos}$ group (65%), and 6 out of 20 (30%) required hospitalization (Guillo et al., 2022).

Overall, it seems that the drug safety profile is reassuring in HIV_{pos} patients, not existing a statistically significant difference between the two populations (Guillo et al., 2022).

Some specific agents have been studied more in detail such is the example of anti-TNF medication and azathioprine.

In a 2014 systematic review, on the risk of infections with the use of biologics in IBD, it was found that anti-TNF treatment does not seem to have much impact on CD4+ cell counts and HIV viral load, and these agents appear safe to use in regards to the risk of opportunistic infections (Nanau R.M. et al., 2014).

Azathioprine is a purine analog, used to maintain remission in steroid-dependent IBD patients. In 2014, a study reported on the efficacy and toxicity of this agent, being used in HIV_{pos} patients with various pathologies (myositis, immune reconstitution inflammatory syndrome (IRIS), myasthenia gravis and ulcerative colitis), while they were on HAART. The median duration of the treatment was 12 months, and they discovered that during the first month no change was noted in blood count parameters, including CD4+ and CD8+ cell counts. Over the next months, the total white cell count fell (median 6.8 to 3.6 x 10^9 /L, p = 0.037) and there was a trend, although not statistically significant, in the decline in neutrophils (median 4.2 to 2.1 x 10^9 /L, p = 0.066). No significant decline was observed in the total lymphocyte count or its subtypes. In terms of opportunistic infections during or in the 6 months after cessation of treatment, none were reported, as well as cancer. Therefore, close monitoring of hematological parameters is needed for patients on thiopurines, as generally recommended for all IBD patients. (Chamberlain et al., 2014).

In terms of impact of HIV medication on IBD, not much data is available, however Viazis et al. (2010) found that HAART therapy itself had no influence on the rate of IBD relapse.

All in all, the drugs safety profile seems to be reassuring overall, however further studies should be conducted with larger populations, so as to, reach a conclusion regarding this subject.

Serious infections

As mentioned before, infections are of utmost relevance when it comes to IBD treatment regimens, and concomitant HIV raises additional concerns.

Pneumocystis jirovecii pneumonia is a known opportunist infection and an AIDS-defining illness. A study was conducted to assess this risk in a population of IBD patients, from 2016 to 2017. They found that among all the admissions, only 0.035% involved management of this infection, and in probable relation to the use of biologicals, especially anti-TNF in combination with steroids and thiopurines. Among the risk factors for this pathology, HIV was present in 20% of cases. Overall, the authors report that despite being associated with increased mortality and increased incidence in this population, the frequency of this infection does not seem to warrant widespread prophylaxis for this population as of now (absolute infectious risk < 3.5%, to indicate benefit in groups without HIV). However, in IBD-HIV_{pos} patients, close monitoring must be ensured, and prophylaxis or treatment must be started as needed. They also suggested that newer agents such as vedolizumab, ustekinumab and tofacitinib were less frequently associated with *Pneumocystis jirovec*i pneumonia, showing that these agents might be safer in this population (Schwartz et al., 2022).

Apart from *Pneumocystis jirovecii* pneumonia there are other concerns infection-wise with IBD treatment in HIV patients, however, there are not any studies further studying this. More data is published regarding treatment of psoriasis in HIV_{pos} patients, and as some agents are common between psoriasis and IBD, some comparisons can be drawn. According to studies published, it seems that anti-TNF therapy (infliximab, adalimumab and certolizumab pegol) as well as ustekinumab (IL-12/23 inhibitor) can be used in patients without detectable viral load and undergoing HAART (highly active antiretroviral therapy). In terms of patients with detectable viral loads, there is more concern when using biologics, but as there is paucity of data, studies recommend constant vigilance and consultation with infectious diseases specialists regarding treatment decisions (Lambert et al., 2020; Nakamura et al., 2018).

Effect of IBD medication on HIV

Recently, with new data being published regarding HIV infection pathophysiology, some theories have surfaced, that some agents used in IBD therapy could have some activity against HIV.

The $\alpha_4ß_7$ integrin acts as a co-receptor for HIV-1, mediated by glycoprotein-120 (gp120), which may be responsible for the gut-homing behavior of acute HIV infection, which primarily depletes gut-associated lymphoid tissue (GALT). So this poses a possible new therapeutic approach, as a study done in non-human primates showed that using an analogue of vedolizumab prior to exposure, SIV infection could be prevented (Byrareddy et al., 2014). However no human studies have been conducted.

Natalizumab is a humanized monoclonal antibody against $\alpha_4ß_7$ integrin, with important anti-inflammatory activity, used in IBD. One paper suggested a possible effect of this agent in reducing HIV proliferation (Falasca F. et al., 2009). However, an experiment to assess this effect concluded that the agent did not have any anti-HIV activity (Ballana E. et al., 2009).

A study published by Uzzan and colleagues, evaluated the safety and the effects of vedolizumab in a cohort of 6 IBD-HIV_{pos} patients, over 30 weeks. All patients had mild proctitis, without significant changes endoscopically. In terms of safety, the only adverse events reported, were those previously reported for vedolizumab in HIV_{neg} populations (mild self-limited nasopharyngitis and headache), implying that it is safe to use this agent in HIV_{pos} patients. They also analyzed tissue samples from the left colon and terminal ileum, to evaluate the effect of vedolizumab on the immune system: they found that there was a major decrease in lymphoid aggregates, naïve and memory B cells in the terminal ileum and a less pronounced decrease in the left colon (as there are less B cells here), however no changes were observed among plasma cells. Among the T cell subtypes, no fluctuations were observed in the CD8+ T cells, nevertheless, in CD4+ T cells, there was a reduction in activated CD4+ T cells in the terminal ileum (either due to decreased activation or reduce homing), an increase in memory CD4+ T cells in circulation and no change in lamina propria CD4+ T cells. In NK cells there was an increase in number and activation in the beginning of the treatment, but then it

stabilized over time. Finally, in terms of anti-HIV activity, results were not consistent, and no conclusion was reached, although it is referred that vedolizumab in combination with other treatments is an interesting approach to HIV treatment, and should warrant further investigation (Uzzan et al., 2018).

Discussion

Herein, we have looked into the diagnostic and therapeutic challenges associated with the management of IBD patients concomitantly infected with HIV.

Overall, the prevalence of concomitant IBD and HIV infection is within the range of 0.1% to 2%, which is a low percentage. However, due to the chronicity and nature of both diseases, symptoms shared and also associated treatment regimens, IBD patients should always be tested for HIV infection before initiating treatment, as suggested by ECCO guidelines (Maaser et al., 2019).

In terms of impact on disease course, from our search there were no studies consistently reporting worsening of HIV infection following IBD diagnosis. One study (Sharpstone et al., 1996) hinted at a possible beneficial effect of colectomy on CD4+ count on IBD-HIV_{pos} patients, as they demonstrated a stabilizing effect and subsequent rise in 3 patients, alluding to the fact that with surgery a huge reservoir of the virus would be removed. However, more studies will be needed to conclude on this effect.

With regards to the impact of HIV in IBD disease course, there is a rational to hypothesize that lower CD4+ counts associated with HIV infection could modulate the course of IBD (Skamnelos et al., 2015). While some studies have tried to correlate IBD outcomes with CD4+ count, no definite conclusion can be made, due to lack of standardized definition of outcomes, such as immunosuppression cut-off in HIV_{pos} patients and IBD flares definition. Nonetheless, in terms of disease progression and uncomplicated course of IBD, there did not seem to be any significant difference between IBD-HIV_{pos} and IBD-HIV_{neg} patients, with similar survival. Some studies even reported a milder IBD phenotype in HIV_{pos} patients (Calafat Sard et al., 2023; Then et al., 2021).

Regarding morbidity, the only data found were regarding intestinal permeability, which was not increased (Michelini et al., 2016) and risk of developing colorectal cancer, which was increased in IBD-HIV_{pos} patients (OR 6.23, 95% CI 2.48 – 15.68) (Kommuru et al., 2022). In terms of overall survival, it was similar in IBD-HIV_{pos} and IBD-HIV_{neg} patients (Guillo et al., 2022; Then et al., 2021).

Treatment-wise, an interesting fact was observed, as patients with IBD and HIV co-existence, showed a lower percentage of treatment regimens with immunosuppressants and biologics. While this could potentially indicate a milder disease course in IBD-HIV_{pos} patients, we could not exclude that this was driven by doctor's concerns in using immunosuppressive medication in patients with HIV infection. However, all studies reporting on the safety of IBD immunosuppressive treatment regimens, no safety alerts were identified. Some studies do report an increase in opportunistic infections and cancer; however no impact was observed in CD4+ counts, and it should be also considered that the HIV infection might account for that increased risk, and not necessarily the immunosuppressive treatment. It was also shown, that newer biologics, such as ustekinumab and vedolizumab, had lower rates of opportunistic infections, suggesting some options in these populations.

This review had some limitations. Firstly, there is significant heterogeneity in terms of clinical criteria between studies. Not every study used the same definition for IBD exacerbation and CD4+ count cut-off to define immunosuppression in HIV_{pos} patients, which are of utmost importance to compare the data between studies. Secondly, most of the papers were retrospective. In some cases, these were limited to data contained in registries, not allowing to account for the impact of other variables if they were not reported in the registry. Thirdly, most of the studies regarding HIV infection impact on IBD did not adjust for possible confounding factors, such as the chronology of the development of both diseases and whether that has any impact on the disease course of each.

One potential solution for the problems reported, would be an international registry of IBD patients with HIV infection, with standardized criteria, which would allow for a prospective follow-up. Thus, with larger standardized populations more robust conclusions could be drawn and some variables could be better studied such as CD4+

count nadir, which disease developed first and what impact does it have on the patient, to name a few.

In conclusion, it seems that IBD and HIV co-existence has a low prevalence. In terms of disease course, no robust conclusion can be drawn, however some studies do point to a less aggressive IBD phenotype in IBD-HIV_{pos} patients, nonetheless, more studies are needed to conclude on this matter. Although, no significant difference was noted in disease progression. In terms of morbidity, there is an increased risk of cancer in these patients, but overall, survival is similar in IBD-HIV_{pos} and IBD-HIV_{neg} patients. The current literature suggests that all IBD treatment regimens can be used safely in HIV_{pos} patients, as long as close monitoring is carried out to prevent complications.

Resumo

Introdução

A doença inflamatória intestinal (DII) é uma patologia crónica que inclui duas entidades clínicas distintas: a doença de Crohn e a colite ulcerosa. Estas doenças manifestam-se essencialmente por dor abdominal, diarreia crónica, perda de peso e fadiga. Evoluindo por remissões e recidivas com acumulação de lesões do trato gastro-intestinal com morbilidade associada.

Em termos epidemiológicos, denota-se que a prevalência da DII está a aumentar a nível mundial. Entre 1990 e 2017, o número de casos aumentou de 3.7 milhões (95% IC 3.5-3.9) para mais de 6.8 milhões (95% IC 6.4-7.3), com aumento da prevalência global ajustada à idade de 79.5 por 10^5 (95% IC 75.9-83.5) em 1990 para 84.3 por 10^5 (79.2-89.9) em 2017 (Alatab et al., 2020). Adicionalmente, temos observado um aumento da incidência nos países em desenvolvimento (Torres *et al.*, 2017; Ungaro *et al*., 2017).

Enquanto que a DII é uma patologia caracterizada por uma resposta imune desregulada com forte atividade inflamatória no trato gastro-intestinal, o VIH atua no extremo oposto. O VIH é responsável pela síndrome de imunodeficiência adquirida, caracterizada por aumento do risco de infeções oportunistas e/ou invasivas e neoplasias. É um

retrovírus, que infeta predominantemente células do sistema imunitário, tornando-o progressivamente mais incapaz de montar respostas imunes.

De acordo com o último relatório da Joint United Nations Program on HIV/AIDS (UNAIDS), em 2021, existiam 38.4 milhões de pessoas com uma infeção por HIV a nível mundial (destas apenas 28.7 milhões com acesso a terapêutica antiretroviral), com 1.5 milhões de novos casos e 650 000 mortes por SIDA ou complicações relacionadas com esta síndrome. Desde 2010, que parece haver uma redução na incidência anual, com redução das novas infeções em 32%, de 2.2 milhões para 1.5 milhões em 2021; no entanto, ainda existe um número significativo de novas infeções nos países em desenvolvimento, maioritariamente África do Sul e Oriental (*Global HIV & AIDS Statistics*, 2023).

Tendo em conta ambas as patologias e os riscos associados às mesmas e à terapêutica utilizada, deparamo-nos com um desafio na orientação e otimização do tratamento de doentes com ambas as patologias (DII-HIV_{pos}). O objetivo principal desta revisão sistemática é reportar dados sobre epidemiologia, história natural da doença e eficácia e segurança do tratamento.

Materiais e métodos

Um protocolo para a revisão sistemática foi desenhado (Material Suplementar Anexo 1), para definir o objeto de estudo e permitir o desenvolvimento de uma estratégia de pesquisa abrangente, de acordo com a checklist PRISMA. As bases de dados utilizadas foram a PubMed/MEDLINE, EMBASE e CENTRAL da Cochrane, consultadas a 22 de novembro de 2022.

Resultados

A estratégia de pesquisa utilizada resultou em 2 483 resultados, que após remoção de duplicados e *screening* de título e abstract perfez 41 artigos passíveis de serem incluídos. Após análise de *full text* foram incluídos no total 32 artigos (14 reportaram dados

epidemiológicos, 16 sobre impacto na história natural da doença e 11 sobre segurança e eficácia dos regimes terapêuticos).

Os dados epidemiológicos obtidos provinham essencialmente de estudos nacionais observacionais e caso-controlo, demonstrando uma prevalência de doentes com DII-HIV_{pos} de 0.1 a 2% (Tabela 1).

Em termos de impacto na história natural de ambas as patologias, denotou-se que a DII não teve impacto significativo na história natural da infeção por VIH, não havendo alterações das contagens de CD4+ no estudos incluídos. No entanto, temos de ter em consideração que existem poucos estudos a estudarem este efeito, portanto, não podemos retirar conclusões robustas sobre este impacto.

O impacto da infeção por VIH nos doentes com DII é controversa. Alguns autores postularam a teoria da remissão da contagem dos CD4+, em que, à medida que a infeção por VIH fosse progredindo, e fosse reduzindo a contagem de CD4+, que iríamos assistir a uma diminuição da atividade inflamatória da DII com redução das exacerbações (Skamnelos et al., 2015). Porém, os resultados observados são conflituosos, com estudos a comprovarem esta teoria e outros a refutarem a mesma. Dos artigos incluídos, 3 comprovaram esta teoria com redução do número de exacerbações assim que se atingissem valores de CD4+ indicativos de imunossupressão; enquanto que doentes com contagens de CD4+ mais elevadas, mantinham a atividade da doença. Não obstante, outros artigos refutaram estes dados ou demonstraram resultados conflituosos, em que se observavam taxas elevadas de recidiva mesmo com contagens de CD4+ baixas. Assim, tem se verificado uma dificuldade crescente em comprovar ou refutar esta teoria, devido em parte a estudos de reduzida qualidade, ausência de ajuste para fatores confundidores e não utilização de definições amplamente aceites para definição de contagens de CD4+ indicativas de imunossupressão ou de exacerbações da DII. Adicionalmente, os estudos consultados reportaram por vezes um fenótipo mais ligeiro de DII em doentes com VIH, no entanto, sem existir uma diferença estatisticamente significativa em termos de progressão da doença.

No que toca a complicações da co-existência de ambas as patologias, os estudos abordaram o impacto na translocação bacteriana e permeabilidade intestinal e também

o risco de cancro coloretal. Em termos da permeabilidade intestinal, verificou-se que apesar de ambas as patologias estarem associadas a um aumento da mesma, não se observou um aumento aditivo da translocação bacteriana nestes doentes. Relativamente às neoplasias, verificou-se um risco aumentado em doentes com DII-VIH_{pos} (OR 6.23, 95% IC 2.48 – 15.68), e que doentes do sexo masculino apresentavam um risco 2 vezes superior de mortalidade (Kommuru et al., 2022). Finalmente, em termos de mortalidade, não se verificou um aumento estatisticamente significativo em doentes com DII-VIH_{pos} quando comparados com doentes DII-VIH_{neg}.

Em relação ao tratamento, sabe-se que os regimes terapêuticos da DII incluem agentes com efeito imunomodulador ou mesmo imunossupressor, com riscos associados, nomeadamente risco aumentado de infeções. Torna-se assim importante determinar a segurança da utilização destes regimes em doentes com DII-VIH_{pos}. Observou-se uma diminuição da utilização de agentes imunossupressores (essencialmente agentes biológicos, tiopurinas e corticóides) em doentes DII-VIH_{pos} (Tabela 2). Duas possíveis explicações para este fenómeno surgiram, sem, no entanto, se poder chegar a uma conclusão: ou os médicos teriam receio de recorrer a estes agentes em doentes com DII-VIH_{pos} ou a infeção por VIH reduziria a atividade inflamatória da DII com melhoria do fenótipo. No que toca a segurança, alguns estudos demonstraram um risco aumentado de infeções oportunistas e neoplasias, porém, algumas destas infeções deviam-se à infeção por VIH e não necessariamente ao uso de esquemas terapêuticos imunomoduladores, enquanto que outros não verificaram riscos aumentados. No geral, os estudos reportaram que o perfil de segurança destes agentes é tranquilizador, desde que houvesse uma vigilância apertada destes doentes. Além disso, alguns agentes biológicos demonstraram taxas mais baixas de infeções oportunistas como o vedolizumab, ustekinumab e tofacitinib, sugerindo que estes agentes podem ser preferidos na população em estudo. Relativamente ao impacto da medicação para a infeção por VIH nos doentes com DII, não se denotaram efeitos no curso da DII.

Estudos mais recentes elucidaram novos componentes da fisiopatologia da infeção por VIH, e a partir destes dados começou-se a avaliar o potencial terapêutico de alguns agentes muito utilizados na DII, os anticorpos monoclonais contra a integrina $\alpha_4ß_7$. Porém, à luz dos dados atuais, não temos resultados consistentes e robustos que

possam comprovar uma possível atividade anti-VIH destes agentes, necessitando de mais estudos.

Esta revisão teve algumas limitações. Em primeiro lugar, observou-se uma heterogeneidade significativa em termos de critérios clínicos entre estudos (*cut-off* de CD4+ para definir imunossupressão e definição de exacerbação de DII). Em segundo lugar, a maior parte dos estudos eram retrospetivos. A informação utilizada provinha de bases de dados, com variáveis pré-definidas que por vezes não tinham em consideração outras variáveis importantes, limitando as conclusões. Em terceiro lugar, muitos dos estudos sobre o impacto na história natural da doença não tiveram em consideração alguns fatores confundidores, como por exemplo a cronologia do desenvolvimento das doenças e se isso teria algum impacto no curso das mesmas.

Uma potencial solução para os problemas reportados seria uma base de dados internacional com esta população, com critérios previamente definidos e padronizados, que permitisse um follow-up prospetivo. Assim, com populações maiores poderíamos chegar a conclusões mais robustas.

Sumarizando, a prevalência de doentes com DII-VIH_{pos} é reduzida. Em termos de história natural da doença, não foi possível chegar a uma conclusão robusta, porém, alguns estudos reportam um fenótipo de DII menos agressivo na população em estudo. Não se observam alterações na progressão da doença. No que toca a morbilidade, existe um aumento do risco de neoplasias nestes doentes, no entanto, não se observa um aumento da mortalidade em doentes com DII-VIH_{pos} em comparação com doentes com DII-VIH_{neg}. A mais recente literatura sugere que os agentes terapêuticos da DII podem ser utilizados nesta população, desde que haja uma vigilância apertada destes doentes.

References

Abesig, J., Chen, Y., Wang, H., Sompo, F. M., & Wu, I. X. Y. (2020). *Newcastle-Ottawa Scale adapted for cross-sectional studies.* https://doi.org/10.1371/journal.pone.0234348.s002

Abramowitz M., Ramachandran R., Koczka C., & Lawlor G. (2013). Human immunodeficiency virus: CD4 count does not impact ulcerative colitis relapse risk. *Inflammatory Bowel Diseases*, *19*(SUPPL. 1), Article SUPPL. 1. https://doi.org/10.1097/01.MIB.0000438747.05146.b0

Abramowitz M., Ramachandran R., Koczka C., & Lawlor G. (2014). CD4 count does not impact disease severity in HIV positive patients with ulcerative colitis. *American Journal of Gastroenterology*, *109*(SUPPL. 2), Article SUPPL. 2. https://doi.org/10.1038/ajg.2014.269

Alatab, S., Sepanlou, S. G., Ikuta, K., Vahedi, H., Bisignano, C., Safiri, S., Sadeghi, A., Nixon, M. R., Abdoli, A., Abolhassani, H., Alipour, V., Almadi, M. A. H., Almasi-Hashiani, A., Anushiravani, A., Arabloo, J., Atique, S., Awasthi, A., Badawi, A., Baig, A. A. A., … Naghavi, M. (2020). The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet Gastroenterology & Hepatology*, *5*(1), 17–30. https://doi.org/10.1016/S2468-1253(19)30333-4

Arroyo-Mercado, F., Likhtshteyn, M., Huynh, C. D., Chokshi, T., Chawla, G. S., Grossman, E., Ramirez, M., Ojeda-Martinez, H., & McFarlane, S. I. (2019). CD4 Levels and Viral Load during Ulcerative Colitis Flares in Patients with Human Immunodeficiency Virus: A Case Series. *American Journal of Medical Case Reports*, *7*(8), Article 8. https://doi.org/10.12691/ajmcr-7-8-3

Bähler, C., Schoepfer, A. M., Vavricka, S. R., Brüngger, B., & Reich, O. (2017). Chronic comorbidities associated with inflammatory bowel disease: Prevalence and impact on healthcare costs in Switzerland. *European Journal of Gastroenterology & Hepatology*, *29*(8), Article 8. https://doi.org/10.1097/MEG.0000000000000891

Ballana E., Pauls E., Moncunill G., Bofill M., Clotet B., Ramo-Tello C., & Este J.A. (2009). Evaluation of the anti-HIV activity of natalizumab—An antibody against integrin alpha4. *Antiviral Research*, *82*(2), Article 2. https://doi.org/10.1016/j.antiviral.2009.02.031

Byrareddy, S. N., Kallam, B., Arthos, J., Cicala, C., Nawaz, F., Hiatt, J., Kersh, E. N., McNicholl, J. M., Hanson, D., Reimann, K. A., Brameier, M., Walter, L., Rogers, K., Mayne, A. E., Dunbar, P., Villinger, T., Little, D., Parslow, T. G., Santangelo, P. J., … Ansari, A. A. (2014). Targeting α4β7 integrin reduces mucosal transmission of simian immunodeficiency virus and protects gut-associated lymphoid tissue from infection. *Nature Medicine*, *20*(12), 1397–1400. https://doi.org/10.1038/nm.3715

Calafat Sard, M., Súria, C., Mesonero, F., de Francisco, R., Yagüe Caballero, C., de la Peña, L., Hernández-Camba, A., Marcè, A., Gallego, B., Martín-Vicente, N., Rivero, M., Iborra, M., Guerra, I., Carrillo-Palau, M., Madero, L., Burgueño, B., Montfort, D., Torres, G., Teller, M., … on behalf of GETECCU. (2023). DOP17 HIV infection is associated with a less aggressive phenotype of inflammatory bowel disease. A multicenter study based on the ENEIDA registry. *Journal of Crohn's and Colitis*, *17*(Supplement_1), i80–i81. https://doi.org/10.1093/ecco-jcc/jjac190.0057

Chamberlain, F. E., Dinani, N., Jagjit Singh, G. K., Bower, M., & Nelson, M. (2014). Azathioprine can be safely used in HIV-infected individuals. *AIDS (London, England)*, *28*(3), Article 3. https://doi.org/10.1097/QAD.0000000000000121

Clerinx, J., Bogaerts, J., Taelman, H., Habyarimana, J. B., Nyirabareja, A., Ngendahayo, P., & Van de Perre, P. (1995). Chronic diarrhea among adults in Kigali, Rwanda: Association with bacterial enteropathogens, rectocolonic inflammation, and human immunodeficiency virus infection. *Clinical Infectious Diseases : An Official Publication of the Infectious Diseases Society of America*, *21*(5), Article 5. https://doi.org/10.1093/clinids/21.5.1282

Dalsania, R., Nustas, R., Patnana, S., Brown, J., & Qayed, E. (2020). Prevalence of gastrointestinal disorders and their healthcare burden in hospitalized hiv patients in the United States. *American Journal of Gastroenterology*,

115(SUPPL), Article SUPPL. https://doi.org/10.14309/01.ajg.0000707152.21857.ef

Damba, J. J., Laskine, M., Jin, Y., Sinyavskaya, L., & Durand, M. (2021). Incidence of autoimmune diseases in people living with HIV compared to a matched population: A cohort study. *Clinical Rheumatology*, *40*(6), Article 6. https://doi.org/10.1007/s10067-020-05500-x

Deeks, S. G., Overbaugh, J., Phillips, A., & Buchbinder, S. (2015). HIV infection. *Nature Reviews. Disease Primers*, *1*, 15035. https://doi.org/10.1038/nrdp.2015.35

Falasca F., Turriziani O., Graziano F., Maida P., Boni A., Gallinaro A., Guidolin L., & Antonelli G. (2009). Evaluation of the anti-HIV activity of natalizumab/Tysabri, a monoclonal antibody against integrin alpha 4. *Infection*, *37*(SUPPL. 2), Article SUPPL. 2. https://doi.org/10.1007/s15010-009-1002-3

Ghosn, J., Taiwo, B., Seedat, S., Autran, B., & Katlama, C. (2018). HIV. *Lancet (London, England)*, *392*(10148), 685–697. https://doi.org/10.1016/S0140-6736(18)31311-4

Global HIV & AIDS statistics. (2023, February 21). UNAIDS. https://www.unaids.org/en/resources/fact-sheet

Guillo, L., Uzzan, M., Beaugerie, L., Gornet, J.-M., Amiot, A., Pelletier, A.-L., Altwegg, R., Laharie, D., Abitbol, V., Filippi, J., Goutorbe, F., Nachury, M., Nancey, S., Viennot, S., Reenaers, C., Amil, M., Caillo, L., Buisson, A., Collins, M., … Peyrin-Biroulet, L. (2022). Impact of HIV Infection on the Course of Inflammatory Bowel Disease and Drug Safety Profile: A Multicenter GETAID Study. *Clinical Gastroenterology and Hepatology : The Official Clinical Practice Journal of the American Gastroenterological Association*, *20*(4), Article 4. https://doi.org/10.1016/j.cgh.2020.12.023

Harsh, P., Gupta, V., Kedia, S., Bopanna, S., Pilli, S., Surendernath, Makharia, G. K., & Ahuja, V. (2017). Prevalence of hepatitis B, hepatitis C and human immunodeficiency viral infections in patients with inflammatory bowel disease in north India. *Intestinal Research*, *15*(1), Article 1. https://doi.org/10.5217/ir.2017.15.1.97

Ho T.H., Fausel R., Yang J., Swartz T., Torres J., Aberg J., Colombel J.-F., & Mehandru S. (2016). The impact of concurrent HIV-1 infection on the management of

patients with inflammatory bowel disease. *Gastroenterology*, *150*(4 SUPPL. 1), Article 4 SUPPL. 1.

Hunt T.J., Kozuch P.L., & Spacek L.A. (2021). Immunosuppressive Agent Use in Patients with Comorbid HIV and Inflammatory Bowel Disease. *Open Forum Infectious Diseases*, *8*(SUPPL 1), Article SUPPL 1. https://doi.org/10.1093/ofid/ofab466.1021

Juneja M., Schwartz M., El Mourabet M., Dunn M.A., Baidoo L., Swoger J.M., Barrie A.M., Regueiro M., Saul M.I., & Binion D.G. (2010). Patterns of co-morbid illness and nutritional deficiencies in geriatric Crohn's disease. *Gastroenterology*, *138*(5 SUPPL. 1), Article 5 SUPPL. 1. http://dx.doi.org/10.1016/S0016-5085(10)60936-5

Kommuru, S., Aziz, S. N., Sagireddy, S., Kaur, G., Rijal, S., Loh, C. C., Ibrahim, Y., & Patel, V. (2022). Risk Factors for Colorectal Cancer in Inpatients With Ulcerative Colitis: A Nationwide Cross-Sectional Analysis. *Cureus*, *14*(7), Article 7. https://doi.org/10.7759/cureus.27114

Lambert, J. l. w., Segaert, S., Ghislain, P. d., Hillary, T., Nikkels, A., Willaert, F., Lambert, J., & Speeckaert, R. (2020). Practical recommendations for systemic treatment in psoriasis in case of coexisting inflammatory, neurologic, infectious or malignant disorders (BETA-PSO: Belgian Evidence-based Treatment Advice in Psoriasis; part 2). *Journal of the European Academy of Dermatology and Venereology*, *34*(9), 1914–1923. https://doi.org/10.1111/jdv.16683

Landy, J., Gazzard, B., & Harbord, M. (2008). *Inflammatory Bowel Disease in HIV Seropositive Individuals: Analysis of a Large Cohort*. A-504. https://doi.org/10.1016/S0016-5085(08)62352-5

Lebrun, D., Hentzien, M., Cuzin, L., Rey, D., Joly, V., Cotte, L., Allavena, C., Dellamonica, P., Servettaz, A., & Bani-Sadr, F. (2017). Epidemiology of autoimmune and inflammatory diseases in a French nationwide HIV cohort. *AIDS (London, England)*, *31*(15), Article 15. https://doi.org/10.1097/QAD.0000000000001603

Maaser, C., Sturm, A., Vavricka, S. R., Kucharzik, T., Fiorino, G., Annese, V., Calabrese, E., Baumgart, D. C., Bettenworth, D., Borralho Nunes, P., Burisch, J., Castiglione, F., Eliakim, R., Ellul, P., González-Lama, Y., Gordon, H., Halligan, S., Katsanos, K., Kopylov, U., … Stoker, J. (2019). ECCO-ESGAR Guideline for Diagnostic

Assessment in IBD Part 1: Initial diagnosis, monitoring of known IBD, detection of complications. *Journal of Crohn's and Colitis*, *13*(2), 144-164K. https://doi.org/10.1093/ecco-jcc/jjy113

Michelini, Z., Baroncelli, S., Fantauzzi, A., Pasquale, C., Galluzzo, C. M., Sanchez, M., Gatto, M., Amici, R., Franco, M., d'Ettorre, G., Fimiani, C., Mezzaroma, I., Vullo, V., Merli, M., & Palmisano, L. (2016). Reduced Plasma Levels of sCD14 and I-FABP in HIV-infected Patients with Mesalazine-treated Ulcerative Colitis. *HIV Clinical Trials*, *17*(2), Article 2. https://doi.org/10.1080/15284336.2015.1125077

Nakamura, M., Abrouk, M., Farahnik, B., Zhu, T. H., & Bhutani, T. (2018). Psoriasis treatment in HIV-positive patients: A systematic review of systemic immunosuppressive therapies. *Cutis*, *101*(1), 38;42;56.

Nanau R.M., Cohen L.B., & Neuman M.G. (2014). Risk of infections of biological therapies with accent on inflammatory bowel disease. *Journal of Pharmacy and Pharmaceutical Sciences*, *17*(4), Article 4. https://doi.org/10.18433/j3gg6d

Newcastle—Ottawa Quality Assessment Scale Case Control Studies. (n.d.). Retrieved October 2, 2023, from https://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf

Olariu C. & Nurciu A. (2014). Chronic diarrhea in patients with acquired immunodeficiency syndrome (AIDS). *BMC Infectious Diseases*, *14*(Supplement 4), Article Supplement 4. https://doi.org/10.1186/1471-2334-14-S4-P20

Pospai, D., René, E., Fiasse, R., Farahat, K., Beaugery, L., Lammens, P., Reimund, C., Duclos, B., Le Quintrec, Y., Vandercam, B., & Mignon, M. (1998). Crohn's disease stable remission after human immunodeficiency virus infection. *Digestive Diseases and Sciences*, *43*(2), Article 2. https://doi.org/10.1023/a:1018883112012

Schwartz, J., Stein, D. J., & Feuerstein, J. D. (2022). Comprehensive National Inpatient Sample data reveals low but rising Pneumocystis jiroveci pneumonia risk in inflammatory bowel disease patients. *Annals of Gastroenterology*, *35*(3), Article 3. https://doi.org/10.20524/aog.2022.0713

Sharpstone, D. R., Duggal, A., & Gazzard, B. G. (1996). Inflammatory bowel disease in individuals seropositive for the human immunodeficiency virus. *European*

Journal of Gastroenterology & Hepatology, *8*(6), Article 6. https://doi.org/10.1097/00042737-199606000-00015

Siwak, E., Suchacz, M. M., Cielniak, I., Kubicka, J., Firląg-Burkacka, E., & Wiercińska-Drapało, A. (2022). Inflammatory Bowel Disease in Adult HIV-Infected Patients-Is Sexually Transmitted Infections Misdiagnosis Possible? *Journal of Clinical Medicine*, *11*(18), Article 18. https://doi.org/10.3390/jcm11185324

Skamnelos, A., Tatsioni, A., Katsanos, K. H., Tsianos, V., Christodoulou, D., & Tsianos, E. V. (2015). CD4 count remission hypothesis in patients with inflammatory bowel disease and human immunodeficiency virus infection: A systematic review of the literature. *Annals of Gastroenterology*, *28*(3), Article 3.

Soria, A., Rossi, M., Muscatello, A., & Gori, A. (2011). HIV testing: A must for patients with inflammatory bowel disease? *The American Journal of Gastroenterology*, *106*(9), Article 9. https://doi.org/10.1038/ajg.2011.186

Then, E., Uhlenhopp, D. J., Barakat, M., John, F., Gayam, V., Lopez, M., Sunkara, T., & Gaduputi, V. (2021). The Impact of Human Immunodeficiency Virus (HIV) on Inflammatory Bowel Disease (IBD): A Retrospective Nationwide Study. *Current HIV Research*, *19*(5), Article 5. https://doi.org/10.2174/1570162X19666210611145635

Torres, J., Mehandru, S., Colombel, J.-F., & Peyrin-Biroulet, L. (2017). Crohn's disease. *Lancet (London, England)*, *389*(10080), 1741–1755. https://doi.org/10.1016/S0140-6736(16)31711-1

Ungaro, R., Mehandru, S., Allen, P. B., Peyrin-Biroulet, L., & Colombel, J.-F. (2017). Ulcerative colitis. *The Lancet*, *389*(10080), 1756–1770. https://doi.org/10.1016/S0140-6736(16)32126-2

Uzzan, M., Tokuyama, M., Rosenstein, A. K., Tomescu, C., SahBandar, I. N., Ko, H. M., Leyre, L., Chokola, A., Kaplan-Lewis, E., Rodriguez, G., Seki, A., Corley, M. J., Aberg, J., La Porte, A., Park, E.-Y., Ueno, H., Oikonomou, I., Doron, I., Iliev, I. D., … Mehandru, S. (2018). Anti-α4β7 therapy targets lymphoid aggregates in the gastrointestinal tract of HIV-1-infected individuals. *Science Translational Medicine*, *10*(461), Article 461. https://doi.org/10.1126/scitranslmed.aau4711

Viazis, N., Vlachogiannakos, J., Georgiou, O., Rodias, M., Georgiadis, D., Papastamopoulos, V., Baraboutis, I. G., Karamanolis, D. G., & Skoutelis, A.

(2010). Course of inflammatory bowel disease in patients infected with human immunodeficiency virus. *Inflammatory Bowel Diseases*, *16*(3), Article 3. https://doi.org/10.1002/ibd.21077

Yoshida, E. M., Chan, N. H., Herrick, R. A., Amar, J. N., Sestak, P. M., Willoughby, B. C., & Whittaker, J. S. (1996). Human immunodeficiency virus infection, the acquired immunodeficiency syndrome, and inflammatory bowel disease. *Journal of Clinical Gastroenterology*, *23*(1), Article 1. https://doi.org/10.1097/00004836-199607000-00008

Supplementary Material

Supplementary Material Table 1 – Search Strategy

PubMed search strategy

PECO PROTOCOL	TERMS	RESULTS
POPULATION	#1 "inflammatory bowel diseases"[MeSH Terms] #2 "crohn disease"[MeSH Terms] #3 "colitis, ulcerative"[MeSH Terms] #4 "inflammatory bowel diseases"[Title/Abstract] OR "IBD"[Title/Abstract] OR "inflammatory bowel disease"[Title/Abstract] OR "crohn disease"[Title/Abstract] OR "crohn s disease"[Title/Abstract] OR "crohns disease"[Title/Abstract] OR "crohn disease"[Title/Abstract] OR "crohn*"[Title/Abstract] OR "ulcerative colitis"[Title/Abstract] #5 #1 OR #2 OR #3 OR #4	133 679
EXPOSURE	#6 "HIV"[MeSH Terms] #7 "acquired immunodeficiency syndrome"[MeSH Terms] #8 "HIV"[Title/Abstract] OR "hiv 1*"[Title/Abstract] OR "hiv 2*"[Title/Abstract] OR "HIV1"[Title/Abstract] OR "HIV2"[Title/Abstract] OR "hiv infect*"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract] OR "human immunedeficiency virus"[Title/Abstract] OR "human immuno deficiency virus"[Title/Abstract] OR "human immune deficiency virus"[Title/Abstract] OR ("human immun*"[Title/Abstract] AND "deficiency virus"[Title/Abstract]) OR "acquired immunodeficiency syndrome"[Title/Abstract] OR "AIDS"[Title/Abstract] OR "acquired immunedeficiency syndrome"[Title/Abstract] OR "acquired immuno deficiency syndrome"[Title/Abstract] OR "acquired immune deficiency syndrome"[Title/Abstract] OR ("acquired immun*"[Title/Abstract] AND "deficiency syndrome"[Title/Abstract]) #9 #6 OR #7 OR #8	466 220
STUDY DESIGNS	#10 "animals"[MeSH Terms] NOT "humans"[MeSH Terms]	5 065 004
FINAL RESULT	#11 #5 AND #9 NOT #10	1 040

Embase search strategy

PECO PROTOCOL	TERMS		RESULTS
POPULATION	#1	inflammatory bowel diseases/	181 313
	#2	crohn disease/	
	#3	ulcerative colitis/	
	#4	#1 OR #2 OR #3	
EXPOSURE	#5	Human immunodeficiency virus/	249 432
	#6	acquired immunodeficiency syndrome/	
	#7	#5 OR #6	
STUDY DESIGNS	#8	animals/ NOT humans/	1 020 945
FINAL RESULT	#9	#4 AND #7 NOT #8	1 225

CENTRAL search strategy

PECO PROTOCOL	TERMS	RESULTS
POPULATION	#1 MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees #2 MeSH descriptor: [Crohn Disease] explode all trees #3 MeSH descriptor: [Colitis, Ulcerative] explode all trees #4 Inflammatory Bowel Diseases OR IBD OR Inflammatory Bowel disease OR Crohn Disease OR Crohn's disease OR Crohns disease OR Crohn Disease OR Crohn* OR Ulcerative colitis #5 #1 OR #2 OR #3 OR #4	13 032
EXPOSURE	#6 MeSH descriptor: [HIV] explode all trees #7 MeSH descriptor: [Acquired Immunodeficiency Syndrome] explode all trees #8 HIV OR HIV-1 OR HIV-2 OR HIV1 OR HIV2 OR HIV infect* OR human immunodeficiency virus OR human immunedeficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR (human immun* AND deficiency virus) OR acquired immunodeficiency syndrome OR AIDS OR acquired immunedeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR (acquired immun* AND deficiency syndrome) #9 #6 OR #7 OR #8	38 711
STUDY DESIGNS	#10 [mh animals] NOT [mh humans]	12
FINAL RESULT	#11 #5 AND #9 NOT #10	218

Supplementary Material Table 2 – Case-Control Studies Quality Assessment

Author	Year	Selection	Comparability	Exposure	Total
Abramowitz	2014	2 stars	1 star	2 stars	**Fair**
Calafat Sard	2023	2 stars	1 star	2 stars	**Fair**
Dalsania	2020	2 stars	1 star	2 stars	**Fair**
Guillo	2022	3 stars	1 star	2 stars	**Good**
Harsh	2017	2 stars	1 star	2 stars	**Fair**
Ho	2016	2 stars	1 star	2 stars	**Fair**
Schwartz	2022	2 stars	1 star	2 stars	**Fair**
Then	2021	2 stars	1 star	2 stars	**Fair**
Viazis	2010	2 stars	1 star	2 stars	**Fair**

Supplementary Material Table 3 – Cross-Sectional Studies Quality Assessment

Author	Year	Selection	Comparability	Outcome	Total
Bähler	2017	4 stars	0 stars	1 star	**Satisfactory Study**
Clerinx	1995	2 stars	0 stars	2 stars	**Unsatisfactory Study**
Damba	2021	4 stars	2 stars	1 star	**Good Study**
Juneja	2010	2 stars	0 stars	0 stars	**Unsatisfactory Study**
Kommuru	2022	4 stars	0 stars	1 star	**Satisfactory Study**
Landy	2008	3 stars	0 stars	2 stars	**Satisfactory Study**
Lebrun	2017	3 stars	0 stars	1 star	**Unsatisfactory Study**
Michelini	2016	2 stars	2 stars	3 stars	**Good Study**
Olariu	2014	2 stars	0 stars	2 stars	**Unsatisfactory Study**

Supplementary Material Annex 1

Protocol and methods of search

PRISMA guidelines for reporting for systematic reviews will be followed

PECO strategy

Patients with Crohn's disease or ulcerative colitis

Exposure: patients with concomitant HIV infection

Control/comparison: Crohn's disease or ulcerative colitis without HIV

Outcomes: disease course (hospitalizations, surgery, flares), infections, serious infections, opportunistic infections, CD4+ count, rate of AIDS defining events, treatment efficacy and any other clinically relevant outcomes.

Inclusion criteria: Studies that report the impact of having IBD and an HIV infection concomitantly, whether it is related to the pathophysiology of both diseases, associated complications and implications for the therapeutic management, will be eligible for inclusion. Only studies published in English will be considered.

No restrictions in population age nor in date of publishing will be applied.

Exclusion criteria: Studies reporting adjustments made to the standard IBD therapeutic regimen to account for other causes rather than the HIV infection will not be considered. Studies published in other languages rather than English will be excluded. Review papers and case reports or studies with only 2 participants will be excluded.

Search strategy

A search query was designed in PubMed/MEDLINE and adapted to the other databases requirements.

PubMed/MEDLINE

- IBD strategy
    - MeSH terms were used for IBD, Crohn's disease and ulcerative colitis as well as any similar terms
- HIV strategy
    - HIV and Acquired Immunodeficiency Syndrome MeSH terms were utilized and other related terms
- Animal exclusion: animal studies were excluded.
- The final search strategy was completed on 22/11/2022, resulting in 1 040 results, which were exported to Zotero on the same date.

PubMed search string

(("inflammatory bowel diseases"[MeSH Terms] OR "inflammatory bowel diseases"[Title/Abstract] OR "IBD"[Title/Abstract] OR "inflammatory bowel disease"[Title/Abstract] OR "crohn disease"[MeSH Terms] OR "crohn disease"[Title/Abstract] OR "crohn s disease"[Title/Abstract] OR "crohns disease"[Title/Abstract] OR "crohn disease"[Title/Abstract] OR "crohn*"[Title/Abstract] OR "colitis, ulcerative"[MeSH Terms] OR "ulcerative colitis"[Title/Abstract]) AND ("HIV"[MeSH Terms] OR "HIV"[Title/Abstract] OR "hiv 1*"[Title/Abstract] OR "hiv 2*"[Title/Abstract] OR "HIV1"[Title/Abstract] OR "HIV2"[Title/Abstract] OR "hiv infect*"[Title/Abstract] OR "human immunodeficiency virus"[Title/Abstract] OR "human immunedeficiency virus"[Title/Abstract] OR "human immuno deficiency virus"[Title/Abstract] OR "human immune deficiency virus"[Title/Abstract] OR ("human immun*"[Title/Abstract] AND "deficiency virus"[Title/Abstract]) OR "acquired immunodeficiency syndrome"[MeSH Terms] OR "acquired immunodeficiency syndrome"[Title/Abstract] OR "AIDS"[Title/Abstract] OR "acquired immunedeficiency syndrome"[Title/Abstract] OR "acquired immuno deficiency syndrome"[Title/Abstract] OR "acquired immune deficiency syndrome"[Title/Abstract] OR ("acquired

immun*"[Title/Abstract] AND "deficiency syndrome"[Title/Abstract])) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])

Embase

- The search for this platform was adapted and only the Emtree entry terms were searched.
- The final search strategy was completed on 22/11/2022, resulting in 1 225 results, which were exported to Zotero on the same date.

Embase search string

#1 inflammatory bowel diseases/

#2 crohn disease/

#3 ulcerative colitis/

#4 #1 OR #2 OR #3

#5 Human immunodeficiency virus/

#6 acquired immunodeficiency syndrome/

#7 #5 OR #6

#8 animals/ NOT humans/

#9 #4 AND #7 NOT #8

CENTRAL

- For this database, the previous search strategies were adapted.
- The final search strategy was completed on 22/11/2022, resulting in 218 results, which were exported to Zotero on the same date.

CENTRAL search string

#1 MeSH descriptor: [Inflammatory Bowel Diseases] explode all trees

#2 MeSH descriptor: [Crohn Disease] explode all trees

#3 MeSH descriptor: [Colitis, Ulcerative] explode all trees

#4 Inflammatory Bowel Diseases OR IBD OR Inflammatory Bowel disease OR Crohn Disease OR Crohn's disease OR Crohns disease OR Crohn Disease OR Crohn* OR Ulcerative colitis

#5 #1 OR #2 OR #3 OR #4

#6 MeSH descriptor: [HIV] explode all trees

#7 MeSH descriptor: [Acquired Immunodeficiency Syndrome] explode all trees

#8 HIV OR HIV-1 OR HIV-2 OR HIV1 OR HIV2 OR HIV infect* OR human immunodeficiency virus OR human immunedeficiency virus OR human immuno-deficiency virus OR human immune-deficiency virus OR (human immun* AND deficiency virus) OR acquired immunodeficiency syndrome OR AIDS OR acquired immunedeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR (acquired immun* AND deficiency syndrome)

#9 #6 OR #7 OR #8

#10 [mh animals] NOT [mh humans]

#11 #5 AND #9 NOT #10

Study selection

The results obtained will be imported to a Zotero library, with deletion of duplicates. The final studies to be included in our review will be described in a PRISMA diagram. Two independent reviewers will screen for abstracts and full-text to assess eligibility, using the software Rayyan.

Any conflicts in study eligibility or data extraction will be discussed between authors, and if needed a third person will intervene.