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ORIGINAL RESEARCH—CLINICAL

Development of Inflammatory Bowel Disease in HIV Patients: A Danish Cohort Study (1983–2018) With American Validation (1999–2018)

Rahma Elmahdi,[1,2] Gursimran S. Kochhar,[3] Aske T. Iversen,[1] Kristine H. Allin,[1,4] Parambir S. Dulai,[5] Aakash Desai,[6] and Tine Jess[1,4]

[1]Department of Clinical Medicine, Center for the Molecular Prediction of Inflammatory Bowel Disease (PREDICT), Aalborg University, Copenhagen, Denmark; [2]Department for Lung and Infectious Disease Medicine, Nordsjællands Hospital, Hillerød, Denmark; [3]Division of Gastroenterology, Allegheny Health Network, Pittsburgh, Pennsylvania; [4]Department of Gastroenterology & Hepatology, Aalborg University Hospital, Aalborg, Denmark; [5]Division of Gastroenterology, University of California San Diego, La Jolla, California; and [6]Department of Medicine, Case Western Reserve University, Cleveland, Ohio

BACKGROUND AND AIMS: Human immunodeficiency virus (HIV) infection is associated with several immune-mediated disorders. However, the risk of inflammatory bowel disease (IBD) in people living with HIV (PLWH) remains unclear. We aimed to assess the risk of IBD among PLWH using a nationwide, population-based Danish cohort and to validate findings in a large American insurance-based database. **METHODS:** Using Danish registries (1983–2018), we identified 8995 PLWH and age- and sex-matched them to 449,750 HIV-negative individuals. Cox regression analysis was undertaken to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) for IBD diagnosis. Results were stratified by sex, age, and year of HIV diagnosis. Using an American insurance-based cohort, Explorys (1999–2018), we assessed the prevalence odds ratio (OR) and 95% CI of IBD diagnosis in PLWH compared with HIV-negative individuals. **RESULTS:** IBD diagnosis among PLWH in Denmark was increased (HR: 2.25, 95% CI: 1.78–2.83) compared with matched HIV-negative individuals. This was seen for both Crohn's disease (HR: 2.25, 95% CI: 1.47–3.44) and ulcerative colitis (HR: 2.24, 95% CI: 1.70–2.96) and in male (HR: 2.75, 95% CI: 2.15–3.52) but not female (HR: 0.93, 95% CI: 0.48–1.79) PLWH. Explorys analysis also showed an increased odds of IBD diagnoses among PLWH (OR: 1.41; 95% CI: 1.35–1.49). **CONCLUSION:** This study finds an increased risk of IBD diagnosis among PLWH in both a Danish and US cohort, highlighting a need to consider IBD in PLWH with new-onset gastrointestinal symptoms. Further research into the role of antiretroviral therapy in this relationship is required.

Keywords: Cohort Study; Human Immunodeficiency Virus; Inflammatory Bowel Disease

Background

Human immunodeficiency virus (HIV) is implicated in the development of several immune-mediated inflammatory diseases (IMIDs), with disorders such as systemic lupus erythematous, psoriasis, and autoimmune thyroid disease diagnosed at higher rates in people living with HIV (PLWH).[1]

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is caused by an interplay of genetic and environmental factors.[2,3] The pathophysiology of IBD is characterized by an abnormal T-cell-mediated immune response to the gut microbiotia in genetically susceptible individuals.[4] Gut-associated lymphoid tissue harbors the majority of T cells in the body, and this tissue is central to HIV infection, as the virus targets and replicates within CD4 T cells in lymphoid tissues.

In addition to being the location of the largest lymphoid organ, certain characteristics of the gut mucosa render it susceptible to HIV infection and replication, including increased expression of HIV target receptor CCR5 compared to peripheral CD4 T cells.[5] Although there is no evidence that absolute CD4 T-cell count correlates with the course of IBD as it does for HIV, there is evidence in support of the "remission hypothesis," that is, depletion in CD4 T cells as a result of HIV infection might be protective in IBD,[6] indicating a potentially important relationship between HIV infection and progression to IBD.[7–9]

Biological data suggest a complex but significant overlap between HIV infection and IBD. The epidemiological relationship between HIV and IBD, in particular, the risk of developing IBD in the context of HIV infection, remains unclear. One registry-based cohort study from 2017 estimates incidence of IBD in a cohort of HIV-positive adults in Taiwan[10] and found a numerically but not statistically significant increase in rate of IBD in PLWH. The follow-up period of the

Abbreviations used in this paper: **ART, antiretroviral therapy; CD, Crohn's disease; CI, confidence interval; HIV, human immunodeficiency virus; HR, hazard ratio; IBD, inflammatory bowel disease; IMID, immune-mediated inflammatory disease; NPR, National Patient Registry; OR, odds ratio; PLWH, people living with HIV; UC, ulcerative colitis.**

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study was however short, with few cases of IBD identified, and findings are therefore potentially limited by lack of power to detect an increased risk of IBD in PLWH. In general, it has been a challenge to study the co-occurrence of these 2 diseases epidemiologically due to limitations in data availability.

The aim of the present study was to assess the risk of IBD in a population-based nationwide Danish cohort of PLWH, by IBD disease subtype, age, sex, and calendar period of HIV diagnosis, (a proxy for antiretroviral therapy [ART] treatment). We further aimed to validate our findings using an insurance-based American cohort representing a larger cohort of PLWH.

Materials and Methods

The Danish Cohort

The Danish study population was derived from the Danish National Patient Registry (NPR). The NPR contains information on all inpatient hospital records including all diagnoses in Denmark since 1977 as well as outpatient hospital records from emergency room and ambulatory care settings since 1995.[11] All those resident in Denmark are assigned a unique personal identification (Civil Personal Registration) number at either birth or immigration, which is linkable to the NPR registry for identification of individual level diagnoses.[12]

We identified all individuals with an HIV diagnosis registered in the NPR by using diagnosis codes classified within the registry by the International Classification of Diseases eighth and tenth revision (ICD-8 and 10). These codes were DB20-24 in ICD-10 and D221, DF024, DO987, 07983, Y4049, and Y4149 in ICD-8. All those diagnosed with HIV in the period from 1980 to 2018 were included in the analysis, and baseline was defined as the date of first HIV diagnosis, with 1983 being the first year that HIV is recorded as a diagnosis in Denmark. As HIV diagnoses are recorded only in the context of a positive serum viral antigen test, we considered one HIV diagnosis as valid for inclusion at baseline. To generate a matched cohort for comparison, fifty HIV-negative individuals were selected from the general Danish population. Reference individuals were matched at the start of follow-up (date of HIV diagnosis) by sex recorded at birth and age (within 2 weeks of the index case). End of follow-up for cohort participants was defined as the point of emigration, death, diagnosis with IBD, or end of study observation period (December 31, 2018). Matched cohort participants going on to develop HIV infection in the course of follow-up were censored at the point of diagnosis with HIV. Due to the common overlap of symptoms of acute HIV infectious colitis (HIV-colitis) and IBD,[13,14] we restricted the outcome of IBD to those with two or more recorded IBD diagnoses (ICD-8 codes 56308-09 and ICD-10 codes K50 for CD; ICD-8 codes 56319 and 56904 and ICD-10 code K51 for UC). Additionally, to exclude prevalent cases of IBD, patients diagnosed with IBD before or on the day of diagnosis of HIV were excluded from the analysis.

Statistical Analyses on the Danish Cohort

The cumulative incidence of IBD in PLWH was assessed as a function of time since baseline, with death treated as a competing outcome to diagnosis with IBD. Hazard ratios (HRs) for IBD diagnosis were calculated along with 95% confidence intervals (CIs) using Cox proportional regression modelling to assess the rate of IBD in PLWH compared with matched HIV-negative individuals. We used time since first recorded diagnosis of HIV as the underlying time scale (or cohort entry for the matched HIV-negative population). We additionally adjusted for area of residence using the Danish national area of residence socioeconomic index. HRs were stratified by sex, age at diagnosis of HIV (<30 years old, 30–40 years old, and >40 years old), period of diagnosis (pre- and post-ART eras; before 1996 and after 1996), place of birth (Denmark, other European country, non-European country), calendar year of diagnosis (1983–1996, 1997–2010, 2011–2018), existing IMID (ICD-10 codes and NPR codes are available in Table A1) at baseline, and subtype of IBD (CD or UC). We used calendar year of diagnosis as proxy for treatment exposure, that is, before antiretroviral treatment availability (1983–1996), treatment in immunosuppression (1997–2010), and treatment at HIV diagnosis (2011–2018).

To test the robustness of our findings, we also performed a number of sensitivity analyses, including restriction of HIV diagnoses to the period after 1995, when outpatient diagnoses are available in the NPR, and extension of the exclusion period for IBD diagnosis to 90 days and 1 year after HIV diagnosis, respectively. To further assess the extent of misclassification of HIV-colitis as UC, we calculated the difference in number of recorded diagnoses of IBD in the HIV population and the non-HIV population using Pearson's χ^2 test, with results considered significant if $P < .05$, and explored prescription of IBD-specific medication for those with HIV compared to those without HIV. All statistical analyses were performed in SAS V.9.4 (SAS Institute).

Validation Using Explorys Data Set

To validate Danish findings, we used Explorys, a prospectively maintained electronic medical records data set (IBM Corporation, Somers, NY) to conduct a retrospective cohort study for IBD in PLWH in the United States cohort. Explorys is a multi-institution, deidentified, electronic health record database with an estimated 60 million covered lives spanning from 1999 to present day. Deidentified data from virtual health-care systems (EPIC, Amalga, Eclipsys, etc.) are standardized by the Explorys Web-based platform. Specific diagnoses, procedures, and medications can be mapped onto the systematized nomenclature of medicine clinical terms (SNOMED-CT). Other variables, such as medication use, comorbidities, and demographic characteristics, can also be identified through Explorys. All data are live and updated once every 24 hours.[15] This database was used to identify PLWH, the HIV-negative reference cohort, and also to identify IBD diagnoses for the American validation analysis.

Explorys Population

Patients with HIV were identified using the SNOMED-CT diagnosis code for HIV infection. We used specified time period parameters in Explorys to identify HIV patients who were diagnosed after database entry, from database inception to December 31, 2018. To exclude patients entering the database with both HIV and IBD diagnosis, we used the "first ever" parameter to exclude previous HIV diagnoses. PLWH were therefore defined as patients in Explorys who received a new diagnosis of HIV during the 19-year period of follow-up (1999–2018). Patients without HIV were identified using the "Pre-existing condition exclusion attribute" component in Explorys, and these made up the HIV-negative reference group.

We identified IBD diagnoses within the database using SNOMED-CT diagnosis codes for UC, CD, indeterminate colitis, or IBD. To further validate IBD diagnoses, additional inclusion criteria included at least one prescription of an IBD immune-mediating medication (mesalamine, infliximab, adalimumab, golimumab, vedolizumab, methotrexate, azathioprine, 6-mercaptopurine, ustekinumab, or tofacitinib).[16] We then used the "Temporal attribute" component within Explorys to establish temporal relationships between HIV diagnosis and de-novo IBD diagnosis.[17,18]

Explorys Design and Statistical Analysis

We calculate prevalence odds ratios (OR) with 95% CIs for de-novo IBD diagnosis in HIV compared to the HIV-negative reference group. Explorys does not provide deidentified, deaggregated data; therefore, total person-year contribution, incidence rates, or standardized age-adjusted incidence rates could not be calculated. Instead, we used Explorys to select demographic characteristics, laboratory results, medications, and procedures to stratify analyses. Stratified variables included age at HIV diagnosis (<30 and ≥30 years, or at selection for HIV-negative reference group inclusion), sex, history of tobacco smoking, and presence of obesity, diabetes mellitus, or other IMIDs.

Results

We identified 8995 individuals diagnosed with HIV in Denmark between 1983 and 2018 and matched these to 449,750 individuals without an HIV diagnosis. Baseline characteristics of PLWH and HIV-negative individuals from the Danish population are presented in Table 1.

Over a total of 7,154,999 person-years of follow-up, 0.82% of patients with HIV developed IBD as compared to 2818 (0.63%) HIV-negative individuals. The cumulative incidence of IBD was 1.31% at 25 years of follow-up in PLWH as compared to 0.95% among HIV-negative individuals (Figure 1). The median time from diagnosis of HIV to diagnosis of IBD was 4.7 years (range, 0.1–25.3 years). The mean age at IBD diagnosis was 45 years for PLWH compared to 48 years among HIV-negative individuals. Of the 74 HIV-IBD cases, 52 developed UC (70.3%). Of note, survival function (Figure 1) illustrate only a 52% survival of the cohort of PLWH at 25 years of follow-up, compared to 85% survival in matched HIV-negative individuals. However, the cumulative incidence of both CD and UC remained increased in PLWH than that in HIV-negative individuals throughout the 25-year of follow-up period (Figures 2 and 3).

Cox proportional regression analysis showed an HR of 2.25 (95% CI: 1.78–2.83) for IBD development in PLWH compared to HIV-negative individuals (Table 2). There was also a significantly increased rate of IBD in male PLWH (HR: 2.75, 95% CI: 2.15–3.52) that was not seen in female PLWH (HR: 0.93, 95% CI: 0.48–1.79). However, male PLWH made up the majority of the Danish HIV cohort (78.3%). The rate of IBD diagnosis was significantly increased in all age groups diagnosed with HIV (Table 2) but particularly high in those diagnosed with HIV over 40 years of age (<30 years

Table 1. Baseline Characteristics of Nationwide Cohort of People Living with HIV (PLWH) and Age- and Sex-Matched HIV-Negative Reference Individuals (Denmark, 1983–2018)

	Individuals diagnosed with HIV		Reference individuals	
Baseline characteristics	N	%	N	%
Total	8995	100	449,750	100
Sex				
Female	1954	21.7	97,700	21.7
Male	7041	78.3	352,050	78.3
Year of cohort entry				
1983–1996	3597	40.0	179,850	40.0
1997–2010	3584	39.8	179,200	39.8
2011–2018	1814	20.2	90,700	20.2
Age at cohort entry				
<30 y	2201	24.5	110,050	24.5
30–40 y	3478	38.7	173,900	38.7
>40 y	3316	36.9	165,800	36.2
Diagnosis era (pre-/post-ART)				
Pre-1996	3226	35.9	161,300	35.9
1996–2018	5769	64.1	288,450	64.1
Place of birth				
Denmark	6227	69.2	406,405	90.4
Other Europe	941	10.5	23,127	5.1
Non-Europe	1827	20.3	20,185	4.5
Inflammatory and autoimmune diseases (IMID)[a]				
Yes	170	1.89	5236	1.16
No	8499	94.49	429,674	95.54

[a]See Table A1 for complete list of IMID included (with ICD-10, and Danish National Health Registry code).

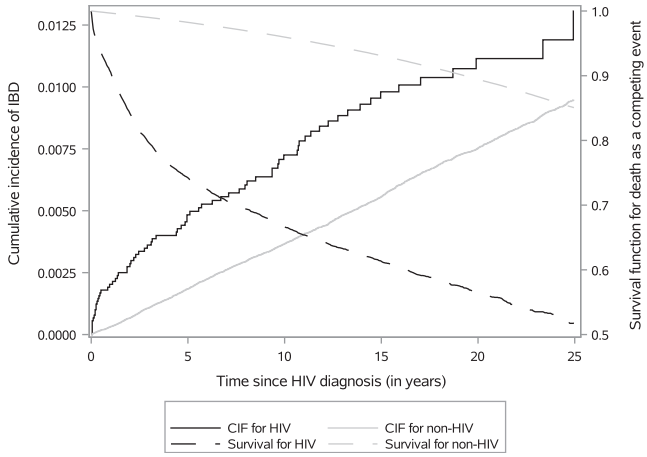

Figure 1. Cumulative incidence of IBD in individuals with HIV and matched HIV-negative reference individuals with survival function in the Danish population over 25 years of follow-up. CIF, cumulative incidnece function.

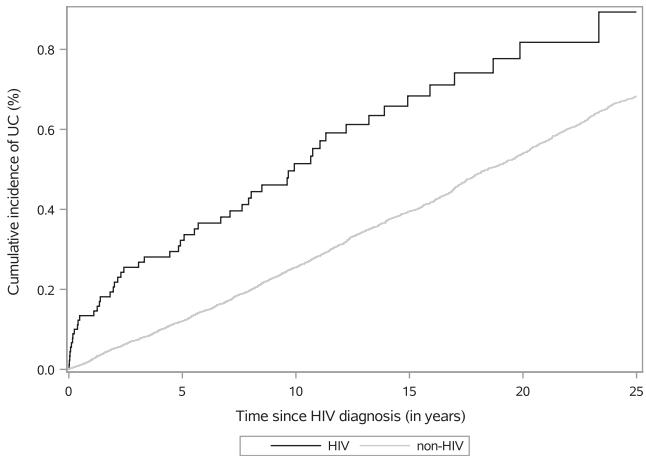

Figure 3. Cumulative incidence of ulcerative colitis (UC) in individuals with HIV and matched HIV-negative reference individuals in the Danish population over 25 years of follow-up.

HR: 1.78, 95% CI: 1.10–2.88; 30–40 years HR: 2.01, 95% CI: 1.38–2.92; >40 years HR: 2.99, 95% CI: 2.06–4.32). The rate of IBD diagnosis was also significantly increased across all time periods of HIV diagnosis (1983–1996 HR: 2.11, 95% CI: 1.44–3.08; 1997–2010 HR: 1.87, 95% CI: 1.33–2.63; 2011–2018 HR: 4.15, 95% CI: 2.36–7.29), including pre- (HR: 2.30, 95% CI: 1.55–3.42) and post-ART (HR: 2.11, 95% CI: 1.59–2.80) period. PLWH born in Denmark also appeared to have a significantly increased rate of IBD diagnosis (HR: 2.50, 95% CI: 1.93–3.24) which was not seen for those born in other European countries (HR: 2.16, 95% CI: 0.95–4.92) or those born in non-European countries (HR: 1.14, 95% CI: 0.74–2.92). PLWH who did not have an IMID diagnosis at baseline also had a significantly increased HR 2.19 (95% CI: 1.73–2.78) for developing IBD. This was again numerically but not statistically increased in those with IMID (HR: 3.04, 95% CI: 0.94–9.86). These non-significant results are likely to be a reflection of low numbers of PLWH born outside Denmark or with existing IMID at baseline.

We observed an increased HR of IBD development in PLWH both before and after the advent of ART. Due to large discrepancies observed in survival between PLWH and the matched population (Figure 1), we additionally undertook Cox regression analysis including death as a competing outcome to calculate subdistributional HR by diagnosis era (pre-1996 compared with 1996–2018). This analysis showed an increased rate of IBD in PLWH diagnosed in the period 1996–2018 with an HR of 1.91 (95% CI: 1.44–2.54) but not in those diagnosed in the pre-1996 period (HR: 0.90, 95% CI: 0.61–1.34), underscoring the significance of death as a competing event in the observed rate of developing IBD in PLWH.

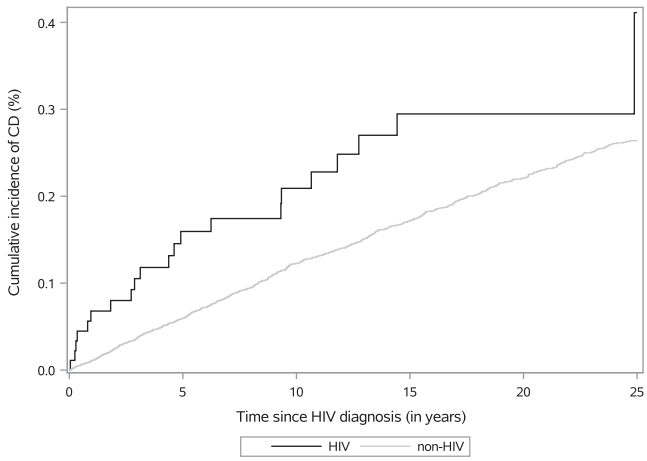

Figure 2. Cumulative incidence of Crohn's disease (CD) in individuals with HIV and matched HIV-negative reference individuals in the Danish population over 25 years of follow-up.

Sensitivity Analysis

The robustness of our analysis was tested using several sensitivity analyses. We accounted for differing diagnostic records before 1995, when complete information on outpatient visits became available by undertaking regression analysis only including patients diagnosed with HIV from 1995 onwards. This showed a sustained increased rate of IBD diagnosis with an HR of 2.22 (95% CI: 1.70–2.91) in PLWH compared to the matched population. To assess for the potential contribution of misclassification bias in diagnosis of IBD in PLWH compared to their matched HIV-negative counterparts which might occur due to infectious enteritis (in the context of immunosuppression in HIV disease) or HIV enteropathy (HIV-colitis), we undertook an analysis excluding IBD cases diagnosed within the first 3 months and further extended this to the first year following HIV diagnosis (the most common period for HIV-colitis diagnosis). This showed an HR of 1.98 (95% CI: 1.54–2.55) and 1.79 (95% CI: 1.38–2.34), respectively. When further assessing the number of diagnoses of IBD in

Table 2. Hazard Ratios and 95% CI for IBD Development in Individuals With HIV Compared With Age- and Sex-Matched HIV-Negative Reference Individuals in Denmark (1983–2018)

	Person-years followed up	IBD cases[a]	Hazard ratio[b] (HR)	95% CI
All	84,590	74	2.25	1.78, 2.83
Crohn's disease	84,590	22	2.25	1.47, 3.44
Ulcerative colitis	84,590	52	2.24	1.70, 2.96
Sex				
Female	22,127	9	0.93	0.48, 1.79
Male	62,462	65	2.75	2.15, 3.52
Age at diagnosis with HIV				
<30 y	23,597	17	1.78	1.10, 2.88
30–40 y	35,082	28	2.01	1.38, 2.92
>40 y	25,910	29	2.99	2.06, 4.32
Year of diagnosis with HIV				
1983–1996	35,934	27	2.11	1.44, 3.08
1997–2010	42,081	34	1.87	1.33, 2.63
2011–2018	6575	13	4.15	2.36, 7.29
Diagnosis era (pre-/post-ART)				
Pre-1996	30,172	25	2.30	1.55, 3.42
1996–2018	54,418	49	2.11	1.59, 2.80
Place of birth				
Denmark	59,937	59	2.50	1.93, 3.24
Other Europe	7023	6	2.16	0.95, 4.92
Non-Europe	17,630	9	1.47	0.74, 2.92
Inflammatory and autoimmune diseases (IMID)				
No			2.19	1.73, 2.78
Yes			3.04	0.94, 9.86

[a]Where cell total is ≤5, the number is censored to ensure individual patient anonymity.
[b]Adjusted for area of residence (socio-economic index area).

the HIV population, compared to the non-HIV population, we found 82.4% (n = 61) of patients with HIV diagnosed with IBD had ≥3 IBD recorded diagnoses compared to 93% (n = 2433) of those without HIV, and this difference was not significant ($P = .062$). We additionally found that 82.4% (n = 61) of all HIV patients diagnosed with IBD also received IBD-specific medication, including 5 amino salicylic acids (e.g. Sulfasalzine, and IBD-specific treatment), and of the total, 20.3% (n = 15) were prescribed either immunomodulatory or anti-tumor necrosis factor treatments, indicating that the association between HIV infection and IBD development in the Danish cohort remains significant, even when restricting cases to exclude possible HIV-colitis (Table A3).

Table 3. Prevalence Odds Ratios and 95% CI for Development of De-Novo IBD in Individuals With HIV Compared With HIV-Negative Reference Population in Explorys, USA (2009–2018)

	IBD cases	Prevalence odds ratio (OR)	95% CI
All	1610	1.41	1.35, 1.49
Age			
<30 y	270	6.3	5.59, 7.13
≥30 y	1340	1.39	1.32, 1.47
Sex			
Female	970	1.87	1.76, 2.00
Male	640	1.09	1.01, 1.18
Inflammatory and immune mediated disease (IMID)			
Including IMID	840	6.84	6.36, 7.35
Excluding IMID	1610	1.41	1.35, 1.49

Explorys American Cohort

Results from Explorys US retrospective cohort analysis, undertaken to validate findings from the Danish cohort, are presented in Table 3. We found an OR of 1.41 (95% CI: 1.35–1.49) for development of de-novo IBD in PLWH compared to HIV-negative individuals. In contrast to Danish findings, this increased risk was observed in both female (OR: 1.87, 95% CI: 1.76–2.00) and male PLWH (OR: 1.09, 95% CI: 1.01–1.18). This increased risk was also found in all age groups (<30 years OR: 6.3, 95% CI: 5.59–7.13, and ≥30 years OR: 1.39, 95% CI: 1.32–1.47) and both including (OR: 6.84, 95% CI: 6.36–7.35) and excluding (OR: 1.41, 95% CI: 1.35–1.49) IMID diagnosis, which is in keeping with the Danish cohort. An increased rate of IBD diagnosis was however particularly seen in those younger than 30 years (OR: 6.3, 95% CI: 5.59–7.13) compared to those aged 30 years or older (OR: 1.39, 95% CI: 1.32–1.47) and in those with a prior IMID diagnosis (OR: 6.84, 95% CI: 6.36–7.35)

compared to exclusion of those with IMID diagnosis (OR: 1.41, 95% CI: 1.35–1.49) in the US population (Table A2).

Discussion

In this nationwide Danish cohort study of almost 9000 individuals diagnosed with HIV and 449,750 sex- and age-matched HIV-negative individuals followed up over 7,154,999 person-years, we find a greater than 2-fold increased in risk of development of IBD in PLWH than matched HIV-negative individuals. This risk was increased across all age groups and all calendar-years of HIV diagnosis (including in both pre- and post-ART periods) but appeared confined to male PLWH in the Danish cohort. Using the American Explorys data set, representing a larger population with a higher prevalence of HIV, we confirmed an increased rate of de-novo IBD diagnosis in PLWH. In contrast to Danish findings, US data revealed an increased risk of IBD in both female and male PLWH.

Only 2 studies[10,19] have previously explored the association between HIV and IBD using a population-based cohort design, and only Yen et al[10] attempted to estimate incidence. Unlike our findings here, authors found no statistically significant increased risk of IBD in PLWH. However, this study may have been limited by a short follow-up period and, therefore, poor power to detect IBD development in a small population of PLWH. In the present study, we were able to account for these limitations and provide an estimate of the rate of developing IBD in HIV infection using population-representative data over a 35-year follow-up period.

The increased risk of IBD observed in Danish male PLWH but not female PLWH might be a result of the small number of female PLWH in the Danish cohort (21.7%) compared with US cohort (60.3%), a reflection of the underlying demographic differences between PLWH in Denmark and the United States. Yen et al[10] also identified a numerical disparity in the standardised incidence ratio between female and male PLWH developing IBD and also reported this as likely due to limited numbers of female PLWH in their cohort (8.4% of the total cohort was female).

Similarly, although we observed a statistically non-significant increased rate of IBD development in PLWH who were not born in Denmark, we suspect that this may reflect low statistical power. Although there is evidence that there is an increased risk of IBD in native Danes compared to first- and second-generation immigrant Danes,[20] there is no indication from our analysis to suggest that place of birth impacts the rate of IBD development in PLWH.

The high death rate in PLWH in our cohort is likely to be a direct reflection of the impact of AIDS-related deaths before the availability of treatment for HIV and has important implications for our analysis. Subdistributional HR (where death and IBD are treated as mutually exclusive alternate outcomes) gives an indication of the impact of high rates of mortality on the risk of developing IBD early in the follow-up period with no increased risk of IBD diagnosis identified in the period before 1996 compared to the 1996–2018 period (HR: 1.91, 95% CI: 1.44–2.54). It may be that the high levels of mortality early in the HIV epidemic explain the lack of an association between HIV and IBD observed in the few previous epidemiological studies undertaken to investigate this. The findings from the present study indicate that the median time to IBD disease diagnosis from HIV diagnosis is 4.7 years, and so it may be that with improved life expectancy, earlier diagnosis, and longer follow-up time, there is statistical power to detect an increased risk of IBD in large HIV cohorts in more recent years.

Several studies on common IMID risk in HIV indicate a decreased risk of developing IMID in patients who are treated with ART.[10,21] Although we do not have individual-level data on ART treatment, the results from our analysis show a comparably increased risk for IBD in PLWH both before and after 1996 (advent of ART in Denmark). Further exploration of the influence of ART would be of particular value in assessing this risk.

The primary strength of the present study is the use of a large nationwide, population-based cohort with complete record of national diagnoses of HIV and IBD and the ability to verify findings in a US population with higher HIV prevalence. Our robust study design with unbiased selection and strict criteria for diagnosis of both HIV and IBD enhances the validity of our findings. Additionally, due to the long-standing universal access to Danish health-care services, we can be confident that inclusion of participants is truly population-representative. The use of Explorys allows for generalizability of our findings and has highlighted key demographic differences that might have an impact on the association identified here (eg, sex differences). Another key strength of this study is the large sample size and over 25 years of follow-up of our cohort of PLWH.

Our study also has potential limitations to consider. Although we sex- and age-matched the reference population and were able to adjust for area of residence (socio-economic residence index), lack of data on other potential confounders, including smoking and other lifestyle exposures, is a limitation. The risk of bias due to misclassification of HIV-colitis as UC is also a potential limitation, and when using insurance claims data sets such as Explorys, it is usual to validate IBD diagnoses with at least 3 separate records.[22] Additionally, as Explorys includes indeterminate colitis diagnoses as part of the IBD cohort, there is an additional risk of misdiagnosis of HIV-colitis for patients in this group. Our use of the Danish national patient registries however ensures the risk of misdiagnosis bias is minimal as IBD diagnoses identified via the NPR for this study have previously been assessed against histological records and found to be highly valid (94%).[23] Additionally, sensitivity analysis assessing both IBD diagnosis bias and IBD-specific treatment prescription revealed no significant difference between HIV and matched non-HIV groups, indicating minimal misclassification bias for IBD. The lack of

availability of individual-level data on ART treatment in this cohort is also a limitation. However, the free and easily accessible nature of health care (particularly diagnosis and treatment of HIV) and the prompt availability and uptake of treatment in Denmark make time period a reliable proxy for ART treatment in our cohort of PLWH.

Conclusion

This unselected, nationwide cohort study of almost 9000 HIV patients reveals a greater than 2-fold increased risk of IBD in PLWH, and these findings are validated in a large US cohort with a higher HIV prevalence. Although we observed no difference in the risk of developing IBD before or after the introduction of ART, further research into the impact of individual level ART on this relationship is required. Finally, findings from this work highlight the need to consider IBD as a differential diagnosis in patients with HIV and new-onset gastrointestinal symptoms.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2022.08.003.

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Correspondence:
Address correspondence to: Rahma Elmahdi, MD, PhD, Center for the Molecular Prediction of Inflammatory Bowel Disease (PREDICT), Aalborg University, A.C. Meyers Vænge 15, Copenhagen DK-2450, Denmark. e-mail: rahmae@dcm.aau.dk.

Authors' Contributions:
Rahma Elmahdi, Tine Jess, Parambir S. Dulai, and Aske T. Iversen designed the study. Rahma Elmahdi undertook the literature search. Rahma Elmahdi, Aske T. Iversen, Gursimran S. Kochhar, and Aakash Desai analyzed the data. All authors interpreted the analyses. Rahma Elmahdi and Tine Jess drafted the first version of the manuscript. All authors contributed substantially and approved the final manuscript.

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The corresponding author, on behalf of all authors, jointly and severally, certifies that their institution has approved the protocol for any investigation involving humans or animals and that all experimentation was conducted in conformity with ethical and humane principles of research.

Data Transparency Statement:
The data underlying this article cannot be shared publicly due to National Health Registry access restrictions. The data will be shared on reasonable request to the corresponding author.