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MAJOR ARTICLE

Colorectal Disorders in Acute Human Immunodeficiency Virus Infection: A Case Series

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Background. The gastrointestinal (GI) tract is important in the pathogenesis of human immunodeficiency virus (HIV) infection. We report a case series of lower GI endoscopic and histopathologic findings of HIV-infected individuals after presentation with acute infection.

Methods. We performed a retrospective case review of individuals infected with HIV who enrolled between August 2010 and April 2013 in a primary infection treatment trial. All participants started the trial during acute infection and underwent colonoscopy with biopsies at baseline and after the start of antiretroviral treatment.

Results. Twenty acutely infected individuals were included in the study (mean age, 33 years; range, 20–54 years). All participants were male who reported having receptive anal sex as an HIV risk factor. Nine individuals (45%) had at least 1 finding by colorectal pathology; 1 person had 2 diagnoses (diverticulosis and focal active proctitis). The histopathological findings revealed anal dysplasia in 3 cases: 2 had high-grade anal intraepithelial neoplasia (AIN) and 1 had low-grade AIN. Two persons had a colorectal polyp, 1 hyperplastic and 1 adenomatous. Three persons were diagnosed with diverticulosis, and 2 persons were diagnosed with proctitis, including 1 with focal active proctitis and 1 with cytomegalovirus proctitis.

Conclusions. To our knowledge, this is the first case series report of lower GI disorders in acute HIV-infected individuals. Although the causal relationship remains uncertain, we describe the endoscopic findings that were observed during acute HIV infection among men who have sex with men. Understanding the prevalence of these pathologies may likely shed light on how acute HIV infection damages the lower GI tract.

Keywords. acute infection; endoscopy; gastrointestinal tract; HIV; primary infection.

A variety of clinical symptoms can occur within weeks of human immunodeficiency virus (HIV) infection. This "acute retroviral syndrome (ARS)," or "acute HIV infection (AHI)," is characterized by fever, myalgias, arthralgias, pharyngitis, lymphadenopathy, gastrointestinal (GI) symptoms, rash, headache, and other symptoms [1, 2]. Because symptoms of AHI are largely nonspecific, early diagnosis of AHI is often missed [3]. The GI tract is a common site of symptomatic HIV infection throughout the course of HIV disease progression, including nausea, vomiting, diarrhea, anorexia, and abdominal pain, which is reported by 35%–88% of individuals infected with HIV [4, 5]. These symptoms are particularly common among those with advanced immunosuppression [5].

The GI tract plays an important role in both AHI and advanced disease [6]. The lymphoid tissue within the GI tract, ie, gut-associated lymphoid tissue (GALT), harbors a large part of the body's entire immune system with large numbers of the activated memory T lymphocytes [7]. Both human studies with HIV and studies with the simian immunodeficiency virus (SIV) macaque model have demonstrated that acute infection is accompanied by a dramatic depletion of mucosal $CD4^+$ memory T cells [6, 8], indicating that GALT is a target for early SIV and HIV replication and future immunosuppression.

In this study, we report a case series of 20 men who reported sex with other men (MSM) who underwent colonoscopy during their acute stage of HIV infection before and after the initiation of antiretroviral therapy (ART).

METHODS

We performed a retrospective chart review of individuals enrolled in the University of California, San Diego Primary Infection Resource Consortium (SD PIRC) between August 2010 and April 2013 and who were offered colonoscopy as part of a randomized control trial in which individuals with AHI were provided standard ART (atazanavir, ritonavir, tenofovir, and emtricitabine) with or without maraviroc. The inclusion criteria were (1) aged 18 years or older, (2) laboratory tests

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Table 1. Baseline Characteristics of Acute and Early HIV-Infected Participants

Baseline Characteristics Before Start of Antiretroviral Therapy	
All participants (number, %)	20 (100%)
Participants with colon pathology (number, %)	9 (45%)
Mean age at time of enrollment (years) (±SD), range	33 (±10.4), 20–54
Mean estimated duration of infection at baseline (days), range	35, 10–70
Male (number, %)	20 (100%)
Race (number, %)	
White	12 (60%)
Asian	4 (20%)
Unknown	4 (20%)
Ethnicity (number, %)	
Non-Hispanic or Latino/Americans	15 (75%)
Hispanic or Latino/Americans	3 (15%)
Unknown	2 (10%)
MSM as the HIV risk factor (number, %)	20 (100%)
Baseline CD4 (cell/mm^3), mean (±SD)	600 (±214.4)
Baseline viral load, median (copies/mL)/mean ($\log_{10}$ copies/mL) (±SD)	87 950/4.7 (±1.4)
Acute retroviral syndrome symptoms (number, %)	10 (50%)
Gastrointestinal symptoms (number, %)	8 (40%)

Abbreviations: HIV, human immunodeficiency virus; MSM, men who reported sex with other men; SD, standard deviation.

consistent with HIV-infection within the previous 30 days (detection of HIV-1 RNA level above 5000 copies/mL with a negative or indeterminate HIV enzyme immunoassay, followed by HIV seroconversion) [9], and (3) willingness to undergo colonoscopy with biopsy. Baseline colonoscopies were performed before ART. The exclusion criteria were (1) contraindication or participant refusal of colonoscopy and (2) self-report of previous colorectal cancer diagnosis. A single experienced endoscopist performed all procedures. All participants started ART within 1 week of enrollment into SD PIRC (a mean of 35 days after their estimated date of infection, range 10–70 days). Mucosal abnormalities detected during colonoscopy were photographed, and suspicious mucosal tissue was biopsied or resected, and a histopathological examination was performed. Demographic, clinical, and laboratory data, including age, sex, race or ethnicity, HIV transmission risk, ART regimen, baseline CD4 count, and viral load, were obtained. Cytologic and endoscopic biopsy results were also collected. At baseline, participants were also tested for (1) syphilis infection through serology and (2) gonorrhea and chlamydia infections in the urethra, pharynx, and rectum via nucleic acid testing (ARUP). All participants provided written informed consent, and the study was approved by the University of California, San Diego human research protection program.

RESULTS

Characteristics of the Study Population

Twenty participants acutely infected with HIV were included in this study. Nine (45%) participants had at least 1 endoscopic abnormality at baseline. Of the 20 participants, 10 (50%) reported symptoms consistent with ARS, and of those 10 individuals, GI symptoms were reported by 8 (80%) (Table 1). Specific GI symptoms and endoscopic findings corresponding to each of those 8 individuals are presented in Table 2. All participants were male (100%); 60% were white and 20% were Asian. At enrollment, mean baseline CD4 count was 600 cell/μL and median viral load was 87 950 HIV RNA copies/mL (range, 136-10 000 000 copies/mL). The mean age was 33 years (range, 20–54 years). Two individuals had rectal chlamydia infections at baseline, and 1 had diverticulosis on colonoscopy, whereas the other participant had no colorectal pathology observed. All were men who reported having receptive anal sex with other men as their HIV risk factor. The histologic results and endoscopic findings are listed in Table 3.

Anal Dysplasia

Among the 20 acutely HIV-infected individuals, 3 had biopsy-proven anal intraepithelial neoplasia (AIN), 2 of which had high-grade anal intraepithelial neoplasia (HGAIN; AIN II). Case 1 was a previously healthy 54-year-old white male presented with fever. His physical examination was unremarkable. His white blood cell and hematocrit were within normal limits. His initial CD4 count was 881 cells/mm^3, and his initial HIV viral

Table 2. Endoscopic and Histopathologic Features of Acute and Early HIV-Infected Individuals With Gastrointestinal Symptoms

Age at Diagnosis (Years)	CD4 Count (Cells/mm^3) Baseline	Gastrointestinal Symptoms	Colonoscopy	Histopathology
28	622	Loose stool	A 1 cm sessile, flat lesion in distal rectum	HPV AIN II
24	362	Diarrhea, bloating	A 1 cm flat lesion in distal rectum	HPV AIN II
28	629	Lower abdominal pain	A 5 mm polyp in transverse colon	Hyperplastic polyp
52	817	Nausea and vomiting	1. Mild proctitis at 30 cm from anal verge 2. Diverticulosis	1. Acute proctitis 2. Mild sigmoid diverticulosis
22	67	Nausea and vomiting, abdominal pain	Normal colon and terminal ileum	–
21	656	Constipation	Normal colon and terminal ileum	–
40	509	Nausea and vomiting	Normal colon and terminal ileum	–
35	496	Nausea and vomiting	Normal colon and terminal ileum	–

Abbreviations: AIN, anal intraepithelial neoplasia; HIV, human immunodeficiency virus; HPV, human papillomavirus.

Table 3. Baseline Characteristics of Acute and Early HIV-Infected Individuals With HIV-Associated Colon Pathology

Case	Age at Diagnosis (Years)	Sex	CD4 Counts (Cells/mm^3)		Viral Load (Copies/mL)		ART Regimen	Estimated Year of HIV Infection	Days Postinfection of Amplified Sample	Pathology	Baseline (Pre-ART) Colonoscopy	Repeat Colonoscopy
			Baseline	Week 48	Baseline	Week 48						
1	54	Male	881	1325	3118	48	ATV/r + TDF + FTC + MVC	2011	70	HPV AIN I	2 small 2 mm polyps at anorectal junction	At 6-month follow-up, previous lesion was not identified
2	24	Male	362	632	506210	48	ATV/r + TDF + FTC	2010	10	HPV AIN II	A 1 cm flat lesion in distal rectum	At 7-month follow-up, previous AIN lesion was identified in rectal retroflexion
3	28	Male	622	819	136	48	ATV/r + TDF + FTC	2010	19	HPV AIN II	A 1 cm sessile, flat lesion in distal rectum	At 3-month follow-up, previous lesion was not identified
4	28	Male	629	655	428	48	ATV/r + TDF + FTC	2010	70	Hyperplastic polyp	A 5 mm polyp in transverse colon	At 4-month follow-up, previous lesion was not identified
5	34	Male	627	828	1091	48	ATV/r + TDF + FTC	2012	10	Tubular adenoma	A pedunculated 5 mm rectal polyp and a sessile 2 mm cecal polyp	Not performed
6	33	Male	741	684	18 939	48	ATV/r + TDF + FTC + MVC	2011	70	Diverticulosis Rectal Chlamydia	Mild sigmoid and descending colon diverticulosis	At 3-month follow-up, previous lesions were not identified
7	41	Male	557	730	333233	26	ATV/r + TDF + FTC	2012	70	Diverticulosis	Mild sigmoid diverticulosis	Not performed
8	52	Male	817	1063	776 930	48	ATV/r + TDF + FTC + MVC	2011	10	1. Acute proctitis 2. Diverticulosis	1. Mild proctitis at 30 cm from anal verge 2. Mild sigmoid diverticulosis	1. At 13-month follow-up, previous lesion was not detected 2. At 7-month follow-up, minimal lesions were identified
9	25	Male	436	505	3256	20	ATV/r + TDF + FTC + MVC	2012	70	CMV proctitis with ulceration	A 4 mm clean-based rectal ulcer	Not performed

Abbreviations: AIN, anal intraepithelial neoplasia; ART, antiretroviral therapy; ATV/r, atazanavir/ritonavir; CMV, cytomegalovirus; FTC, emtricitabine; HIV, human immunodeficiency virus; HPV, human papillomavirus; MVC, maraviroc; TDR, tenofovir disoproxil fumarate.

load was 3118 copies/mL. His colonoscopy showed two 2 mm polyps at the anorectal junction, and the pathology demonstrated AIN I. Case 2 was a previously healthy 24-year-old Asian male presented with fatigue, malaise, diarrhea, and bloating. His physical examination was unremarkable. His initial CD4 count was 362 cells/mm^3, and his initial HIV viral load was 506 210 copies/mL. His colonoscopy showed a 1 cm flat lesion in the distal rectum (Figure 1), and the subsequent biopsy showed AIN II. Case 3 was a previously healthy 28-year-old Asian male presented with fatigue and loose stools. His physical examination was unremarkable. His initial CD4 count was 662 cells/mm^3, and his initial HIV viral load was low at baseline 1621 copies/mL and then 136 copies/mL 3 weeks later at time of colonoscopy. His colonoscopy showed a 1 cm sessile, flat lesion in the distal rectum (Figure 2) with the pathology showing AIN II. The repeat endoscopy was performed in all 3 cases at a mean duration of 5.4 months (range, 3.3–7.3 months). The result showed that only 1 of the 3 participants had a residual AIN lesion (Table 3).

Colorectal Polyps

Among the 20 participants, 2 cases with a colorectal polyp were identified. One was a hyperplastic polyp and the other was an adenomatous polyp. Case 4 was a previously healthy 28-year-old male presented with lower abdominal pain. There were no signs or symptoms of GI bleeding or malabsorption. His physical examination was unremarkable. His initial CD4 count was 629 cells/mm^3, and his initial HIV viral load was 428 copies/mL. His colonoscopy showed a 5 mm polyp in the transverse colon, and the pathology report described a hyperplastic polyp. Case 5 was a previously healthy 34-year-old male who had no GI symptoms. His physical examination was unremarkable. His initial CD4 count was 627 cells/mm^3, and his initial HIV viral load was 1091 copies/mL. His colonoscopy showed a pedunculated 5 mm polyp in the rectum and a sessile 2 mm polyp in the cecum. Subsequent pathology findings revealed both lesions to be tubular adenomas (Table 3).

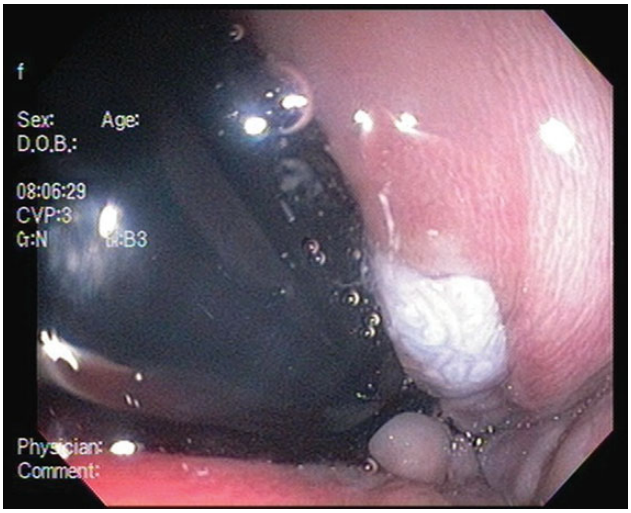

Figure 1. A 24-year-old male presented with fatigue, malaise, diarrhea and bloating. Colonoscopy demonstrated a 1 cm flat lesion in the distal rectum with pathology showing anal intraepithelial neoplasia II.

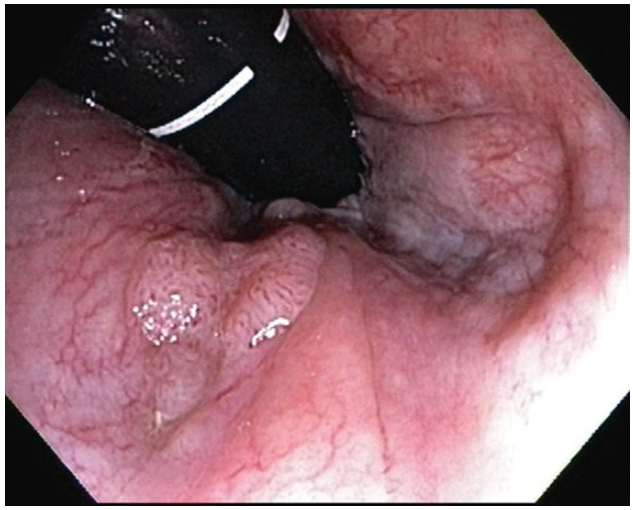

Figure 2. A 28-year-old male presented with fatigue and loose stools. Colonoscopy showed a 1 cm sessile, flat lesion in the distal rectum with pathology showing anal intraepithelial neoplasia II.

Diverticulosis

Of the 20 individuals acutely infected with HIV, 3 had diverticular disease (15%). Case 6 was a previously healthy 33-year-old white male who had no GI symptoms. His physical examination was unremarkable. His initial CD4 count was 741 cells/mm^3, and his initial HIV viral load was 18 939 copies/mL. His colonoscopy showed mild diverticulosis of the sigmoid and descending colon. Of note, at baseline, a rectal chlamydia infection was diagnosed and treated. Case 7 was a previously healthy 41-year-old male who had no GI symptoms. His physical examination was unremarkable. His initial CD4 count was 557 cells/mm^3, and his initial HIV viral load was 333 233 copies/mL. His colonoscopy showed mild sigmoid diverticulosis. Case 8 was a previously healthy 52-year-old white male presented with fever, nausea, and vomiting. His physical examination was unremarkable. His white blood cell and hematocrit were within normal limits. His initial CD4 count was 817 cells/mm^3, and his initial HIV viral load was 776 930 copies/mL. His colonoscopy showed mild sigmoid diverticulosis (Table 3).

Proctitis

Of the 20 participants, 2 cases (10%) were identified with proctitis. Case 8 was the 52-year-old white male described above. In addition to diverticulosis, his colonoscopy showed mild proctitis 30 cm from the anal verge, with pathology revealing focal acute cryptitis and crypt abscesses (focal active proctitis).

Case 9 was a previously healthy 25-year-old male who had no GI symptoms. His physical examination was unremarkable. His initial CD4 count was 436 cells/mm^3, and his initial HIV viral load was 3256 copies/mL. His colonoscopy showed a 4 mm clean-based rectal ulcer (Figure 3), and the biopsy demonstrated cytomegalovirus (CMV) proctitis with ulceration. A repeat endoscopy was performed only in Case 8 at 12.8 months after enrollment and found that the previously observed lesion was not identified (Table 3).

DISCUSSION

Forty to ninety percent of individuals with acute HIV infection report symptoms consistent with an ARS [1, 10]. The most commonly reported symptoms are fever (80%–90%), fatigue (70%–90%), rash (40%–80%), headache (32%–70%), and lymphadenopathy (40%–70%) [2]. In addition, several GI manifestations, including nausea, vomiting, and diarrhea, have been reported in approximately 30%–60% of individuals with AHI [2]. Our data are consistent with these previous studies, with half of our cases having an ARS, and 40% of those with AHI reported having GI symptoms. In this study, we describe the GI tract pathology among these individuals acutely infected with HIV.

In the United States, MSM continue to be the largest risk group of new HIV infections [11], and unprotected anal intercourse is the main sexual risk behavior for HIV transmission among MSM [12]. Among MSM, the anorectum is a common site of sexually transmitted infections, including chlamydia, gonorrhoea, herpes simplex virus, syphilis, and human papillomavirus (HPV). There is also an increased risk of anal ulcers and anal cancer in MSM [13, 14]. Prompt recognition of anorectal disorders in MSM may be important to avoid serious complications and may help reduce HIV acquisition.

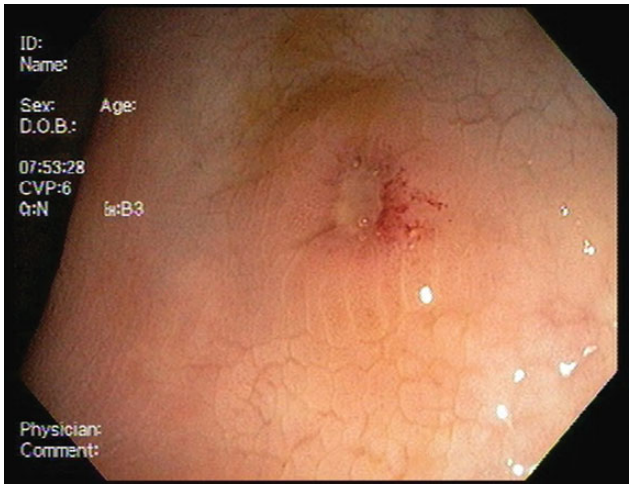

Figure 3. A 25-year-old male without gastrointestinal symptoms. Colonoscopy showed a 4 mm clean-based rectal ulcer with pathology showing cytomegalovirus proctitis with ulceration.

The prevalence of anal dysplasia and anal cancer is higher in HIV-positive than in HIV-negative individuals, especially among MSM [14, 15], with the prevalence of AIN between 29% and 57% in HIV-positive MSM and 21%–35% in HIV-negative MSM [16, 17]. Advanced immunosuppression with low nadir CD4 cell count is significantly associated with AIN, a precursor to anal cancer [18]. In addition, anal HPV and AIN are very common among HIV-positive and HIV-negative MSM [16, 17, 19]. Given those findings in chronically infected individuals, we found that 3 cases of acute HIV-infected individuals had AIN, and 2 of these 3 had HGAIN. All 3 of these individuals had baseline CD4 count more than 200 cells/mm^3, suggesting AIN can also be found despite high CD4 count. This is the first report of anal dysplasia in individuals acutely infected with HIV, and it may suggest that much of this pathology was brewing before their HIV infection. Once HIV infection happens and immunosuppression starts to occur, then it could be expected that these lesions would progress [20]. It should be noted, however, that most of the colorectal pathology identified at the baseline colonoscopy before ART was not detected on follow-up colonoscopies, while the participant was receiving ART (Table 3). Although GALT is severely depleted during AHI and does not return even during ART [6, 21], to our knowledge such systematic resolution of clinically evident gut pathology during ART has not previously been reported.

Published data suggest that hyperplastic polyps are detected in 12.5%–34% of older adults (age >50 years) in the general population by colonoscopy, whereas adenomas are detected in 22.2%–58.2% in this same population [22–24]. One study found a lower prevalence of colorectal polyps (8.9%) in younger populations (40 years of age or younger) with rectal bleeding in the United States [25]. Our study identified 1 participant with a hyperplastic polyp at 28 years of age and 1 with an adenomatous polyp at 34 years of age. Our results with this generally younger population appear consistent with previous reports in the general population. Some recent studies suggest a higher incidence of colorectal adenomas among individuals infected with HIV compared with the general population (25.5%–62.5% vs 13.1%–41.2%, respectively) [26, 27], and that the risk of such lesions is higher in the setting of lower CD4 counts (<200 cells/mm^3), longer duration of HIV infection, and advanced age [28]. Our study found only 2 individuals with a colorectal polyp (10%), which may be attributable to generally young age of our study population, the fact that participants had only been infected with HIV for a very short time, and all CD4 counts were greater than 200 cells/mm^3.

Diverticulosis of the colon is quite common in the United States. The prevalence increases with age, affecting approximately 10% of people under 40 years of age to 30% to 50% of the population over 60 years of age [29, 30]. Currently, comprehensive reviews of diverticular disease do not include any discussion of HIV infection [30, 31], and even when corrected for age, there

is no evidence for an increased risk of diverticular disease in individuals infected with HIV [32]. In our study, we found 3 participants with diverticular disease, and all were younger than 60 years of age and had no complications. Because there is a lack of evidence of diverticular disease among individuals infected with HIV, further studies are needed to clarify this issue.

To date, only 3 cases of acute CMV colitis in the context of AHI have been described in the literature [33–35]. Those cases have been associated with severe symptoms (eg, fevers, weight loss, watery diarrhea, vomiting, central abdominal pain, hemorrhagic colitis) and sometimes pancolitis. Such symptoms were the reason these described cases underwent the colonoscopic work up that led to the diagnosis of CMV colitis. Our case was asymptomatic and disease was confined to the rectum. Because CMV colitis in immunocompetent individuals has also been documented in men and women who report receptive anal intercourse [36, 37], we feel that the observed CMV colitis may be an incidental finding related to the participant's recent receptive anal intercourse and less likely related to his AHI.

In this study, we report the first case of focal active proctitis in the setting of primary HIV infection. Focal active proctitis refers to the isolated finding of neutrophilic crypt injury, namely focal acute inflammation of the crypt epithelium of the colorectal mucosa [38]. There have been 3 reports in the adult literature describing correlation of focal active proctitis with clinical outcomes [38–40]. Focal active proctitis is a nonspecific pathologic finding, and it can be seen in inflammatory bowel disease, infectious colitis, ischemic colitis, with the use of nonsteroidal anti-inflammatory drugs (NSAIDs), or as an incidental finding in biopsies taken from individuals with suspected colonic neoplasia [40]. Most individuals with focal active proctitis seem to have acute self-limited or infectious-type colitis, and a large proportion of these individuals are immunosuppressed. Our case was followed and turned out to be self-limited.

CONCLUSIONS

To the best of our knowledge, we report the first case series of acutely HIV-infected individuals receiving colonoscopy, and half of these MSM had some colorectal pathology on endoscopy and biopsy. The spectrum of colorectal diseases during the acute stage of HIV infection was varied, and some of the conditions likely pre-existed the HIV infection; however, many of the identified conditions could be worsened by immunosuppression that can be caused by HIV over time.

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