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Gastrointestinal symptoms in patients infected with human immunodeficiency virus: relevance of infective agents isolated from gastrointestinal tract

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Abstract

The correlation of gastrointestinal symptoms and infections in 186 consecutive patients with human immunodeficiency virus (HIV) infection undergoing diagnostic endoscopy (oesophagogastroduodenoscopy, n=124; colonoscopy, n=37; both, n=25) was investigated. Biopsy and stool samples were examined for infective agents. Only weight loss (p=0·003) and dysphagia (p=0·027) were more common in patients at stage CDC IV compared with earlier stages. In three of 27 patients at stage II/III and in 93 of 159 patients at stage IV an infective agent was identified in stool or gastrointestinal biopsy specimen (p<0·001). Cytomegalovirus (n=35), *Candida sp* (n=28), *M avium* complex (n=10), and *Cryptosporidium* (eight) were the most frequent agents detected. At stage IV, diarrhoea was more frequent in infected compared with non-infected patients (p=0·006); however, an infective agent was also found in 39 of 82 patients at stage IV without diarrhoea. The frequency of gastrointestinal symptoms was not consistently increased in patients harbouring specific infective agents compared with non-infected patients. Our findings indicate that the pathogenic relevance of a gastrointestinal infection in HIV infected patients has to be verified and indirectly support the existence of an HIV associated enteropathy.

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The pathogenesis of gastrointestinal symptoms in patients with the acquired immunodeficiency syndrome (AIDS) is still under debate. Recent reports have stressed the importance of extensive microbiological evaluation of stool samples and intestinal biopsy specimens, however, there is always a considerable proportion of symptomatic patients without an identifiable intestinal pathogen.[1] This observation has led to the hypothesis of a human immunodeficiency virus (HIV) induced enteropathy which has been confirmed recently by the finding of small bowel atrophy with hyporegeneration and impaired enterocyte maturation in patients infected with HIV.[2 3] The possibility of HIV itself being an intestinal pathogen challenges the pathogenic relevance of other infectious agents recovered from the gastrointestinal tract of HIV infected patients. The causal relevance of an agent would be optimally confirmed if it was detected in symptomatic but not in asymptomatic patients. Thorough examination including endoscopy with biopsy of asymptomatic patients, however, is hardly conceivable because of ethical reasons. Therefore, we have investigated the presence and absence of different gastrointestinal symptoms in patients with and without intestinal infections.

Methods

PATIENTS

We studied 186 consecutive patients undergoing diagnostic endoscopy of the gastrointestinal tract in two major referral based hospitals in West Berlin over two years. Clinical data of 45 patients have been reported previously.[2] Symptoms included weight loss (defined as an unintended decrease of body weight of more than 5% in six months), diarrhoea (defined as more than three loose bowel movements a day), epigastric and abdominal pain, nausea, vomiting, dysphagia, and fever of unknown origin. The classification of the Centers for Disease Control[4 5] was used to determine the disease stage of each patient: 16 patients were at stage II, 11 at stage III, 13 at stage IVa, 82 at stage IVcl, 26 at stage IVc2, 26 at stage IVd, and 12 at stage IVc1/IVd. The patients ranged in age from 19 to 68 years (median 36). One hundred and twenty six men were homosexual or bisexual, five women and 21 men were intravenous drug abusers, one woman and three men had received blood transfusions; in 30 men no risk factor could be ascertained.

INVESTIGATIONS

All patients had a complete physical examination and their medical history was recorded using a standardised protocol. In 150 patients the number of $CD4^+$ lymphocytes per microlitre and the CD4/CD8 ratio in the peripheral blood was determined within two weeks before or after endoscopy. Oesophagogastroduodenoscopy was performed in 124 patients, flexible colonoscopy in 37 patients, and 25 patients had both examinations. If no lesions were seen, seven biopsies each of the stomach and duodenum in upper, and of different parts of the large intestine in lower endoscopy were taken: two for histopathological, three for microbiological, and two for virological examination. An additional seven biopsies were taken from visible lesions. At least three stool samples per patient were examined by culture for enteropathogenic *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, *Yersinia* spp, *Streptococcus* spp, *Staphylococcus* spp, *Clostridium* spp, and mycobacteria. In addition, stools were examined by microscopy for ova and parasites, including *Cryptosporidium* and *Isopora*.

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TABLE I *Gastrointestinal symptoms in patients with HIV infection correlated with the stage of disease and risk group*

	Stage of disease					
	II or III			*IV*		
	*Homosexual risk**			*Homosexual risk**		
	Negative	*Positive*	*Total*	*Negative*	*Positive*	*Total*
Dysphagia	0 (0%)	1 (8%)	1 (4%)	5 (26%)	27 (24%)	36 (23%)†
Nausea	1 (10%)	3 (23%)	5 (19%)	5 (26%)	42 (37%)	51 (32%)
Vomiting	2 (20%)	3 (23%)	6 (22%)	4 (21%)	25 (22%)	33 (21%)
Pain						
Epigastric	4 (40%)	4 (31%)	9 (33%)	7 (37%)	34 (30%)	46 (29%)
Abdominal	2 (20%)	2 (15%)	4 (15%)	1 (5%)	40 (35%)‡	46 (29%)
Weight loss§	0 (0%)	2 (15%)	2 (7%)	3 (16%)	52 (46%)‖	58 (36%)¶
Diarrhoea**	5 (50%)	3 (23%)	10 (37%)	11 (58%)	57 (50%)	77 (48%)
Total number	10	13	27	19	114	159

*30 patients in which no risk factor could be ascertained were excluded; †p=0·014 compared with patients at stage II/III; ‡p=0·005 compared with non-homosexual patients at stage IV; §Defined as decrease in body weight of more than 5% in six months; ‖p=0·012 compared with non-homosexual patients at stage IV; ¶p=0·001 compared with patients at stage II/III; **Defined as more than three loose bowel movements a day.

Paraffin sections of formaldehyde fixed biopsies were stained with various histochemical stains including haematoxylin and eosin, Ziehl-Neelsen acid fast, Grocott, Giemsa, periodic acid Schiff, and Gram stain. Sections were examined by light microscopy for bacterial, protozoal, fungal, and viral enteric pathogens. Biopsies were also cultured for enteropathogenic bacteria including mycobacteria. Rectal swabs were cultured for chlamydia. Investigations for viral pathogens were done by electron microscopical examination of stool samples (identification of rota, corona, and adenoviruses), and cultures of stool samples and intestinal biopsies on three different cell lines were observed for characteristic cytopathic effects. In addition, biopsies from lesions were examined for the presence of cytomegalovirus by immunohistology.

STATISTICAL ANALYSIS

Measurement results were described as medians and range, and the two tailed Mann-Whitney U test was used to evaluate comparative statistical significance. The frequency of symptoms or pathogens in different groups of patients was compared by Fisher's exact test. The critical hypotheses to be tested in our study were rather that there are no differences between groups than that there are differences. Therefore, in order to minimise the risk of falsely rejecting an existing difference, p values less than 0·05 were considered as significant although multiple tests were carried out on the same data.

Results

CLINICAL FINDINGS

All patients in this study presented with gastrointestinal complaints. Gastrointestinal symptoms were correlated with the stage of disease and risk group (Table I). Dysphagia and weight loss were the only symptoms found significantly more frequently in patients at stage IV compared with patients at stages II or III. No significant differences were observed in the frequency of gastrointestinal symptoms when comparing homosexual and non-homosexual patients at stage II/III, at stage IV abdominal pain and weight loss were more frequent in homosexual compared with non-homosexual patients.

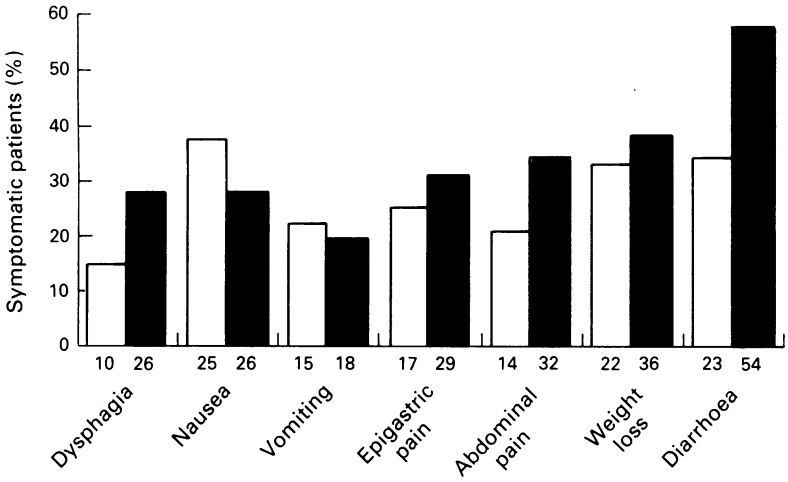
GASTROINTESTINAL INFECTIONS

Gastrointestinal pathogens were investigated in 186 HIV infected patients by endoscopy with biopsy and microbiological examination of biopsies and repeated stool samples. In 96 patients (52%) an infectious agent was identified in stool or biopsy: in three (11%) of 27 patients at stage II/III and in 93 (58%) of 159 patients at stage IV ($p<0·0001$). In 25 patients (26% of infections) an agent was recovered only from stool samples, in 58 patients (60% of infections) an agent was identified only in biopsy, in 23 patients (24% of infections) an agent was detected in both stool and biopsy. There were two patients harbouring three and 18 patients harbouring two different infectious agents in the gastrointestinal tract (Table II). Five patients, all with a gastrointestinal infection, had intestinal Kaposi's sarcoma, four in the duodenum and one in the rectum. In 90 patients (48%) no potential pathogen was found. At stage II *Chlamydia trachomatis* was detected in rectal biopsies of two homosexual men (one had fever and weight loss, the other had abdominal pain), and *Staphylococcus aureus* in stool specimens of one non-homosexual man with epigastric pain and diarrhoea. In none of the patients at stage III was an infectious agent isolated from the gastrointestinal tract. At stage IV 72 (63%) of 114 homosexual and eight (42%) of 19 non-homosexual patients had a gastrointestinal infection (p=0·070, not significant). Intestinal infections, however – that is, if candida oesophagitis was excluded, were found more commonly in 58 (51%) of 114 homosexual, compared with four (21%) of 19 non-homosexual patients at stage IV (p=0·014).

TABLE II *Multiple gastrointestinal infections in HIV infected patients**

	CMV†	*Candida sp*	*MAC‡*	*Cryptosporidium*	*E histolytica*	*Adenovirus*	*Campylobacter sp*	*Chlamydia sp*	*Shigella sp*	*Coronavirus*	*Spirochetes*	*M tuberculosis*	*Coinfection§*
Cytomegalovirus	#	7‖	3‖¶		1¶	1	1				1	1	13/35 (37%)
Candida sp	7‖	#	2‖			1							9/28 (32%)
M avium complex	3‖¶	2‖	#		1¶	1							5/10 (50%)
Cryptosporidium				#						1			1/8 (13%)
E histolytica	1¶		1¶	#									1/6 (17%)
Adenovirus	1	1	1			#				1			4/5 (80%)
Campylobacter sp	1						#						1/3 (33%)
Chlamydia sp								#	2				2/5 (40%)
Shigella sp								2	#				2/3 (67%)
Goronavirus				1		1				#			2/2 (100%)
Spirochetes	1										#		1/2 (50%)
M. tuberculosis	1											#	1/1 (100%)

*20 of 186 patients were multiply infected, 76 patients were monoinfected; † CMV=Cytomegalovirus; ‡MAC=*M avium* complex; §Patients with coinfection/infected patients (%); ‖One patient had CMV, MAC, and candida infection; ¶One patient had CMV, MAC, and *E histolytica* infection.



Frequency of gastrointestinal symptoms in 159 HIV infected patients at stage IV in correlation to the presence of a gastrointestinal infection. Infectious agents were recovered from stool or biopsy in 93 patients (closed bars), in 66 patients no infectious agent was identified (open bars). The number of patients with the symptoms indicated is given below the horizontal axis. The frequency of dysphagia (p=0·042) and diarrhoea (p=0·003) was increased in infected compared with non-infected patients.

The frequency of gastrointestinal symptoms was compared in infected and non-infected patients at stage IV (Figure); earlier stages were excluded to avoid bias because of the small proportion of infected patients at stages II/III. Only two of the seven symptoms investigated were found to occur more frequently in the presence of identifiable infectious agents – namely, dysphagia which was found in 15% of non-infected and in 28% of infected patients (p=0·042), and diarrhoea which was found in 35% of non-infected and in 58% of infected patients (p=0·003). Diarrhoea was present in 44 (59%) of 74 patients with intestinal infection – that is, if candida oesophagitis was excluded, and thus also more common compared with non-infected patients. Of note, infectious agents were also detected in 39 (48%) of 82 patients at stage IV without diarrhoea (Table III), 30 (37%) of whom had intestinal infection.

Fifteen different infectious agents were isolated from the gastrointestinal tract of HIV infected patients at stage IV of the disease, the most frequent agent was cytomegalovirus (Table IV). The most common result of the microbiological examinations, however, was negative (42%), and this was true for patients with every symptom except dysphagia and abdominal pain, who had candida oesophagitis and cytomegalovirus infection, respectively, as the most frequent findings. Cytomegalovirus was the only agent detected more frequently in homosexual compared wth non-homosexual patients. Compared with patients without detectable infective agents dysphagia, abdominal pain, weight loss, and diarrhoea were more frequent in patients with cytomegalovirus infection. *Candida* sp was found only in oesophageal biopsies, and candida oesophagitis correlated significantly with the presence of dysphagia. Patients with *M avium* complex infection had more frequent dysphagia, vomiting, and epigastric pain, patients with salmonella infection vomiting and abdominal pain, and patients with shigella or chlamydia infection diarrhoea compared with non-infected patients. No other significant association between gastrointestinal symptoms and a specific organism was found. Four agents were detected in less than three patients each, however, and could therefore not be tested at 5% significance level. Both patients with coronavirus infection had weight loss, one with cytomegalovirus coinfection had diarrhoea too. In one patient with diarrhoea *M tuberculosis* and cytomegalovirus was found. Two patients with intestinal spirochetosis and one patient with *C perfringens* infection had fever as the only symptom.

The number of CD4 positive cells per microlitre and the CD4/CD8 ratio in the peripheral blood was reduced in patients at stage IV compared with patients at stage II/III, and – at stage IV – in patients with gastrointestinal infections compared with non-infected patients (data not shown). Both values were not significantly different in homosexual compared with non-homosexual patients (data not shown).

TABLE III *Infective agents detected in stool or gastrointestinal biopsy of 82 HIV infected patients at stage IV without diarrhoea*†*

Agents detected	*Patients (n)*
Candida sp	9
CMV‡	7
Candida sp, CMV	4
MAC§	4
Cryptosporidium	3
E histolytica	2
Adenovirus	1
Adenovirus, *Candida* sp	1
Adenovirus, Coronavirus	1
MAC, CMV	1
Campylobacter sp	1
C perfringens	1
CMV, Spirochetes	1
G lamblia	1
Salmonella sp	1
Spirochetes	1
Total	39

*Diarrhoea = more than three loose bowel movements a day; †In addition, *C trachomatis* was detected in two of 17 patients at stage II/III without diarrhoea; ‡CMV = Cytomegalovirus; §MAC = *M avium* complex.

Discussion

The absence of identifiable pathogens in a considerable proportion of HIV infected patients with gastrointestinal symptoms and the detection of intestinal pathogens in asymptomatic patients[6] raise doubts about the pathogenic relevance of secondary infections and malignancies.[1] We have therefore investigated gastrointestinal symptoms in correlation to the detection of infective agents in stool or gastrointestinal biopsies of patients at different stages of HIV infection.

Compared with patients at earlier stages of HIV infection, we found a significantly increased rate of gastrointestinal infections in patients at stage IV. This is not merely an artifact caused by the classification system but probably results from progressive immune dysfunction as indicated by a decrease of $CD4^+$ cells and of the CD4/CD8 ratio in the peripheral blood correlating with the stage of disease and the presence of gastrointestinal infections. Only two gastrointestinal symptoms were more common in advanced stages of the disease, however, dysphagia which was strongly associated with candida oesophagitis leading to a stage IV classi-

TABLE IV *Detection of infective agents in stool or gastrointestinal biopsy from 159 HIV infected patients at stage IV of the disease correlated with gastrointestinal symptoms and risk group*

Agents	*Total*	*Dysphagia*	*Nausea*	*Vomiting*	*Epigastric pain*	*Abdominal pain*	*Weight loss**	*Diarrhoea†*	*Homosexual risk‡*	
									Positive	*Negative*
None	66	10	25	15	17	14	22	23	42	11
Cytomegalovirus	35	10§	9	5	11	17‖	17§	22‖	32¶	0
Candida sp	28	14‖	9	8	11	7	6	14	22	4
M avium complex	10	5§	4	5§	7**	3	5	5	9	1
Cryptosporidium	8	1	2	1	1	2	3	5	7	0
E histolytica	6	2	0	0	1	2	1	4	3	1
Adenovirus	5	1	2	2	1	2	4	2	4	0
Salmonella sp	4	1	2	2§	1	2§	3	3	2	1
Campylobacter sp	3	0	1	0	0	2	2	2	1	1
Chlamydia sp	3	0	1	2	2	1	1	3§	1	0
G lamblia	3	0	0	0	1	1	1	2	2	0
Shigella sp	3	0	0	2	2	1	1	3§	1	0
Coronavirus††	2	0	0	0	0	0	2	1	1	0
Spirochetes††	2	0	0	0	0	0	0	0	2	0
C perfringens††	1	0	0	0	0	0	0	0	1	0
M tuberculosis††	1	0	0	0	0	0	0	1	1	0
Total	159	36	51	33	46	46	58	77	114	19

*Defined as decrease in body weight of more than 5% in six months; †Defined as more than three loose bowel movements a day; ‡30 patients in which no risk factor could be ascertained were excluded; §$p<0.05$ compared with non-infected patients; ‖$p<0.005$ compared with non-infected patients; ¶$p<0.005$ compared with non-homosexual patients; **$p<0.01$ compared with non-infected patients; ††Agents found in less than three patients could not be tested at 5% significance level.

fication, and weight loss which did not correlate with gastrointestinal infections at stage IV. Two recent studies exclusively involving patients with diarrhoea similarly reported the absence of potential pathogens in most patients with AIDS related complex while in most patients with AIDS a potential cause of diarrhoea was detected[7 8]; as the abnormalities detected in AIDS patients were obviously not necessary to produce diarrhoea at earlier stages of the disease, their causative relevance is doubtful.

Intestinal infections were more common in homosexual compared with non-homosexual patients at stage IV, which is in contrast with the report by René and coworkers[9] and probably results from the inclusion of non-homosexual patients from Africa and Haiti in their study. Despite the higher rate of intestinal infections homosexual patients had a higher frequency of abdominal pain and weight loss only, while the frequency of diarrhoea or other symptoms was not different.

In the present study, in 42% (95% confidence interval: 38% to 46%) of patients at stage IV with gastrointestinal symptoms no potential pathogen was detected in stool or gastrointestinal biopsy. Diarrhoea was the only symptom occurring more frequently in infected compared with non-infected patients at stage IV which is in accordance with two previous studies.[9 10] No infectious agent was found in 30% (95% confidence interval: 25% to 36%) of 77 patients at stage IV with diarrhoea and furthermore, nearly 50% of the patients without diarrhoea harboured an infective agent in their gastrointestinal tract. These agents obviously did not cause diarrhoea at the time of study, although their presence might represent chronic or convalescent carriage after earlier symptomatic infection.

The frequency of agents found in our patients was similar to those reported in earlier studies from Western Europe and the USA,[6-11] except for cryptosporidium which was detected in 5% of our patients, in about 10% of patients in the USA,[6 8 10] but in more than 20% of patients in Great Britain[7] and France.[9] These differences might result from epidemiological differences in the populations studied. We confirmed the clear correlation of histologically proven candida infection, which was always confined to the oesophagus, with the presence of dysphagia.[12] Patients infected with cytomegalovirus had significantly more frequent dysphagia, abdominal pain, weight loss, and diarrhoea, and a significant association with diarrhoea can also be inferred from two earlier studies.[9 10] No correlation of intestinal *M avium* complex infection with gastrointestinal symptoms has been shown previously. We found an increased frequency of dysphagia, vomiting, and epigastric pain in patients infected with *M avium* complex while the frequencies of weight loss or diarrhoea were not different. Neither diarrhoea nor the other symptoms investigated were more common in patients with cryptosporidiosis compared with non-infected patients in our study. In fact, a significant association of cryptosporidiosis with diarrhoea can be inferred from only one[9] of previous studies, and Janoff and coworkers[13] recently reported asymptomatic colonisation of the digestive tract by *Cryptosporidium*. Isolation rates of other agents isolated from the gastrointestinal tract of our patients at stage IV were below 4% each which limits an estimation of their pathogenic relevance based on the association with gastrointestinal symptoms. No symptomatic improvement of diarrhoea in AIDS patients, however, has been observed by others after eradication of *E histolytica*, Salmonella, *Campylobacter* sp, or *G lamblia*.[7 10] Therapeutic studies on intestinal *M avium* complex infection are missing and an effective therapy for cryptosporidiosis is not available at present. In contrast, improvement of gastrointestinal symptoms after specific treatment with ganciclovir is well documented in cytomegalovirus infection[7 10] which is in accordance with the significant association this agent has with the gastrointestinal symptoms reported here. Nonetheless, it should be noted that cytomegalovirus was present in 13 of our patients without diarrhoea.

Electron microscopy of intestinal biopsies was not done in our study, thus we cannot rule out the possibility that microsporidia were present. An ongoing study revealed microsporidia in only one (3%) of 39 HIV-infected patients investi-

gated so far, however,[14] (and unpublished results), thus the prevalence of microsporidiosis seems to be rather low in Berlin. It is therefore unlikely that microsporidia were responsible for the symptoms in a relevant proportion of the patients reported here, especially those at early disease stages and those without detectable secondary infection, as intestinal microsporidiosis is apparently associated with low CD4 counts in the peripheral blood.[15]

Thus we have shown a high frequency of gastrointestinal symptoms including diarrhoea and weight loss in non-infected patients which was not consistently increased in patients harbouring specific infective agents. Furthermore diarrhoea or weight loss were absent in a considerable proportion of infected patients. Extensive microbiological evaluation obviously increases the number of abnormalities detected; however, these may or may not be of pathogenic relevance as also indicated by the persistence of symptoms after eradication of several infective agents reported by others. Thus, further controlled studies are clearly needed to define the true role of the various secondary infective agents detectable in the intestine of HIV infected patients. Apart from the mere detection of an agent in stool or biopsy additional criteria have to be established which differentiate asymptomatic carriers from those patients with infection in the strict sense – that is, with related signs of illness. Nonetheless we recommend a thorough diagnostic evaluation of HIV infected patients with gastrointestinal symptoms because specific therapy especially of cytomegalovirus infection may indeed lead to symptomatic improvement.

The high proportion of symptomatic patients without detectable pathogens especially at early stages of HIV infection, and furthermore the poor correlation of infections and symptoms might be explained by an enteropathogenic role of HIV itself. HIV infection of the intestinal mucosa is found in about 40% of patients with gastrointestinal symptoms and thus the most frequent infective agent detected in this population.[1 2 16] As for most of the secondary infectious agents a clear correlation between intestinal HIV infection and gastrointestinal symptoms has not been established so far. Mucosal HIV infection, however, is associated with defects in enterocyte maturation and hyporegenerative villus atrophy[2 16] which are less pronounced in patients receiving zidovudine.[17] Thus HIV probably causes gastrointestinal dysfunction; furthermore HIV is the only intestinal pathogen which is frequently found even at stages II or III[2 16] and could therefore account for the occurrence of gastrointestinal symptoms and mucosal abnormalities at early stages of the disease when other potential causes are rarely detected.[2 16 18 19] An HIV enteropathy would probably worsen with disease progression, and our study shows that other intestinal infections are of uncertain relevance; however, it is tempting to assume a synergistic effect of HIV with other infectious agents to explain the progressive gastrointestinal dysfunction seen with the advancement of the disease. The recent report by Connolly *et al* of diarrhoea and malabsorption being more severe in the presence of detectable secondary infections supports this hypothesis.[20] In fact, such synergy has been shown between HIV and cytomegalovirus,[21] an agent which is unequivocally found to cause gastrointestinal symptoms.

In conclusion, our findings show that gastrointestinal symptoms are not generally explained by secondary infections as the pathogenic relevance of most agents detected in HIV infected patients is doubtful. Thus the proportion of patients with unexplained symptoms is in fact even larger than recognised so far which indirectly supports an enteropathogenic role of HIV itself.

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