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REVIEW ARTICLE

Approach to Diarrhea in HIV Patients: Narrative Literature Review and Diagnostic Proposal

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ABSTRACT

Diarrhea in patients infected with the human immunodeficiency virus (HIV) represents a challenge for the clinician. Its differential diagnosis includes infectious causes (bacteria, viruses, fungi, and parasites) as well as non-infectious ones. Among the infectious causes are microorganisms that can affect both immunocompetent and immunocompromised hosts, making the differential diagnosis broad. The presentation can be acute or chronic, with the latter having a greater impact on morbidity and quality of life for patients. The diagnostic approach should be sequential, first with non-invasive laboratory methods, progressing to endoscopic studies with biopsy in those individuals for whom reaching a diagnosis is difficult.

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Enfoque de la Diarrea en el paciente VIH: Revisión narrativa de la literatura y propuesta diagnóstica

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RESUMEN

La diarrea en el paciente infectado con el virus de la inmunodeficiencia humana (VIH) representa un reto para el clínico, dentro de su diagnóstico diferencial se incluyen causas infecciosas (Bacteria, virus, hongos y parásitos) como no infecciosas; dentro de las causas infecciosas se encuentran microorganismos los cuales pueden afectar a hospederos tanto inmunocompetentes como inmunocomprometidos, por lo que el diagnóstico diferencial es amplio. La presentación puede ser aguda o crónica, siendo esta última la que presenta mayor impacto en la morbilidad y la calidad de vida de los pacientes. El enfoque diagnóstico debe ser secuencial, primero con métodos de laboratorio no invasivos, hasta llegar a estudios endoscópicos con toma de biopsias en aquellas personas en quienes es difícil llegar a un diagnóstico.

INTRODUCTION

Symptomatic diarrheal disease affecting the small intestine and colon remains a frequent clinical manifestation in patients with acquired immunodeficiency syndrome (AIDS). Observational studies in the era of antiretroviral therapy (ART) suggest that approximately 28%–60% of patients present with this clinical symptom per year (1-4), either with episodes of acute infectious diarrhea or as chronic diarrhea leading to malabsorption, weight loss, and nutritional deficit (5). A study conducted in Mexico in a population with AIDS described that the acute presentation of the disease (more than 3 days of symptomatic evolution but less than 21 days) was present in 17% of the patients, while chronic diarrhea (more than 21 days) was present in 36%, with the latter being related to a lower probability of survival at one year (60% vs. 95% for patients with acute presentations of the disease) (6). That retrospective study demonstrates how chronic diarrhea may not only be a marker of advanced immunodeficiency but also of poor prognosis in HIV patients.

A Colombian descriptive study conducted in Antioquia with 192 patients of the HIV care program of the Corporación para Investigaciones Biológicas (CIB, *Biological Research Corporation*) found that 9.3% of them presented with diarrhea, out of which 68.4% were acute presentations (less than 2 weeks); 21.05% were chronic (> 4 weeks); and 10.5% were subacute (between 2 and 4 weeks) (7). It is important to highlight that, in that study, 83.7% of the patients had CD4 T-lymphocyte counts greater than 200.

Another retrospective descriptive study conducted in the city of Medellin included patients hospitalized with a diagnosis of HIV/AIDS between 2007 and 2011, 66.1% of whom had CD4+ T-lymphocyte counts of less than 200 cells/mm^3. A total of 50.3% of the patients presented with gastrointestinal symptoms on admission; using microbiological studies and histopathology with special stains, it was possible to identify *Mycobacterium tuberculosis* in 8.4%, *Histoplasma capsulatum* in 3.3%, and *Cryptococcus neoformans* in 1.7% of the patients. However, no definitive etiological diagnosis could be established for about 86.25% of patients (8).

In summary, in patients living with HIV, diarrhea is a frequent and heterogeneous disease, with a varied clinical presentation and a wide variety of etiological agents when it is infectious. However, there are multiple non-infectious causes as well, which implies a challenge for diagnosis and treatment.

With the advent of highly active antiretroviral therapy (HAART), the impact of infectious etiologies has been diminishing in favor of non-infectious causes (3,9). A historical data series of HIV-infected patients in the US with CD4+ lymphocyte counts <200 showed a significant decrease in infectious etiology from 53% to 13% over a 3-year period (1995-97), with a significant increase in non-infectious diarrhea from 32% to 71% (9). Similar data have been observed in other latitudes among patients with successful antiretroviral treatment (10).

Observations made in patients under antiretroviral therapy show that 60% may present diarrhea (11). Clinical trial results suggest that up to 19% of these events could be due to adverse effects of the antiretroviral treatment itself (12).

Given the complexity of the approach in primary care and emergency departments, in this paper we review the effect of diarrhea in the HIV patient, discuss current diagnostic approaches, and present a diagnostic algorithm.

HIV and the gut

To understand the impact of HIV in the gut one must first understand that the vast majority of lymphoid tissue in the human body is found in the gut-associated lymphoid tissue (GALT). It is estimated that T lymphocytes associated with the small intestinal epithelium may account for approximately 60% of the total lymphocyte count (13). From 40% to 70% of the lymphocytes of the gastrointestinal tract express the CCR5 co-receptor (14), and the coexpression of CXCR4 and CCR5 receptors is substantially higher than that expressed by lymphocytes in peripheral blood (15). These characteristics explain why this mucosal compartment is especially permissive to HIV infection.

Because of this, the gastrointestinal tract is a susceptible target organ during all phases of HIV infection. However, the effect on mucosal immunity is most striking during acute infection. The greatest depletion of CD4+ lymphocytes in the lamina propria of the intestinal mucosa can be observed in the first 24 weeks of primary infection (16,17), with preferential targeting of the subpopulation of T lymphocytes expressing a TH17 phenotype (which play an important role in the maintenance of the gastrointestinal mucosal epithelial junctions, and their loss may lead to increased microbial translocation from the gastrointestinal lumen to systemic circulation) (18). This loss of lymphocytes is more rapid than that observed in peripheral blood (19).

In addition, despite the use of antiretrovirals, HIV will persist in GALT lymphocytes even after peripheral blood CD4+ lymphocyte counts have recovered (20). This phenomenon, known as viral reservoir, can often be a source of relapses or viral rebounds despite antiretroviral therapy, and, therefore, the development of new drugs targeting these cells is currently a strong focus of research.

ETIOLOGY

The etiology of diarrhea in HIV-infected patients is multicausal, with the causes of this symptom being divided into two broad categories: infectious (Table 1) and non-infectious causes (antiretroviral therapy-induced diarrhea, HIV-associated enteropathy, as well as non-infectious causes of diarrhea in non-HIV patients) (21).Tabla 1. Causas infecciosas de Diarrea en el paciente VIH diagnosticadas mediante colonoscopia o endoscopia.

Table 1. Infectious causes of diarrhea diagnosed by colonoscopy or endoscopy in HIV patients

Pathogen	Endoscopy / Colonoscopy
Bacteria	*Salmonella*
	E. coli (small intestine)
	Clostridioides difficile (Colonoscopy)
	Mycobacterium avium complex (small intestine; duodenum)
Protozoa	*Cryptosporidium* (small intestine and colon)
	Microsporidium (more frequent in proximal jejunum)
	Giardia (small intestine; duodenum and jejunum)
	Cyclospora (small intestine)
	E. histolytica (large intestine)
	Isospora (small intestine)
Viruses	Cytomegalovirus (commonly colon) (endoscopy and colonoscopy)
	Herpes simplex virus (endoscopy and colonoscopy)
Fungi	*Histoplasma* (most commonly in terminal ileum; may affect any part of the gastrointestinal tract)

Source: based on (41,48,65)

It is important to note that antiretroviral treatment has resulted in a decrease in the risk of infectious diarrhea (22), and, as a consequence, the non-infectious cause has been more frequent in some studies (9). We highlight antiretroviral treatment as a potential cause of non-infectious diarrhea, especially frequent with the use of protease inhibitors (23) (Table 2).

Table 2. Incidence of diarrhea with different antiretroviral drugs

Group	Antiretroviral drug	Incidence of diarrhea	
		Dikman *et al.* 2015 (21)	Clay, *et al.* 2014(66)
Single drug regimens	Tenofovir/Emtricitabine/Efavirenz	N.A.	9%
	Tenofovir/Emtricitabine/Rilpivirine	N.A.	>10%
	Tenofovir/Emtricitabine/Elvitegravir/Cobicistat	N.A.	12%
Nucleoside-analogue reverse-transcriptase inhibitors	Lamivudine	N.A.	18%
	Emtricitabine	N.A.	>10%
	Abacavir	7%	7%
	Tenofovir	9%–16%	11%
Non-nucleoside reverse transcriptase inhibitors	Efavirenz	3%–14%	3%
	Nevirapine	< 1–2%	< 1–2%
	Rilpivirine	<2%	<2%
Protease inhibitors	Darunavir	9%–14%	9%
	Atazanavir	2%–3%	1%–3%
	Lopinavir	7%–28%	15%–28%
Integrase inhibitors	Raltegravir	<1%	<1%
	Dolutegravir	1%	<1%
	Elvitegravir	12%	N.A.

N.A: Not Applicable. Source: based on (21,66)

For guidance on the possible etiology of diarrhea in people with HIV, knowledge of the CD4+ lymphocyte count is critical, as low lymphocyte counts imply an increased risk for some diseases (Figure 1).

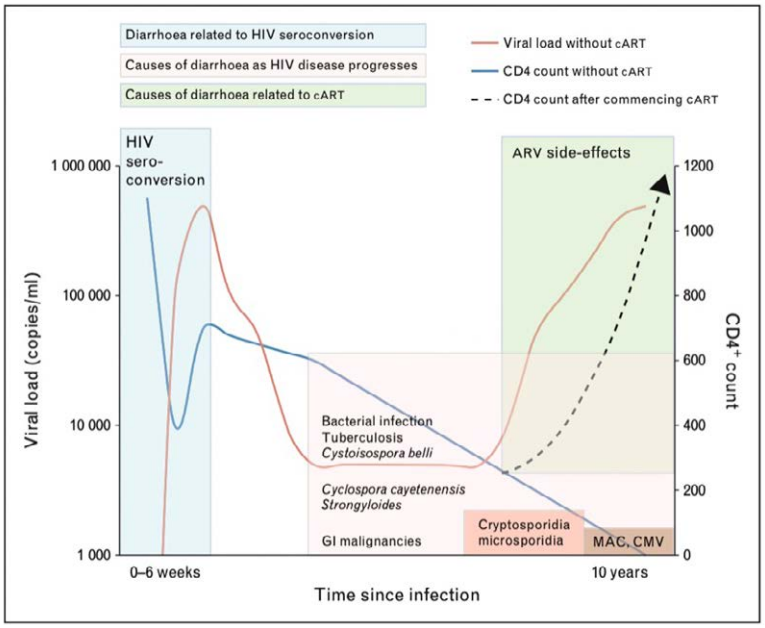

Figure 1. Causes of diarrhea at different stages of HIV disease. GI: Gastrointestinal
Source: taken from (22) with permission of the author

Bacterial infections

HIV-infected patients may present with acute diarrhea due to the same agents that cause enterocolitis in HIV-negative patients; however, they are at increased risk of developing invasive infections, especially with non-typhoidal strains of *Salmonella enterica* (24) and *Campylobacter jejuni* (25,26).

Invasive *Salmonella enterica i*nfection is considered an AIDS-defining illness. An observational study in New York City found that HIV-positive individuals had a higher frequency of multiple site infections, septicemia, urinary tract infection, and gastroenteritis due to bacterial pathogens (especially *S. enteritidis*) compared to HIV-negative individuals (27). In an observational study in HIV-positive African patients, *Salmonella enterica* bacteremia presented a high mortality rate (47%) and a recurrence rate close to 43%, mainly during the first 23–186 days. No recurrences were observed after 245 days of treatment. These relapses seemed to be more related to a recrudescence of the infection due to possible reservoirs in the host than to reinfections. Multiple relapses were observed in 26% of patients (24).

On the other hand, *Campylobacter jejuni* infections in HIV-positive patients are up to 39 times more common than in HIV-negative patients (25), with a mortality as high as 33% in some series (26).

Other bacterial agents causing diarrhea in HIV-positive individuals include *Escherichia coli, Shigella* and *Clostridioides difficile (*22)**,** with the latter being reported as the most frequent agent of bacterial diarrhea in HIV patients in the United States. *Clostridioides* species were found in 54.4% of the samples studied (out of these, 98.5% corresponded to *C. difficile*), followed by *Shigella* (14%) and *Campylobacter* (13.8%) (28).

In turn, *Mycobacterium avium complex* (MAC) infections cause diarrhea in profoundly immunosuppressed patients (CD4+ <50 cells/mm^3) (29). Infections by this species complex generally

involve the duodenum, generating mucous nodules and yellowish patches (30). A characteristic of intestinal alteration by *Mycobacterium tuberculosis* is the involvement of the ileocecal valve in 75%–84% of cases (31,32).

Viruses

The usual viral etiologies in a community are the most frequent in people with HIV and acute diarrhea. Common pathogens include adenovirus, coronavirus, herpes simplex virus, rotavirus and norovirus, among others, with the latter being very important due to its frequency as a cause of acute community-acquired gastroenteritis (21).

Cytomegalovirus (CMV) is the most frequently reported viral pathogen in HIV patients with gastrointestinal pathology (29). Although it can affect any segment of the gastrointestinal tract, it usually generates colitis characterized by bleeding, abdominal pain in the upper hemiabdomen, fever and weight loss (33); colonoscopy results show mucosa with erythema in patchy erosions and ulcers (34,35). However, this seems to be a selection bias in patients with advanced HIV who consult emergency departments of tertiary care hospitals.

Parasites

Multiple parasitic infections cause diarrhea in HIV patients, including some that cause diarrhea in HIV-negative patients (*Giardia lamblia, Entamoeba histolytica, Blastocystis hominis, Strongyloides stercoralis*) and some that are characteristic of HIV infection (*Cryptosporidium parvum, Cyclospora cayetanensis*) (22). The prevalence of parasitic infections in HIV varies greatly among studies, with values ranging from 17% in France (36) to 33% in Denmark (37) and 82% in Cameroon (38).

The most common cause of chronic, debilitating diarrhea in people with HIV is *C. parvum,* manifesting with profuse watery diarrhea, weight loss, paraumbilical pain, nausea, and vomiting (39), which can lead to malabsortion syndrome, severe dehydration, and fluid and electrolyte imbalances (33,40). Other protozoa that also affect HIV patients are *Cystoisospora,* which characteristically causes the presence of eosinophilia in the hemogram, and *Cyclospora;* these microorganisms affect the small intestine and can generate malabsorptive diarrhea (41).

Fungi

Microsporidia such as *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are causes of diarrhea in profoundly immunosuppressed patients, and special trichrome stains and microscopy are required for their diagnosis (42,43). *Cryptococcus* has also been described as a cause of diarrhea with the ability to involve any segment of the intestine (44).

Diarrhea may also be caused by disseminated histoplasmosis. In some observational studies, up to 63% of invasive histoplasmosis present with diarrhea (45) and usually affect the ileocecal region (23).

DIAGNOSIS

For an adequate diagnostic approach to the patient, a complete anamnesis should be performed, taking into account current immunosuppression status, adherence to ART, treatment received,

travel to endemic areas, anal intercourse or recent exposure to antibiotics. The CD4 count (Figure 1), chronicity and severity of diarrhea (Table 3) should be documented. Regarding chronicity, diarrhea is defined as acute if the symptomatic course lasts more than 3 days but less than 21 days, or as chronic if it lasts more than 21 days (5,6)..

Table 3. Classification of diarrhea

Grade 1 - Mild	Transient or intermittent with less than 3 stools/day
Grade 2 - Moderate	Persistent liquid diarrhea or an increase of more than 4–6 stools
Grade 3 - Severe	Bloody diarrhea or more than 7 stools/day requiring management with intravenous fluids
Grade 4 - Incompatible with life	Incompatible with life due to shock or organ dysfunction

Source: own work based on (5)

The classification of severity can be used to define the most appropriate place to treat the patient, the need for additional studies and the need for empirical treatment (23). Most authors recommend stool analysis as the first diagnostic study for patients with diarrhea, since it is simple to perform, inexpensive and non-invasive (46,47). In 50% of the cases in which a microbiological study of stool is performed, it is possible to identify the microorganism responsible for the diarrhea (23).

At least three stool samples should be collected in order to improve the performance of germ detection (23,46-48). A prospective study by Blanshard *et al.* showed that the diagnostic yield of stool cultures increases with the number of samples collected: 18% for a single stool culture and 38.7% for three stool cultures (49).

As in immunocompetent patients, it is suggested that a stool culture be performed in search of *Salmonella, Shigella, Campylobacter and Yersinia* (50). Coproculture of bacterial pathogens is performed on selective agar plates and enrichment broth media, which may vary among laboratories of different institutions. Some microorganisms can be more demanding and difficult to isolate by means of cultures, such as *Campylobacter spp.* and *Shigella spp;* this has led to the use of molecular tests to search for different microorganisms (51).

Opportunistic microorganisms require a concentrated stool sample and the performance of special stains (47). Egg and parasite studies should be requested for evidence of amoebae, *Cyclospora* and schistosomes (50). Additionally, modified Ziehl Neelsen (ZN) staining is used for the detection of *Cryptosporidium spp.,* while microscopy and trichrome staining are used for microsporidia (47). For *Giardia* detection, microscopy diagnosis is performed with a stool concentration method and can be complemented with molecular tests (52). For the detection of *C. difficile,* stool samples are initially tested for the presence of glutamate dehydrogenase (GDH) and toxins A/B, with a sensitivity of 70%–78% (23).

Multiplex polymerase chain reaction (PCR) tests based on nucleic acid amplification technology are now available. These molecular tests can perform a simultaneous analysis of multiple pathogens and can be used when stool culture fails to identify any enteropathogen (53).

The most commonly used molecular test in our context is the FilmArray Gastrointestinal panel (BioFire Diagnostics, Salt Lake City, UT), which is a multiplex real-time PCR for the syndromic

diagnosis of infectious gastroenteritis; it can detect 22 pathogens (13 bacteria, 5 viruses and 4 parasites), and it has a sensitivity of >90% and a specificity of >97% for most of the pathogens (54,55).

A retrospective study by Stockman *et al.* with 378 fecal samples analyzed with gastrointestinal FilmArray PCR detected pathogens in 63% of the samples, and standard laboratory tests were positive in 38% of the samples (56). Once all the initial microbiological studies of the stool have been performed, if diarrhea persists and no pathogen isolation has been achieved to explain the persistence, radiological and endoscopic studies should be considered (57).

The guidelines of the American Society for Gastrointestinal Endoscopy (ASGE) on the endoscopic study of diarrhea recommend starting the study with sigmoidoscopy, and, if it is not positive and the suspicion of opportunistic infection continues, upper gastrointestinal endoscopy and colonoscopy should be performed. The upper endoscopy with biopsy of the duodenum should be as distal as possible (third and fourth duodenal portion) to increase the yield of detection of *Microsporidium,* and the colonoscopy should include biopsies of ileum and colon. The diagnostic yield of colonoscopy ranges from 27% to 39%. For isolated cytomegalovirus infection localized in the right colon, it is as high as 29%–39%, which is why total colonoscopy is preferred over sigmoidoscopy (23,58). It should be emphasized that biopsies taken for microbiological studies should be transported in a dry tube or in saline solution (23).

There is no typical endoscopic pattern of opportunistic infection; however, involvement of the right colon with lesions ranging from erythema to ulcers suggests *Salmonella.* Involvement of the cecum and rectosigmoid colon with ulcers and areas of necrosis suggests amoeba infection, while involvement of the left colon with ulcerations suggests CMV infection (46).

A 2005 paper compared endoscopic biopsies with microbiological studies performed on fecal material and found that endoscopic biopsies have a higher yield in people with CD4 counts of <200 cells/mm^3 (46). Another study by Wilcox reported opportunistic pathogens found by endoscopic studies in 21 out of 48 patients (44%; confidence interval [CI] 95%: 30%–58%). Biopsy by colonoscopy found the diagnosis in 13 patients, including CMV in 9 of them; most of the time, the diagnosis is made by rectosigmoid biopsy. Biopsy by upper endoscopy diagnosed *Microsporidium* infection in 7 patients; and *Cryptosporidium,* in 2 of them (47).

A prospective study of 79 patients who had undergone upper endoscopy and colonoscopy found infection in 22 of the participants, with a sensitivity of 77% for left colon biopsies (17/22 patients) and 100% for CMV infection. The combination of left and right colon biopsies had a sensitivity of 82% (59,60).

Another paper evaluated the use of capsule endoscopy, reporting small bowel abnormalities in 89% of the patients with diarrhea and CD4 counts of <200 cells/mm^3. It was also observed that the region distal to the ligament of Treitz was more commonly involved, with more severe findings such as Kaposi sarcoma, ulcerative jejunitis due to *CMV* infection, jejunum involvement by mycobacteria and *Strongyloides stercoralis* infection (61).

Radiological studies have described that in up to 90% of the cases tuberculosis tends to affect the ileocecal region, with thickening of the ileum and cecum (62). MAC infection presents with jejunum involvement and thickening of folds, and up to 25% of infected patients may have CT scans within normal ranges. Ulcers in the colon, thrombosis due to vasculitis with ischemia and visceral perforation are characteristic findings of CMV infection (22). In Kaposi sarcoma, long, flat or submucosal lesions associated with thickening of folds are found (63). Non-Hodgkin's lymphoma can produce thickening of the terminal ileum, with predisposition to the formation of masses and ulcers, and with extension of the tumor to the mesentery and adjacent ganglia (23,64).

Diagnostic approach

The approach to the HIV-positive patient who presents with diarrhea is a great challenge for the clinician, since within the differential diagnosis we find both infectious causes, such as those we have discussed so far, as well as non-infectious causes (Table 4).

Table 4. Causes of chronic diarrhea

Malabsorption syndromes	Gastric bypass surgery
	Rapid emptying syndrome
	Chronic pancreatitis
	Bacterial overgrowth
	Lactase deficiency
	Celiac disease
	Tropical sprue
	Crohn's disease
	Radiation enteritis
Watery diarrhea	Osmotic diarrhea
	Alcohol
	Factitious
	Functional watery diarrhea
Secretory diarrhea	Hormone-secreting tumors
	Systemic mastocytosis
	Hairy adenoma
Inflammatory diarrhea	Ulcerative colitis
	Eosinophilic gastroenteritis
	Food allergy
	Microscopic colitis

Source: adapted from (67)

For an adequate diagnostic approach, the first consideration to take into account is the temporality of the syndromic evolution, since the approach varies depending on whether it is acute (Figure 2) or chronic diarrhea (Figure 3).

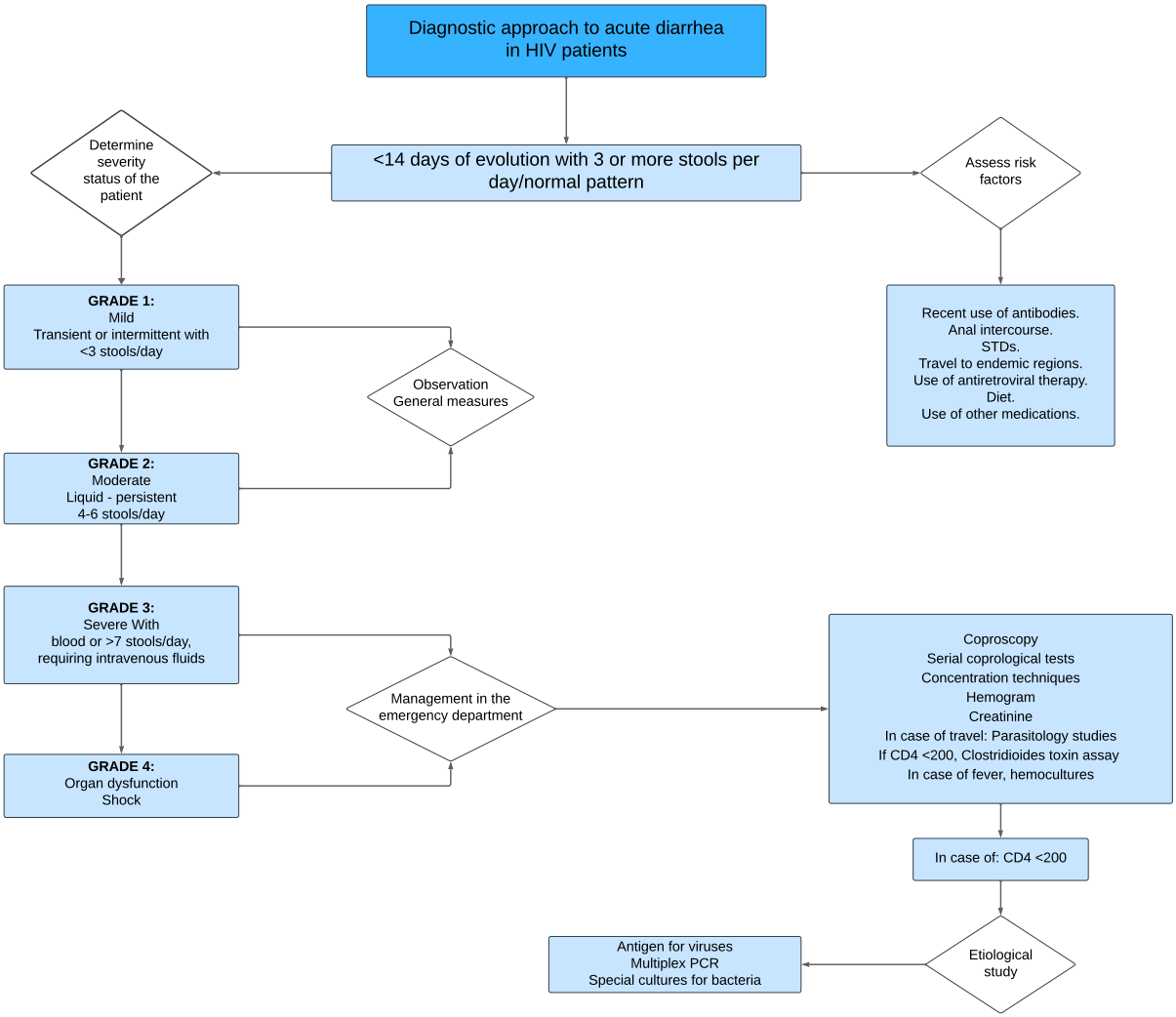

Figure 2. Diagnostic approach to acute diarrhea in HIV patients

Source: Own work

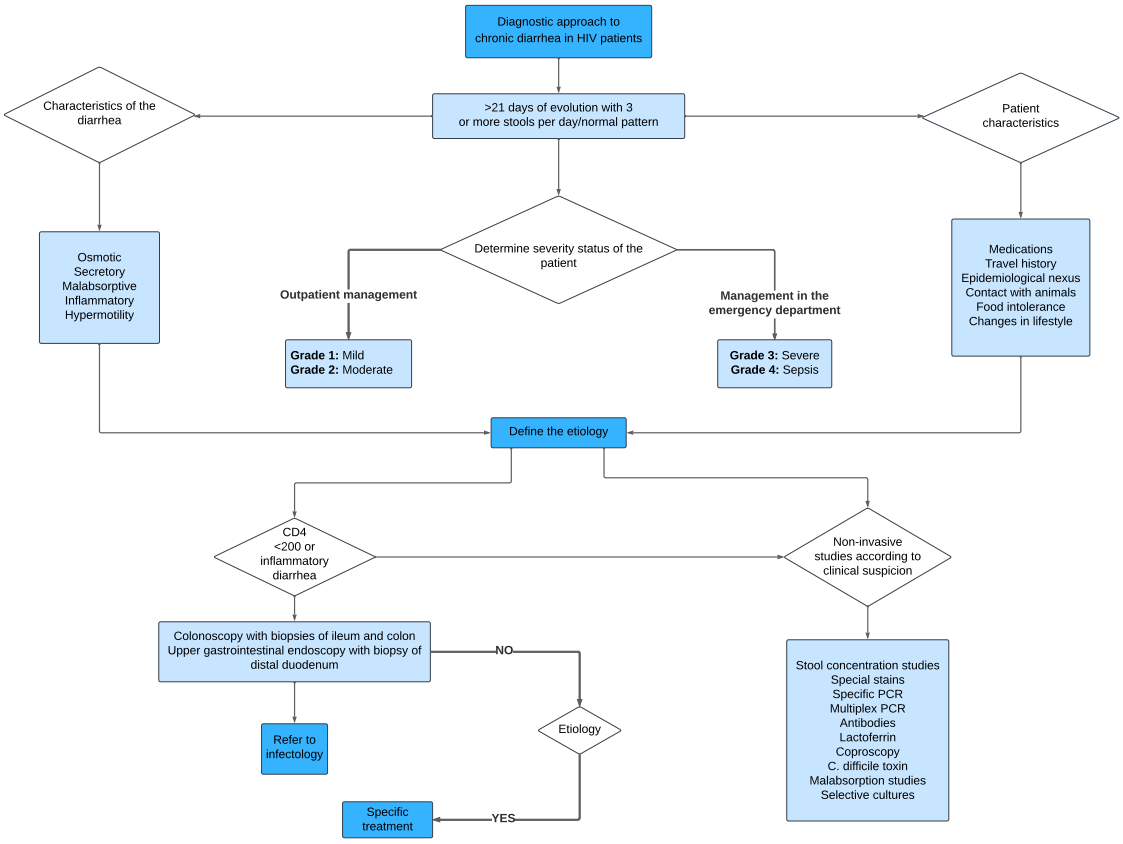

Figure 3. Diagnostic approach to chronic diarrhea in HIV patients

Source: Own work

Once the chronological evolution of the syndrome has been determined, the severity of the clinical presentation must be established, taking into account that grade 1 or 2 diarrhea can be managed at home. If hospital admission is required, the search for the etiologic agent will depend on the scenario, since advanced techniques for etiologic search are not required in the acute scenario, except in patients with less than 200 CD4+ T lymphocytes.

In the chronic diarrhea scenario, serial stool culture studies should be requested initially, in addition to other studies to rule out non-infectious causes based on clinical suspicion. In individuals presenting with chronic inflammatory diarrhea, with less than 200 CD4+ T lymphocytes, the approach includes endoscopic studies with biopsies of the colon and ileum, in addition to upper gastrointestinal endoscopy seeking biopsies of the duodenum.

If the etiology remains uncertain despite the endoscopic study and the taking of biopsies of the gastrointestinal tract, a drug cause or HIV-associated enteropathy could be considered among the diagnostic options. In any case, if after the initial studies a cause for the diarrhea cannot be identified, an evaluation by a specialist in infectious diseases is a priority.

CONCLUSION

Diarrheal syndrome in HIV patients implies a diagnostic challenge for the clinician considering that there are both infectious and non-infectious causes; among infectious diseases there are both common causes and opportunistic microorganisms. Diagnosis is based on a systematic approach, starting with a thorough medical history to determine acute or chronic diarrhea and then and evaluation of the need for invasive studies for the etiological search.

CONFLICT OF INTEREST

None to declare.

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