Austin Journal of HIV/AIDS Research

Open Access

Austin Publishing Group

Review Article

Diarrheal Syndrome in HIV-Infection/AIDS: A Review

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Received: September 26, 2023
Accepted: November 06, 2023
Published: November 13, 2023

Abstract

HIV infection continues to be a huge socio-economic problem. The infection is characterized by a variety of symptoms, with the involvement of the gastrointestinal tract in all infected. Diarrhea is the most common gastrointestinal symptom among HIV-infected patients and is seen in over 90% of them. The etiology of diarrhea syndrome is varied and is both infectious and non-infectious. In recent years, the number of patients with non-infectious diarrhea has increased due to the introduction of specific antiretroviral therapy, prolonging the survival of HIV-infected patients, and the occurrence of a variety of accompanying chronic and malignant diseases affecting intestinal structures. The incidence, severity and variation in the clinical picture of diarrhea is determined by specific immune changes in the gastrointestinal tract as well as changes occurring in the intestinal microbiome in HIV-infected / AIDS patients.

Keywords: Diarrheal syndrome; HIV; AIDS; HAART; Microbiome

Introduction

According to WHO data, at the end of 2022, nearly 40.0 million people were living with HIV, and in just one year (2022), the number of newly infected people was 1.3 million. In 2022, 630 000 people died from AIDS-related infections. The most affected by the infection still remains the African region with an estimated 25.6 million infected at the end of 2022. Populations at risk for the infection are men who have sex with men (MSM), intravenous drug users, promiscuous people including prostitutes and their clients, people forcibly deprived of liberty. It has been found that still only approximately 70% of those infected with HIV are aware of their diagnosis. To reach the 90% target, approximately 7.5 million people need to be screened for the insidious infection [1. According to UNAIDS data, the number of infected people at the end of 2022 in Bulgaria was 3,600 people, and for that year the number of newly registered cases was nearly 200. Of them, 88% were infected sexually, and 50% of them were in result of homosexual contacts. In recent years, the tendency for the number of newly registered men to be more than five times greater than the number of women has been maintained. According to the route of infection, 39% of new cases were infected by heterosexual contact, 49% by homosexual contact, and 12% by injecting drug use. HIV-1 and HIV-2 are retroviruses belonging to the lentivirus family that invade CD4+ cells. The gradual decrease in the number of these cells leads to a severe immune deficiency with the development of numerous bacterial, viral or fungal infections. Immune deficiency is also the cause of the development of other severe non-infectious diseases, known as AIDS-indicators [2]. The infection is characterized by a diverse clinical picture, and its course can generally be divided into 3 periods: primary HIV infection, latent period, AIDS.

For the convenience of professionals working with HIV-infected patients, the CDC created classifications, one of which is clinical and the other based on CD4+ T cell counts. The clinical classification divides the disease into three categories - category A, B and C. In the last category C, AIDS-defining conditions are observed. According to the number of CD4+ T cells, the disease is again divided into three categories - 1, 2 and 3. In the 1st category we observe CD4+ T-cells >500/µl, in category 2 - CD4+ T-cells from 200 to 499/µl, and in the last category 3 - CD4+ T-cells <200/µl.

Diarrhea is the most common gastrointestinal symptom among HIV-infected patients and occurs in over 90% of them. It can be observed in each of the indicated periods of HIV infection, and, of course, the etiology in the individual stages is different. The frequency and severity of diarrheal episodes increases progressively with the development of immunosuppression [3,4]. According to literature data, 30-60% of seropositive patients with diarrhea remain without a diagnosed cause of the diarrheal syndrome [5]. Unlike immunocompetent patients, in these with HIV-infection we often observe acute, persistent and chronic diarrhea. In acute diarrheal diseases, pathogens affecting the small intestine lead to profuse watery diarrhea, severe abdominal pain immediately after feeding, and rapid dehydration with rapid development of the consumptive syndrome [6,7]. Pathogens affecting the large intestine lead to frequent loose stools, most often mixed with mucus and/or blood, do not lead to rapid dehydration, there is pain in the lower parts of the abdominal area and sometimes – tenesmus[8,9].

Citation: Andonova RS, Popov GT. Diarrheal Syndrome in HIV-Infection/AIDS: A Review. Austin J HIV/AIDS Res. 2023; 9(1): 1055.

Etiology of Diarrheal Syndrome in Patients with HIV Infection/AIDS

The most common HIV-associated pathogens causing acute diarrhea, regardless of CD4+ cell count, are: viruses (Adeno-, Astro-, Picorna-, Calici-), Clostridium difficile, Salmonella spp., Shigella spp., Campylobacter jejuni, Escherichia coli O157:H7, Aeromonas species, Vibrio species, Yersinia species, and Edwardsiella tarda [10,11]. The most common causes of chronic diarrhea, regardless of the number of CD4+ cells, are: Clostridium difficile, Giardia lamblia, Entamoeba histolytica [10,11]. Other common causes of diarrhea, independent of the number of CD4+ cells, are mycotic infections - Candida albicans, Candida crusei, Candida glabrata, Hystoplasma capsulatum. In patients with a CD4+ cell count <100/mm3, the most common causes of chronic diarrhea are: Microsporidia, Cryptosporidium spp., Mycobacterium avium complex, Isospora beli, Cyclospora cayetanensis, Cytomegalovirus (CMV) (especially in patients with number of CD4+ cells <50/mm3) [12,13]. The presence of chronic diarrhea in HIV-infected patients can also be due to a number of non-infectious causes - irritable bowel syndrome, inflammatory bowel diseases (Crohn's disease, ulcerative colitis), lymphomas (B-cell lymphomas such as opportunistic neoplasias of the GIT), lactase deficiency, bacterial overgrowth syndrome, pancreatic insufficiency, fecal incontinence, as well as due to the use of some of the medications included in HAART. And finally, but not least - the so-called HIV-enteropathy, when we have not isolated an infectious cause of the diarrheal syndrome, as well as we have excluded any other non-infectious causes of it. The cumulative risk of developing chronic diarrhea after the onset of AIDS increases from 48.5% in the first year to 95.6% in the third year [14,15].

As noted, bacterial pathogens are common causes of acute diarrhea, regardless of the CD4+ cell count. One of the largest studies in this field, done in the USA, supported by the CDC, examined 50,000 HIV-infected patients with diarrheal pathology during 10 years (2006-2016) [16]. According to the study, C. difficile is the most common pathogen among patients with bacterial diarrhea – 53.6%. Shigella, Campylobacter and Salmonella have the following frequency respectively: 14.0%; 13.8% and 7.4% [17-19]. The higher percentage of Shigella spp. infection among HIV-infected compared to the general population is mainly explained by the possibility of the infection being transmitted through sexual contact. S. flexneri is most common, followed by S. sonnei, with the most affected contingent being MSM [20,21]. The greater incidence of Campylobacter spp. and Salmonella spp. is due to changes in mucosal immunity based on HIV-related immunosuppression [22,23].

In recent years, a number of studies have demonstrated the increasing importance of gastrointestinal protozoan infections such as microsporidia species, Cryptosporidium species, Isospora belli and Cyclospora cayetanensis [24,25]. Among HIV-infected patients, a number of risk factors such as homosexuality and practice of oro-anal sex increase the possibility of infection with a number of intestinal parasites such as giardiasis, cryptosporidiosis and strongyloidosis, and the clinical picture is significantly more severe compared to patients with preserved immune status [26,27]. Intestinal parasitic infections are the most common cause of morbidity and mortality among HIV-infected patients worldwide. Unlike bacterial intestinal infections, intestinal parasites can persist in the body for a long time without causing clinical symptoms [28,29]. According to the above-mentioned study in the USA, among the examined patients with a proven parasitic etiology and diarrhea were 48.15% (among which Isospora spp. 25.92%; Cryptosporidium spp. 14.81%; Cyclospora spp. 3.7%; Strongyloides stercoralis 3.7%; Entamoeba hystolitica 3.7%) and with proven parasitic etiology, but without diarrhea complaints were 33.33% (Isospora spp. 11.11% ; Cryptosporidium spp. 11.11%; Cyclospora spp. 11.2%) [30,31].

As noted, a number of noninfectious causes can lead to chronic diarrhea. Before the advent of HAART, malignant neoplasms were seen in about 12% of AIDS patients, with almost 1/3 of them involving the GIT [32]. Kaposi's sarcoma and non-Hodgkin's lymphomas were the most common AIDS-related malignancies, both of which often affect the GIT as well. Since the introduction of HAART (Highly Active Antiretroviral Therapy), the incidence of disease-related malignancies has decreased dramatically, in parallel with opportunistic infections in the developed world [33,34]. Nevertheless, malignancies remain the leading cause of death among HIV-infected patients in the developed world. with GIT involvement observed in more than half of them. Malignant diseases include: mesenchymal neoplasias, lymphoid and epithelial neoplasias. Mesenchymal neoplasias include Kaposi's Sarcoma (etiologically related to Human Herpesvirus 8), which despite HAART remains the most common HIV-related gastrointestinal and visceral neoplasia [35,36]. Often the symptoms of GIT involvement can be nausea and abdominal pain, less often, but significantly more manifest - diarrhea with the presence of blood impurities. Mesenchymal tumors also include EBV-associated smooth muscle tumors affecting the GIT. They are rarely seen, mostly affecting young children and adolescents [37,38]. Lymphoid tumors have a diverse etiology and clinical picture. Before HAART, Burkitt's lymphoma and B-cell Non-Hodgkin's lymphomas (NHL) affecting the CNS were~ 1000 times more common among HIV-infected compared to the general population [39]. Since the introduction of HAART, the incidence of NHL has significantly decreased, especially those affecting the CNS. Despite this, however, NHLs are still observed~ 200 times more frequently among HIV-infected, and in recent years an increased incidence of Hodgkin's lymphomas has also been observed among seropositive [40]. The GIT remains the second most frequent system affected by NHL. Approximately 25% of patients with AIDS and systemic lymphoma have GIT involvement, which is usually associated with a poor prognosis [41]. In contrast to mesenchymal tumors, GIT involvement by NHL is significantly more likely to result in bloody diarrhea as well as bleeding. . It has long been known that HIV is a risk factor for the occurrence and development of anal intraepithelial neoplasia, as well as for the occurrence of rectal squamous cell carcinoma [42,43].

Another common cause of diarrhea among HIV-infected patients can be the so-called IRIS (Immune Reconstitution Inflammatory Syndrome), which occurs in about 15% of patients weeks or months after starting HAART and is due to immune hyperactivation leading to dysregulation in the inflammatory response [42]. Mortality is 4.5%, with most affected patients with CD4+ <50/mm^3 [43]. Drug-induced diarrhea among HIV patients presents a unique challenge to the clinician treating a HIV-positive patient. Since the introduction of HAART, drugs have been the most common cause of diarrhea among HIV patients in the developed world [43]. Combination antiretroviral therapy remains the only proven life-sustaining treatment for HIV-infected people. The development of antiretroviral therapy marks one of the most dramatic advances in the history of

medicine. Modern therapeutic regimens differ substantially from those used at the beginning of the HIV era. With modern antiretroviral therapy, the life expectancy of HIV-positive people does not differ significantly from that of the uninfected. However, therapy must be continuous. As knowledge of the risks of antiretroviral therapy increases, many treatment recommendations are being revised. Many of the widely used medications are gradually being withdrawn from therapy (HIVID, Agenerase, Fortovase, Viracept). Antiretroviral drugs d4T, ddI, Nelfinavir, Indinavir were widely used in the 1990s, but are no longer present in the guidelines for the treatment of HIV-infected patients. There are currently 28 approved antiretroviral drugs, grouped according to their mechanism of action into six groups. Therapy includes a number of nucleoside (NRTIs) and Non-Nucleoside (NNRTIs) Reverse-Transcriptase Inhibitors, protease (PIs) and integrase inhibitors, fusion/entry inhibitors. More than 28% of patients receiving modern HAART reported more than 4 watery diarrheal stools/24h [43]. PIs are associated with the greatest risk of developing diarrhea (13.6%) compared to NRTIs, which are associated with the occurrence of diarrhea in 10.0% of cases (with the exception of didanosine and stavudine, which are now rarely used in practice due to their GIT toxicity). The remaining preparations – NNRTIs (which lead to diarrhea in 2.2% of cases), as well as integrase inhibitors and CCR5-antagonists (each class leads to diarrheal episodes in <1% of cases) are less closely associated with diarrheal pathology [44,45].

The goals of antiretroviral therapy include reduction of HIV-related morbidity and mortality, improved quality of life, restoration and preservation of immune function, and control of HIV replication. An optimal virological response to therapy is achieved when HIV-RNA is suppressed to a value lower than that which can be determined with available diagnostics. Today, this limit is an HIV-RNA level <20-50 copies/mL. An optimal immunological response from ongoing antiretroviral therapy is achieved when maintaining a CD4 T cell count >500/mm3. As we noted earlier, last but not least, HIV-related enteropathy is also a cause of diarrheal syndrome. This condition remains an enigma to this day and is referred to as the presence of chronic diarrhea in the absence of an infectious agent or other non-infectious etiology. Despite intensive microbiological and histological investigations of GIT, nearly 20% of HIV-infected patients with chronic diarrhea remain without an etiological diagnosis [44,45]. In these patients, a diverse histopathological picture is often observed on gastrointestinal biopsy, including villous atrophy and hyperplasia of the crypts, as well as prominent epithelial apoptosis and non-specific inflammation affecting both the small and large intestine. Initially, it was considered that HIV-enteropathy was a consequence of undiagnosed opportunistic infections, the use of HAART, a little later it was also explained by the direct virotoxicity of HIV. According to current research, it is considered that a major role in the pathogenetic mechanisms of HIV-enteropathy is played by the change in the intestinal microbiota, resulting in local and systemic immune activation.

HIV-Infection and Its Induced Changes in the Intestinal Microbiota

HIV-associated changes in the gut microbiome can lead to a systemic inflammatory response, disrupting the balance of some metabolic processes mediated by the gut microbiome, such as the metabolism of bile and short-chain fatty acids, or by increasing circulating bacterial products. Elevated plasma kynurenine (a tryptophan metabolite) is associated with CD8+-cell activation and mortality in HIV-infected individuals. On the other hand, under the influence of immunological changes occurring in the GIT during HIV-infection, the intestinal microbiome leads to a rapid transformation of phosphatidylcholine and bile acids into reactive metabolites such as trimethylamine-N-oxide, which in turn leads to macrophage and platelet activation , thrombosis and formation of arterial plaques [46]. Changes in the gut microbiome that differ from the normal structure of healthy individuals are referred to as dysbiosis. It is the dysbiotic state that is the cause of a number of pathological changes in the GIT in a number of diseases. A number of studies comparing the gut microbiome among HIV-infected and uninfected patients have shown significant changes in the microbiota. In HIV-infected individuals, there is little diversity among the microbiome, with the spectrum of microorganisms close to that of patients with chronic inflammatory bowel diseases (ulcerative colitis, Crohn's disease), diabetes mellitus type I, obesity grades III and IV, recurrent C. difficile colitis. In HIV-infection, we also observe an increase in tissue and circulating in the systemic circulation indicators of inflammation (CD14, IL-6, CD38+, HLA-DR+, CD8+-cells), mostly associated with representatives of the family Enterobacteriaceae and a decrease in commensal intestinal microorganisms such as Lactobacillaceae, Lachnospiraceae and Ruminococcaceae [47].

Among some major groups of pathogens, the difference between HIV-infected and uninfected patients is highlighted, namely: Proteobacteria, Fusobacteria, Bacteroidetes and Firmicutes. Proteobacteria (including Salmonella, Shigella, Helicobacter, Pseudomonas, etc., belonging to the family Enterobacteriaceae) are observed significantly more often among HIV-infected people. Pseudomonas is an opportunistic pathogen that causes disruption in the mucosal production of HIV-infected individuals [48]. Desulfovirbrio produces hydrogen sulfide, leading to inflammation of the intestinal epithelium. Acinetobacter and the lipopolysaccharides released during the breakdown lead to the induction of IL-8 production, which in turn causes neutrophilic inflammation and tissue damage. Campylobacter secretes a number of toxins that induce mucosal inflammation [48,49]. The Fusobacteria phylum, which is mainly blamed for the development of inflammatory bowel diseases and colorectal carcinoma, is also observed with greater frequency in HIV-infected patients. The phylum Bacteroidetes, comprising several families (Prevotellaceae, Porphyromonadaceae, Bacteroidaceae and Rikenellaceae) is characterized by considerable heterogeneity in terms of changes among HIV-infected individuals. Prevotellaceae, the higher frequency of which was previously associated with the development of autoimmune diseases and activation of intestinal dendritic cells, was also demonstrated with a higher frequency among HIV-infected individuals [50]. In contrast, representatives of the family Porphyromonadaceae are significantly reduced among patients with HIV infection. Reduced members of this family, especially Barnesiella and Odoribacter, are associated with recurrent C. difficile infection, colonization with Vancomycin-resistant enterococci, and frequent Citrobacter rodentium infections. Bacteroidaceae is characterized by a significant reduction among HIV-infected patients. The presence of representatives of this family in the intestinal microbiome provides a powerful anti-inflammatory function, as Bacteroides fragilis, for example, promotes the differentiation of regulatory T-cells and of IL-10. Rikenellaceae is also in reduced representation among the gut microbiome of HIV-infected patients. Decreased levels are associated with

a predisposition to recurrent C. difficile infection, obesity, and the development of type II diabetes mellitus. The Firmicute type is also reduced in HIV-infected patients. A number of the representatives there are associated with anti-inflammatory functions, such as the formation of butyrate and other short-chain fatty acids, again stimulating the differentiation of regulatory T-cells [51].

A reduction in commensal gut micro-organisms also plays a negative role in HIV-infected patients. Ruminococcaceae is characterized by its protective function on the intestinal mucosa and the production of a number of anti-inflammatory products. Respectively, reduced levels of microorganisms from this family are associated with the development of chronic inflammatory bowel diseases [51].

Table 1: Characterization of dysbiosis in HIV-infection compared with that in uninfected individuals.

	Mucouse tissue	Fecal specimen
Type Proteobacteria	↑	↑
Family		
Enterobacteriaceae	↑	↑
Brucellaceae	↑	
Xanthomonadaceae	↑	
Rhodspirillaceae	↓	
Genus		
Escherichia	↑	
Serratia	↑	
Shigella	↑	
Klebsiella	↑	
Ralstonia	↑	
Actinobacter	↑	
Burkholderia	↑	
Desulfovibrio		↑
Thalossospira	↓	
Type Bacteroidetes		
Family		
Rikenellaceae	↓	↓
Bacteroidaceae	↓	↓
Prevotellaceae	↑	↑
Genus		
Bacteroides	↓	↓
Alistipes	↓	↓
Barnesiella	↓	↓
Prevotella	↑	↑
Type Firmicutes	↓	
Family		
Lachnospiraceae	↓	
Ruminococcaceae	↓	↓
Christensenellacea	↓	
Erysipelotrichaceae	↑	↑
Veillonellaceae		↑
Genus		
Coprococcus	↓	
Faecalibacterium	↓	↓
Blautia	↓	
Rumminococcus	↓	
Dorea	↓	
Oscillospira	↓	
Lachnospira	↓	↓
Roseburia	↓	↓
Dialister	↓	↑
Eubacterium	↓	
Lactobacillus	↓	↑
Mitsuokella		↑
Catenibacterium	↑	↑
Mogibacterium	↑	
Bulleidia		↑

Among HIV-infected individuals, there is a significant change not only in the bacterial but also in the viral enteric set, which determines the normal functioning of the GIT [52]. The diverse human enteric virome includes a wide range of eukaryotic viruses, bacteriophages and endogenous retroviruses, which are largely unexplored, with less than 1% of the human virome believed to be defined. To date, only a few studies have documented changes in the virome during lentiviral infection [52]. Enteric eukaryotic viruses themselves can cause gastroenteritis, enteritis, and colitis. Bacteriophages, which are the most diverse enteric viruses, can initiate changes in the microbiome, affecting the normal functioning of the GIT as well as the overall functioning of the immune system. The few studies conducted have demonstrated elevated levels of Picornaviridae, Adenoviridae, and Parvoviridae among HIV-infected patients. Elevated levels of Adenoviridae are associated with severe GIT dysfunction, particularly among patients with CD4+ cell counts below 200/mm^3. Anelloviridae (small, non-enveloped DNA viruses) are also observed with increased frequency among patients with CD4+ cell counts below 200/mm3, and their role in GIT pathology has not yet been proven (Table 1) [52].

Discussion

Diarrheal pathology is common among HIV-infected patients, often significant in severity. Persistent and chronic diarrhea should always serve as an indicator light for the patient to be tested for HIV. If the patient has already been diagnosed with HIV-infection/AIDS, the following diagnostic algorithm for clarifying diarrheal syndrome among HIV-infected patients should be performed at each visit for diarrheal complaints. First of all, in patients with acute diarrhea, a coprocytogram and a microbiological examination of feces must be performed. When a cause is established, adequate etiological treatment is started. If the causative agent is not identified, but the diarrhea persists, it is appropriate to start empiric treatment with a fluoroquinolone. If the patient has a history of taking an antibiotic in the last month, the feces must be examined for C. Difficile [46]. Patients who have chronic diarrhea should also be questioned about medication intake in the previous days. If there is no such anamnesis, the feces are examined microbiologically and blood cultures are taken when the temperature is available. When a causative agent is established, etiological treatment is mandatory. If the results are negative, colonoscopy with terminal ileal biopsy is recommended. In patients with a CD4+-cell count of 100-200/mm^3, sigmoidoscopy with biopsy is sufficient, since the development of CMV-infection is unlikely with a higher CD4+- cell count. To establish protozoan infections, it is necessary to examine the feces with specific staining methods - Ziehl-Neelsen, Giemsa, Heidenhain, Masson. If the result is still negative, colonoscopy with intestinal biopsy, electron microscopy, as well as molecular techniques to demonstrate fecal antigen are recommended [46]. In the absence of an infectious pathogen, HAART should always be taken into account, as well as a number of other medications that these patients take for accompanying diseases. Some behavioral characteristics of seropositive patients are also associated with diarrheal pathology - alcohol abuse, use of psychoactive substances. In the absence of another cause, a colonoscopy should be performed to determine the cause of the diarrheal symptoms. This can be a malignant disease affecting the GIT or the result of another chronic intestinal disease (e.g. Crohn's disease, ulcerative colitis, etc.). In the absence of a diagnosis, and of course on the basis of histological examination, it is assumed to be HIV-related enteropathy.

Establishing the cause of the diarrheal syndrome in time is important in order to take early and adequate measures for its elimination. Otherwise, patients develop severe malabsorption and HIV-related cachexia, which can often lead to death.

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