

REVIEW ARTICLE

Chronic Non-Infectious Diarrhea in HIV-infected Persons

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Abstract

Chronic non-infectious diarrhea is estimated to occur in approximately 5% of all HIV-infected persons in the United States. The two main etiologies are HIV enteropathy and antiretroviral-associated diarrhea. The initial evaluation should focus on determining if the diarrhea is truly chronic, and excluding infectious etiologies. Treatment options for chronic non-infectious diarrhea are limited, but there is one FDA-approved drug (crofelemer) specifically approved for use in this setting. In addition, powdered serum bovine immunoglobulin (a “medical food” per the FDA) shows promise, but studies in humans have been small. This brief article will review the etiology, diagnosis, evaluation, and management of this condition.

Key Words: chronic, non-infectious, diarrhea, HIV-infected

Non-infectious chronic diarrhea, defined as 3 or more abnormally formed stools per day for more than 4 weeks¹, not due to infectious etiologies, is estimated to occur in 3% - 7% of all HIV infected persons². Some gastroenterologists and infectious diseases physicians with extensive HIV treatment experience estimate that percentage to be as high as 10% - 20%. The discrepancy can

be explained, in part, by the different definitions of diarrhea, the different phraseology of questions included in patient surveys, and the typical absence of questions related to nocturnal bowel movements, rectal fullness, lower abdominal cramping and/or urgency, etc. In addition, most surveys fail to differentiate between acute, intermittent, self-limited, and chronic diarrhea.

Two recent reviews have discussed the etiology and management of non-infectious diarrhea^{1,3}. Briefly, etiologies include HIV-related factors (e.g., HIV enteropathy), antiretroviral-related factors (e.g., protease inhibitors), and miscellaneous factors (e.g., irritable bowel syndrome). Treatment options still are limited to a handful of products. The main purpose of this paper will be to serve as an update for clinicians who are likely to encounter issues related to chronic, non-infectious, diarrhea while caring for their HIV-infected patients.

Etiology

- 1) **HIV enteropathy**. The exact mechanism by which HIV leads to chronic diarrhea is not known. Nevertheless, it is clear that practically all HIV-infected persons will experience changes to their gut within weeks of infection with HIV. Gut-associated lymphoid tissue (GALT) is depleted early in HIV infection, which is postulated to result in poorer immune control of translocated microbes across the gut lumen, leading to a state of chronic inflammation. Initiation of combination antiretroviral therapy (cART) improves (reduces) inflammation, but not to baseline status (pre-HIV infection). Given that essentially all HIV-infected persons have substantially reduced GALT, but only a minority have chronic diarrhea, it is likely that some additional “triggering event” is required to cause the diarrhea.
- 2) **Antiretrovirals**. The protease inhibitor (PI) class, in particular, has been associated with many gastrointestinal side effects. Substantial data exist to support the observation that the PIs cause a secretory diarrhea, by activating two chloride-ion channels in the gut lumen: the cyclic adenosine monophosphate (cAMP)-stimulated cystic fibrosis transmembrane conductance regulator chloride channel (CFTR), and the calcium-activated chloride channel (CACC)⁴. A high-volume efflux of water into the gut lumen is the result of activating these channels. Another proposed mechanism by which antiretrovirals cause diarrhea is by increasing permeability at the cell junction (i.e., “leaky flux diarrhea”) due to apoptosis and necrosis of intestinal epithelial cells^{4,5}.
- 3) **Miscellaneous causes**. Irritable bowel syndrome occurs with unknown frequency in HIV-infected persons, but often is associated with alternating bouts of diarrhea and constipation^{1,6}. Functional diarrhea, defined as stools that are loose (i.e., “mushy”) greater than or equal to 75% of the time for 3 months or more, like irritable bowel syndrome, occurs in HIV-infected as well as HIV-uninfected persons^{1,6}. Inflammatory bowel disease (IBD; e.g., Crohn’s and ulcerative colitis) also can occur in HIV-infected persons, but factors such as fever, presence of blood

and/or mucous, anemia, and elevated markers of inflammation (e.g., erythrocyte sedimentation rate) usually are sufficient to differentiate between IBD and HIV-specific causes of diarrhea.

Diagnosis and Treatment

Diagnosis begins with obtaining a thorough history, with attention to the duration of the diarrhea (e.g., acute vs. chronic; ongoing vs. self-limited, etc), the character of the stools (e.g., watery vs. loose), aggravating and alleviating factors, and associated symptoms (e.g., urgency, nocturnal awakening). If IBD is suspected, colonoscopy should be performed. Pancreatitis usually can be excluded by history, although on occasion it can be useful to order serum lipase and amylase.

Very importantly, infection needs to be excluded. Stool should be sent for ova and parasites to exclude *Giardia lamblia*, *Entamoeba histolytica*, and other protozoan and helminthic causes of diarrhea. Stool also should be sent for culture and sensitivity for bacterial pathogens, as occasionally diarrhea associated with these organisms can approach weeks in duration. *Clostridium difficile* infection (CDI) needs to be excluded by sending a specimen for a PCR-based toxin assay, especially in the setting of recent antibiotic use.

Once infectious and miscellaneous causes of chronic diarrhea in HIV-infected persons

have been excluded, the diagnosis likely is either HIV enteropathy or antiretroviral-associated diarrhea. Either condition can appear suddenly, years after HIV infection has occurred, and months or years after a particular antiretroviral regimen has been initiated. Unfortunately, treatment options for either condition are limited to the following:

- 1) Dietary modification. Specific recommendations are hard to make, as many different foods have the potential to exacerbate these conditions. A reasonable starting point is to suggest a diet containing lower levels of fat, and avoidance of fried foods.
- 2) Change the antiretroviral regimen. Patients, especially those who have been well-controlled on a particular regimen for years, often are reluctant to switch to “something new”. Consequently, this approach is considered by many to be a “last resort” intervention.
- 3) Antimotility agents, such as immodium and Lomotil[®]. While tempting, these agents should never be used, especially in an era of increasing CDI rates (i.e., risk of toxic megacolon in the setting of CDI). The mechanism of action of these drugs is non-specific, and involves substantially reducing gut motility. Post-diarrhea constipation/obstipation typically follows. Importantly, these drugs have never been studied for safety and efficacy in HIV-infected

persons. The optimal dose is not known for either HIV enteropathy- or antiretroviral-caused diarrhea, and patients typically self-medicate.

- 4) Probiotics. Like the antimotility agents, these products have not been adequately studied in HIV-infected persons. While generally safe and well-tolerated, there have occasional cases of *saccharomyces* species fungemia associated with the use of probiotics in the setting of chronic diarrhea^{7,8}.
- 5) Crofelemer. This drug is derived from the bark-sap of the *Croton lechleri* tree, which grows in parts of the Brazilian and Peruvian Amazon. It is the only FDA-approved botanical for systemic use, and has the indication for treatment of chronic diarrhea in HIV-infected persons⁹. Trees are harvested on site in FDA-approved areas (latitude, longitude, altitude), and the bark sap is drained into large drums. The drums are shipped to India for purification, and subsequently sent back to Cincinnati, Ohio, USA, to be made into pills. Typically, 2 – 3 trees are planted for every one removed. Trees grow to maturity within about 2 years. Approval of crofelemer was based on safety and efficacy demonstrated in the ADVENT trial¹⁰. The drug attaches to both the CFTR and CACC chloride ion channels, blocking secretion of chlo-

ride ions and reducing the efflux of water into the gut lumen. Reduction in daily and weekly watery stools improves over a 4 – 6 month period of time⁹. Recently-presented data demonstrated a 50% reduction in watery stools at 20 weeks of use in 73% of participants, and a 100% reduction in watery stools at 20 weeks in 50% of participants¹¹. Crofelemer is intraluminally-active and minimally absorbed systemically. The FDA-approved dose is 125mg twice daily on a chronic basis. Diarrhea typically returns within days or weeks after stopping the drug. As would be expected from a drug that is minimally absorbed systemically, side effects are relatively few¹⁰. Specifically, there is no substantial likelihood of constipation. Importantly, neither CD4+ cell counts, nor HIV RNA levels, are changed in association with the use of crofelemer¹⁰.

- 6) Serum bovine immunoglobulin (Enteral Health, Akeny, Iowa, USA). This product is classified as a medical food, which means it is considered “generally safe” for human use by the FDA, when used for a specific condition under the supervision of a physician. It has been used extensively in animal husbandry, and has been shown to have anti-inflammatory properties which result in improved animal gastrointestinal (GI) function and animal growth. In

small numbers of HIV-infected persons, serum bovine immunoglobulin has been shown to result in improved GI function, and increased intestinal mucosal CD4+ lymphocyte infiltration¹². The typical dose studied is 2.5g twice daily¹².

In summary, chronic, noninfectious, diarrhea is seen in a low-percentage of HIV-infected persons. Treatment options are limited, but do exist. For those individuals with HIV-associated diarrhea, treatment can have a positive effect on both the disease process and quality of life measures. Diagnosis starts with a thorough history and an evaluation to exclude infectious and non-HIV-associated causes.

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