Management of Noninfectious Diarrhea Associated With HIV and Highly Active Antiretroviral Therapy

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Abstract

In geographic locations where highly active antiretroviral therapy (HAART) is widely available, the nature of HIV-related diarrhea has shifted from being predominantly a consequence of opportunistic infection to being largely a side effect of HAART agents. With this shift has come a smaller risk for the life-threatening wasting and weight loss, although serious instances of noninfectious diarrhea remain a concern. While estimates vary, in part due to the lack of a standard diarrhea definition, over a quarter of patients receiving HAART experience diarrhea. The negative effect on quality of life in patients with HAART-related diarrhea is profound; diarrhea may also increase the risk of poor adherence to treatment, with potentially serious effects on viral suppression and increased risk of drug resistance. Diagnosis of HAART-related diarrhea largely involves ruling out pathogen involvement, which, in addition to laboratory testing, may require endoscopic examination. Treatment was, until recently, mainly supportive in nature. The recent US Food and Drug Administration approval of crofelemer offers the first reliably effective treatment for HAART-related diarrhea.

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For author information and disclosures, see end of text.

Introduction

Prior to the advent of highly active antiretroviral therapy (HAART; also referred to as combination antiretroviral therapy), diarrhea in patients with HIV was primarily a result of opportunistic infections that often manifested with devastating effects. Malabsorption and maldigestion exacerbated weight loss and wasting, contributing, in turn, to high rates of mortality. Gastrointestinal (GI) disease, in fact, was the primary cause of morbidity and mortality among patients with AIDS in the pre-HAART era.[1] The emergence of, and continuous improvements to, HAART have considerably reduced mortality and morbidity in the HIV/AIDS populations, including a significant reduction in GI disease. Despite these improvements, diarrhea is still very common, but the nature of the diarrhea and the degree of risk associated with diarrhea in patients receiving HAART has changed. While the prevalence of infectious diarrhea has diminished considerably, there has been a corresponding rise in noninfectious, often chronic, diarrhea in patients being treated with HAART.[2] The primary cause of noninfectious diarrhea in HIV-positive patients receiving HAART is the treatment itself, of which diarrhea is a fairly common side effect, although certain antiretroviral (ART) agents are more likely to cause diarrhea than others.[3] Noninfectious diarrhea can also derive from the pathological effects of HIV on cells and on the immune system in the GI tract, while HIV enteropathy can also produce a noninfectious form of diarrhea at almost any stage of HIV/AIDS.[3,4]

A precise estimation of the current rate of chronic diarrhea in HIV is problematic because of the multiple ways of defining diarrhea. With regard to the terminology and definitions used in clinical trials of diarrhea in HIV, there exists no widespread agreement as to whether acute diarrhea should be measured together with or separately from chronic diarrhea; what minimum level of stool frequency is definitive, what form the stool should take, and what descriptive terms should be used ("watery," "loose," "unformed," etc); and, at a global level, whether a given patient population has access to HAART. Nevertheless, while diarrhea may be delineated in multiple ways, the Division of AIDS of the National Institute of Allergy and Infectious Diseases has defined 4 grades of diarrhea severity as shown in Table 1.[5,6]

Three studies of diarrhea in the HAART era offer a sense of its range of prevalence. A study conducted by Siddiqui et al in New

Table 1. National Institute of Allergy and Infectious Diseases Division of AIDS: Criteria for Grading Diarrhea[6]

Parameter	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Potentially Life-Threatening
Diarrhea	Transient or intermittent episodes of unformed stools OR increase of ≤3 stools over baseline per 24-hour period	Persistent episodes of unformed to watery stools OR increase of 4-6 stools over baseline per 24-hour period	Bloody diarrhea OR increase of ≥7 stools per 24-hour period OR IV fluid replacement indicated	Life-threatening consequences, eg, hypotensive shock

York City (Bellevue Hospital and Veterans Affairs Harbor Healthcare System) included 163 consecutive HIV-positive patients, 150 of them (92.0%) receiving HAART, and 253 HIV-negative patients who served as controls. The authors found that 28.2% of patients infected with HIV had experienced diarrhea, defined as 3 or more bowel movements per day over the previous 7 days, compared with 7.1% of HIV-negative subjects, a nearly 4-fold difference (P <.001). Patients with HIV were also more likely to experience diarrhea if they were older or had received treatment with a protease inhibitor (PI).[7]

Zingmond et al evaluated the prevalence and characteristics of diarrhea in HIV-positive patients participating in 2 Veteran's Affairs studies: the HIV Cost and Service Utilization Study (HCSUS), which included 2864 patients, and the Veterans Aging Cohort 3 Site Study (VACS 3), which included 881 patients. Participants in the VACS 3 study were largely non-white (67%), and 42% were aged 50 years or over. Patients in the HCSUS study were approximately 50% non-white, with 10% aged 50 years or over. More than 85% of patients in the VACS 3 study were receiving antiretroviral therapy (ART) compared with more than 80% in the HCSUS study. Diarrhea was observed in 53% of the HCSUS patients under the age of 50 years and 37% of those aged 50 years or over (P <.01). In the VACS 3 study, 60% of those aged under 50 years experienced diarrhea compared with 55% of those aged 50 years or over (P = NS).[8]

Finally, a study from the United Kingdom evaluated 778 patients with HIV in the London area, 67% of whom were receiving ART and 20% of whom were treatment naïve. Similar to the HCSUS and VACS 3 studies, the authors found that 54% of patients had experienced diarrhea in the previous 7 days.[9]

It is, of course, difficult to clearly identify exactly why rates of diarrhea varied among studies. Numerous possible causes may be identified, including the definition of diarrhea applied and the time frame of its measurement. Differences between study populations are also plausible confounding factors, including such variables as differences in ART regimens, baseline health, stage of infection, diet, and patient age. Indeed, the relationship between patient age and diarrhea risk is an important one, particularly in light of the aging of the HIV patient population.

Patient Burden of HIV-Related Diarrhea

As with any serious side effect caused by a medication, there always exists a risk of diminished adherence to therapy. It is widely assumed that the diarrhea associated with HAART reduces adherence. The available data are ambiguous on the relationship between diarrhea and adherence with HAART. Rather than seeing an independent association of diarrhea with poor treatment adherence, the medical literature suggests that diarrhea, in combination with other treatment-related symptoms, exerts a negative effect on adherence.[9-11] That said, the relationship between gastrointestinal adverse events (AEs), such as diarrhea, and discontinuation of ART has been better established. A retrospective cohort study, published in 2012, assessed the key factors in treatment discontinuation in 1096 HIV-positive patients who had initiated first-line ART. The authors found that among AEs, gastrointestinal AEs constituted the largest factor, comprising nearly 29% of AE-related ART discontinuations.[12]

Poor adherence in HIV is of concern not only because it lessens the likelihood of optimal viral suppression, but also because irregular administration of HAART increases the risk of the development of HIV drug-limiting mutations.[13,14] A study published in 2012 found that HIV-positive children in Ethiopia who experienced diarrhea after the initiation of first-line HAART had a significantly increased risk of treatment failure.[15] Cadosch et al determined that the risk of treatment failure, and of developing drug resistance, due to poor adherence is contingent on both the particular drug being taken, specifically with regard to its half-life, and the duration of a patient's "drug holiday." Brief and repeated dose skipping was shown, in the case of drugs with shorter half-lives, to be associated with a greater risk for emerging drug resistance than a longer uninterrupted period of non-adherence.[13]

In addition to the risk of poor adherence, diarrhea in HIV has a considerable and adverse effect on quality of life

■ **Table 2.** Health-Related Quality of Life in HIV-Positive Patients With or Without Diarrhea[7,a]

	Diarrhea (n = 46)	No Diarrhea (n = 117)	*P*
General health	45.3 ± 19.9	53.4 ± 22.7	.04
Physical function	45.8 ± 22.3	73.4 ± 24.2	<.001
Role function	19.6 ± 35.7	49.6 ± 48.5	<.001
Social function	39.6 ± 22.5	56.1 ± 28.4	<.001
Cognitive function	81.8 ± 20.9	78.6 ± 22.2	.39
Pain	47.1 ± 28.4	72.6 ± 27.1	<.001
Mental health	61.8 ± 18.0	64.9 ± 23.0	.38
Energy/fatigue	35.2 ± 18.0	53.2 ± 21.2	<.001
Health distress	44.8 ± 33.6	70.9 ± 24.0	<.001
Quality of life	41.3 ± 24.3	65.2 ± 23.2	<.001
Health transition	48.4 ± 25.5	58.3 ± 23.7	.02

HRQoL indicates health-related quality of life.
[a]Diarrhea was defined as ≥3 bowel movements per day for previous 7 days. HRQoL was measured by the Medical Outcome Study-HIV Health Survey instrument; scores range from 0 to 100, with higher scores indicating better HRQoL.
Reprinted with permission from Siddiqui U, Bini EJ, Chandarana K, et al. *J Clin Gastroenterol.* 2007;41(5):484-490.

(QoL). Diarrhea at its most severe, including diarrhea secondary to HAART, can be life-threatening.[16] In the Siddiqui study, the authors sought to determine the effect of diarrhea in HIV on health-related QoL (HRQoL) by comparing HIV-infected patients with and without diarrhea using the Medical Outcomes Study HIV (MOS-HIV) Health Survey. Compared with patients who did not experience diarrhea, patients who did experience diarrhea scored significantly worse on 9 out of 11 domains of the MOS-HIV instrument, including measures of physical health, social function, health distress, and pain (Table 2).[7]

The Palladio Study Group undertook an evaluation of HIV-related diarrhea on HRQoL using data from a multicenter prospective observational study of 100 HIV-positive patients at 11 AIDS clinics in Italy who were receiving HAART. A total of 271 patients with HIV who had participated in an earlier prospective observational study, none of whom had experienced diarrhea, served as individually matched controls for the initial 100 patients; all of these had also been receiving HAART and were matched by CDC disease stage. The MOS-HIV instrument was used to measure HRQoL. In this study, HRQoOL was found to be significantly worse in all 11 MOS-HIV domains, with notably larger gaps in scores for social function, role function, energy/fatigue, and health transition for those patients who experienced diarrheal symptoms.[17]

Diagnosis

Diagnosis of diarrhea in HIV can be thought of as progressing through 1 to 4 stages. The first stage seeks to determine whether or not a pathogen is the cause of the diarrhea. If a pathogen is not the cause, the second stage involves examination of the GI tract to ascertain whether one of a number observable causes of the diarrhea can be perceived. This evaluation is particularly important in cases of acute or subacute diarrhea, and for the evaluation of diarrhea in HIV-infected persons with CD4+ lymphocyte counts less than 100 cells per microliter. The third stage is an evaluation of the patient's HAART regimen to discern whether the diarrhea is a treatment side effect. If none of these approaches yields a diagnosis, and if the diarrhea has persisted for at least 1 month, an HIV enteropathy diagnosis should be considered.[3]

Prior to the first stage, however, the clinician must determine whether the patient does, in fact, have diarrhea as opposed to fecal incontinence. A functional definition of diarrhea involves passing 3 or more abnormal stools in a 24-hour period or liquid stools in excess of 200 grams over the same time period. If diarrhea is confirmed, the duration of the diarrhea should be established to distinguish between acute and chronic diarrhea, with diarrhea in excess of 4 weeks duration being considered chronic.[3]

Stage 1: Evaluation for Pathogen Involvement[3,4]

1. Physical examination, patient/HIV history, treatment history, determination of possibility of exposure to pathogen
2. Stool examination; requires up to 3 stool samples taken over a period of 10 days. Specimens should be over 2 g and transported to the testing lab without delay. Microbiologic examination for ova, cysts, and parasites (eg, cryptosporidia); culture for enteric pathogens; depending on evidence, tests for: *Salmonella sp*, *Shigella sp*, *Campylobacter sp*, *Clostridium difficile*, *mycobacterium avium complex (MAC)*; assay for stool protozoa (polymerase chain reaction analysis or an antigen detection test)
3. Plasma CD4+ count to measure degree of immunosuppression and establish spectrum of possible opportunistic infection
4. HIV viral load to determine response to ART. An increase in viral load is the earliest sign of nonad-

herence, treatment failure, or resistance; viral load increases occur before reductions in CD4+ count

Stage 2: Examination of Gastrointestinal Tract

If no pathogen has been identified, and the diarrhea has persisted, and is severe (ie, at least 10 abnormal stools in 24 hours), endoscopic examination of the GI tract may be appropriate to rule out observable causes such as cytomegalovirus (CMV) colitis, microsporidial infection, or giardia. The greater the diarrhea severity and the lower the CD4+ count, the stronger the rationale for endoscopic examination.[3,4]

1. Upper endoscopy and flexible sigmoidoscopy or colonoscopy are viable endoscopic modalities to procure samples for biopsy; full colonoscopy, ideally with terminal ileoscopy, is recommended, particularly in cases of severe symptoms, and strongly recommended in cases of CD4+ cell count less than 100 cells per μL.[3]
2. For patients with Kaposi's sarcoma or non-Hodgkin lymphoma, radiologic imaging of the GI tract may be necessary to evaluate lesions. Radiologic imaging may also help identify edematous or ulcerated mucosa that could narrow a search for a pathogen, particularly in correlation with CD4+ count, but samples for biopsy must be obtained to confirm diagnosis.[3,4]

Stage 3: Evaluation of HAART Regimen

Clinical trials in ART have exhibited rates of grade 2 to 4 diarrhea ranging from 2% to 19%, with most trials being nearer the higher end of the range.[16] Evidence exists for mechanisms by which ART may produce diarrhea in patients with HIV. For example, some ART agents are thought to potentiate stimulation of calcium-dependent chloride ion channels resulting in excess secretion in the human intestine.[18] Certain drugs have also been shown to cause damage to the intestinal epithelial barrier—including reduction in villi length and crypt depth (components of the epithelial lining), and induction of apoptosis—causing intestinal permeability and leakage of water and electrolytes from the intestines.[19]

Because diarrhea as a side effect of HAART is a major contributor to the prevalence of noninfectious HIV-related diarrhea, an evaluation of the treatment regimen in patients with diarrhea should be undertaken. If HAART-related diarrhea is suspected at initial presentation, this diagnostic stage can precede stage 2.

Diarrhea has been shown to be a potential side effect of PIs, nucleoside reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, and integrase inhibitors.[20-22] The PI ritonavir is particularly associated with diarrhea as a side effect, and while it is now used as a pharmacokinetic enhancer ("booster drug") for other PIs, it remains a high-risk agent for diarrhea. Among ritonavir-inclusive HAART combinations, those most strongly associated with moderate (grade 2), severe (grade 3), and life-threatening (grade 4) diarrhea are lopinavir-ritonavir and fosamprenavir-ritonavir, while lower risks are associated with atazanavir-ritonavir, darunavir-ritonavir, and saquinavir-ritonavir. Several of these combinations are currently used as first-line treatment.[3]

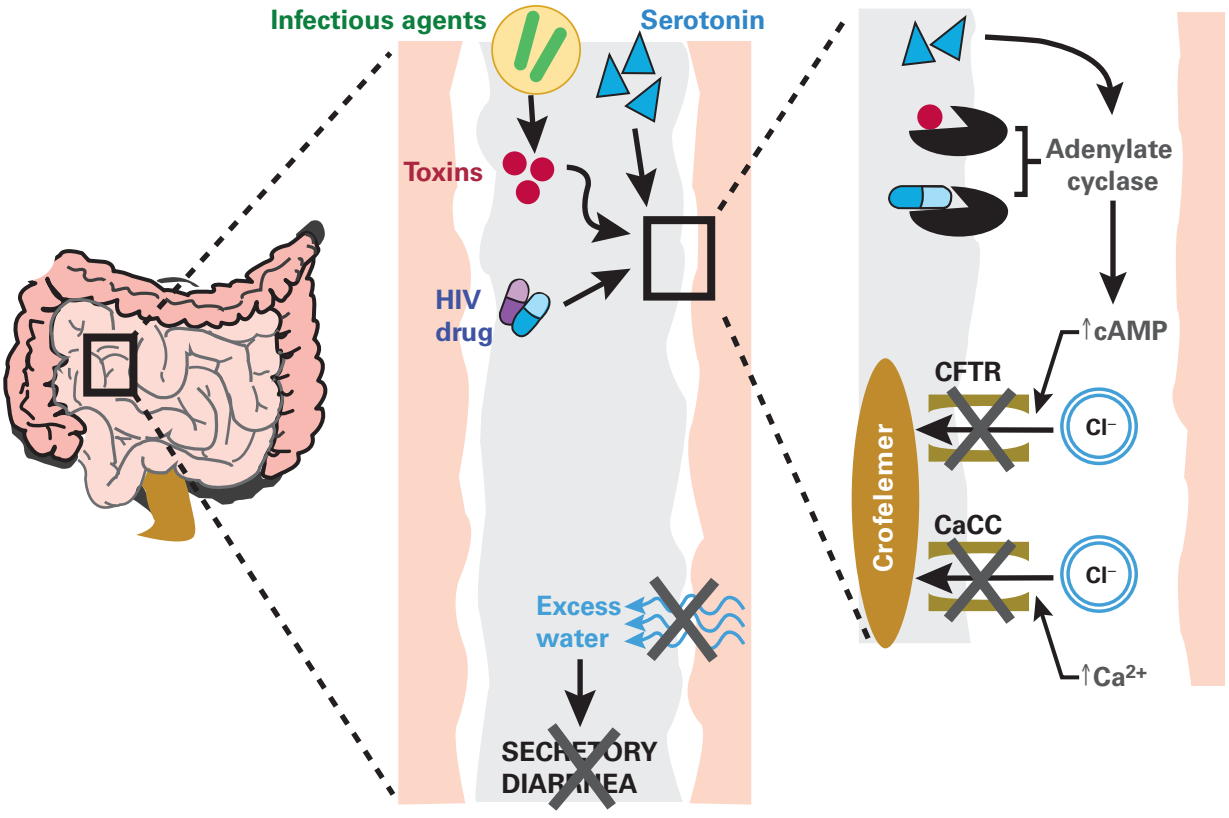
If none of the above diagnostic stages reveal the cause of diarrhea, and if the diarrhea has remained persistent, consideration of HIV enteropathy as a diagnosis is appropriate. HIV enteropathy, it may be noted, describes idiopathic diarrhea, where no pathogen is identified and which may occur at any stage of HIV infection and AIDS. The histological evidence for HIV enteropathy includes blunting and atrophy of villi, hyperplasia of epithelial crypts, and inflammatory lymphocytic infiltration of the lamina propria, a layer of tissue lying below the epithelium. HIV enteropathy may or may not be ameliorated with HAART treatment.[3]

Therapeutic Options

General supportive care should be implemented in patients experiencing diarrhea, and over-the-counter medications may be employed. Over-the-counter fiber additives, such as psyllium, commonly found at drugstores and health food stores, are recommended to ameliorate diarrhea.[3] Incorporating fiber-rich foods into the diet is also advisable. These include leafy green vegetables, broccoli and cauliflower, oat bran, cabbage, celery, raspberries, and squash, as well as beans and legumes such as split peas, lentils, and black or lima beans.

A number of supportive agents, including adsorbent, antimotility, and antisecretory agents, have been used to help manage diarrhea. Bismusth subsalicylate, a commonly used adsorbent agent for diarrhea, may be risky for HIV-positive patients, particularly patients with more advanced disease, due to the (remote) risk of bismuth encephalopathy. Other adsorbent agents that improve stool consistency include attapulgite, kaolin, and pectin.[3] Loperamide, an opioid derivative, possesses both antimotility and antisecretory properties, and has shown limited efficacy in a chart review that included 47 patients who were receiving treatment with nelfinavir. Diphenoxylate/atropine is another antimotility agent possessing opioid characteristics; there are limited clinical study data to support its use in patients experiencing diarrhea associated with PI therapy. Diphenoxylate/atropine, like other opioid-related drugs that are sometimes used for antimotility qualities, can be habit forming and, at higher doses, exhibit opioid analgesic activity.[3,23]

Figure 1. Mechanism of Crofelemer Efficacy in Secretory Diarrhea[27]



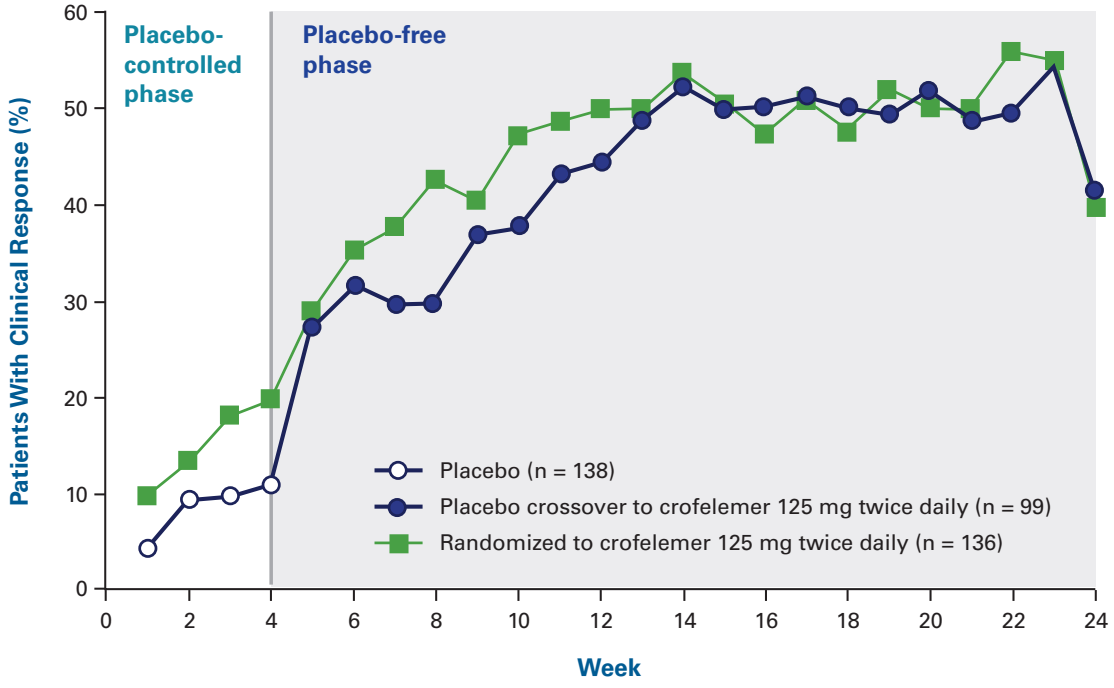
CaCC indicates calcium-activated chloride channel; cAMP, cyclic adenosine monophosphate; CFTR, cystic fibrosis transmembrane conductance regulator. Clinical benefit is derived through reduction of fluid and chloride (Cl^-) secretion via potent dual inhibition of cystic fibrosis transmembrane conductance regulator and calcium-activated chloride channels in the intestinal epithelium.

It should be noted that antimotility agents have not been studied for their safety in patients with HIV-related diarrhea, and do not treat the causes of diarrhea in patients with HIV; also, antimotility agents are associated with constipation. In addition, in an era of increasing prevalence of *C difficile*, extreme caution should be exercised prior to prescribing antimotility agents.

At present, only 1 agent, crofelemer, has been approved by the US Food and Drug Administration (FDA) (on December 31, 2012) for the treatment of noninfectious diarrhea in patients with HIV/AIDS receiving antiretroviral therapy.[24] Crofelemer is a botanical compound derived from the stem bark latex of an Amazonian tree called the *Croton lechleri*, the red-colored latex being known as Sangre de Drago or Dragon's Blood.[25] The mechanism of action of crofelemer involves the inhibition of prosecretory intestinal chloride ion channels, which are a necessary part of intestinal fluid secretion (Figure 1).[26,27] Interestingly, absorption of crofelemer is minimal in human subjects (with or without HIV infection), and more than 95% of subjects in pharmacokinetic studies had crofelemer levels below that quantifiable by standard assays.[26] Crofelemer does not appear to confer risk of GI-absorption–based interactions, and is not associated with significant pharmacokinetic interaction with antiretroviral therapies.[24,28]

Prior to the pivotal phase 3 trial, ADVENT, upon which crofelemer's FDA approval was based, crofelemer had been studied in other conditions, including traveler's diarrhea and diarrhea-predominant irritable bowel syndrome (IBS). Crofelemer showed efficacy in conditions in which the diarrhea was secretory in nature (eg, traveler's diarrhea) but did not demonstrate efficacy in IBS; the lack of efficacy in IBS may be due to the multifactorial nature of diarrhea in IBS.[29] Crofelemer was also studied in a phase 2 trial for the treatment of diarrhea in patients with AIDS; the results were published in 1999. The phase 2 study population (N = 51), 77% of whom were receiving treatment with a PI, were randomized to crofelemer or placebo, and the investigators observed a significant reduction in both stool weight (P = .008) and stool frequency (P = .04) with crofelemer treatment.[26,30]

Figure 2. Response Rates for Placebo-Controlled Phase and Placebo-Free Phase of ADVENT Trial of Crofelemer for HIV-Related Diarrhea[32,a]



[a]Response defined as ≤2 watery stools per week for ≥2 of 4 weeks.

The recent ADVENT trial included HIV-positive subjects who were experiencing diarrhea for at least 4 weeks, were receiving ART, had a CD4+ cell count greater than 100 cells per μL, and showed no evidence of intraluminal pathogen-related diarrhea. The mean number of daily watery bowel movements in the study population was slightly less than 3, with a marginally higher rate (3.04) in the placebo-treated patients versus patients receiving crofelemer. Patients had received their HIV diagnosis an average of approximately 12.5 years prior to the study, and had been experiencing diarrhea for between 5.5 and 6.9 years. The mean age of the study subjects was 44 to 46 years, and the patient population was ethnically diverse.[27] A total of 79 patients (58%) receiving crofelemer 125 mg and 83 patients (60%) receiving placebo had previously used antidiarrheal medication.[31]

The trial was divided into 2 separate stages. The first stage was a dose evaluation study that established an optimal dose of 125 mg twice daily. The second stage, composed of an entirely new set of subjects meeting the same entry criteria (crofelemer n = 92, placebo n = 88), was a double-blind, randomized, controlled trial with a 4-week blinded phase and a 20-week open-label extension in which all subjects were treated with crofelemer 125 mg twice daily. The primary end point for the 4-week blinded phase was response rate, where response was defined as no more than 2 watery bowel movements per week for 2 or more of the 4 weeks.[26,27,32]

At the end of the 4-week placebo-controlled phase, the rate of response in crofelemer-treated patients was nearly double that of the placebo group (approximately 19% vs approximately 10%).[27] The crofelemer response rate during the placebo-controlled period increased continuously throughout the 4 weeks, and improved almost continuously throughout the 20-week open-label extension (n = 136), reaching a plateau of an approximately 50% response rate (**Figure 2**).[32] Exploratory analyses of the outcomes data from the ADVENT trial revealed numerically higher response rates (reported as percentage differences comparing crofelemer-treated versus placebo-treated) in several subgroups of patients, including patients who had used antidiarrheal medications in the past 4 weeks versus those who had not used antidiarrheal medications (14.9% vs 6.2%), patients with CD4+ cell counts less than 404 cells/mm^3 compared with those with higher CD4+ cell counts (15.6% vs 7.2%), patients diagnosed more than 12 years ago compared with those with a more recent diagnosis (14.1% vs 5.5%), and patients who used PIs compared with those who used other classes of antiretrovirals (11.0% vs 6.2%).[31]

The safety data, which included study subjects from both the first and second phases of the study (crofelemer n = 130, placebo n = 137), showed that the percentages of patients who experienced any adverse event (AE) were similar in the crofelemer and placebo groups (34.6% crofelemer vs 32.8% placebo), and the rate of serious AEs was very low and similar for both groups (1.5% crofelemer vs 2.9% placebo). There were 4 serious AEs (any cause) in the placebo group and 2 in the crofelemer group, and 4 AE-related discontinuations in the placebo group compared with none in the crofelemer group. GI effects and infections were the most common AEs in both groups, and 2 cases each of the following AEs were observed in the crofelemer group: dyspepsia, flatulence, abdominal pain, hemorrhoids, and constipation. Upper respiratory tract infections were seen in 5 crofelemer and 4 placebo patients, while urinary tract infections were seen in 3 crofelemer patients and 1 placebo patient.[32]

Other Non-Approved and Non-Pharmacologic Treatments

Octreotide—The somatostatin analogue octreotide has demonstrated efficacy in patients with HIV and AIDS experiencing diarrhea. However, studies of octreotide have largely been conducted in the pre-HAART era, and do not reflect treatment of HAART-induced diarrhea.[33-35]

Racecadotril—The enkephalinase inhibitor racecadotril (also known as acetorphan) has demonstrated efficacy in small studies of patients with HIV experiencing diarrhea, but the data are limited and do not reveal the efficacy of racecadotril in HAART-related diarrhea.[34,36]

Bovine colostrum—Bovine colostrum has been shown to alleviate diarrhea in HIV-positive patients in several studies. However, these studies were conducted in patients who were, for the most part, not receiving HAART, or whose diarrhea predated initiation of HAART, and its efficacy in HAART-treated patients is therefore unclear.[37-39]

Curcumin—Curcumin (extracted from turmeric) as a treatment for HIV-related diarrhea was evaluated in a nonblinded, non-controlled study by the Southern California Kaiser Permanente Medical Group in 8 patients in whom no pathogen or parasite was detected by stool culture or observation or by endoscopy or colonoscopy. Seven of the 8 subjects were receiving HAART. The mean number of bowel movements before therapy was 6.75, which was reduced to 1.69 by the end of therapy (P = .006). Time to resolution varied from 3 to 28 days; side effects were minimal and not serious.[40]

Lactobacillus rhamnosus GG—The effects of the probiotic *Lactobacillus rhamnosus* GG (LGG) were evaluated in 17 patients with HIV-related diarrhea in a randomized, placebo-controlled study with crossover design (2 weeks on LGG and 2 weeks on placebo) conducted in Finland. Neither daily stool frequency nor bowel movements were statistically different between LGG and placebo, nor did LGG improve stool consistency.[41]

Summary

The success of HAART in reducing HIV/AIDS morbidity and mortality also conferred a substantial reduction in the risk of the kind of opportunistic infection that can ravage patients and considerably speed their deterioration. The success of these treatments should not, however, overshadow the fact that diarrhea remains a serious problem in the HAART era, particularly with regard to certain drugs and drug classes. Diarrhea can adversely impact QoL. Knowledge of the serious impact of diarrhea in patients with HIV should prompt the selection of therapies to minimize diarrhea risk. In cases when diarrhea is unavoidable, the recent approval of crofelemer provides a therapeutic option for a substantial proportion of the affected patient population.

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