

Etiology and Pharmacologic Management of Noninfectious Diarrhea in HIV-Infected Individuals in the Highly Active Antiretroviral Therapy Era

Rodger D. MacArthur¹ and Herbert L. DuPont^{2,3,4}

¹Division of Infectious Diseases, Wayne State University, Detroit, Michigan; ²The University of Texas School of Public Health, ³St Luke's Episcopal Hospital, and ⁴Baylor College of Medicine, Houston, Texas

Diarrhea remains a common problem for patients with human immunodeficiency virus (HIV) infection despite highly active antiretroviral therapies (HAART) and can negatively affect patient quality of life and lead to discontinuation or switching of HAART regimens. In the era of HAART, diarrhea from opportunistic infections is uncommon, and HIV-associated diarrhea often has noninfectious causes, including HAART-related adverse events and HIV enteropathy. Diarrhea associated with HAART is typically caused by protease inhibitors (eg, ritonavir), which may damage the intestinal epithelial barrier (leaky-flux diarrhea) and/or alter chloride ion secretion (secretory diarrhea). HIV enteropathy may result from direct effects of HIV on gastrointestinal tract cells and on the gastrointestinal immune system and gut-associated lymphoid tissue, which may be active sites of HIV infection and ongoing inflammation and mucosal damage. New therapies targeting the pathogenic mechanisms of noninfectious diarrheas are needed.

The widespread availability of highly active antiretroviral therapy (HAART) has prolonged survival of patients with human immunodeficiency virus (HIV) infection and has improved many of the gastrointestinal (GI) conditions associated with HIV, including diarrhea, nausea, vomiting, dysphagia, and abdominal pain [1]. However, GI conditions, especially diarrhea, remain a common problem in patients with HIV infection in the presence and absence of HAART [1, 2]. Diarrhea negatively affects health-related quality of life (HRQOL) [3] and is a common reason for discontinuing [4] or switching HAART regimens [5]. Here the etiology of HIV-associated diarrhea will be reviewed,

with a focus on noninfectious causes of diarrhea, current pharmacologic management options, and future research directions.

IMPACT OF DIARRHEA IN PATIENTS WITH HIV INFECTION

Although up to 60% of patients with HIV infection report diarrhea [6], the prevalence of diarrhea in these patients has been unclear in the HAART era, given variations in defining HIV-associated diarrhea (eg, definition, assessment tools, and duration [acute vs chronic]). However, patients with HIV infection are significantly more likely than noninfected persons to report diarrhea [3]. In a study by Siddiqui et al, acute diarrhea (ie, ≥ 3 bowel movements per day during the past 7 days) was 4 times more prevalent in patients with HIV infection (28%; 92% were receiving HAART) than in HIV-seronegative controls (7%; $P < .001$), including after adjustment for multiple factors (eg, age, sex, race) [3]. Significant differences

Received 23 January 2012; accepted 24 May 2012; electronically published 14 June 2012.

Correspondence: Rodger D. MacArthur, MD, Division of Infectious Diseases, Wayne State University, 4201 St Antoine, UHC Ste 7D, Detroit, MI 48201 (rmacarthur@med.wayne.edu).

Clinical Infectious Diseases 2012;55(6):860–7

© The Author 2012. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/cis544

were independent of variations in criteria employed to define acute diarrhea (prevalence 2–4 times greater in HIV-positive patients vs HIV-seronegative controls; $P < .001$ for all comparisons). Chronic diarrhea was reported in 28% of patients in a noncomparative trial of 671 patients with HIV infection [7]. Both of these studies were done in the era of HAART.

Diarrhea has a substantial negative impact on HRQOL and social quality of life (QOL) in patients with HIV infection [3]. In a national survey of 2267 adults with HIV infection, diarrhea or loose or watery stools was associated with significantly worse perceived QOL (unadjusted regression coefficient, -2.45 ; 95% confidence interval, -4.4 to -0.5 ; $P < .05$) [8]. In another survey, 40% of patients with HIV infection indicated that diarrhea moderately or greatly negatively affected their social life. In addition to restricting schedules or staying closer to home because of diarrhea, HIV-positive patients with diarrhea reported feelings of loss of control and shame [9]. In the study by Siddiqui et al, HIV-infected adults with diarrhea reported significantly worse HRQOL, with significantly worse scores for 9 of 11 domains of the Medical Outcomes Study (MOS)–HIV Health Survey (MAPI Research Trust, Lyon, France) compared with HIV-infected patients without diarrhea; only domains for cognitive function and mental health were not significantly worse [3]. These results supported findings of a previously published study in which adults with HIV infection and diarrhea while receiving HAART had significantly lower HRQOL for all 11 domains of the MOS–HIV Health Survey compared with matched HIV-infected controls ($P < .05$ for all) [10]. In addition to detriments in HRQOL, diarrhea in patients with HIV infection may reduce treatment efficacy and adherence.

ETIOLOGY OF DIARRHEA IN PATIENTS WITH HIV INFECTION

Gastrointestinal opportunistic infections are common causes of diarrhea in patients with advanced AIDS and are caused by a variety of definable pathogens typically occurring in HIV-infected patients with CD4⁺ counts <200 cells/ μ L [2]. However, diarrhea may affect patients at all stages of HIV infection and may have multiple causes, including noninfectious causes such as HAART, effects of HIV on the GI tract (ie, HIV enteropathy), HIV-associated malignancies, and pancreatitis [11].

HAART-Associated Diarrhea

In an analysis of clinical trials using consistent reporting, up to 19% of patients treated with HAART reported moderate to potentially life-threatening diarrhea that was considered at least possibly related to study drug [1]. Diarrhea may be associated with several of the therapies used in HAART regimens,

including nucleoside reverse-transcriptase inhibitors (NRTIs) and nonnucleoside reverse-transcriptase inhibitors, protease inhibitors (PIs), and integrase inhibitors [3, 5, 11].

Of particular issue is the PI ritonavir (Norvir; Abbott Laboratories). In early studies of ritonavir (up to 1200 mg/d) as single-agent therapy, diarrhea was a common adverse event. Ritonavir (100–400 mg/d) is now used only as a pharmacokinetic booster to increase levels of other PIs, including lopinavir, atazanavir (Reyataz; Bristol-Myers Squibb), darunavir (Prezista; Tibotec), fosamprenavir (Lexiva; GlaxoSmithKline), and saquinavir (Invirase [Genentech] or Fortovase [Roche Laboratories]) [1, 11]. Despite the reduced dose of ritonavir used in the booster combination, diarrhea remains a common adverse event with varying prevalence depending on the choice of boosted PI [1]. Overall, lopinavir-ritonavir (Kaletra; Abbott Laboratories) and fosamprenavir-ritonavir tended to have the highest rates of drug-related moderate to potentially life-threatening diarrhea compared with atazanavir-ritonavir, darunavir-ritonavir, or saquinavir-ritonavir (Table 1) [12–23]. Notably, all 5 of these ritonavir-boosted PI therapies are considered preferred, alternative, or acceptable first-line therapies for treatment of patients with HIV-1 infection.

Data suggest that HAART-associated diarrhea may be caused by a variety of mechanisms, including increased calcium-dependent chloride conductance and cellular apoptosis, necrosis, and decreased proliferation of intestinal epithelial cells [24]. Furthermore, it has been shown that PIs induced endoplasmic reticulum (ER) stress and activation of the unfolded protein response leading to apoptosis of intestinal epithelial cells in vitro and in vivo. However, it is noteworthy that concentrations of PIs used in studies demonstrating apoptosis are substantially greater than those reached in humans treated with Food and Drug Administration (FDA)–approved doses. Furthermore, clinically relevant doses of PIs have been associated with reduced levels of apoptosis in vitro and in vivo, but this has not been demonstrated specifically for intestinal cells.

The effects of PIs on apoptosis, necrosis, and proliferation have been linked to changes in intestinal barrier function that may be linked to diarrhea (ie, leaky-flux diarrhea). A study by Braga Neto et al found that PIs increased intestinal permeability in mice and induced necrosis and apoptosis and decreased proliferation of intestinal epithelial cells in vitro, suggesting that a disrupted intestinal barrier function and/or altered small intestinal absorption may contribute to PI-associated diarrhea [25]. The study further showed that PIs and NRTIs altered intestinal morphology and water and electrolyte secretion in mice, suggesting that both classes of drugs may contribute to or aggravate infectious enteropathies and may induce diarrhea via a secretory mechanism.

Table 1. Incidence of Treatment-Related Grade 2–4 Diarrhea in Head-to-Head Comparisons of Boosted Protease Inhibitor Regimens Compared With Lopinavir Plus Ritonavir

Study	Patient Population	Patients, No. ^b	Patients With Grade 2–4 Diarrhea, % ^a		P Value
			Boosted PI/r	LPV/r	
ATV/r					
BMS-045 [12, 13] ^c	Treatment experienced	347			
48 weeks			3	11	.01
96 weeks			3	13	<.01
CASTLE [14, 15] ^d	Treatment naive	878			
48 weeks			2	11	NR
96 weeks			2	12	NR
DRV/r					
TITAN [16, 17] ^e	Treatment experienced	595			
48 weeks			8	14	NR
96 weeks			8	15	NR
ARTEMIS [18, 19] ^d	Treatment naive	689			
48 weeks			4	10	<.01
96 weeks			4	11	<.001
SQV/r					
BMS-045 [12] ^c	Treatment experienced	347	6	11	NR
Gemini [20] ^d	Treatment naive	331	7 ^f	14 ^f	NR
fAPV/r					
KLEAN [21, 22] ^g	Treatment naive				
48 weeks		879	13	11	NR
144 weeks		196	15	12	NR
COL100758 [23] ^h	Treatment naive	115	14	18	NR

Abbreviations: ATV/r, atazanavir plus ritonavir; DRV/r, darunavir plus ritonavir; fAPV/r, fosamprenavir plus ritonavir; LPV/r, lopinavir plus ritonavir; NR, not reported; PI/r, protease inhibitor plus ritonavir; SQV/r, saquinavir plus ritonavir.

^a Diarrhea at least possibly related to or related to study drug treatment.

^b Safety population.

^c Treatment also included tenofovir plus 1 nucleoside reverse-transcriptase inhibitor.

^d Treatment also included tenofovir (Viread; Gilead Sciences) plus emtricitabine (Emtriva; Gilead Sciences).

^e Treatment also included ≥ 2 antiretroviral agents (nucleoside reverse-transcriptase inhibitor with or without nonnucleoside reverse-transcriptase inhibitor).

^f Includes all grades of diarrhea (1–4).

^g Treatment also included abacavir (Ziagen; ViiV Healthcare) plus lamivudine (Epivir; ViiV Healthcare).

^h Treatment also included abacavir plus lamivudine, or zidovudine (Retrovir; ViiV Healthcare) plus lamivudine if abacavir plus lamivudine had treatment-limiting toxic effects.

Notably, no data favoring the leaky-flux model of PI-associated diarrhea have been obtained in human studies. In contrast, a study of patients with HIV infection treated with a PI revealed increased concentrations of fecal electrolytes (including chloride) and elevated stool pH and fecal supernatant osmotic gap consistent with secretory diarrhea [26]. Results of in vitro studies further suggested PIs induce secretory diarrhea via potentiation of calcium-activated chloride conductance. A phase 2 study provided further support for a secretory mechanism for PI-associated diarrhea by demonstrating that the investigational agent crofelemer, an inhibitor of the calcium-activated chloride channel and the cystic fibrosis

transmembrane regulator, improved symptoms of diarrhea and decreased stool chloride concentrations in patients with AIDS, most of whom were receiving ≥ 1 PI [27].

HIV Enteropathy

HIV enteropathy is an idiopathic form of diarrhea that can occur during the acute phase of HIV infection through advanced AIDS and for which there is no identified pathogen. Histologically, villous atrophy, crypt hyperplasia, and villous blunting exemplify damage to the GI tract, and inflammatory infiltrates of lymphocytes in the lamina propria may be observed. Notably, HIV enteropathy may improve with HAART,

but it may also occur in patients receiving HAART. The pathogenic mechanisms leading to HIV enteropathy remain unclear but may involve effects of HIV infection on the GI tract and the gut-associated lymphoid tissue (GALT) [28].

Effects of HIV Infection on Cells of the GI Tract

HIV can directly infect enterocytes, lamina propria cells, and the submucosa. Direct infection of enterocytes by HIV may lead to altered cellular differentiation, crypt hyperplastic villous atrophy, and altered absorptive and secretory function. Viral proteins secreted or shed from infected cells may also have toxic effects on cells of the GI tract. For example, the HIV-1 Tat protein may induce calcium-dependent chloride ion secretion in enterocytes and colonic mucosa and inhibit proliferation of enterocytes [29]. Results of an in vitro study further showed that Tat may activate oxidative stress pathways, leading to apoptosis and disruption of the actin cytoskeleton, which may be associated with HIV enteropathy [30]. The HIV-1 envelope protein Gp120 may alter ion secretion and intracellular architecture [31]. Finally, recent data have also suggested that the HIV-1 viral protein R may also be associated with the ER stress and inflammation as well as disrupted barrier function associated with HIV enteropathy [32].

HIV Effects on GI Immune System Activation and the GALT

Local activation of the GI immune system and inflammation may contribute to HIV enteropathy. Increased protein or messenger RNA levels of proinflammatory cytokines (eg, interleukin 1, 4, 6, and 10; tumor necrosis factor α ; and interferon γ), the β -chemokine RANTES, and macrophage inflammatory proteins 1 α and 1 β have been observed in biopsies of the duodenum or colonic mucosa of patients with HIV infection [33]. Furthermore, increased expression of messenger RNA for Xbp-1s and C/EBP (CCAAT enhancer binding protein) homologous protein were observed in duodenal biopsy specimens, suggesting that activation of ER stress pathways may contribute to the inflammation associated with HIV enteropathy. Overall, the increased levels of proinflammatory proteins and mucosal cellular inflammation in patients with HIV infection suggest the presence of intestinal or colonic inflammation and may represent an inflammatory bowel disease–like condition in these patients.

Decreased mucosal immune system repair and regeneration may also contribute to HIV enteropathy. The GALT is an early site of HIV replication and CD4⁺ T-cell depletion. Sanakaran et al demonstrated that HIV-induced damage to the GALT occurs early during the infection process, even before seroconversion can be detected [28]. The rapid destruction of CD4⁺ T cells was paralleled by increased epithelial cell apoptosis and changes in gene expression patterns, indicating

early loss of proteins involved in intestinal epithelial barrier and mucosal functions. The results of this study suggest that HIV enteropathy may occur early in the course of HIV infection, even before HIV-mediated immune activation and inflammation.

Given that destruction of the GALT is directly mediated by HIV infection, treatment with HAART would be expected to resolve enteropathy caused by GALT destruction. However, HAART usually, but not always, improves HIV enteropathy. With long-term HAART there is delayed and often incomplete reconstitution of CD4⁺ T cells in the GALT compared with peripheral blood. Low levels of viral replication may also persist in the GI mucosa despite HAART [33].

Autonomic Neuropathy

Damage to autonomic neurons is a well-known complication of HIV infection. Autonomic damage may manifest in the GI tract many ways, with diarrhea being the most distressing and debilitating issue. In the GI tract, severe structural damage to and depletion of autonomic nerves have been observed and can occur at all stages of HIV infection [34]. However, as seen with other conditions associated with autonomic neuropathy (eg, diabetes), there does not appear to be a relationship between the severity of the neuropathy and the HIV-associated diarrhea.

Chronic Pancreatitis and Exocrine Insufficiency

Pancreatitis, which may be caused by HIV infection itself and by a variety of noninfectious agents (eg, didanosine) and pathogenic agents (eg, opportunistic infection, viral hepatitis), may also contribute to chronic diarrhea [11]. Chronic pancreatitis and exocrine insufficiency may lead to steatorrhea, particularly in the advanced stages of pancreatic disease. Patients may present with foul-smelling, bulky stools that may be associated with the passage of oil droplets.

DIAGNOSIS AND MANAGEMENT OF HIV-ASSOCIATED DIARRHEA

Diagnosis

A basic algorithm for the diagnosis and management of diarrhea in patients with HIV infection is presented in Figure 1. Initially, it should be determined that the patient does indeed have diarrhea. Clinical and lay definitions of diarrhea may be different, and fecal incontinence, which can be confused with diarrhea, should be ruled out. A working definition of diarrhea is the abnormal passage of ≥ 3 unformed stools per day or a liquid stool volume >200 g/d. The initial assessment of a patient with HIV infection and diarrhea should include a physical examination and history that includes a review of the patient's HIV and treatment history and potential for

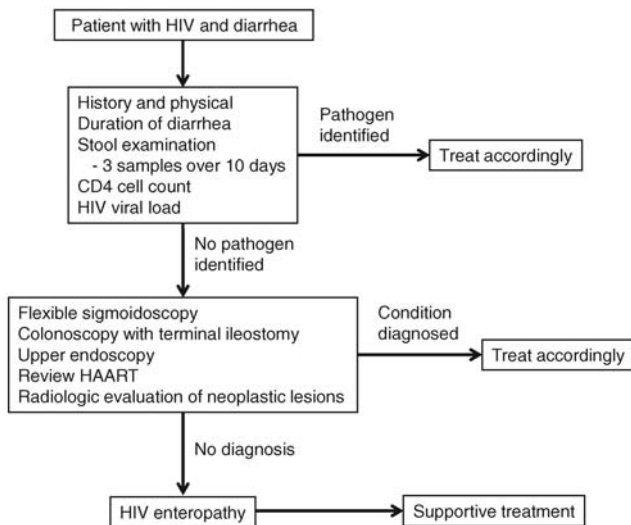


Figure 1. Basic algorithm for the diagnosis and management of human immunodeficiency virus–associated diarrhea. Diarrhea was defined as the abnormal passage of loose or liquid stools ≥ 3 times a day, and/or a liquid stool volume >200 g/d. Specific examples of stool assays for intestinal protozoa that may be performed in addition to microscopic examination are presented in Table 2. Upper endoscopy and colonoscopy should be strongly considered for patients with $CD4^+$ cell counts <100 cells/ μ L. Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.

pathogen exposure (eg, travel history) [11]. The duration of diarrhea should also be considered to determine whether acute or chronic pathogenic causes may be relevant. Generally speaking, diarrhea of duration >4 weeks is considered chronic.

A plasma $CD4^+$ cell count should be determined to assess the patient's degree of immunosuppression and spectrum of possible opportunistic infections, and the HIV load should be determined to measure response to HAART [11]. Microbiologic examination of feces should be performed, including culture for enteric pathogens; microscopic examination for ova, cysts, and parasites; and testing for the *Clostridium difficile* toxin when appropriate [11]. In addition to microscopic examination, diagnosis of stool protozoa may be accomplished using polymerase chain reaction analysis or a variety of antigen detection tests, including direct fluorescent antibody, enzyme immunoassay, or rapid, dipstick-like tests (Table 2) [35]. Fecal examination will yield a diagnosis approximately half of the time.

If no pathogen is identified during fecal examination and the diarrhea is severe (eg, ≥ 10 viscous, liquid, or watery stools in a 24-hour period) and persistent, further examination by upper endoscopy and flexible sigmoidoscopy or colonoscopy may be performed to obtain biopsy samples and rule out other potential causes of diarrhea, such as inflammatory bowel disease [11]. Upper endoscopy and colonoscopy should

Table 2. Examples of Specific Diagnostic Tests for Intestinal Protozoal Pathogens [35]

Pathogen	Test
<i>Cryptosporidium</i> spp.	DFA ^{a,b}
	IFA ^b
	PCR
	EIA ^b
	RAPID ^b
<i>Cyclospora</i>	PCR
<i>Giardia lamblia</i>	DFA ^{a,b}
	IFA ^b
	PCR
	EIA ^b
	RAPID ^b
<i>Microsporidia</i>	PCR

Abbreviations: DFA, direct fluorescent antibody; EIA, enzyme immunoassay; IFA, indirect fluorescent antibody; PCR, polymerase chain reaction; RAPID, rapid immunographic assay.

^a Current test of choice.

^b Available as combined test for *Cryptosporidium* spp and *G. lamblia*.

be strongly considered for patients with $CD4^+$ cell counts <100 cells/ μ L. Microsporidial or mycobacterial infections of the small intestine, cytomegalovirus infections, and giardiasis may be identified using these procedures. The HAART regimen should also be reviewed to determine the possibility of medication-induced diarrhea. Radiologic assessments or direct visualization (eg, colonoscopy) may be warranted for patients with Kaposi's sarcoma or non-Hodgkin's lymphoma to identify lesions in the GI tract. For patients in whom diagnostic testing has yielded negative results and in whom diarrhea has persisted for >1 month, a diagnosis of HIV enteropathy or HAART-associated diarrhea may be made or considered. Other idiopathic forms of diarrhea such as irritable bowel syndrome or functional diarrhea may also be considered, depending on the signs and symptoms the patient is experiencing (Table 3) [36, 37].

Treatment and Management

Patients in whom a pathogenic cause for diarrhea has been identified should be treated accordingly. Specific treatment recommendations for pathogenic diarrhea are beyond the scope of this review and have been reviewed elsewhere [11]. Briefly, treatment of pathogenic diarrhea typically targets the specific pathogen causing the condition. Some therapies that may be used include antibacterial agents, such as ciprofloxacin (for bacterial pathogens) or clarithromycin plus ethambutol with or without rifabutin (for *Mycobacterium avium* complex infection); antiviral therapies, such as ganciclovir or valganciclovir (for cytomegalovirus infection); and antifungal or

Table 3. Idiopathic Diarrhea in Patients With HIV Infection

Condition	Clinical Presentation/Definition
HIV enteropathy [36]	<p>May be associated with</p> <ul style="list-style-type: none"> GI inflammation Malabsorption of vitamin B12 and bile acid Increased intestinal permeability Weight loss <p>Histologically associated with</p> <ul style="list-style-type: none"> Inflammatory lymphocyte infiltrates Damage to the GI epithelium, including villous atrophy, crypt hyperplasia, and villous blunting
Irritable bowel syndrome [37]	<p>Defined by the ACG as abdominal pain or discomfort associated with altered bowel habits over a period of ≥ 3 months</p> <p>Defined by Rome III criteria as recurrent abdominal pain or discomfort for ≥ 3 d/mo in the last 3 months with symptom onset at ≥ 6 months before diagnosis and associated with ≥ 2 of the following:</p> <ul style="list-style-type: none"> Improvement with defecation Onset associated with change in stool frequency Onset associated with change in stool form
Functional diarrhea [37]	<p>Defined by Rome III criteria as $\geq 75\%$ of stools that are loose (mushy) and without pain for ≥ 3 months with symptom onset ≥ 6 months before diagnosis</p>

Abbreviations: ACG, American College of Gastroenterology; GI, gastrointestinal; HIV, human immunodeficiency virus.

antiprotozoal agents, such as metronidazole (for *Giardia* infection) or albendazole (for *Encephalitozoon intestinalis*).

For noninfectious forms of HIV-associated diarrhea, there are currently no FDA-approved treatment options. For patients with HAART-associated diarrhea, modification of HAART regimen may be attempted. Otherwise, pharmacologic options for treatment of HAART-associated diarrhea and HIV enteropathy are primarily supportive (Table 4).

Clinical data on the efficacy of antimotility agents in HIV-associated diarrhea are lacking. These agents may lead to objectionable postdiarrhea constipation and do not target the cause of HAART-associated diarrhea. In addition, extra caution should be used when prescribing bismuth subsalicylate in persons with advanced HIV infection because of the rare risk of developing bismuth encephalopathy. Antisecretory agents that have promise in the treatment of HAART-associated diarrhea include octreotide, a subcutaneously administered somatostatin analogue, and crofelemer, a first-in-class, naturally occurring, nonabsorbable, nonsystemic, GI-specific, intraluminally active, oral antidiarrheal agent currently under

Table 4. Pharmacologic Treatments for Noninfectious HIV-Associated Diarrhea

Class	Example
Adsorbents	Attapulgit
	Bismuth subsalicylate
	Kaolin
	Pectin
Antimotility agents	Diphenoxylate-atropine
	Loperamide
	Octreotide ^a
Antisecretory agent	Bismuth subsalicylate
	Crofelemer ^b
	Octreotide

From reference 27.

^a Inhibits motility at higher doses (eg, 100–250 μ g subcutaneous).

^b Investigational.

development [38]. Results from a phase 2, randomized, placebo-controlled, multicenter trial suggest that crofelemer may be effective in reducing stool weight and abnormal stool frequency in patients with AIDS and chronic diarrhea [27]. A phase 3, randomized, double-blind, placebo-controlled trial of crofelemer in HIV-infected patients receiving HAART with CD4⁺ cell counts >100 cells/ μ L (median, >500 cells/ μ L) has been completed (ADVENT; n = 376) [39]. The results suggest that crofelemer was effective for relief of HIV-associated diarrhea compared with placebo ($P = .0096$). Results of the phase 3 study also suggest that the tolerability of crofelemer was similar to that of placebo.

Nonpharmacologic approaches for the supportive treatment of noninfectious diarrhea may include dietary modification. Fiber supplements, such as oat bran, may be used to increase intestinal transit time and promote formation of more viscous (ie, less watery) stools [40]. Psyllium, a concentrated vegetable powder and source of fiber, may be used for treatment of PI-associated diarrhea.

FUTURE RESEARCH DIRECTIONS

Future research into HIV-associated diarrhea will be in 3 areas. The first goal is to better define the pathogenesis of diarrhea in properly treated patients with HIV infection. The second is to evaluate the efficacy of currently available and investigational antidiarrheal drugs (eg, crofelemer) in the treatment of HIV-associated diarrhea and prevention of complications of diarrhea. The third is to explore refinements in antiretroviral therapy with fewer GI complications and improved immune responsiveness.

CONCLUSIONS

HIV-associated diarrhea remains a common problem in patients with HIV infection in both the presence and absence of HAART, and it reduces QOL and decreases adherence to HAART. HIV-associated diarrhea may affect patients at any stage of HIV infection and may have several noninfectious causes, including adverse events associated with HAART (particularly when boosted PIs, such as ritonavir, are included in the regimen) and HIV enteropathy. While the pathophysiologic conditions mediating noninfectious forms of diarrhea remain incompletely defined, diarrhea associated with HAART may be caused by intestinal epithelial barrier disruption, which can lead to secretory diarrhea (ie, PIs and NRTIs). HIV enteropathy may be caused by direct effects of HIV on the GI tract, GI immune system, and GALT. Treatment of these noninfectious diarrheas remains merely supportive because there are no FDA-approved therapies. Further understanding of the mechanisms leading to noninfectious forms of diarrhea may lead to targeted therapies.

Notes

Acknowledgments. Writing and editorial assistance was provided under the direction of the authors by MedThink SciCom (Raleigh), with support from Salix Pharmaceuticals.

Potential conflicts of interest R. D. M. is a consultant to and has received grants administered through his university from Salix Pharmaceuticals. H. L. D. has consulted with, received honoraria for speaking for, and received research grants administered through his university from Salix Pharmaceuticals, and he has received research grants administered through his university from Intercell and Santarus.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

- Hill A, Balkin A. Risk factors for gastrointestinal adverse events in HIV treated and untreated patients. *AIDS Rev* **2009**; 11:30–8.
- Cello JP, Day LW. Idiopathic AIDS enteropathy and treatment of gastrointestinal opportunistic pathogens. *Gastroenterology* **2009**; 136:1952–65.
- Siddiqui U, Bini EJ, Chandarana K, et al. Prevalence and impact of diarrhea on health-related quality of life in HIV-infected patients in the era of highly active antiretroviral therapy. *J Clin Gastroenterol* **2007**; 41:484–90.
- O'Brien ME, Clark RA, Besch CL, Myers L, Kissinger P. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr* **2003**; 34:407–14.
- Silverberg MJ, Gore ME, French AL, et al. Prevalence of clinical symptoms associated with highly active antiretroviral therapy in the Women's Interagency HIV Study. *Clin Infect Dis* **2004**; 39:717–24.
- Zingmond DS, Kilbourne AM, Justice AC, et al. Differences in symptom expression in older HIV-positive patients: the Veterans Aging Cohort 3 Site Study and HIV Cost and Service Utilization Study experience. *J Acquir Immune Defic Syndr* **2003**; 33(Suppl 2): S84–92.
- Knox TA, Spiegelman D, Skinner SC, Gorbach S. Diarrhea and abnormalities of gastrointestinal function in a cohort of men and women with HIV infection. *Am J Gastroenterol* **2000**; 95:3482–9.
- Lorenz KA, Shapiro MF, Asch SM, Bozzette SA, Hays RD. Associations of symptoms and health-related quality of life: findings from a national study of persons with HIV infection. *Ann Intern Med* **2001**; 134:854–60.
- Siegel K, Schrimshaw EW, Brown-Bradley CJ, Lekas HM. Sources of emotional distress associated with diarrhea among late middle-age and older HIV-infected adults. *J Pain Symptom Manage* **2010**; 40:353–69.
- Tramarin A, Parise N, Camprotrini S, et al for the Palladio Study Group. Association between diarrhea and quality of life in HIV-infected patients receiving highly active antiretroviral therapy. *Qual Life Res* **2004**; 13:243–50.
- Feasey NA, Healey P, Gordon MA. Review article: the aetiology, investigation and management of diarrhoea in the HIV-positive patient. *Aliment Pharmacol Ther* **2011**; 34:587–603.
- Johnson M, Grinsztejn B, Rodriguez C, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. *AIDS* **2005**; 19:685–94.
- Johnson M, Grinsztejn B, Rodriguez C, et al. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. *AIDS* **2006**; 20:711–8.
- Molina J-M, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir versus twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 48 week efficacy and safety results of the CASTLE study. *Lancet* **2008**; 372:646–55.
- Molina J-M, Andrade-Villanueva J, Echevarria J, et al. Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naïve HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study. *J Acquir Immune Defic Syndr* **2010**; 53:323–32.
- Bánhegyi D, Katlama C, da Cunha CA, et al. Week 96 efficacy, virology and safety of darunavir/r versus lopinavir/r in treatment-experienced patients in TITAN. *Curr HIV Res* **2012**; 10:171–81.
- Madruga JV, Berger D, McMurchie M, et al on behalf of the TITAN study group. Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: a randomised controlled phase III trial. *Lancet* **2007**; 370:49–58.
- Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naïve, HIV-1-infected patients: 96-week analysis. *AIDS* **2009**; 23:1679–88.
- Ortiz R, DeJesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naïve HIV-1-infected patients at week 48. *AIDS* **2008**; 22:1389–97.
- Walmsley S, Avihingsanon A, Slim J, et al. Gemini: a noninferiority study of saquinavir/ritonavir versus lopinavir/ritonavir as initial HIV-1 therapy in adults. *J Acquir Immune Defic Syndr* **2009**; 50:367–74.
- Eron J Jr, Yeni P, Gathe J Jr, et al for the KLEAN Study Team. The KLEAN study of fosamprenavir-ritonavir versus lopinavir-ritonavir, each in combination with abacavir-lamivudine, for initial treatment of HIV infection over 48 weeks: a randomised non-inferiority trial. *Lancet* **2006**; 368:476–82.
- Pulido F, Estrada V, Baril JG, et al. Long-term efficacy and safety of fosamprenavir plus ritonavir versus lopinavir/ritonavir in combination with abacavir/lamivudine over 144 weeks. *HIV Clin Trials* **2009**; 10:76–87.
- Hicks CB, DeJesus E, Sloan LM, et al for the COL100758 Study Team. Comparison of once-daily fosamprenavir boosted with either 100 or 200 mg of ritonavir, in combination with abacavir/lamivudine: 96-week results from COL100758. *AIDS Res Hum Retroviruses* **2009**; 25:395–403.

24. Bode H, Lenzner L, Kraemer O, et al. The HIV protease inhibitors saquinavir, ritonavir, and nelfinavir induce apoptosis and decrease barrier function in human intestinal epithelial cells. *Antivir Ther* **2005**; 10:645–55.
25. Braga Neto MB, Aguiar CV, Maciel JG, et al. Evaluation of HIV protease and nucleoside reverse transcriptase inhibitors on proliferation, necrosis, apoptosis in intestinal epithelial cells and electrolyte and water transport and epithelial barrier function in mice. *BMC Gastroenterol* **2010**; 10:90.
26. Rufo P, Lin PW, Andrade A, et al. Diarrhea-associated HIV-1 APIs potentiate muscarinic activation of Cl⁻ secretion by T84 cells via prolongation of cytosolic Ca²⁺ signaling. *Am J Physiol Cell Physiol* **2004**; 286:C998–1008.
27. Holodniy M, Koch J, Mistal M, et al. A double blind, randomized, placebo-controlled phase II study to assess the safety and efficacy of orally administered SP-303 for the symptomatic treatment of diarrhea in patients with AIDS. *Am J Gastroenterol* **1999**; 94:3267–73.
28. Sankaran S, George MD, Reay E, et al. Rapid onset of intestinal epithelial barrier dysfunction in primary human immunodeficiency virus infection is driven by an imbalance between immune response and mucosal repair and regeneration. *J Virol* **2008**; 82:538–45.
29. Canani RB, Cirillo P, Mallardo G, et al. Effects of HIV-1 Tat protein on ion secretion and on cell proliferation in human intestinal epithelial cells. *Gastroenterology* **2003**; 124:368–76.
30. Buccigrossi V, Laudiero G, Nicastrò E, Miele E, Esposito F, Guarino A. The HIV-1 transactivator factor (Tat) induces enterocyte apoptosis through a redox-mediated mechanism. *PLoS One* **2011**; 6:e29436.
31. Dayanithi G, Yahi N, Baghdiguian S, Fantini J. Intracellular calcium release induced by human immunodeficiency virus type 1 (HIV-1) surface envelope glycoprotein in human intestinal epithelial cells: a putative mechanism for HIV-1 enteropathy. *Cell Calcium* **1995**; 18:9–18.
32. Maingat F, Halloran B, Acharjee S, et al. Inflammation and epithelial cell injury in AIDS enteropathy: involvement of endoplasmic reticulum stress. *FASEB J* **2011**; 25:2211–20.
33. Schulbin H, Bode H, Stocker H, et al for the Kompetenznetz HIV/AIDS Germany. Cytokine expression in the colonic mucosa of human immunodeficiency virus-infected individuals before and during 9 months of antiretroviral therapy. *Antimicrob Agents Chemother* **2008**; 52:3377–84.
34. Brownley KA, Hurwitz BE. Assessment of autonomic and cardiovascular function in HIV disease. In: Barbaro G, ed. *HIV infection and the cardiovascular system*. Basel, Switzerland: S. Karger, **2003**:105–39. Borer JS, ed. *Advances in cardiology*, vol 40.
35. Reed SL, Davis CE. Laboratory diagnosis of parasitic infections. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's principles of internal medicine*. Vol 18. New York, NY: McGraw-Hill, **2012**:25–21–25–28.
36. Brenchley JM, Douek DC. HIV infection and the gastrointestinal immune system. *Mucosal Immunol* **2008**; 1:23–30.
37. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* **2006**; 130:1480–91.
38. Crutchley RD, Miller J, Garey KW. Crofelemer, a novel agent for treatment of secretory diarrhea. *Ann Pharmacother* **2010**; 44:878–84.
39. MacArthur R, Hawkins T, Brown S, LaMarca A, Chaturvedi P, Ernst JA. ADVENT trial: crofelemer for the treatment of secretory diarrhea in HIV+ individuals [poster 889]. Presented at: 19th Conference on Retroviruses and Opportunistic Infections; 5–8 March 2012; Seattle, WA. Available at: <http://www.retroconference.org/2012b/Abstracts/43107.htm>. Accessed 11 April 2012.
40. Sherman DS, Fish DN. Management of protease inhibitor-associated diarrhea. *Clin Infect Dis* **2000**; 30:908–14.