Diarrhea and AIDS in the Era of Highly Active Antiretroviral Therapy

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Since the beginning of the AIDS epidemic, it has been obvious that diarrhea is one of the most common manifestations of this infection. In Africa, HIV infection has been characterized by a relentlessly progressive condition called Slims disease, which is the result of unremitting watery diarrhea, weight loss, severe malnutrition, low-grade fever with night sweats, and, finally, a wasting away followed by death. Although multiple parasites, pathogenic bacteria, and, occasionally, viruses have been isolated from the stool of up to two-thirds of patients with AIDS, pathogen-specific therapy has generally been only minimally effective and diarrhea generally considered a manifestation of the underlying immunodeficiency.

Diarrhea has been described previously in association with various other immunodeficiency syndromes; up to 60% of patients with common variable hypogammaglobulinemia have diarrhea, with 40% developing malnutrition [1, 2]. In the case of severe combined immunodeficiency, patients are extremely prone to infections and they commonly succumb to chronic diarrhea and malabsorption. In selective IgA deficiency—the most common immunodeficiency state in humans that affects 1 of 500–3,000 people in the general population—recurrent bronchusinopulmonary infections are often associated with a high incidence of gastrointestinal disease, including diarrhea, steatorrhea, and celiac sprue.

In the Western world, diarrhea has also dominated the clinical picture of patients with advanced HIV and, in fact, has been a clinical indicator of progression of immunodeficiency along with thrush, weight loss, fevers, and night sweats. In many cases pathogenic organisms could be isolated, and various algorithms were developed to standardize the work-up of this condition. However, not all cases of chronic diarrhea in advanced AIDS can be attributed to an infectious etiology, thus the therapeutic approach is limited. Drug side effects, gastrointestinal malignancies (Kaposi’s sarcoma, lymphoma), and HIV enteropathy are often listed as likely causes.

The purpose of this article is to review the causes of diarrhea in HIV-infected individuals, review the information concerning the impact of highly active antiretroviral therapy (HAART) on this clinical manifestation, and, because data on the role of HAART in causing diarrhea are only just becoming available, to speculate about the future impact of HAART on diarrheal illness in HIV-infected patients.

Causes of Diarrhea in HIV-Infected Patients

Bacteria

Pathogen-specific therapy is often successful in cases where pathogenic bacteria are identified. Such cases include infections due to Shigella, Salmonella, and Campylobacter species for which treatment with the fluoroquinolones usually resolves the diarrhea and fever. However, relapses after discontinuation of therapy have been observed more frequently among HIV-infected individuals than in the general population. A curious syndrome of nontyphoidal salmonella bacteremia that repeatedly relapses when effective therapy is discontinued has been reported, a phenomenon observed in other opportunistic infections such as cryptococcal meningitis and disseminated histoplasmosis [3]. Campylobacter upsaliensis has recently been identified as a cause of chronic diarrhea in Australia [4].

Diarrhea associated with Clostridium difficile can be a particularly difficult diagnostic dilemma in patients with AIDS, given that they are often taking various types of antibiotics because diarrhea is so common among these patients. A C. difficile—anxiety assay should always be part of a work-up for new-onset watery diarrhea, with or without fecal leukocytes, especially if the diarrhea is associated with fever, leukocytosis, and cramps. Treatment with metronidazole, 250 mg po t.i.d. for 7 to 10 days, is usually curative. However, as in the general population, up to 20% of patients will have a relapse, and these relapses should be retreated with metronidazole at the same dosage. The annual incidence of C. difficile--associated diarrhea in HIV-positive individuals who were hospitalized ranged from 1.7–6.4 cases per 100 HIV-infected patients who were discharged from the hospital [5]. Three independent risk factors were associated with C. difficile--associated diarrhea among HIV-infected patients: a CD4 cell count of <50/mm³, clindamycin use, and penicillin use.

There have been several reports of enteroaggregative Escherichia coli (EaggEc) that caused chronic diarrhea in AIDS
patients who had CD4 cell counts of \(<50/\text{mm}^3\) [6]. Others have found no difference in prevalence of \(EaggEc\) in HIV-positive patients with and without diarrhea [7]. \(EaggEc\) have been associated with persistent diarrhea in children in developing countries. The pathophysiologic mechanism by which this organism causes diarrhea is not entirely clear. It is known that a heat-stable toxin that appears to mediate secretion through cyclic guanosine monophosphate (GMP) is produced. In addition, some strains produce a larger toxin that stimulates IL-8, and other strains have the ability to invade enterocytes directly.

Studying the epidemiology of \(EaggEc\) has been challenging, mainly because it is difficult to recover the organisms from stool. These organisms cannot be identified by use of routine stool culture; the expensive tissue culture adherence assay is required (all strains aggregate in HeLa or HEp-2 tissue culture assays). This assay remains the most reliable tool for identification of the organisms. The true prevalence of \(EaggEc\) in the stool of nonimmunocompromised adults around the world is not known. In a small study of non-HIV-infected adults with diarrhea, \(EaggEc\) was identified in 19 (28%) of 68 patients [6]. In the same study, HIV-positive individuals with and without diarrhea were screened for evidence of \(EaggEc\) in the stool. The organisms were identified in the stool of individuals in both groups, although more frequently in the patients with diarrhea. The CD4 cell counts were lower in the diarrheal group (mean, 94/mm\(^3\) vs. 157/mm\(^3\)), suggesting that these organisms are more likely to produce diarrhea when immunosuppression is more advanced.

Quinolone therapy for infections due to \(EaggEc\) may be beneficial, and resistance of these organisms to ciprofloxacin remains low. In a recent placebo-controlled cross-over treatment trial, therapy with ciprofloxacin, 500 mg po b.i.d. for 7 days, resulted in a 50% reduction in the number of stools per day and a 40% decrease in intestinal symptoms, as well as elimination of \(EaggEc\) from the stool in all 24 patients [8].

In a recent study from Switzerland, small bowel bacterial overgrowth (SBBO) was present in 19% of HIV-infected patients with chronic, pathogen-negative diarrhea [9]. SBBO was defined as \(\geq10^5\) cfu of bacteria per gram of aspirate, as determined by quantitative culture of small bowel fluid aspirates (endoscopy was extended to the jejunum by use of a pediatric colonoscope). The most common organisms isolated were viridans streptococci, \(Lactobacillus\) species, yeast, and \(Neisseria pharyngitides\). No gram-negative organisms or anaerobes were isolated. No data are currently available to determine whether the eradication of SBBO affects the outcome of pathogen-negative diarrhea in HIV-infected patients.

Parasites

The most common pathogens isolated from patients with AIDS continue to be new and unusual parasitic organisms that had rarely been implicated in human disease before the AIDS epidemic. The most notorious of these is \(Cryptosporidium parvum\). This organism was a recognized pathogen in cattle and hogs and had been associated with small outbreaks of cryptosporidiosis in veterinarians and others before 1980. Since then, multiple outbreaks have been reported and the organism has been shown to be highly infectious (as few as 132 oocysts can cause diarrhea in a normal adult) [10].

In patients with advanced AIDS, usually with CD4 cell counts of \(<150/\text{mm}^3\), \(C. parvum\) produces a large-volume watery diarrhea that is usually progressive but is occasionally associated with spontaneous remissions and reexacerbations that last for years. In HIV-infected patients with CD4 cell counts of \(>180/\text{mm}^3\), the diarrhea resolved spontaneously in 7 to 28 days, but the diarrhea persisted in 87% of those with CD4 cell counts of \(<180/\text{mm}^3\) [11]. HAART is protective against disease [12]. \(C. parvum\) is easily identified in stool with use of a modified acid-fast stain and is seen attached to the brush borders on the external surface of the small intestinal epithelium.

Pathogen-specific therapy for cryptosporidiosis has been disappointing. Initially, in a small study that lacked controls, azithromycin was found to be effective, however, when tested in a larger controlled study, it was no better than placebo. Paromomycin, a nonabsorbable aminoglycoside, was also touted as effective, but no benefit was reported in a prospective double-blind randomized study [13]. Roxithromycin, a new macrolide studied in Brazil, has also demonstrated efficacy in an uncontrolled study [14]. More recently, a powdered immunoglobulin concentrate from bovine colostrum demonstrated a modest response [15]. A second approach that was tried as therapy for cryptosporidiosis was inhibition of the normal-gut secretory mechanisms with octreotide (Sandostatin, Sandoz Pharma, Basel, Switzerland), an inhibitor of somatostatin, a gut hormone. These studies proved that octreotide reduced the total volume of stool produced when a patient was infected with cryptosporidia by one-third to one-half in some patients, but had little effect in most [16]. The therapy is extremely expensive and has never been adopted as a standard of care.

The most effective therapy for cryptosporidiosis is HAART. Immune reconstitution following potent antiretroviral therapy can induce diarrheal cessation, weight gain, and complete remission of cryptosporidiosis. In most patients with persistent cryptosporidial diarrhea who were treated with HAART, the symptoms disappeared once they had CD4 cell count increases to \(>250/\text{mm}^3\), and the organism could not be found by stool microscopy or in biopsy samples. However, clinical relapses were documented when HAART failed, CD4 cell counts fell, and HIV-1 RNA levels increased, suggesting that the infection was not eradicated [17–19].

Another previously unusual gut pathogen, \(Isospora belli\), also emerged as a significant cause of diarrhea in patients with advanced AIDS. It produces a clinical syndrome similar to cryptosporidiosis that usually occurs in patients with CD4 cell counts of \(<100/\text{mm}^3\). It can also be identified by a modified
acid-fast stain, but the cysts are much larger than those attributable to Cryptosporidium species (20–30 μm vs. 4–6 μm). The distinction is important because Isospora species usually respond to therapy with trimethoprim-sulfamethoxazole (TMP-SMZ); one double-strength tablet po q.i.d. for 10 days followed by b.i.d. for 3 weeks, and then chronic suppression with one tablet 3 times a week for the duration of immunosuppression. Without chronic suppression, relapses are common. The number of patients reported to date is not adequate to determine with certainty whether suppression can be stopped with TMP-SMZ, but it most likely can be discontinued if the response of the CD4 cell count to this therapy is robust (>250/mm³).

The various microsporidia, which include Encephalitozoon intestinalis (Septata intestinalis), Enterocytozoon bieneusi, and Encephalitozoon hellem are food-borne and water-borne spores of 1–2 μm that can be seen in stool with Giemsa or special trichrome stains [20]. They account for up to 20% of diarrheal disease in patients with CD4 cell counts of <50/mm³ and as much as 60% in patients with chronic diarrhea [21]. The pathophysiologic mechanism by which microsporida cause diarrhea is not entirely clear. It appears in part to be malabsorptive, caused by a reduction of absorptive mucosal surface area and enterocyte immaturity with impairment of function [22].

The clinical syndrome cannot be distinguished from that caused by Cryptosporidium or Isospora species: a large-volume watery diarrhea without WBCs, with malabsorption and wasting that is remittent over years. There is no standard treatment for microsporidiosis, although case reports and small case series have indicated that metronidazole (500 mg b.i.d.) decreased diarrhea in 10 of 19 patients but did not clear the organism from the stool in any of the patients. Albendazole, 400 mg po b.i.d., rapidly controlled diarrhea due to E. bieneusi and E. intestinalis in 3 of 10 patients, but 4 had no response [23]; atovaquone, 750 mg t.i.d., decreased diarrhea in 8 of 8 patients but did not eradicate the organism from the stool [24]. For E. hellem, single case reports indicate that therapy with albendazole, itraconazole, or fluconazole has been somewhat successful. With HAART, E. bieneusi was cleared from the stools in two of six patients after 24 weeks [25]. In another study, complete remission of diarrhea due to E. bieneusi occurred with HAART [17]. In these patients, the need for chronic suppression should disappear, but more conclusive studies are needed before we can do more than speculate.

Other pathogenic parasites that are more common in the general population such as Entamoeba histolytica, Giardia, and Cyclospora species can also cause diarrhea in patients with AIDS and should be considered in the differential diagnosis. Cyclospora cayetanensis usually occurs in patients with CD4 cell counts of <100/mm³; these patients will usually respond in 2–3 days to therapy with TMP-SMZ, one double-strength tablet b.i.d. for 10 days, then one tablet three times a week for the duration of immunosuppression. For patients treated with HAART whose CD4 cell counts increase to >250/mm³, one would be tempted to discontinue suppression.

**Mycobacteria**

Mycobacterium avium complex (MAC) is a common infectious agent in patients with AIDS, especially when the CD4 cell count decreases to <50/mm³. The most common presentation is a febrile illness with weight loss, anorexia, night sweats, and a generalized catabolic state. Cultures of blood are positive, and patients will usually respond to therapy with a macrolide and ethambutol, but suppressive therapy is necessary to prevent relapse. Diarrhea is common in these patients, and a biopsy of the small bowel may show macrophages filled with acid-fast bacilli, similar to Whipple’s disease. The diarrhea is usually watery, without fecal WBCs, and may be associated with malabsorption and diffuse abdominal cramping in the late stages of disease. Whether the diarrhea consistently responds to antymycobacterial therapy is not clear from published reports. Although it is not yet an established standard of care, many clinicians are discontinuing suppressive anti-MAC therapy when a robust CD4 cell count response (>250/mm³) follows HAART.

Mycobacterium tuberculosis should also be included in the differential diagnosis for patients from areas with high tuberculosis prevalence [26].

**Viruses**

Although various viruses such as rotavirus, adenovirus, coronnavirus, astrovirus, and calicivirus (as defined by electron-microscopy of stool specimens) have been implicated as causes of diarrhea in patients with AIDS, most infections appear to be self-limited and are untreatable [27]. In Argentina, a picobirnavirus was recently detected in 9% of HIV-infected individuals with chronic diarrhea but not in HIV-infected patients without diarrhea or in non-HIV-infected patients with diarrhea [28]. Cytomegalovirus, however, accounts for up to 20% of diarrhea in patients with AIDS and is potentially treatable. This virus typically produces a colitis that colonoscopy reveals as punctate hemorrhages with ulcerations, which demonstrate typical intranuclear inclusions on biopsy. In 10% to 30% of cases, the virus will affect only the right side ascending colon and be missed on sigmoidoscopy [29]. The clinical picture is typically one of fever and small-volume, occasionally bloody diarrhea with fecal leukocytes, occasionally leading to perforation or toxic megacolon. Treatment is with either ganciclovir or foscarnet in similar dosages as those used to treat CMV retinitis. Some patients definitely respond to anti-CMV therapy, but overall response rates are generally not as good as those for retinitis [30].

Suppressive therapy is critical, but when there is a rise in CD4 cell counts (>250/mm³) with HAART, many clinicians are starting to discontinue either the ganciclovir or foscarnet therapy for CMV retinitis and wait for symptoms to reappear [31, 32]. Because therapy is expensive, toxic, and difficult to administer intravenously, this approach certainly makes sense,
Although one may be forced to reinstitute induction therapy if relapse occurs. To date there are just no convincing data to guide recommendations.

**When No Pathogen Can Be Identified**

In 15% to 46% of HIV-infected patients with diarrhea, no pathogen can be identified and HIV itself may be important (HIV enteropathy) [2]. Stockmann and colleagues [33] have recently demonstrated that for HIV-infected individuals with diarrhea and without other identified causes of diarrhea there was no evidence for active ion secretion return or malabsorption but there was evidence for impaired epithelial-barrier function. They suggested that opening of the tight junctions between epithelial cells by HIV-stimulated cytokine release (TNF or IFN-γ) could cause diarrhea by a leak flux mechanism. A recently purified plant product (SP303-Provir, Shaman Pharmaceuticals, South San Francisco, CA) from Croton lechleri, a species found in the Western Amazon region, has been shown in one study to have some benefit in reducing diarrhea in these patients [34].

**Diarrhea as a Side Effect of HAART**

During the past 4 years, the number of patients infected with chronic diarrhea who undergo endoscopic evaluations has declined. The proportion of patients diagnosed with an enteric opportunistic infection has fallen precipitously [35]. In the era of potent antiretroviral therapy, one can expect dramatic changes in the incidence and etiology of chronic diarrhea in patients with advanced AIDS. Recent studies have shown that combination antiretroviral therapy can result in complete and sustained clinical, microbiological, and histologic resolution of various opportunistic infections [36-39]. Therefore, chronic diarrhea will be much less likely to be caused by the pathogens listed above or even by HIV itself, but will now more likely be a result of side-effects of the antiretroviral drugs themselves.

Most of these drugs will cause diarrhea: didanosine, in up to 28% of patients; lamivudine (3TC), in up to 18%; stavudine (d4T), in up to 7%; zalcitabine (dDC), in up to 1%; zidovudine (AZT), in up to 12%; indinavir, in up to 5%; nelfinavir, in up to 30%; ritonavir, in up to 13%; saquinavir, in up to 5%; nevirapine, in up to 2%; and delavirdine, in up to 11%. Up to 41% of patients receiving protease inhibitor therapy in one series had diarrhea [40]. The combination of stavudine and lamivudine plus nelfinavir with either twice daily or three-times-daily dosage schedules caused diarrhea in 12% and 13% of patients, respectively [41]. According to some studies, up to 40% of patients receiving combinations of antiretroviral agents will experience moderate-to-severe diarrhea, significantly complicating treatment.

**Conclusion**

It is clear that the spectrum of diarrheal illnesses in HIV-infected individuals changed significantly during the late 1990s because of the introduction of HAART. However, diarrhea will likely remain one of the most troublesome clinical manifestations of HIV infection and will now most likely reflect toxicity from the various antiretroviral drugs used to treat the underlying HIV infection and restore the damaged immune system.

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1. All of the following regarding *Clostridium difficile*-associated diarrhea in AIDS patients are true except:
   A. It occurs most often with CD4 cell counts of <50/mm³.
   B. Clinical clues include watery diarrhea without fecal leukocytes and peripheral leukocytes.
   C. The antibiotic most associated with the disease is clindamycin.
   D. The first-line treatment of choice is oral vancomycin.
   E. The clinical disease in HIV-infected individuals is similar to that seen in the general population.

2. Which of the following is true regarding enteroaggregative *Escherichia coli* (EaggEc):
   A. It is a common cause of acute diarrhea in patients with AIDS.
   B. It can be readily diagnosed by routine stool culture.
   C. It only causes diarrhea in immunocompromised patients.
   D. Antibiotic resistance to ciprofloxacin remains low.
   E. These organisms are rarely found in asymptomatic individuals.

3. Small bowel bacterial overgrowth should be considered a cause of diarrhea in HIV-infected individuals in all of the following situations except:
   A. When other known pathogens are not identified
   B. When >10⁵ cfu/mL of small bowel aspirate is cultured
   C. When the predominant isolates are gram-negative bacilli

4. All of the following are true regarding *Cryptosporidium parvum* except:
   A. It is a recognized pathogen in cattle and hogs.
   B. It can cause human disease with a very low inoculum.
   C. Diarrhea caused by *C. parvum* responds well to paromomycin therapy.
   D. The organism can be readily identified in stool by use of a modified acid-fast stain.
   E. The most effective treatment is highly active antiretroviral therapy (HAART).

5. All of the following are true regarding *Isospora belli* except:
   A. It produces a chronic watery diarrhea indistinguishable from that of *C. parvum*.
   B. Cysts are much larger than *C. parvum* cysts.
   C. Treatment with trimethoprim-sulfamethoxazole is effective.
   D. Relapses after treatment are rare.

6. The various microsporidia produce diarrheal disease characterized by:
   A. High fever and chills
   B. Blood and large numbers of fecal leukocytes
   C. Small-volume stools
   D. Watery large-volume stools without leukocytes

7. All of the following regarding infection due to *Mycobacterium avium* complex (MAC) are true except:
   A. Biopsy of the small bowel often reveals macrophages filled with acid-fast bacilli.
   B. The most common symptoms are fever, night sweats, and weight loss.
   C. Macrolides alone are sufficient to effectively treat the disease.
   D. Most cases of MAC infection occur with CD4 cell counts of <50/mm³.
   E. MAC-associated diarrhea is usually watery without fecal leukocytes.
8. Cytomegalovirus (CMV) produces colitis characterized by all of the following except:
   A. Sigmoidoscopy usually reveals punctate hemorrhages with ulcerations.
   B. The disease is most often confined to the descending colon.
   C. The diarrhea is usually small volume with fecal leukocytes.
   D. The colitis is more responsive to ganciclovir therapy than is CMV retinitis.

9. With effective antiretroviral therapy, the most common cause of diarrhea in patients with AIDS is:
   A. HIV
   B. CMV
   C. Cryptosporidium parvum
   D. Drug toxicity
   E. Immune reconstitution

10. Following a robust CD4 cell count response to HAART, prophylactic therapy for the following pathogens can likely be discontinued:
    A. Cryptosporidium species
    B. CMV
    C. MAC
    D. Isospora species
    E. All of the above