DIARRHEAL DISEASE IN PATIENTS INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS IN BANGKOK, THAILAND

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Abstract. Diarrheal disease and its associated morbidities occur frequently in patients infected with human immunodeficiency virus (HIV) and may be associated with a decreased quality of life. We studied the spectrum of symptoms, measures of nutritional status, and the enteric pathogens associated with diarrheal disease in a group of 24 patients infected with HIV in Bangkok, Thailand compared with a group of 19 patients infected with HIV without diarrhea cared for at the same clinic. Patients with diarrhea appeared to have more advanced disease by CD4 cell counts and complained more frequently of symptoms such as anorexia, gas, and bloating than patients without diarrhea. Patients with diarrhea had a tendency toward a lower nutritional status, as measured by body mass index and mid arm circumference. Stool culture and examination revealed that enteric pathogens including Salmonella species and Cryptosporidium parvum sporidia were recovered at equal frequencies in patients with and without diarrhea (27% of the patients with diarrhea and 25% of the patients without diarrhea). Microsporidia was identified in one patient with diarrhea. It was not possible to identify a pathogen in 73% of the patients with diarrhea and 75% of the patients without diarrhea, suggesting that additional agents or factors may be responsible for the diarrheal symptoms in the patients with diarrhea. More extensive studies to identify potentially treatable pathogens in HIV-infected patients with diarrhea in Thailand are warranted and further attempts to better define the syndrome of pathogen-negative diarrheal disease in patients infected with HIV might result in the development of more targeted interventions in these patients.

Diarrheal disease and malnutrition are frequent complications in patients infected with the human immunodeficiency virus (HIV). Diarrheal disease in this patient population has been demonstrated to be associated with a significant decrease in quality of life, whatever the etiology of the diarrheal illness might be.1–4 Multiple infectious pathogens including bacteria, mycobacteria, viruses, and parasites have been implicated as causes of diarrheal illness in patients infected with HIV.5–7 The etiology of diarrheal disease appears to vary by geographic region.8,9 In patients with HIV in Africa, diarrheal disease and wasting are a more common complication of HIV infection than they are in the United States and Western Europe, and parasitic pathogens, such as Cryptosporidium parvum, appear to be a more frequent etiologic agent than in the United States and Western Europe. Additionally, in series of extensively studied patients with HIV and diarrhea, a significant proportion of patients remain without an identified etiology for their diarrheal illness.10,11 Lack of aggressiveness in investigation can explain a portion of the cases for which no pathogen can be found. Hypotheses to explain the remaining large percentage of cases that have no identifiable etiologic agent include the possibility of as-yet-unrecognized pathogens, dysregulation of intestinal cytokines, disturbances of enteric autonomic enervation, or potentially the direct effects of HIV infection of the intestine.12,13 Understanding the etiology of the diarrheal disease is crucial to developing directed interventions for the patients with this debilitating syndrome.

Little is known about the causes and morbidity of diarrheal illness in HIV-infected patients in the rest of the world. There is one report of the isolation of C. parvum and Mycobacterium tuberculosis from 20% and 18%, respectively, from a group of patients hospitalized in Bangkok with severely advanced HIV disease.14 This study did not report the frequency of pathogens in a control population and reported on a group of individuals that were extremely late in the course of their HIV disease. Therefore, we studied the etiologic agents and morbidities associated with diarrheal disease in a cohort of out-patients infected with HIV in Thailand.

METHODS

Patients. Adult patients infected with HIV who were followed at the Special Immunology Clinic at Chulalongkorn University Medical School in Bangkok were recruited for the study. At a clinic visit, patients were asked if they had diarrhea and if so were asked to participate in the study; an equal number of patients seen during those clinic visits who specifically denied that they had complaints of diarrhea were also recruited for the study as controls. For the purposes of the study, diarrhea was defined as more than three stools per day or a two-fold increase in stool frequency over the usual number of bowel movements with a decrease in consistency.

The study was approved by the ethical review boards of Deaconess Hospital (Boston, MA) and Chulalongkorn University Medical Center in Bangkok. Informed consent was obtained and patients were interviewed and examined. Medical records were reviewed for pertinent HIV history, medications, and laboratory data including CD4 cell count. All patients enrolled in the study were asked to submit a stool specimen to the clinic laboratory.

Stool studies. Freshly submitted stool from all patients was examined for the presence of inflammatory cells and blood and was cultured for routine enteric pathogens including Salmonella spp., Shigella spp., Vibrio cholerae, Campylobacter spp., Aeromonas spp., and Plesiomonas shigelloides. Freshly collected stool samples were inoculated on
Table 1
Demographic and clinical data for human immunodeficiency virus (HIV)–infected patients with and without diarrhea at the special Immunology Clinic at Chulalongkorn University Medical School

<table>
<thead>
<tr>
<th></th>
<th>Diarrhea (n = 24)</th>
<th>No diarrhea (n = 19)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (83%)</td>
<td>17 (97%)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>4 (17%)</td>
<td>2 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (mean ± SD), years</td>
<td>34.2 ± 7.3</td>
<td>37.3 ± 9.6</td>
<td>NS</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean ± SD)</td>
<td>52 ± 55</td>
<td>114 ± 143</td>
<td>0.04</td>
</tr>
<tr>
<td>Range</td>
<td>(0–202)</td>
<td>(0–545)</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>34.5</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Region of birth</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangkok</td>
<td>15 (63%)</td>
<td>Bangkok 11 (58%)</td>
<td>NS</td>
</tr>
<tr>
<td>South</td>
<td>1 (4%)</td>
<td>South: 1 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>North</td>
<td>1 (4%)</td>
<td>North: 5 (26%)</td>
<td>NS</td>
</tr>
<tr>
<td>Central</td>
<td>7 (29%)</td>
<td>Central 2 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>HIV risk factor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterosexual</td>
<td>24 (100%)</td>
<td>Heterosexual: 13 (68%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Bisexual</td>
<td>0</td>
<td>Bisexual: 2 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Male sex with male: 0</td>
<td>1</td>
<td>Male sex with male: 1 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>Unknown: 3 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of recognized HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mean ± SD), months</td>
<td>25.2 ± 21.6</td>
<td>92.4 ± 146.4</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>11.2 ± 3.3</td>
<td>10.4 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>White blood cells</td>
<td>5.6 ± 3.1</td>
<td>4.2 ± 2.5</td>
<td>NS</td>
</tr>
</tbody>
</table>

* NS = not significant.

Table 2
Previous human immunodeficiency virus (HIV)–related illnesses and medications in patients with and without diarrhea*

<table>
<thead>
<tr>
<th>Prior HIV-associated diagnoses</th>
<th>Diarrhea (n = 24)</th>
<th>No diarrhea (n = 19)</th>
<th>p†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral hairy leukoplaikia</td>
<td>5 (21%)</td>
<td>12 (63%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mucosal candidiasis</td>
<td>6 (25%)</td>
<td>3 (16%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cryptococcal disease</td>
<td>4 (17%)</td>
<td>0 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>4 (17%)</td>
<td>4 (21%)</td>
<td>NS</td>
</tr>
<tr>
<td>HSV/VZV</td>
<td>7 (29%)</td>
<td>5 (26%)</td>
<td>NS</td>
</tr>
<tr>
<td>Kaposis’s sarcoma</td>
<td>0</td>
<td>1 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>PCD</td>
<td>1 (4%)</td>
<td>1 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Penicilliosis</td>
<td>1 (4%)</td>
<td>0 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>Rashes</td>
<td>1 (4%)</td>
<td>9 (47%)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Medications

<table>
<thead>
<tr>
<th></th>
<th>Diarrhea (n = 24)</th>
<th>No diarrhea (n = 19)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine (AZT)</td>
<td>10 (42%)</td>
<td>6 (32%)</td>
<td>NS</td>
</tr>
<tr>
<td>ddI</td>
<td>11 (46%)</td>
<td>6 (32%)</td>
<td>NS</td>
</tr>
<tr>
<td>dDC</td>
<td>3 (13%)</td>
<td>1 (5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Combination antiretroviral therapy</td>
<td>7 (29%)</td>
<td>2 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>PDC prophylaxis (TMP-SMX, dapsone)</td>
<td>20 (83%)</td>
<td>13 (68%)</td>
<td>NS</td>
</tr>
<tr>
<td>Antifungal (Keto, Flu, Itra)</td>
<td>15 (63%)</td>
<td>3 (16%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Anti-TB (treatment, prophylaxis)</td>
<td>11 (46%)</td>
<td>3 (16%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>1 (4%)</td>
<td>0 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>Anti-diarrheals</td>
<td>3 (13%)</td>
<td>0 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>Vitamins</td>
<td>5 (21%)</td>
<td>2 (11%)</td>
<td>NS</td>
</tr>
<tr>
<td>Nutritional supplement</td>
<td>9 (38%)</td>
<td>0 (NS)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* HIV = herpes simplex virus; VZV = varicella zoster virus; PCP = Pneumocystis carinii pneumonia; AZT = azidothymidine; ddI = didanosine; dDC = deoxycoformycin; TMP-SMX = trimethoprin-sulfamethoxazole; Keto = ketoconazole; Flu = flaconazole; Itra = iraconazole; TB = tuberculosis.
† NS = not significant.
‡ Infection with Penicillium marneffii.

MacConkey agar, Salmonella-Shigella (SS) agar, tellurite taurocholate gelatin agar, ampicillin-blood agar, Butzler’s agar, and selenite F broth. Selenite F broth was subcultured onto SS agar after overnight incubation at 37°C. Butzler’s medium was incubated in an atmosphere of 10% CO₂ for up to 48 hr for the isolation of Campylobacter spp. The other plates were incubated for 24–48 hr at 37°C in a normal atmosphere. Stool was examined for routine parasites and was stained with the modified acid-fast and modified trichrome stains looking for C. parvum, cyclospora, and microsporidia.15–17 Stool was examined for rotavirus by ELISA.

Statistical analysis. All patient data was entered into a Microsoft (Redmond, WA) Access database for analysis. Statistical analysis was done using the Statview software package (SAS Institute, Cary, NC). Group comparisons of continuous variables were done by the Student’s t-test or Wilcoxon rank sum test. Comparison of discrete variables was done by the chi-square test.

RESULTS

A total of 24 HIV infected patients with diarrhea and 19 HIV infected patients without diarrhea were enrolled in the study. Stool examination was available for 22 of 24 patients with diarrhea and 16 of 19 patients without diarrhea.

The demographic and clinical data describing the patients with and without diarrhea are shown in Table 1. There were no significant differences between the two groups in terms of age, sex, or region of birth. Individuals who presented with diarrhea appeared to have more advanced disease by CD4 cell count, although the acknowledged duration of HIV seropositivity between the two groups did not differ. The group of patients who presented with diarrhea had all acquired HIV via the heterosexual route whereas the group who presented without diarrhea had a variety of exposure risks for acquisition of HIV.

Other HIV-related medical conditions and medications taken by the patients are shown in Table 2. There were no significant differences in the presentations of the two groups with the exception of more oral hairy leukoplaikia and more nonspecific rashes in the group of patients who did not have...
diarrhea. Likewise, the medication exposures of the two groups were similar with the exception of more usage of anti-tuberculous and antifungal medications in the group of patients with diarrhea. The use of anti-tuberculous medications in this group correlates with a study of prophylaxis against *M. tuberculosis* in HIV-infected individuals that was ongoing in the clinic at the time of the study. The patients with diarrhea were more likely to be taking a nutritional supplement that was being offered to the patients in the clinic at the time of the study.

The symptoms reported by the two groups of patients are shown in Table 3. Those patients who presented with diarrhea had a mean of 5.9 stools for a mean of 5.8 months. There was a trend for patients with diarrhea to have a decreased body mass index compared with the patients who did not have diarrhea. The patients with diarrhea also had a tendency to have a smaller mid-arm circumference than the patients who presented without diarrhea. None of the patients with diarrhea reported having formed stool. The patients with diarrhea were more likely to complain of anorexia and weight loss than those patients who did not have diarrhea. Additionally, patients with diarrhea reported more gas, bloating, and malaise than did patients without diarrhea.

When the stools of both groups of patients were examined for routine enteric pathogens, there was little difference in the presence of pathogens between the two groups. Two of the patients with diarrhea had fecal leukocytes detected; none of the patients without diarrhea had fecal leukocytes. No patient in either group had red blood cells in his or her stool. There was no significant difference in the rate of identification of pathogens between the group of patients with and without diarrhea; 72% of the patients with diarrhea and 75% of the patients without diarrhea had no identifiable pathogens.

Two patients with diarrhea and three patients without diarrhea had *Salmonella* species isolated from their stool. One patient without diarrhea had *C. parvum* identified in the stool (this patient had a CD4 cell count of 287 cells/mm²). Two patients with diarrhea had *C. parvum* in their stool (these patients had CD4 cell counts of 29 and 21 cells/mm², respectively). One patient with diarrhea had microsporidia identified by the modified trichrome stain. This individual had a CD4 cell count of 53 cells/mm². One patient with diarrhea had *Strongyloides* identified in the stool.

**DISCUSSION**

It has been demonstrated that diarrheal disease and its attendant symptoms in patients with HIV may be associated with a diminished quality of life. Attempts to further describe these syndromes and to develop interventions, if possible, for common HIV-associated symptoms, such as diarrheal disease might be able to provide a cost-effective means to diminish symptoms and thereby improve the quality of life for otherwise healthy patients infected with HIV. Therefore, a survey of individuals infected with HIV cared for at a special outpatient immunology clinic at a university medical center in Bangkok, Thailand was conducted to describe the spectrum of diarrheal symptoms and the occurrence of enteric pathogens in this setting.

Patients with diarrheal disease reported a large daily number of diarrheal stools for a prolonged period of time. These patients also reported symptoms, such as anorexia, gas, bloating, and malaise, which could be consistent with a lower quality of life, although no direct measure of quality of life was done in this survey. Those individuals with diarrhea also had a tendency for a lesser nutritional status when compared with patients without diarrhea, as determined by measurement of body mass index and mid-arm circumference.

Not surprisingly, patients with diarrhea and without diarrhea had some enteric pathogens identified in their stool (27% in the patients with diarrhea and 25% in the patients without diarrhea). *Salmonella* species were identified at the same rate in both groups of patients. *Cryptosporidium parvum*, which has been previously reported in patients with HIV in Thailand, was also identified in both groups. *Cryptosporidium parvum* appeared to be associated with prolonged symptoms in the patients with more advanced disease.

*Table 3*

<table>
<thead>
<tr>
<th>Characterization of diarrheal disease and attendant symptoms in patients with and without diarrheal disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of diarrhea (mean ± SD months)</td>
</tr>
<tr>
<td>5.8 ± 7.27 (n = 24)</td>
</tr>
<tr>
<td>Mean weight loss (kg) ± SD</td>
</tr>
<tr>
<td>7.6 ± 8.7 (n = 19)</td>
</tr>
<tr>
<td>Mean BMI ± SD</td>
</tr>
<tr>
<td>18.3 ± 3.5</td>
</tr>
<tr>
<td>Mean MAC ± SD</td>
</tr>
<tr>
<td>23.0 ± 5.9</td>
</tr>
<tr>
<td>Mean no. of bowel movements/day ± SD</td>
</tr>
<tr>
<td>5.9 ± 5.0 range = 2–30</td>
</tr>
</tbody>
</table>

*p* = not available; NS = not significant; BMI = body mass index; height (m)/weight (kg); MAC = mid-arm circumference (cm).
as measured by CD4 cell counts. One individual with diarrhea and advanced disease by CD4 cell count had microsporidia identified in the stool. Microsporidia have also been identified previously in HIV-infected patients in northern and southern Thailand.\textsuperscript{19,20} While the epidemiology and precise role of microsporidia in diarrheal disease in patients infected with HIV remains controversial, patients who have symptomatic diarrheal disease have had advanced HIV disease as measured by CD4 cell counts.\textsuperscript{10,21,22} The apparent lack of routine parasites in this population may reflect the socioeconomic status of this urban population.

It was not possible to identify a pathogen in 73\% of the patients with diarrhea and 75\% of the patients without diarrhea, suggesting that additional agents or factors may be responsible for the diarrheal symptoms in the patients with diarrhea. This proportion of patients with HIV and diarrhea and no identifiable pathogen is consistent with other studies in patients infected with HIV in other parts of the world.\textsuperscript{3} While this does not agree with the recovery of pathogens from 64\% of HIV-infected patients with diarrhea in another published report from Thailand, that study was performed in patients with much more advanced HIV disease.\textsuperscript{14} More extensive studies to identify potentially treatable pathogens or factors in HIV infected outpatients with diarrhea in Thailand are warranted. The identification of other potentially treatable pathogens such as the enteropathogenic or enteroaggregative \textit{Escherichia coli} might allow the development of directed treatment strategies for these otherwise functional patients. Further attempts to better define the syndrome of pathogen-negative diarrheal disease in otherwise healthy outpatients infected with HIV in Thailand might permit the development of effective and cost effective strategies for intervention for this syndrome and its associated morbidities.

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REFERENCES


