Clinical Features of Human Immunodeficiency Virus–Infected Patients Presenting with Cholera in Port-au-Prince, Haiti

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Abstract. Human immunodeficiency virus (HIV) infection has been postulated to alter the natural history of cholera, including increased susceptibility to infection, severity of illness, and chronic carriage of *Vibrio cholerae*. Haiti has a generalized HIV epidemic with an adult HIV prevalence of 1.9% and recently suffered a cholera epidemic. We conducted a prospective study at the cholera treatment center (CTC) of GHESKIO in Haiti to characterize the coinfection. Adults admitted at the CTC for acute diarrhea were invited to participate in the study. Vital signs, frequency, and volume of stools and/or vomiting were monitored, and single-dose doxycycline was administered. After counseling, participants were screened for HIV by enzyme-linked immunosorbent assay and for cholera by culture. Of 729 adults admitted to the CTC, 99 (13.6%) had HIV infection, and 457 (63%) had culture-confirmed cholera. HIV prevalence was three times higher in patients without cholera (23%, 63/272) than in those with culture-confirmed cholera (7.9%, 36/457). HIV prevalence in patients with culture-confirmed cholera (7.9%) was four times higher than the adult prevalence in Port-au-Prince (1.9%). Of the 36 HIV-infected patients with cholera, 25 (69%) had moderate/severe dehydration versus 302/421 (72%) in the HIV negative. Of 30 HIV-infected patients with weekly stool cultures performed after discharge, 29 (97%) were negative at week 1. Of 50 HIV-negative patients with weekly stool cultures, 49 (98%) were negative at week 1. In countries with endemic HIV infection, clinicians should consider screening patients presenting with suspected cholera for HIV coinfection.

INTRODUCTION

With recent cholera outbreaks in the Caribbean and sub-Saharan Africa, there is now significant geographic overlap of the human immunodeficiency virus (HIV)–1 and *Vibrio cholerae* epidemics. Cholera is a waterborne disease caused by *V. cholerae* that spread across the world from its original reservoir in the Ganges delta in India. More than 20 countries in Africa have reported cholera, with recent outbreaks reported in Cameroon, Democratic Republic of Congo, Ghana, Guinea, Niger, Sierra Leone, and Uganda.^{1–3} Cholera has also been reported in countries in South America and the Caribbean including Bolivia, Brazil, Ecuador, Guatemala, Nicaragua, and Peru.^{4–6} Most recently, the disease emerged in Haiti, the country with the highest rates of HIV-1 infection in the Western Hemisphere.^{7–9} The cholera outbreak in Haiti has been one of the largest in recent history with 745,588 cases reported to date.¹⁰

The natural history of cholera varies depending upon bacterial strain, inoculum, host genetics, and immune status.¹¹ Most people infected with *V. cholerae* develop no symptoms or only mild disease, whereas 10–30% develop profuse diarrhea, rice-watery stools, nausea, and vomiting.¹² The severe form is cholera gravis which can lead to shock and death in majority of cases without effective care. Appropriate treatment consists of rehydration by oral or intravenous fluids and antibiotics.

The effect of HIV-1 infection upon the natural history of cholera is not certain. A small study in Mozambique suggested that people with HIV-1 infection may be at higher risk of developing symptomatic cholera than HIV-uninfected people.¹³ A case series in a Rwandan orphanage suggested

that HIV-1-infected children were more likely to develop severe cholera than uninfected children.¹⁴ Other case reports suggest that HIV-infected individuals may have longer duration of excretion of *V. cholerae*, with the pathogen detected in stools 6 months after initial diarrheal illness.¹⁵ Large-scale studies have not been conducted because cholera epidemics occur sporadically and unpredictably, and it is difficult to conduct research in the context of an emergency response.

Given the increasing geographic overlap between HIV-1 and cholera epidemics and the limited data on the effects of HIV-1 upon the natural history of cholera, we conducted a study in Haiti to characterize the coinfection. Our objectives were to determine the prevalence of HIV-1 in adult patients presenting with symptomatic cholera and to examine differences in disease severity and duration of excretion of *V. cholerae* between HIV-1 infected versus uninfected.

METHODS

The study was approved by the institutional review boards of Weill Cornell Medical College and the GHESKIO Center. All participants provided written informed consent.

Study site. The study was conducted at the GHESKIO Center in central Port-au-Prince, Haiti. GHESKIO is a clinical and research institution dedicated to service, research, and training in infectious diseases. It is located in downtown Port-au-Prince adjacent to large, densely populated slums with poor water supply and sanitation. Since the cholera epidemic began in 2010, GHESKIO has participated in the emergency response including provision of clean water, prevention programs in slums, and emergency care at an inpatient cholera treatment center (CTC) on its downtown campus.

Patients with acute diarrhea come to the GHESKIO CTC on their own, are brought by family, are referred by primary care clinics, or are transported to the CTC by ambulance. Patients are immediately evaluated, and medical staff determines the degree of dehydration (mild, moderate, or severe)

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based upon World Health Organization (WHO) guidelines.¹⁶ Patients with mild dehydration are provided oral rehydration fluids, observed for several hours, and admitted if symptoms worsen. Patients with moderate or severe dehydration are admitted immediately to the CTC for rehydration. At admission, sociodemographic information and medical history are routinely collected including age, gender, address, education, economic status, duration of diarrhea, antibiotic use, and other drugs taken before admission.

During hospitalization, patients who can take oral fluids are rehydrated with oral rehydration fluids (glucose, sodium, bicarbonate and potassium with osmolarity: 245 m osm/L). Other patients are provided intravenous fluids (Lactated Ringer's solution or when indicated normal saline or dextrose normal saline solutions). Vital signs and the frequency and volume of stools are monitored by medical staff to guide the volume of fluid resuscitation. An admission stool specimen is collected before administration of antibiotics, stored in a refrigerator at 4°C, and is available for microbiological examination. Serum electrolytes are monitored as per clinician's judgment (VITROS; Ortho Clinical Diagnostics, Raritan, NJ) and replacement electrolytes are provided as needed.¹⁶ Other laboratory tests are performed when clinically indicated. All patients are given doxycycline 300 mg as a single oral dose as per WHO recommendations.¹⁷

Study recruitment and procedures. Patients 18 years or older, living in the Port-au-Prince metropolitan area, and admitted with diarrhea to the GHESKIO CTC were eligible to participate in the current study. Approximately 12–24 hours after admission and emergency rehydration, a study nurse explained the study and procedures to potential participants and obtained written informed consent.

All study participants had an HIV test. Pretest and post-test counseling were provided, and at discharge, all HIV-1-infected participants were referred for outpatient HIV-1 care to the GHESKIO HIV unit located on the same campus. Data from the participant's medical chart was abstracted for research purposes including demographic information, disease severity, and fluid intake and output. A subset of participants with positive stool cultures for *V. cholerae* was invited to participate in a longitudinal study to determine the length of *V. cholerae* excretion. At discharge, 30 HIV-infected indi-

viduals with a positive stool culture and 50 HIV-uninfected people with a positive stool culture were followed up weekly. Both groups received sterile containers and were asked to return to GHESKIO with a stool specimen weekly. Counseling was provided to the participants on collection procedures following the recommendations of the *American Society for Microbiology*.¹⁸ We performed weekly study visits and stool culture until two consecutive negative cultures were obtained.

Laboratory procedures. Serum samples were tested for HIV-1 antibodies by the Determine HIV1/2 assay (Abbott, Abbott Park, IL) and confirmed by HIV (1 + 2) Antibody (Shanghai Kehua Bioengineering Co. Ltd., Shanghai, China).

Stool specimens were inoculated in alkaline peptone water and plated on thiosulfate citrate bile sucrose for identification of *V. cholerae*. Suspicious colonies were selected for further identification on MacConkey or blood agar.¹⁸

Data analysis. Data were entered into an ACCESS database (Microsoft, Redmond, WA). We determined the prevalence of HIV infection in all adult patients who presented with watery diarrhea. We compared clinical characteristics of patients with and without HIV. For comparison of proportions, we used Fisher's exact test. For comparison of means and medians, we used Student's *t* test and Wilcoxon rank-sum test, respectively. Excretion duration was measured in HIV-positive and HIV-negative patients and compared using the log rank test. All statistical tests were two sided with a *P* value of 0.05 for significance.

RESULTS

Study enrollment. In the 1-year period from June 1, 2012, to May 31, 2013, 888 patients of age ≥ 18 years from Port-au-Prince were admitted to the GHESKIO CTC with acute diarrhea. There was a peak in hospitalizations in November 2012 with 156 cases admitted; this corresponded to the rainy season (Figure 1).

Of the 888 adult patients, 72 (8%) did not consent to participate in the current study, 65 (7%) did not want HIV testing, 22 (2%) were discharged home before study enrollment, and 729 (83%) were enrolled in the current study (Figure 2). Of the 729 participants, 99 (13.6%) tested HIV seropositive. Of the 99 HIV-infected patients, 63 (64%) did not know

FIGURE 1. Adult patients admitted to a cholera treatment center in Haiti, June 2012–May 2013.

FIGURE 2. Study flow diagram of adult patients admitted to a cholera treatment center in Haiti, June 2012–May 2013.

their HIV status upon admission; the diagnosis of HIV infection was new. CD4⁺ T-cell counts were obtained for 72 HIV-infected patients. The median CD4 T-cell count was 222 (interquartile range = 79–530). Forty-nine of 72 (68%) had a CD4 count < 500 cells, and were eligible for antiretroviral therapy initiation under WHO guidelines at the time of the study.

The characteristics of the 729 study participants, stratified by HIV status, are provided in Table 1. HIV-infected patients were older with a median age of 36 years versus 31 years for the HIV uninfected. HIV-infected patients also

TABLE 1

Characteristics of patients admitted to a cholera treatment center in Haiti

	HIV ⁺ N = 99	HIV ⁻ N = 630	Total N = 729
Age**			
Median age	36	31	32
Age range	18–70	18–87	18–87
Gender			
Male	50 (50.5%)	329 (52.2%)	379 (51.9%)
Female	49 (49.5%)	301 (47.8%)	350 (48.1%)
Education*			
None	17 (17.2%)	87 (13.8%)	104 (14.3%)
Primary school	33 (33.3%)	159 (25.2%)	192 (26.3%)
Secondary school	47 (47.5%)	357 (56.7%)	404 (55.4%)
Other	1 (1.0%)	16 (2.5%)	17 (2.3%)
Unavailable	1 (1.0%)	11 (1.7%)	12 (1.6%)
Economy*			
None	47 (47.5%)	269 (42.7%)	316 (43.4%)
1.55–110 USD	32 (32.3%)	163 (25.9%)	195 (26.7%)
111–440 USD	18 (18.1%)	179 (28.4%)	197 (27.0%)
≥ 441 USD	1 (1.0%)	8 (1.3%)	9 (1.2%)
Unavailable	1 (1.0%)	11 (1.7%)	12 (1.6%)
Stool cholera culture*** (positive)	36 (36.4%)	421 (66.8%)	457 (62.7%)

HIV = human immunodeficiency virus. The *P* value comparing HIV⁺ vs. HIV⁻ are indicated by asterisks (*).

* *P* < 0.05; ** *P* < 0.01; *** *P* < 0.001.

had a significantly lower educational and economic status than the HIV-uninfected patients.

Clinical characteristics during hospitalization. In total, 457 (63%) of the 729 participants had a positive stool culture for *V. cholerae*. Of the 272 subjects without cholera, 63 (23%) were HIV infected. Of the 457 culture-confirmed cholera cases, 36 (7.9%) were HIV infected, (95% confidence interval = 5.6–10.7%). This is four times higher than the 1.9% estimated adult HIV seroprevalence in Port-au-Prince.

Demographic and clinical characteristics of the 36 HIV-infected patients with culture-confirmed cholera and the 421 HIV-negative patients with culture-confirmed cholera are presented in Table 2. The HIV-infected patients had similar disease severity as HIV-uninfected patients upon admission. There was no significant difference in length of hospital stay or stool output. Only one patient died. One HIV-infected patient with cholera died 1 week after discharge.

Longitudinal follow-up. A total of 80 patients with culture-confirmed cholera were followed weekly to determine the length of *V. cholerae* excretion. This included 50 HIV-uninfected patients and 30 HIV-infected patients. Of note, all participants had received a single oral dose of doxycycline before discharge from the hospital as per WHO recommendation. There was no significant difference in the length of excretion of *V. cholerae* between the HIV infected versus uninfected. In 49 of 50 HIV-uninfected patients, all follow-up stool cultures were negative. One HIV-uninfected patient had a negative culture at week 1, a positive culture at week 2, and then all negative cultures. In 29 of 30 HIV-infected patients,

TABLE 2

Clinical characteristics of patients admitted to a cholera treatment center in Haiti and with positive *Vibrio cholerae* cultures

	HIV ⁺ N = 36	HIV ⁻ N = 421	<i>P</i> value
Age (years)			0.8291
Mean ± SD	35.23 ± 8.97	34.74 ± 13.1	
Median	35	31.5	
Interquartile range	28–40	24–43	
Sex			0.9911
Male	20 (56%)	228 (54%)	
Female	16 (44%)	193 (46%)	
Clinical severity on admission			0.9926
Light	11 (31%)	119 (28%)	
Moderate	21 (58%)	255 (61%)	
Severe	4 (11%)	47 (11%)	
Systolic BP on admission			0.0971
Too weak to measure	7 (19%)	38 (9%)	
< 90	5 (14%)	89 (21%)	
90–120	23 (64%)	283 (67%)	
> 120	1 (3%)	11 (3%)	
Hospitalization duration (hours)			0.2327
Mean ± SD	65 ± 37	73 ± 39	
Median	55	69	
Interquartile range	43–90	49–91	
Total stool output (mL)			0.2192
Mean ± SD	14,123 ± 14,652	17,288 ± 14,596	
Median	9,900	13,400	
Interquartile range	5,900–17,500	6,200–23,300	
Rate of stool output (mL/hour)			0.613
Mean ± SD	206 ± 113	218 ± 139	
Median	166	198	
Interquartile range	131–249	125–268	

BP = blood pressure; HIV = human immunodeficiency virus; SD = standard deviation.

all follow-up stool cultures were negative. One HIV-infected patient had a positive stool culture at week 1; the next two weekly cultures were found negative.

DISCUSSION

This study demonstrates that a high percentage of patients presenting to a CTC in Haiti were HIV infected. In our study, ~13% of the adults presenting with acute watery diarrhea were HIV infected; the prevalence of HIV in the general population is only 1.9%. Therefore, we recommend that in countries with endemic HIV, clinicians should consider screening patients presenting with acute diarrhea to a CTC for HIV infection.

Our findings of an association between cholera and HIV are supported by prior studies. A case-control study in 2008 in Mozambique suggested that HIV patients might be more at risk to present with cholera than in the general population.¹³ In a mathematical modeling study examining the correlation of HIV and cholera, Mushayabasa and others also suggested that cholera appears to be more frequent in HIV-endemic areas than areas without HIV.¹⁹ In our prospective study, even among patients with culture-documented *V. cholerae*, we found that the HIV prevalence (8%) was significantly higher than in the general population (2%).^{20,21}

Furthermore, many HIV-infected patients with diarrhea but without cholera sought care at our CTC. This would suggest that HIV-infected patients with acquired immunodeficiency syndrome diarrhea may seek care at CTCs. We also found that two-thirds of the HIV-infected patients were newly diagnosed with a CD4 T-cell count that satisfied guidelines to start antiretroviral therapy. This provides a unique opportunity to diagnose HIV and initiate antiretroviral therapy.

There are several possible explanations for the high rate of HIV among cholera patients. Both cholera and HIV are diseases of poverty and those at risk for one may be at risk for the other. HIV-infected patients may be more accustomed to seeking medical care and therefore more likely to seek care when they develop symptomatic diarrhea. Alternatively, HIV-infected patients may be more likely to develop symptomatic disease when exposed to *V. cholerae*. HIV preferentially infects gut-associated lymphoid tissue and impairs gastrointestinal mucosal immunity.²² This decreased mucosal immunity may render HIV-infected hosts more susceptible to *V. cholerae*. However, future studies to explore a causal relationship between HIV and symptomatic cholera are warranted.

Our study also compared the clinical features of cholera between patients with and without HIV infection. HIV-infected individuals seem to have the same level of severity of illness on presentation. Our findings also demonstrate that HIV-infected patients receiving doxycycline as recommended by WHO did not have longer duration of excretion than expected in the general population. Case studies have suggested that HIV-1-infected patients may be at higher risk of chronic carriage.¹⁵ Our study demonstrated that a single dose of doxycycline is effective at preventing chronic carriage.

One limitation of our study is that children were not evaluated. A study conducted in Rwanda demonstrated that HIV-infected children are also more likely to acquire cholera than HIV-uninfected patients.¹⁴ Further research is needed to explore the correlation in children. The study also did

not measure host mucosal immunity to *V. cholerae*; further research is needed.

Recommendations. In endemic HIV countries, clinicians should consider screening patients presenting with acute diarrhea for HIV infection. Education should be reinforced among HIV-infected patients to prevent other causes of diarrhea related to waterborne disease, especially during the rainy season when water supplies may be contaminated. HIV-infected patients in endemic countries may also benefit from cholera vaccination.

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