

DIARRHEAL DISEASE AMONG HIV-INFECTED ADULTS IN KARNATAKA, INDIA: EVALUATION OF RISK FACTORS AND ETIOLOGY

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Abstract. The objectives of this study were to evaluate characteristics associated with diarrhea, the effect of trimethoprim-sulfamethoxazole (TMP/SMX) prophylaxis on diarrhea, the response to treatment with ciprofloxacin and tinidazole (Cipro-TZ™), and presence of enteric pathogens. Adults infected with human immunodeficiency virus with and without diarrhea served as cases and controls, respectively. Participants provided a medical history and underwent a physical examination. Blood was collected for CD4 cell counts and stool for culture. Cases were treated with Cipro-TZ™. Factors associated with a risk of diarrhea included crowded living and no toilet (all $P < 0.05$). Protective variables ($P < 0.05$) included a CD4 count greater than 200 cells/mm³ and TMP/SMX prophylaxis. Cases were more likely to have a pathogen identified ($P = 0.05$). Eighty-six percent of the cases responded to treatment. Important risk factors for diarrhea were identified. Protection by TMP/SMX reinforces the importance of prophylaxis. These data suggest that treatment with an antibiotic and anti-parasitic medication may be effective.

INTRODUCTION

Human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) are among the leading causes of infectious disease morbidity and mortality worldwide. India is estimated to have the second largest HIV-positive population in the world, with more than 5.7 million persons living with HIV/AIDS.¹ Concomitant infections play a major contributing role in the morbidity associated with HIV/AIDS. Effective prevention, diagnosis, and management of accompanying infections are critical for improving the health and well-being of people infected with HIV.

Infectious diarrhea is among the most common associated illnesses in people infected with HIV. The etiologic spectrum of enteric pathogens is broad, including bacteria, parasites, fungi, and viruses.^{2,3} Among AIDS patients in developing countries, as many as 95% may have diarrhea.^{4,5} In a large proportion of this population, the diarrhea may become prolonged and life-threatening, and chronic diarrhea is an independent marker of poor prognosis in patients with AIDS.⁶ Some pathogens tend to occur more frequently or cause more severe disease in persons infected with HIV than in HIV-uninfected persons with diarrhea. These include, but are not limited to, *Salmonella* spp., *Isospora* spp., *Cryptosporidium* spp., *Microsporidia* spp., cytomegalovirus, *Mycobacterium avium* complex, and *M. tuberculosis*.^{2,6–9}

Despite the spread of HIV infection in India, and the high prevalence of diarrheal disease, there is little information available on the epidemiology of diarrheal disease among people with HIV infection. In a review of HIV-related opportunistic infections (OIs) in northern India, chronic diarrhea was the second most common OI encountered.¹⁰ Parasitic infections with *Isospora belli*, *Entamoeba histolytica*, and *Cryptosporidium* sp. have been reported as being among the most frequently identified organisms in India,^{10–13} but few

studies have systematically examined the etiology of diarrhea in this population. In addition, there is little information on possible risk factors for diarrhea in HIV-seropositive persons, although the importance of food and water safety in immune compromised populations is well known.^{14,15}

We present the results of a case-control study to evaluate HIV-seropositive persons with and without diarrhea in the state of Karnataka, India. Karnataka is located in southern India and has a population of approximately 55 million people. It is one of the six states in India considered to have a high prevalence of HIV, with an estimated prevalence in the adult population of 1.5%.¹⁶ We examined risk factors associated with diarrheal disease in HIV-infected adults in this population, the role of antimicrobial prophylaxis for OIs on the development of infectious diarrhea, the etiologies of diarrheal disease, and the response to antimicrobial treatment.

METHODS

Study population and design. The study was reviewed and approved by the University of Manitoba Biomedical Research Ethics Board and the Institutional Ethics Review Board at St John's Medical College in Bangalore, India. Written informed consent was obtained prior to study enrollment. The study was conducted between December 2003 and August 2005, with participants enrolled from locations within both southern and northern Karnataka. We enrolled roughly equal numbers of individuals from community-based HIV clinics in the large urban center of Bangalore in southern Karnataka and from the smaller rural community of Bagalkot District in northern Karnataka. Adult outpatients positive for HIV were informed of the study by a clinic physician. If eligible and willing to participate, individuals were enrolled after written informed consent was obtained.

Case subjects were HIV-positive adults presenting to the clinic with diarrhea. Diarrhea was defined as the passage of three or more unformed stools during the past 24 hours. Persons who had received antibiotics within the past 14 days were excluded; however, this did not include medications such as trimethoprim/sulfamethoxazole (TMP/SMX) prescribed as

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prophylaxis against opportunistic infections. Control subjects were HIV-positive adults without diarrhea at the time of presentation, and without a history of diarrhea in the preceding six months. Case and control participants were enrolled concurrently throughout the study period as they came to the clinic. All participants provide a medical history and underwent a physical examination. Blood samples were collected for enumeration of CD4 cells and a stool sample was collected for microscopic examination, staining, and culture. Case subjects were provided treatment with a locally used combination drug (Cipro-TZ™; CIPLA, Mumbai, India) that contains ciprofloxacin (500 mg) and tinidazole (600 mg) and was administered two times a day for five days. Case subjects were asked to return for follow-up four weeks after their initial presentation. At the follow-up visit, a short medical history was obtained and a repeat physical examination was conducted. All participants were also asked if an interviewer could come to their home to administer a questionnaire assessing socioeconomic factors, general living conditions, toilet facilities, hygiene, food sources, and availability of clean water. Participants who refused home visits could have the identical questionnaire administered in the clinic.

Laboratory studies. Enumeration of CD4 cells was conducted by standard flow cytometry using FACScan (Becton-Dickenson, Somerville, NJ) at the National Institute of Mental Health and Neurosciences in Bangalore. Stool samples were collected and transferred to the microbiology laboratory at St. John's Medical College in Bangalore. Each specimen was divided into two parts: one aliquot was transported in Cary-Blair transport media and the other in polyvinyl alcohol. The stool samples were examined by light microscopy for inflammatory cells and blood. In addition, an iodine mount was prepared and examined for parasitic ova and cysts. All samples also underwent both modified acid-fast staining and a trichrome preparation for *Cryptosporidium* species, *Microsporidium* species, *Isospora* species, and *Cyclospora* species. Selective and differential media were used for detection of enteric pathogens from stool samples in Cary-Blair transport media. All suspicious colonies were identified by standard bacteriology procedures for enteric pathogens.

Statistical analysis. Data were analyzed using SPSS version 13.0 (SPSS Inc., Chicago, IL). For univariate analysis, the chi-square test was used for dichotomous data. The non-parametric Mann-Whitney test was used for ordinal or continuous variables that did not meet the normality assumption. Mantel-Haenszel stratified analysis was used to control for site (Bangalore or Bagalkot), and a Breslow-Day test was used to test for homogeneity of odds ratios. A backwards stepwise multiple logistic regression model was developed with diarrhea as the outcome variable and included site and significant interactions with site. Only variables that were significant ($P < 0.05$) in univariate analysis were entered in the model.

RESULTS

A total of 298 subjects were enrolled, 153 cases (those with diarrhea) and 145 controls (those without diarrhea). Thirty-nine (25%) cases and 102 (70%) controls were enrolled in Bangalore, and 114 (75%) cases and 43 (30%) controls were enrolled in Bagalkot. The mean age was 32.7 years for cases

and 31.9 years for controls ($P = 0.37$). Similar percentages of men and women were enrolled as cases and controls (Table 1).

The duration of diarrhea for more than 97% of the participants was five days or less (mean \pm SD = 3.16 ± 1.24 days). Table 1 compares socioeconomic and clinical characteristics between cases and controls. Forty-five percent of cases compared with 19% of controls gave a previous history of diarrhea (odds ratio [OR] = 4.6, 95% confidence interval [CI] = 2.5–8.4). Forty-eight percent of the controls reported taking TMP/SMX for OI prophylaxis compared with only 16% of the cases (OR = 0.48, 95% CI = 0.25–0.92). Cases were also much more likely to have a CD4 cell count less than 200 cells/mm³ than controls (OR = 2.8, 95% CI = 1.5–5.4). One hundred twenty-two cases (80%) came for their four-week follow-up visit; 106 (86%) reported that their diarrhea had resolved and that they were feeling better. Sixty-nine percent (106 case subjects) reported complete resolution of their illness.

Detailed questionnaires were administered for 230 individuals (126 [82%] cases and 104 [72%] controls; $P = 0.04$). Of the 126 cases, 25 (19.8%) questionnaires were administered in the clinic and 101 (80.2%) at home. For controls, 44 (42.3%) questionnaires were administered in the clinic and 60 (57.7%) at home. No significant differences were seen with respect to age or sex between those individuals who did and did not undergo detailed questionnaires. In comparison with controls, cases had lower levels of education, monthly income, and savings rates and were less likely to work outside the home (Table 1). Cases were significantly more likely than controls to live in crowded conditions and report the presence of flies, cockroaches, and rats in their home. Cases also reported more animals at home, including dogs, cats, cows, goats, and chickens, as well as more contact by themselves or other household members with livestock outside the home. Cases were more likely not to have a toilet in their home than controls (64% versus 31%, OR = 2.2, 95% CI = 1.2–4.0), but there was no significant difference between the two groups with respect to hand-washing practices. Cases cooked only 1–2 meals per day compared with controls, who were more likely to cook three meals per day. There was no significant difference between the two groups in the length of time for food preparation, eating meals outside the home, or eating vegetarian versus non-vegetarian food. Cases had to travel further to access drinking water than controls, with 29% of cases versus 8% of controls having to travel more than 40 meters to obtain drinking water (OR = 3.6, 95% CI = 1.5–8.9). Almost all participants had a storage container for water and there was no significant difference in sources of drinking water between the two groups.

In multivariate analysis, including controlling for location of enrolment (Bangalore versus Bagalkot), a previous history of diarrhea, having a primary education or less, and living with more than five persons at home were significantly associated with an increased adjusted odds of diarrhea (Table 2). In contrast, a CD4 cell count greater than 200 cells/mm³ and taking TMP/SMX for prophylaxis were associated with a lower adjusted odds of diarrhea, after controlling for other factors, including location of enrollment.

Stool samples were tested for pathogens in 142 cases (93%) and 102 controls (70%). Twenty (14%) cases had a pathogen identified in their stool compared with 8 (8%) controls (one-

TABLE 1

Comparison of demographic, clinical, laboratory, socioeconomic, and behavioral characteristics among subjects with diarrhea (cases) and without diarrhea (controls)*

Characteristic	Cases (n = 153) % (no.)	Controls (n = 145) % (no.)	Common stratified OR (95% CI)
Female	44.0 (68/153)	40.0 (58/145)	1.1 (0.63–1.8)
Age mean ± SD	32.7 ± 8	31.9 ± 7.1	
History of diarrhea	45.1 (65/144)	18.6 (27/145)	4.6 (2.5–8.4)†
Taking trimethoprim-sulfamethoxazole for prophylaxis	15.7 (24/153)	47.6 (69/145)	0.48 (0.25–0.92)†
CD4 count cell < 200 cells/mm ³	66.4 (71/107)	45.1 (46/102)	2.8 (1.5–5.4)†
Primary education only	71.2 (89/125)	37.9 (39/103)	3.4 (1.9–6.1)†
Home owner	81.7 (103/126)	54.4 (56/103)	2.3 (1.2–4.3)†
Refrigerator owner	0.8 (1/126)	3.9 (4/103)	0.16 (0.01–2.2)
Phone owner	11.1 (14/126)	14.6 (15/103)	0.86 (0.38–1.9)
Work outside home	44.4 (56/126)	63.5 (66/104)	0.44 (0.24–0.80)†
Income < 3,000 Rs/month	96.4 (54/56)	80.3 (53/66)	5.5 (1.1–26.0)†
Contribute monthly to savings	19.0 (24/126)	29.8 (31/104)	0.38 (0.19–0.77)†
More than 5 people at home	53.2 (67/126)	32.7 (34/104)	2.1 (1.2–3.9)†
Flies at home	56.3 (71/126)	27.2 (28/103)	2.4 (1.3–4.5)†
Ants at home	44.4 (55/126)	30.1 (31/103)	1.4 (0.77–2.6)
Cockroaches at home	52.4 (66/126)	33.0 (34/103)	2.0 (1.1–3.6)†
Rats at home	59.5 (75/126)	35.0 (36/103)	2.2 (1.2–4.0)†
Animals/livestock at home	42.4 (53/125)	22.1 (23/104)	2.3 (1.2–4.4)†
Contact with livestock outside home	39.7 (50/126)	15.4 (16/104)	2.7 (1.4–5.5)†
Family member with livestock contact	40.5 (51/126)	23.1 (24/104)	2.0 (1.1–3.8)†
No toilet at home	63.5 (80/126)	30.8 (32/104)	2.2 (1.2–4.0)†
Hand washing before eating	93.5 (115/123)	91.3 (95/104)	1.2 (0.36–4.0)
Hand washing after toilet	92.1 (116/126)	88.5 (92/104)	0.92 (0.33–2.5)
Less than 3 meals cooked/day	73.0 (92/126)	52.0 (53/102)	2.7 (1.5–5.0)†
Food served > 30 minutes post-preparation	33.3 (42/126)	23.3 (24/103)	2.4 (1.1–5.3)†
Eat out	54.4 (68/125)	54.8 (57/104)	1.1 (0.59–1.9)
Non-vegetarian	59.5 (75/126)	69.9 (72/103)	0.89 (0.48–1.6)
Distance to get water (> 40 meters)	29.3 (36/123)	7.8 (8/102)	3.6 (1.5–8.9)†
Storage container for water	94.4 (118/125)	100.0 (104/104)	Not estimated
Well source for water	29.6 (37/125)	21.2 (22/104)	1.3 (0.7–2.6)
Water treated (filter or chemical treatment)	28.6 (36/126)	30.8 (32/104)	0.50 (0.26–0.96)†

* OR = odds ratio; CI = confidence interval.

† $P < 0.05$.

sided $P = 0.05$). As shown in Table 3, among cases, *Giardia* (5) was the most frequently identified pathogen followed by *Isospora* (4) and hookworm (4). Bacterial pathogens (*Salmonella* spp. and *Shigella* spp.) were only identified in four stool specimens among those with diarrhea.

DISCUSSION

In this study, we identified several important factors associated with acute diarrheal disease in HIV-infected individuals. A CD4 cell count less than 200 cells/mm³ was strongly and significantly associated with diarrhea. This has been noted in several previous studies and reflects a compromised immune system with increased risk of disease.^{7,17–20} Individuals who

had a previous history of diarrhea (at any point in their lifetime) were also at an increased risk of diarrhea. This could be due to persistent exposure to risk factors in the home environment, to hygiene-related risk factors, or a recurrence of diarrhea that persisted due to inadequate treatment and continued carriage of the pathogen. Individuals who were taking TMP/SMX as prophylaxis were protected from developing diarrhea. Although one report did not demonstrate a similar protective effect of TMP/SMX,¹⁷ a protective effect was recently reported when TMP/SMX was combined with home-

TABLE 3

Comparison of enteric organisms among subjects with diarrhea (cases) and without diarrhea (controls)*

Organism	Cases (n = 142) % (no.)	Controls (n = 102) % (no.)	P	OR (95% CI)
<i>Giardia</i> spp.	3.5 (5)	2.9 (3)	1.0	1.2 (0.28–5.1)
<i>Cryptosporidium</i> spp.	0.7 (1)	2.0 (2)	0.57	0.36 (0.03–4.0)
<i>Isospora</i> spp.	2.8 (4)	0	0.14	Not estimated
Hookworm	2.8 (4)	0	0.14	Not estimated
Roundworm	0.7 (1)	1.0 (1)	1.0	0.72 (0.04–11.6)
<i>Entamoeba</i>	0.7 (1)	1.0 (1)	1.0	0.72 (0.04–11.6)
<i>Salmonella</i> spp.	1.4 (2)	0	0.5	Not estimated
<i>Shigella</i> spp.	1.4 (2)	1.0 (1)	1.0	1.4 (0.13–16.1)
Any pathogen	14.2 (20)	7.8 (8)	0.05†	Not estimated

* OR = odds ratio; CI = confidence interval.

† One-sided P value.

TABLE 2

Independent risk factors for diarrhea based on multivariate logistic regression*

Characteristic	P	OR (95% CI)
CD4 cell count > 200 cells/mm ³	0.034	0.42 (0.18–0.94)
Taking TMP-SMX	0.046	0.33 (0.11–0.98)
History of diarrhea	0.002	4.2 (1.7–10.6)
Primary education only	0.001	4.4 (1.9–10.1)
More than 5 people at home	0.004	3.3 (1.4–7.5)
Bagalkot	0.012	3.5 (1.3–9.1)

* OR = odds ratio; CI = confidence interval; TMP-SMX = trimethoprim-sulfamethoxazole.

based water chlorination and safe storage.²¹ However this difference may be due to the different populations evaluated in the studies: the report that indicated no protection was from a developed nation population, whereas the one demonstrating a protective effect was seen in rural sub-Saharan Africa, a study population more similar to one which we evaluated. Differences in the effectiveness of TMP/SMX prophylaxis may be due to differences in environmental exposures or local microbiology. Initiation of TMP/SMX was not a component of the study protocol. Eligibility and use of TMP/SMX was determined independently by the participants and their treating physicians. It should also be noted that antiretroviral treatment was not widely and easily available at the time of the study in India. However, eligible participants were referred for further care and antiretroviral treatment to nearby centers.

In our population, lower education was significantly associated with diarrhea. This is likely due to lower education serving as a proxy for lower socioeconomic status. Several socioeconomic and behavioral factors were identified as being significantly associated with diarrheal disease, as noted above. Similar risk factors have been reported in other studies evaluating diarrheal disease in both developed and developing countries.^{15,22,23} A previous study that evaluated water sources as causes for diarrheal disease yielded varying results, which suggested that pathways other than drinking water may be important in the transmission of infectious diarrhea.¹⁹ Our study did not find a significant association between diarrhea and water source. However, we identified an association between the distance that individuals had to travel to obtain drinking water and the development of diarrhea.

Our diagnostic yield from stool examinations was lower than anticipated. Other studies evaluating both acute and chronic diarrhea have reported a yield of specific pathogens in stool samples between 13% and 55%.^{7,17,20,24,25} Our study may have been limited in diagnostic yield because our laboratory was unable to identify viruses, *Clostridium difficile*, and *Campylobacter* spp. Interestingly, we found very little *Isospora* spp. in our patient population compared with other reports.^{11,12,26} This could be due to the frequent use of TMP/SMX as prophylaxis for OIs.

Participants seemed to respond well to treatment with the locally used combination therapy Cipro-TZTM. Almost 90% of cases responded to treatment. The 1991 World Health Organization guidelines for the management of diarrheal disease in HIV-infected adults recommends TMP/SMX alone as initial therapy.²⁷ The treatment response seen in this study to the combination of a fluoroquinolone and an anti-protozoal agent and the presence of parasitic infections, specifically *Giardia*, suggests that TMP/SMX alone may not be optimal treatment for diarrhea among HIV-infected individuals in India. Furthermore, another study demonstrated high levels of resistance to TMP/SMX, as well as a high prevalence of *Giardia* sp. in similar populations.⁷ Nevertheless, in our setting, TMP/SMX appeared to be very useful as a routine OI prophylaxis and it reduced the adjusted odds of diarrhea by 67% (95% CI = 2–89%) among HIV-infected individuals.

There are a number of limitations to this study. Social desirability bias may have influenced responses to questions regarding food and hygiene practices, and this may have limited our ability to detect differences between the two groups. In addition, we were unable to obtain questionnaires and blood

and stool samples from all participants. Significantly more cases than controls completed the detailed questionnaires. This may have been because more controls were enrolled from Bangalore and were more hesitant to have the questionnaire administered in their home for reasons of confidentiality. It was not always possible to obtain stool samples, especially from controls, and as noted above, we were unable to test for viruses, *Clostridium difficile*, and *Campylobacter* spp. due to limited resources at the testing laboratory. Other diagnostic techniques for diarrhea-causing pathogens, including endoscopy with biopsy and polymerase chain reaction can improve diagnostic yield, but these diagnostic tests are not an option in most resource-poor settings.⁹ In addition, due to logistical difficulties, we were only able to collect one stool sample from participants. Yield from stool samples may be increased with multiple samples. However, because many of our participants traveled from rural areas, it was not possible to collect multiple samples.

In summary, this study has identified several risk factors for diarrheal disease among HIV-infected individuals in India. Some behavioral factors, such as hygiene, food preparation, and water access, are potentially amenable to intervention. For example, there is potential for the provision of latrines to households, and for providing housing for animals outside the home. In addition, education campaigns emphasizing the importance of hygiene and proper food preparation would also be important. The use of TMP/SMX was protective against the development of diarrheal disease, which suggested that among HIV-infected individuals, TMP/SMX should be used not only as prophylaxis for pneumocystis pneumonia, but also for protection against infectious diarrhea. Finally, our data, although not definitive, suggest that empiric treatment for HIV-positive persons with diarrhea should include an anti-parasitic treatment, such as tinidazole, in addition to a broad-spectrum antibiotic. However, prospective treatment studies would need to be conducted for a more definitive conclusion.

Received October 1, 2006. Accepted for publication January 15, 2007.

Acknowledgements: We thank the staff at the clinics who supported the study, especially Mr. K. Chandrashekaraiiah for his enthusiasm and dedication. We also thank Dr. R. Macaden and Dr. G. D. Ravindran (St. John's Medical College) for their assistance and support.

Financial support: This work was supported by a grant from the Canadian Institutes of Health Research Global Health Research Initiative. Marissa L. Becker is the recipient of a Canadian Institutes of Health Research (CIHR) fellowship award. Stephen Moses is the recipient of a CIHR investigator award. James F. Blanchard is supported by a Canada Research Chair in Epidemiology and Global Public Health Research.

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