Epidemiol. Infect. (2002), **128**, 73–81. © 2002 Cambridge University Press
DOI: 10.1017/S0950268801006252 Printed in the United Kingdom

Risk factors in HIV-associated diarrhoeal disease: the role of drinking water, medication and immune status

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(*Accepted 12 July 2001*)

SUMMARY

In a cross-sectional survey of 226 HIV-infected men, we examined the occurrence of diarrhoea and its relationship to drinking water consumption patterns, risk behaviours, immune status and medication use. Diarrhoea was reported by 47% of the respondents. Neither drinking boiled nor filtered water was significantly associated with diarrhoea (OR = 0·5 [0·2, 1·6], 1·2 [0·6, 2·5] respectively), whereas those that drank bottled water were at risk for diarrhoea (OR = 3·0 [1·1, 7·8]). Overall, 47% always or often used at least one water treatment. Of the 37% who were very concerned about drinking water, 62% had diarrhoea, 70% always or often used at least one water treatment. An increase in CD4 count was protective only for those with a low risk of diarrhoea associated with medication (OR = 0·6 [0·5, 0·9]). A 30% attributable risk to diarrhoea was estimated for those with high medication risk compared to those with low medication risk. The significant association between concern with drinking water and diarrhoea as well as between concern with drinking water and water treatment suggests awareness that drinking water is a potential transmission pathway for diarrhoeal disease. At the same time we found that a significant portion of diarrhoea was associated with other sources not related to drinking water such as medication usage.

INTRODUCTION

Diarrhoea is a common problem for HIV-infected individuals and may be due to both infectious and non-infectious causes. An important and increasing non-infectious cause of diarrhoea is related to effects due to medications that are prescribed to HIV-infected individuals. In particular, the incidence of medication-related diarrhoea has increased since the introduction of highly active antiretroviral therapy (HAART) in the last quarter of 1996 [1]. Common infectious causes of diarrhoea include viral, bacterial and protozoan pathogens [2–4]. The impact of these diseases has been well documented. For example, prior to the introduction of HAART, one of the most serious of the protozoan infections was caused by *Cryptosporidium*, which was chronic in 10–15% of AIDS patients, 50% of whom died of cryptosporidiosis [5]. Other enteric pathogens with similar routes of exposure have been implicated as causes of diarrhoea in HIV-infected individuals, such as *Giardia*

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[6, 7], enteric viruses [8], *Microsporidia* [9] and adenovirus [10]. There are, however, few data collected after the introduction of HAART with which to estimate the relative epidemiological significance of these non-infectious and infectious causes of diarrhoea. To understand better the contribution of these pathways to the overall incidence of diarrhoea, we conducted a cross-sectional survey to measure various risk factors and their association with gastrointestinal symptoms, with a particular emphasis on drinking water exposure.

We focus on drinking water risks because there is heated debate in the United States about the extent to which waterborne infectious diseases may be transmitted to human beings through drinking water which has met federal standards for pathogen removal [11, 12]. Studies in Canada suggested that approximately 35% of endemic gastrointestinal illness in a community might be due to drinking water [13, 14]. Outbreaks of disease linked to public water supplies with and without known lapses in water treatment [15, 16] have resulted in a number of deaths, the majority of which were in HIV-infected individuals. Because of these findings, Centers for Disease Control and Prevention (CDC) guidelines for persons with immunocompromising conditions suggest that boiling water is an effective strategy to lower such risks. It is difficult to evaluate how widely these guidelines are followed by HIV-infected individuals or to measure how effective they are in reducing risk.

Very little data, however, exist on drinking-water risks in non-outbreak conditions. Two recently published cross-sectional surveys have focused on drinking water behaviour in an HIV-infected population, one conducted in San Francisco [17] and the other in New York [18]. Although both studies contained important findings, neither addressed the association of risk factor behaviour with disease status. Kim et al. [17] explored how risk perception affects risk behaviour, while Davis et al. [18], compared risk behaviour between an HIV-infected cohort and an immunocompetent cohort.

To improve our understanding of disease transmission associated with enteric pathogens, we conducted a cross-sectional survey among HIV-infected patients at the San Francisco Veterans Administration Medical Center (SFVAMC), between October 1998 and June 1999. Our objectives were to estimate: (1) the prevalence of diarrhoea among HIV-infected individuals; (2) the degree to which drinking water habits are associated with gastrointestinal illness; and (3) the attributable risk of diarrhoea associated with medication risk.

MATERIALS AND METHODS

Data collection and analysis

We administered a questionnaire to patients attending the ID/AIDS clinic at the San Francisco Veterans Administration Medical Center (SFVAMC), between 18 October 1998 and 1 June 1999. Those agreeing to participate signed the informed consent form and then were given the survey to complete. The study instrument was approved by the Institutional Review Boards from the University of California at Berkeley, the University of California at San Francisco, and the Center for Disease Control and Prevention. The survey addressed specific drinking water behaviours, medication use, CD4 count, and other risk factors for gastrointestinal illness.

The survey included questions on: (1) drinking water behaviour; (2) other risk factors for diarrhoeal disease such as medication, sexual practice, food, contact with animals, travel, etc.; (3) self-reported symptoms; (4) demographic information (age, race and income); and (5) knowledge and attitudes of drinking water risks. In addition, clinical records of CD4 count and medication use were obtained from a chart review of the patients. The outcome variable, diarrhoea, was defined as the presence of two or more loose or unformed stools in a day. The patient answered yes or no to whether they had experienced diarrhoea in the last 7 days.

Since each patient on average took several medications, each with a different risk of diarrhoea due to side effects, we developed a continuous scale to estimate the overall diarrhoeal risk associated with possible medication side effects. Each drug was assigned a percent probability of diarrhoea value based on published information [1]. Medications that had no known diarrhoeal side effects were assigned a probability of diarrhoea of 0. Medications producing diarrhoeal side effects between 0 and 1% of the time were assigned a probability of 0·01. Medications producing diarrhoeal side effects between 1 and 10% were assigned a 0·1 probability of diarrhoea, and medications with more 10% diarrhoeal side effects were assigned a probability of 0·2 [l]. Assuming that each drug acted independently in producing diarrhoeal side effects, and that $P_1, P_2, \ldots, P_m$ were the

Table 1. *Association of risk factors with diarrhoea for the categorical variables*

	n (with diarrhoea)	*n* (without diarrhoea)	OR (95%CI)	*P*-value*
Drinking water				
Heard of CDC drinking water guidelines?				
Yes	23	18	1·5 (0·8–2·9)	0·30
No	82	95	1·0 (reference)	
How concerned about drinking water and its health effects?				
Not at all concerned	13	32	1·0 (reference)	0·004†
A little concerned	35	39	2·1 (1·0–4·8)	0·056
Very concerned	37	23	4·0 (1·7–9·0)	0·0015
Always or often uses at least one type of water treatment?				
Yes	57	48	1·8 (1·1–3·0)	0·044
No	48	72	1·0 (reference)	
How often drinks boiled water?				
Never	78	85	1·0 (reference)	0·7†
Rarely	11	8	1·5 (0·6–3·8)	0·47
Sometimes	5	5	1·1 (0·3–3·7)	1·00
Often	2	3	0·7 (0·0–3·7)	1·00
Always	5	10	0·5 (0·2–1·6)	0·42
How often drinks bottled water?				
Never	10	24	1·0 (reference)	0·245†
Rarely	30	32	2·3 (0·9–5·4)	0·086
Sometimes	26	27	2·3 (0·9–5·7)	0·079
Often	17	18	2·3 (0·9–6·0)	0·14
Always	21	17	3·0 (1·1–7·8)	0·034
How often drinks filtered water?				
Never	62	73	1·0 (reference)	0·6†
Rarely	6	11	0·6 (0·2–1·8)	0·45
Sometimes	7	9	0·9 (0·3–2·5)	1·00
Often	10	6	2·0 (0·7–5·5)	0·29
Always	17	17	1·2 (0·6–2·5)	0·70
Medications				
Number of medications with greater than 10% diarrhoeal side effects				
0	40	69		0·019†
1	43	37	2·0 (1·1–3·6)	0·0026
2	13	13	1·7 (0·7–4·0)	0·26
3	4	0		
4	0	0		
5	1	0		
Any medications with greater than 10% diarrhoeal side effects				
Yes	61	50	2·1 (1·2–3·6)	0·007
No	40	69	1·0 (reference)	
Taken any medications in the past 6-months				
Yes	95	104	2·3 (0·9–5·9)	0·11
No	6	15	1·0 (reference)	
Immune status				
CD4 $\geqslant$ 500	16	39	0·4 (0·2–0·7)	0·0027
CD4 $<$ 500	82	73	1·0 (reference)	
Pets and animal contact				
Have any pets at home?				
Yes	45	47	1·2 (0·7–2·0)	0·58
No	57	70	1·0 (reference)	

Table 1 (*cont.*)

	n (with diarrhoea)	*n* (without diarrhoea)	OR (95%CI)	*P*-value*
Clean pet's urine?				
Yes	30	23	1·7 (0·9–3·2)‡	0·11
No	70	93	1·0 (reference)	
Any contact with farm animals				
Yes	6	3	2·4 (0·7–9·1)	0·31
No	94	114	1·0 (reference)	

* 2-sided Fisher's exact test except where noted by a † the χ^2 test of association for whole table was calculated.
‡ For those with CD4 < 200: OR = 4·0 (1·1–14·3).

probabilities associated with each of the *m* drugs taken by a given individual, the medication risk metric (MRM) was calculated as follows:

$$\text{MRM} = 1-[(1-P_1)(1-P_2)\ \ldots\ (1-P_m)].$$

For the purposes of estimating attributable risk, the variable medication risk was categorized into four groups: 0–0·2, 0·2–0·4, 0·4–0·6 and 0·6–0·8. We estimated attributable risk as:

$$\frac{P_n(\text{D})-P_n(\text{D}|\tilde{E})}{P_n(\text{D})},$$

where $P_n(\text{D})$ was the overall proportion of diarrhoea, and $P_n(\text{D}|\tilde{E})$ the proportion of disease among the low risk.

The associations between the risk factors included in the survey and symptoms of diarrhoea were assessed using bivariate tabulations and calculations of odds ratios. To account for variation in diarrhoea at different levels of CD4 and medication use, adjusted odds ratios were also calculated from a logistic model. The outcome was a bivariate indicator of diarrhoeal incidence in the past 7 days and the covariates in this model included CD4 and medication risk. A term describing the interaction between CD4 and medication risk was also included in the model. The data were entered and organized in Access97 (Microsoft®), and Stata (Version 6.0, Stata Corporation).

RESULTS

In this study 226 patients (77%) of the 305 who were approached completed the survey. All participants were HIV-infected males (68% were diagnosed with AIDS) with a median age of 49. The racial breakdown was: 152 Whites (68%), 43 Blacks (19%), 19 Hispanics (8%), and 11 other (5%). The socio-economic status was that of low income (68% earned < $20000 per year), high unemployment (70%), and on average 2 years of post high school education. Among demographic characteristics, only age was associated with diarrhoea. Those with diarrhoea were slightly younger (mean = 47·8) than those without diarrhoea (50·5) ($P = 0{\cdot}058$).

Forty-seven percent of the participants reported diarrhoea in the preceding 7 days, the principal outcome measure of the study. Table 1 contains the risk factors included in the survey and their association with diarrhoea. In this section we report our analysis of the survey in three parts: first, we present drinking water risk factors associated with diarrhoea; second we introduce the factors obtained from clinical records, such as medication use and CD4 count, and present calculations for the attributable risk of diarrhoea from medication; and finally we present all other risk factors contained in the survey and present calculations of their association to diarrhoea.

Drinking water risk factors associated with diarrhoea

Although most participants were unaware of the CDC drinking water guidelines for HIV-infected individuals that advise boiling drinking water (81%), 34% were very concerned and 75% were at least a little concerned about the health effects of drinking tap water. The association between concern about water and diarrhoea was significant: the odds of diarrhoea were fourfold higher among those concerned about drinking water compared to those without this concern (OR = 4·0 [1·7, 9·0]).

Participants responded that they always or often treated their water (by drinking boiled, filtered or

Table 2. *Association of risk factors with diarrhoea for the continuous variables*

		With diarrhoea	Without diarrhoea	
	n	Mean (SD)	Mean (SD)	*P*
Demographic characteristics				
Age	221	47·8 (10·3)	50·5 (10·9)	0·058
Drinking water				
Percent of drinking water treated	213	52 (39)	46 (41)	0·31
Glasses of tapwater per day at home	216	4·4 (4·0)	4·3 (3·9)	0·89
Total glasses of tapwater per day	224	6·7 (5·5)	5·5 (5·5)	0·77
Medications				
Probability of diarrhoea from medication	221	0·36 (0·15)	0·30(0·16)	0·005
Health				
CD4	211	352 (228)	413 (241)	0·059

bottled water) 47% of the time. Always or often treating water was positively associated with diarrhoea in the last 7 days (OR = 1·8 [1·0, 3·0]). Stratifying by treatment strategy, 9% responded always or often to boiling their water, 23% to filtering their water, and 33% to drinking bottled water. The odds of diarrhoea in the past 7 days were lower among those who always boil their water (OR = 0·5 [0·2, 1·6]). The precision of the estimate was limited since few participants boiled drinking water (power calculations suggest that a sample size of 520 would be needed to achieve 80% power). In comparison, drinking bottled water showed a trend towards being a risk factor ($P = 0{\cdot}068$). Those who always used bottled water were nearly three times as likely to have experienced diarrhoea in the past 7 days (OR = 3·0 [1·1–7·8]).

The odds of always or often drinking either boiled, filtered or bottled water was over 8 times greater for those who were very concerned about water compared to those who were not concerned about water (OR = 7·5 [2·1–27·1]), suggesting that those who were concerned about their drinking water were acting upon their concerns.

Medication and CD4 count

CD4 count was in the range 1–1000 with one case above 1400. The mean and median were around 385 and 359 respectively. The association of CD4 count greater than 500 with diarrhoea was significant (OR = 0·4 [0·2, 0·7]).

The medication risk was in the range 0–0·71 with a mean and median of 0·33. The association between diarrhoea in the last 7 days and taking medication with > 10% risk of diarrhoea was significant (OR = 2·1 [1·2, 3·6]). Comparing the observed risk (proportion with diarrhoea obtained from the survey data) with our predicted risk (calculated for the medication risk variable) we found that a 0–0·2 medication risk was associated with a 0·3 prevalence of diarrhoea, a 0·2–0·4 medication risk was associated with a 0·4 prevalence, a 0·4–0·6 medication risk was associated with a 0·4 prevalence, and 0·6–0·8 medication risk was associated with a 0·4 prevalence.

Clinical evidence suggests that there is an interaction between medication usage and CD4 count, since HAART medication both causes diarrhoea directly due to side effects and decreases the risk of infectious diarrhoea indirectly by increasing a patient's CD4 count. When an interaction term for CD4 count and medication risk was included in a logistic model a significant interaction was reflected in the data. Only for low medication risks ($< 0{\cdot}21$) was CD4 count protective (OR = 0·6 [0·5, 0·9]), for an increase of 100 in CD4 count. For high medication risk ($> 0{\cdot}21$) increasing CD4 count was not protective.

The association of diarrhoea and medication risk group was calculated by grouping participants into a low medication risk group (0–0·21), a medium risk group (0·21–0·43), and a high-risk group ($> 0{\cdot}43$). The proportions of subjects with diarrhoea was 0·58 for medication risk $> 0{\cdot}43$, 0·46 for medication risk between 0·21 and 0·43, and 0·33 for medication risk $< 0{\cdot}21$. Using the low medication risk group as the baseline (unexposed), the odds ratio for the medium risk group was 1·7 (0·9, 3·4) and for the high risk group was 3·6 (1·2, 6·3). Based on our 0·47 estimate for overall probability of diarrhoea, the attributable risk due to medication use was 0·3 ((0·47–0·33)/0·47).

There was also an association (of borderline statistical significance) between CD4 count and boiling drinking water. We found that those who never boil their water had a higher CD4 count (407) than those that always or often boiled their water (297) (P-value = 0·08, t test for difference between means).

Other risk factors for diarrhoea

Diarrhoea in the last 7 days was statistically unrelated to sexual contact and to specific high-risk sexual behaviours. However, the point estimates for anal contact (OR = 0·8 [0·5, 1·4]) and contact with women (0·4 [0.l, 1·41]) indicated these factors were associated with a decreased risk of diarrhoea and sexual contact with men was associated with an increased risk of diarrhoea. No relationship was observed between selected foods and diarrhoea ($P > 0·25$). Exposure to pets and other animals was associated with increased risk of diarrhoea. Contact with farm animals was associated with diarrhoea (OR = 2·4 [0·6–l0·0]), however, the precision of this estimate was limited since few subjects (4·1%) had contact with farm animals. Cleaning up after pets was also positively associated with risk of diarrhoea (OR = 1·7 [0·9–3·3]), and was of borderline statistical significance. This relationship was stronger and statistically significant among those with CD4 counts less than 200 (OR = 4·0 [1·1–14·3]).

DISCUSSION

Overall 47% reported that they always or often treat their drinking water. This estimate is comparable to the finding by Kim et al. (1988) that 51% never or rarely drank tap water, but a higher value than reported by Davis et al. (1988), who found that only 18% of their HIV-infected cohort drank no tap water. The Davis study also collected data from a non-HIV-infected cohort, which reported 31% tap water avoidance. Comparing the frequency of specific water treatments, Davis et al. estimated that their HIV-infected cohort was drinking boiled and bottled water approximately twice as often as in our study, and they were drinking filtered water approximately 2·5 times less. The increase in the estimate of filter-use from the time of the Davis et al. study to our current study may be due to the increasing popularity of home drinking water filter devices, or may have been due to the fact that our study and the Davis et al. study did not use identical questions.

Of the 37% who were very concerned about drinking water, 62% had diarrhoea (compared to 47% overall), 70% always or often used at least one water treatment (compared to 47% overall). This significant association between concern about drinking water and water treatment was also found by Kim et al. (1998). Therefore, even with limited knowledge of the CDC guidelines our data suggest a high level of concern with water quality, especially for those with diarrhoea.

Although a high level of concern with water quality may suggest a causal linkage between drinking water and diarrhoeal disease, analysis of our survey data indicate that pathways other than drinking water also may be important in the transmission of infectious diarrhoea in HIV-infected individuals. In particular, analysis of our data suggests that exposures to pets may account for a significant proportion of diarrhoea in individuals with highly compromised immune condition (CD4 < 200), i.e. those who may be particularly at risk of infectious diarrhoea. This result, however, is based on data from only a few individuals. Consistent with our result that the data had suggestive correlations with certain high-risk exposures to animals (farm animals, cleaning up urine) and diarrhoea, another study has recently found that HIV-infected individuals with cryptosporidiosis were slightly more likely to own dogs as pets [19].

The evidence for statistical interaction between medication use and CD4 count for diarrhoea risk suggests that some of these other pathways of diarrhoea are of infectious origin. For patients with low medication risks, CD4 count was protective (associated with decreased diarrhoea), whereas for those patients with high medication risk, CD4 count was not protective. One interpretation for this observation is that patients with high medication risk were predominately at greater risk for diarrhoea from a noninfectious cause such as medication use. Those with low medication risk were, conceivably, at greater risk for infectious diarrhoea, and therefore, an increase in CD4 count was protective. This finding has important public health implications because appropriate intervention depends on knowing the cause of diarrhoea. Additional information useful for policy decisions would be data on the differential in the severity of infectious diarrhoea compared with that due to noninfectious causes such as medication. Unfortunately, in this survey we did not collect the disease severity data needed to address this issue.

Although an attributable risk of 30% suggests that

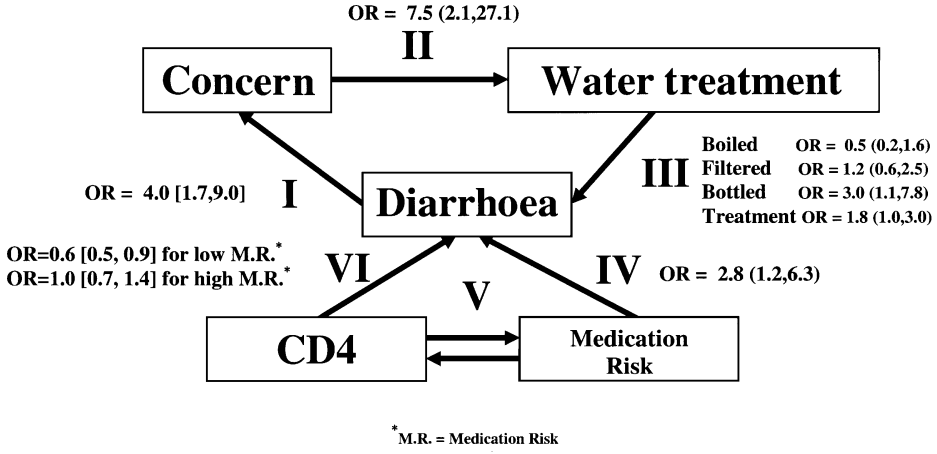

Fig. 1. Causal model diagram linking concern with drinking water quality, water treatment, self-reported diarrhoea, medication risk and CD4 count. The odds ratios listed were estimated from the survey. The directions of the arrows are hypothesized by the authors.

medication was a major cause of noninfectious diarrhoea in our HIV + cohort, there were still 70% of diarrhoea cases that were due to other causes. One such causal pathway could involve drinking water. Our data suggest certain water treatments, e.g., boiling water, may be associated with a lower risk of diarrhoea; however, analysis of our limited sample did not confirm a significant association between any of the water treatment practices and diarrhoea. Boiling water, the practice that was presumed to be the most effective against drinking water risk, may have lacked a significant association because of the small number of people that actually boiled their water. One water treatment practice, drinking bottled water, was found to be a risk factor. The lack of a statistically significant association for drinking boiled water and the finding that drinking bottled water was a risk, may be due, in part, to the existence of the causal loop postulated in Figure 1, linking concern with water quality, water treatment, and diarrhoea.

Though cross-sectional studies can provide valuable descriptive information, they are often limited in providing unbiased estimates of association. This limitation is due in part to the lack of temporally based data, e.g. 'Did you boil your water after having a case of diarrhoea or before?'. In the absence of such information, structural assumptions on causality explicitly provide for a framework to assess consequences of these causal relationships with respect to risk estimates. Therefore, causal models in conjunction with cross-sectional data can be useful in postulating possible causal inferences and suggesting an improved study design that can alleviate some of the confounding issues. For example, temporal information can be included to assess a causal inference both by periodic surveys over time or incorporating questions that elucidate temporal patterns.

To address these possible biases inherent with risk estimates made from data collected in cross-sectional surveys, we postulated the existence of causal linkages to explicitly define our conceptualization of the relationship among various factors. The resulting causal diagram was used to motivate the direction of potential biases (Fig. 1). Linkages I, II and III represent the fact that increased diarrhoea can result in a concern of drinking water quality, which in turn will result in increased water treatment (such as boiling water), which in turn can decrease the prevalence of diarrhoea.

Therefore, an individual may treat water because they are experiencing diarrhoea, even though the diarrhoea may have another cause such as medication use. The existence of this causal loop suggests that a standard odds ratio estimate will underestimate the protective level that boiling water has on the prevalence of diarrhoea and overestimate the risk associated with drinking bottled water, since at least some of the diarrhoea will not be of infectious origin. One such example of noninfectious diarrhoea is made explicit in our causal diagram by linkage IV, the increase of diarrhoea due to side effects from medication use. The estimate of attributable risk due to medication use will potentially be biased due to the confounding effects of CD4 count. This is illustrated in Figure 1 by linkage V and VI. Linkage V reflects that fact that one's CD4 count will influence a physician's decision to use antiretroviral medication, and the medication itself will affect CD4 count. Linkage VI reflects the fact that

a low CD4 count will increase an individual's susceptibility to infectious enteric pathogens.

The complexities of these pathways are illustrated by the dual role of medication in both decreasing the rate of infectious diarrhoea by increasing CD4 count, and increasing the rate of diarrhoea due to side effects. The observed association between CD4 count and boiling water is also consistent with this causal diagram. In this model, a low CD4 count results in an increase in diarrhoea, which results in an increase in concern with water quality, which results in an increase in boiling water (Fig. 1). Therefore, diarrhoea and concern with drinking water are in the causal pathway that connects CD4 count with boiling water.

Kim et al. (1998) also found that diarrhoeal symptoms were often perceived as water-related. In their study, they demonstrated with an HIV cohort that perception of risk to enteric pathogens was significantly associated with boiling water but not with other potential risk factors such as sexual practice. These findings are not surprising in light of the focus on drinking water risks by federal agencies and the media. Public health education should expand to address the significant risks of diarrhoea from other causes in addition to drinking water. In our survey we did ask about risk factor behaviour, such as sexual practice, but found no significant association. One explanation for the lack of significance associated with sexual practice is that our cohort was on average older (mean age = 49) than the age profile of HIV cohorts in both studies by Kim et al. (1998), mean age = 38, and Davis et al. (1998), mean age = 41.

To better estimate the real effects of water treatment on diarrhoea, one would need temporal information to ascertain whether or not, for example, water treatment and medication use relate to diarrhoea as we have postulated in Figure 1. Therefore, additional carefully designed cross-sectional studies or longitudinal cohort studies are needed to validate our causal model, and to delineate the causal pathways of diarrhoeal disease.

ACKNOWLEDGEMENTS

This work was supported by a grant from the University of California, University-wide AIDS Research Program (grant M98-B-1300), and through a cooperative agreement with the Center for Disease Control and Prevention (grant UR2/CCU916252-02).

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