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Associations between water-treatment methods and diarrhoea in HIV-positive individuals

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SUMMARY

This manuscript extends our previously published work (based on data from one clinic) on the association between three drinking water-treatment modalities (boiling, filtering, and bottling) and diarrhoeal disease in HIV-positive persons by incorporating data from two additional clinics collected in the following year. We conducted a cross-sectional survey of drinking water patterns, medication usage, and episodes of diarrhoea among HIV-positive persons attending clinics associated with the San Francisco Community Consortium. We present combined results from our previously published work in one clinic ($n = 226$) with data from these two additional clinics ($n = 458$). In this combined analysis we employed logistic regression and marginal structural modelling of the data. The relative risk of diarrhoea for 'always' *vs.* 'never' drinking boiled water was 0·68 (95% CI 0·45–1·04) and for 'always' *vs.* 'never' drinking bottled water was 1·22 (95% CI 0·82–1·82). Drinking filtered water was unrelated to diarrhoea [1·03 (95% CI 0·78, 1·35) for 'always' *vs.* 'never' drinking filtered water]. Adjustment for confounding did not have any notable effect on the point estimates (0·61, 1·35 and 0·98 for boiled, bottled, and filtered water respectively, as defined above). The risk of diarrhoea was lower among those consuming boiled water but this finding was not statistically significant. Because of these findings, the importance of diarrhoea in immunocompromised individuals, and the limitations of cross-sectional data further prospective investigations of water consumption and diarrhoea among HIV-positive individuals are needed.

INTRODUCTION

There is no doubt that widespread outbreaks of gastrointestinal (GI) infectious illness have occurred in the United States at times when public water-treatment systems have failed [1, 2]. Recent studies, however, have begun to question the assumption that there is little or no risk of GI infectious illness attributable to the consumption of drinking water when public water-treatment systems are functioning properly (i.e. are meeting federal regulatory standards for pathogen removal and there is no evidence of an outbreak) [3–6]. Three of these studies were randomized trials that provided estimates of diarrhoeal disease attributable to drinking water in

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immunocompetent groups. Recently, attention has been directed toward specific sub-populations who may be at increased risk for susceptibility to infection and severe sequelae after infection. These sub-populations include immunocompromised persons, children, and the elderly [7]. The goal of this study was to evaluate the relationship between specific drinking water-treatment modalities (boiling, filtering or bottling) and the occurrence of diarrhoea among HIV-positive persons. We chose to use diarrhoea as our outcome variable, since the pathogens of interest that cause the GI illness consist of a heterogeneous group of viruses, bacteria, and protozoa called water-borne pathogens.

The epidemiology of diarrhoea in immuno-compromised populations is very different than that in general populations. Prior to the introduction of highly active anti-retroviral therapy (HAART), chronic diarrhoea affected 50–90% of the HIV-infected population [8], and was attributed to viral, bacterial, and parasitic infections. A recent study suggested that the prevalence of diarrhoea has dropped since the introduction of HAART but it is still notable in the HIV-positive population [9]. Some opportunistic infections (such as cryptosporidiosis) may be life-threatening to HIV-positive persons but of limited importance in non-immunocompetent individuals. Additionally, there are non-infectious causes of diarrhoea in HIV-positive persons. These include medications that are frequently prescribed for HIV-positive individuals such as the protease inhibitors, especially nelfinavir. These factors could confound any study of risk factors for diarrhoea in this population.

Few studies have evaluated the association between diarrhoeal disease and drinking water in HIV-positive individuals. In a cross-sectional serosurvey for markers of prior *Cryptosporidium* infection among HIV-positive men, sexual practice was significantly associated with infection whereas drinking-water practices were not [10]. In our original survey of 226 patients in San Francisco we found no statistically significant association between boiled water use and diarrhoea in the past 7 days (OR 0·5, 95% CI 0·2–1·6) [11]. The small size of this study, however, limited our ability to firmly estimate the relationship between water modality and diarrhoea. Additionally, results from this study suggested that even in the HAART era, it is likely that diarrhoeal diseases unrelated to medication use remain a significant cause of morbidity in HIV-positive individuals.

METHODS

Between October 1998 and April 1999, the first survey was administered at the San Francisco Veterans Affairs Medical Center (SFVAMC). The SFVAMC cohort consisted of 226 patients and its results were published previously [11].

Between December 1999 and June 2000, the same survey was administered to 458 additional patients at two health clinics associated with the Community Consortium within San Francisco: the Positive Health Unit at the San Francisco General Hospital and Clinica Esperanza at the Mission Neighborhood Health Center. The Community Consortium (CC) is a community-based clinical research programme that has established a network of health-care providers within the San Francisco Bay Area. The study instrument and protocol were approved by the Institutional Review Boards from the University of California at Berkeley, the University of California at San Francisco, and the Centers for Disease Control and Prevention.

We used a cross-sectional design because we were interested in obtaining broad HIV-positive population prevalence estimates of both GI illness and drinking water patterns. We administered the survey to patients from three of the larger HIV clinics in San Francisco as an efficient way to obtain a large sample size.

The survey addressed specific drinking water behaviours, medication usage, CD4 count, and other potential factors associated with GI illness. Specifically, the survey included questions on: (1) drinking water behaviour; (2) other risk factors for diarrhoeal disease such as medication usage, sexual practice, foods consumed, contact with animals, and travel; (3) self-reported symptoms; (4) demographic information (age, race, and income); and (5) knowledge of and attitudes about drinking water risks. Boiled, bottled, and filtered water use were coded as 'never', 'rarely', 'sometimes', 'often' or 'always', and were modelled as dummy variables with 'never' as the baseline. Since some of the intermediate categories ('often', 'sometimes' and 'rarely') had very low numbers, they were collapsed into one category ('sometimes').

For the SFVAMC cohort, clinical records of the most recent CD4 count measure and medication usage were obtained from a chart review of the patients. These data were not available from the CC cohort, and therefore we collected CD4 count and medication usage data from self-reports. All medications were classified by a pharmacist with respect to

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Table 1. *Demographic characteristics*

	VAMC ($n = 226$)	Community Consortium ($n = 458$)	Total ($n = 684$)
Age			
11–20	0 (0%)	2 (<1%)	2 (<1%)
21–30	7 (3%)	53 (12%)	60 (9%)
31–40	39 (17%)	173 (38%)	212 (31%)
41–50	81 (36%)	178 (39%)	259 (38%)
51–60	61 (27%)	43 (9%)	104 (15%)
61–70	22 (10%)	2 (<1%)	24 (4%)
71–80	11 (5%)	2 (<1%)	13 (2%)
>80	0 (0%)	1 (<1%)	1 (<1%)
Missing	5 (2%)	4 (1%)	9 (1%)
Gender			
Male	226 (100%)	325 (71%)	551 (81%)
Female	0 (0%)	133 (29%)	133 (19%)
Years of education			
Less than high-school	5 (2%)	34 (7%)	39 (6%)
Some high-school	9 (4%)	119 (26%)	128 (19%)
High-school degree	59 (26%)	135 (30%)	194 (28%)
Post high-school	153 (68%)	165 (36%)	318 (46%)
Missing	0	5 (1%)	5 (1%)
Race			
Black	43 (19%)	221 (48%)	264 (39%)
White	152 (68%)	117 (26%)	269 (39%)
Hispanic	19 (8%)	90 (20%)	109 (16%)
Native American	2 (1%)	7 (2%)	9 (1%)
Asian	2 (1%)	11 (2%)	13 (2%)
Other	7 (3%)	9 (2%)	16 (2%)
Missing	1 (<1%)	3 (1%)	4 (1%)
Income			
<$20000	152 (68%)	380 (83%)	532 (78%)
$20000–$30000	33 (15%)	38 (8%)	71 (10%)
$30001–$40000	15 (7%)	12 (3%)	27 (4%)
$40001–$50000	8 (4%)	9 (2%)	17 (2%)
$50001–$100000	12 (5%)	1 (<1%)	13 (2%)
> $100000	3 (1%)	2 (<1%)	5 (1%)
Missing	3 (1%)	16 (3%)	19 (3%)
Currently employed			
Yes	66 (29%)	81 (18%)	147 (21%)
No	152 (67%)	371 (81%)	523 (76%)
Missing	8 (4%)	6 (1%)	14 (2%)
CD4/mm^3			
0–200	55 (24%)	78 (17%)	
201–358	51 (23%)	70 (15%)	
359–511	53 (23%)	71 (16%)	
>511	52 (23%)	77 (17%)	
Missing	15 (7%)	162 (35%)	
Medication risk			
None	21 (10%)	116 (25%)	
0·1–0·27	54 (24%)	84 (18%)	
0·28–0·34	36 (16%)	35 (8%)	
0·35–0·42	50 (23%)	85 (19%)	
>0·42	60 (27%)	138 (30%)	

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

	No. (with diarrhoea)	No. (without diarrhoea)	Unadjusted RR (95% CI)	Estimated counterfactual RR (95% CI)
Drinking water				
Heard of CDC drinking water guidelines?				
Yes	50	62	1·02 (0·81–1·28)	
No	232	299	1·0 (reference)	
How concerned about drinking water and its health effects?				
Not at all concerned	54	103	1·0 (reference)*†	
A little concerned	110	135	1·31 (1·01–1·69)*	
Very concerned	98	99	1·45 (1·12–1·87)*	
Always or often uses at least one type of water treatment?				
Yes	141	173	1·08 (0·90–1·28)	
No	142	198	1·0 (reference)	
How often drinks boiled water?				
Never	184	233	1·0 (reference)	1·0 (reference)
Sometimes	77	90	1·05 (0·86–1·27)	0·97 (0·74, 1·26)
Always	16	37	0·68 (0·45–1·04)*	0·61 (0·29–1·31)
How often drinks bottled water?				
Never	24	51	1·0 (reference)	1·0 (reference)
Sometimes	208	244	1·44 (1·02–2·03)*	1·33 (0·87, 2·04)
Always	47	73	1·22 (0·82–1·82)	1·35 (0·84, 2·18)
How often drinks filtered water?				
Never	172	233	1·0 (reference)	1·0 (reference)
Sometimes	69	87	1·04 (0·84–1·28)	0·98 (0·74, 1·28)
Always	35	45	1·03 (0·78–1·35)	0·98 (0·67, 1·44)
Medications				
Number of medications with >10% diarrhoeal side effects				
0	105	181	1·0 (reference)*†	
1	97	114	1·25 (1·01–1·55)*	
2	46	45	1·38 (1·07–1·77)*	
3	22	16	1·58 (1·16–2·15)*	
4	5	12	0·80 (0·38–1·70)	
5	4	2	1·82 (1·01–3·26)	
Any medications with >10% diarrhoeal side effects				
Yes	174	189	1·31 (1·08–1·57)*	
No	105	181	1·0 (reference)	
Taken any medications in the past 6 months				
Yes	238	282	1·44 (1·10–1·89)*	
No	41	88	1·0 (reference)	
Immune status				
CD4 > = 500/mm^3	51	93	0·71 (0·55–0·90)*	
CD4 < 500/mm^3	175	175	1·0 (reference)	
Pets and animal contact				
Have any pets at home?				
Yes	88	84	1·26 (1·05–1·52)*	
No	183	269	1·0 (reference)	
Clean pet's urine?				
Yes	53	44	1·33 (1·08–1·64)*	
No	216	309	1·0 (reference)	

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Table 2. (*cont.*)

	No. (with diarrhoea)	No. (without diarrhoea)	Unadjusted RR (95% CI)	Estimated counterfactual RR (95% CI)
Any contact with farm animals				
Yes	10	4	1·68 (1·19–2·36)‡	
No	267	360	1·0 (reference)	
Food (eaten in the last 7 days)				
Vegetable salad				
Yes	170	211	1·08 (0·91–1·30)	
No	109	155	1·0 (reference)	
Red meat				
Yes	70	65	1·26 (1·04–1·53)*	
No	209	300	1·0 (reference)	
Shellfish				
Yes	52	61	1·08 (0·86–1·35)	
No	227	305	1·0 (reference)	
Raw fish				
Yes	10	22	0·71 (0·42–1·20)	
No	269	344	1·0 (reference)	

* Significant χ^2 test of association.
† Significant χ^2 test for trend.
‡ Significant 2-sided Fisher's exact test.

their probability of causing diarrhoea. Since each patient on average took several medications, each with a different risk of causing diarrhoea due to side effects, we developed a continuous, composite variable ('medication risk') to estimate the overall diarrhoeal risk associated with a given set of medications [11]. Briefly, the medication risk variable ranged from 0 to 1, where 1 represented the highest risk of causing diarrhoea. The outcome variable, diarrhoea, was defined as the presence of two or more loose or unformed stools on a given day of the week. The patient answered yes or no to whether they had experienced diarrhoea in the previous 7 days.

The associations between the risk factors included in the survey and symptoms of diarrhoea were assessed using bivariate tabulations and calculations of relative risks. The relative risk was defined as the ratio of prevalence estimates between the exposed and unexposed. To control for potential confounding factors, we used the Marginal Structural Model (MSM) approach [12]. Specifically, MSMs require a model for the distribution of the risk factor given relevant (to diarrhoea) covariates. Thus we estimated the probability of being in one of the three levels of water treatment ('never', 'sometimes', 'always') given a particular covariate pattern ($P(A|\text{covariates})$) using multinomial logistic regression where $A =$ the observed boiling water pattern ('always', 'sometimes', 'never'). The inverse of these probabilities was subsequently used as weights in a logistic regression of diarrhoea status as the outcome variable and category of water treatment frequency as the predictor. As explained in Robins et al. [12] this has the effect of creating a ''pseudo-population'' (known as counterfactual population) where covariate patterns are no longer associated with water treatment. One important assumption with regards to interpreting the model is that the level of consumption (e.g. 'always') is statistically independent of diarrhoea, *given the covariates*. This is essentially the untestable assumption of no unmeasured confounding. The model yields relative risk estimates comparing counterfactual populations of interest; e.g. everyone always boils their drinking water *vs.* no one ever boils their drinking water. Note, the resulting relative risk has a different interpretation than the typical results from regression where we are comparing the conditional probabilities of disease given a change in the risk factor of interest, keeping all other covariates (potential confounders) fixed. To select the appropriate weights for the logistic regression we used a multinomial logistic regression model-fitting procedure described by Kooperberg et al. [13]. As suggested by Robins [12], we report conservative confidence intervals based on robust or 'sandwich' estimators of the variance of the coefficient estimates.

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Table 3. *Association of risk factors with diarrhoea for the continuous variables*

	n	With diarrhoea Mean (S.D.)	Without diarrhoea Mean (S.D.)
Demographic characteristics			
Age	646	43·3 (10·1)	43·8 (10·5)
Drinking water			
Percent of drinking water treated	636	54·0 (34·8)	55·9 (35·8)
Cold glasses of tap water per day at home	633	2·68 (3·4)	2·20 (2·91)
Total glasses of tap water per day*	652	7·6 (7·3)	6·6 (6·4)
Medications			
Probability of diarrhoea from medication*	649	0·34 (0·2)	0·28 (0·2)
Health			
CD4*/mm^3	495	358 (247)	607 (1760)
CD4*†/mm^3	490	358 (247)	440 (310)

* Significant two-sample *t*-test.
† With 5 outliers removed.

The primary outcome of interest was diarrhoea in the previous 7 days. Once the weights were estimated, we used a weighted General Linear Model (GLM) procedure based on a log link with a binary indicator of diarrhoea in the previous 7 days as the dependent variable and indicator variables for water treatment as the predictor variables. We estimated separate weights and used separate models for each water treatment method. The data were entered and organized in Access97 (Microsoft®), and analysed in S-Plus 4.5 (MathSoft®) and Stata (Version 6.0, Stata Corporation).

RESULTS

The basic demographic composition of the SFVAMC cohort ($n = 226$) and the CC cohort ($n = 458$) are displayed in Table 1. Although the SFVAMC cohort was slightly older, totally male, and had fewer blacks and Hispanics, the two study populations were similar with respect to immunosuppression (as measured by CD4 counts).

Data evaluating the univariate association between several risk factors and the prevalence of diarrhoea for the combined cohorts are shown in Tables 2 and 3. Although 74% were concerned and 33% were very concerned about drinking water quality, only 18% of the cohort had heard about the CDC federal drinking water guidelines for immunocompromised persons (http://www.cdc.gov/mmwr/PDF/rr/rr5108.pdf).

Counterfactual relative risk estimates were calculated by the MSM. Covariates considered in model selection to determine the weights for the MSM included factors suspected to be associated with diarrhoea. These factors included: medication use; consumption of high-risk foods (shellfish, raw fish, vegetable salads, uncooked meat); race; CD4 level; cleaning up after pets; presence of pets in the home; type of water used (boiled, bottled, filtered, tap); current employment status; swimming or drinking in a lake or river; anal sexual contact; education; household income; and homelessness. In determining weights for the MSM, the model selection process identified variables that were the best predictors of water treatment. Race and filtering water were the most important predictors of boiled water use; age, boiling water and current employment were predictors of bottled water use; and boiling water and presence of pets in the home were the most important predictors of filtered water use.

Covariates such as CD4 and medication use, while highly associated with diarrhoea, did not predict water treatment method. Since many of the self-reported CD4 measurements were missing ($n = 162$), and since CD4 was not an important factor in determining the weights, we generated weights again, excluding CD4 from the model, thereby allowing those 162 individuals with missing CD4 values to be included in the model. Results were nearly identical to the model where those with missing CD4 were excluded.

The associations of 'always', 'sometimes', or 'never' drinking boiled, filtered, or bottled water with diarrhoea were examined and are presented as both unadjusted and adjusted relative risk measures (Table 2). The univariate analysis estimated a borderline

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statistically significant association between 'always' boiling drinking water and diarrhoea 0·68 (0·45–1·04). The final model for 'always' compared to 'never' boiling drinking water did not appreciably change the point estimate but did widen the confidence intervals [RR = 0·61 (0·29, 1·31)]. The relative risk point estimate of 'always' compared with 'never' drinking bottled water was elevated though also not significant. These point estimates were similar for both the unadjusted and adjusted estimate, while the CI was wider in the final model [RR = 1·22 (0·82, 1·82) and RR = 1·35 (0·84, 2·18) respectively]. Filtered water use remained unassociated with diarrhoea [RR = 1·03 (0·78–1·35)].

The univariate associations between both medication use and CD4 count and diarrhoea were also statistically significant. For example the RR of diarrhoea for those with CD4 $>500/mm^3$ compared with CD4 $<500/mm^3$ was 0·71 (0·55–0·90), and the RR of diarrhoea for those taking any medication that was reported to cause diarrhoea greater than 10% of the time compared to those that did not was 1·31 (1·08–1·57). Other significant univariate associations were contact with animals: RR = 1·26 (1·05–1·52) for contact with pets; RR = 1·68 (1·19–2·36) for contact with farm animals; and RR = 1·33 (1·08–1·64) for contact with animal urine.

When the CC and SFVAMC cohorts were analysed separately, similar relative risks were observed. For example, 'always' *vs.* 'never' drinking boiled water had a RR of 0·37 (0·1–1·32) for the SFVAMC and 0·73 (0·31–1·7) for the CC. The analogous comparison for bottled water was RR = 1·16 (0·71–1·87) and 1·71 (1·02–2·89) for the CC and SFVAMC cohorts respectively and for filtered water was RR = 0·72 (0·35–1·48) and 1·16 (0·75–1·81) for the CC and SFVAMC cohorts respectively.

DISCUSSION

The principal results of this cross-sectional study suggested that among HIV-positive persons: (1) boiled water consumption was associated with a statistically non-significant decreased risk of diarrhoea; (2) consumption of bottled water was associated with a statistically non-significant elevated risk of diarrhoea; and (3) filtered water consumption was not associated with diarrhoea. The point estimates of the association between diarrhoea and boiling water from the two independent samples, the VAMC ($n = 226$), and the CC ($n = 458$), were strong and protective (RR = 0·37 and 0·73, respectively). Analogously, the bottle water risks were elevated in both groups (RR = 1·16 and 1·71).

It is biologically plausible that boiled water might be associated with a reduced risk of diarrhoea: pathogens associated with diarrhoeal disease are, in general, quite sensitive to temperatures approaching 100 °C, the boiling point of water. Boiling water is, therefore, generally thought of as the most effective treatment for infectious pathogens. Nor is it surprising that filtered water was not associated with diarrhoea since the efficacy of filters sold to the public varies from those that only improve taste and aesthetic qualities to those that effectively filter viruses, bacteria, and protozoa. Although hundreds of millions of dollars are annually spent on these home water-treatment devices, little is known about the benefits of such treatment.

The possibility that bottled water may be associated with an elevated risk of diarrhoea is somewhat surprising, although the microbiology of bottled water does indicate the potential for bacterial regrowth. In Canada, a survey of the microbiology of bottled water Lalumandier and Ayers [14] demonstrated that 23·3 and 5·5% exceeded 10^2 c.f.u./ml and 10^4 c.f.u./ml respectively for heterotrophic plate count bacteria (HPC). They compared tap water and bottled water and found that 6 of 57 samples of bottled water had bacterial counts >1000 c.f.u./ml, whereas the tap water samples never exceeded 2·7 c.f.u./ml. In an earlier review of studies in the United Kingdom on the microbiology and public health of ground waters used for bottled mineral waters, Hunter [15] concluded that there was no evidence that consumption of bottled water provided additional protection as compared to tap water. Our study highlights the need for additional studies to clarify the role that bottled water may play in diarrhoea in immunocompromised individuals.

Although studies linking water consumption to diarrhoea have been repeatedly conducted in developing countries, there are relatively few such studies from developed countries. In a case control study of diarrhoea, there was no observed relationship between consumption of tap water and acute diarrhoea in the winter in France [16]. A case control study of *E. coli* O157:H7 presented limited evidence of a relationship between drinking unchlorinated well water and infection [17]. In one earlier cross-sectional study using an HIV-positive cohort, there was no relationship observed between drinking tap water and infection with *Cryptosporidium* [10].

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There are limitations in our study. As is true for any cross-sectional study, the temporal relationship between the exposure (drinking water) and the outcome (diarrhoea) is uncertain. It is possible that HIV-positive persons with diarrhoea altered their water consumption patterns due to the onset of diarrhoea. Another limitation was our necessary reliance on self-reported symptoms of diarrhoea, which may be associated with certain biases; e.g. a participant, for a variety of reasons, may either mistakenly or intentionally choose not to identify a diarrhoeal episode, resulting in a misclassification of that disease outcome. A final limitation in our data is the fact that for the CC cohort ($n = 458$), the CD4 count and medication use was self-reported and only 63% of these participants provided CD4 count data; a comparison, however, of the distribution of 296 self-reported CD4 count data with the 226 CD4 count values obtained through clinical records for the SFVAMC cohort suggested that the two distributions were comparable. This lessens the likelihood that systematic bias was introduced into the results either by the self-reporting or by the incomplete reporting. Furthermore, since our modelling procedure identified no relationship between CD4 and water treatment after considering other factors, and since we obtained identical results even when CD4 level was completely removed from the model selection process, it is unlikely that incomplete CD4 reporting could bias the observed result. There were some differences in the two cohorts with respect to medication use, gender and racial composition. Separate analysis of each cohort, however, led to results similar to the analysis of the entire cohort.

Although not significant at a 95% confidence level, the relative risk point estimates suggest the need to further evaluate whether or not there is a reduced risk of diarrhoea with the use of boiled water, and an increased risk of diarrhoea with the use of bottled water. A more complete understanding of the relationship between drinking water consumption and diarrhoea is likely to require either prospectively collected observational data or evidence from randomized trials evaluating drinking water treatment methods and their impact on rates of diarrhoea.

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