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Endemic cryptosporidiosis and exposure to municipal tap water in persons with acquired immunodeficiency syndrome (AIDS): A case-control study

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Abstract

Background: In persons with acquired immunodeficiency syndrome (AIDS), *Cryptosporidium parvum* causes a prolonged, severe diarrheal illness to which there is no effective treatment, and the risk of developing cryptosporidiosis from drinking tap water in non-outbreak settings remains uncertain. To test the hypothesis that drinking tap water was associated with developing cryptosporidiosis, we conducted a matched case-control study among persons with AIDS in San Francisco.

Methods: Among patients reported to the San Francisco AIDS Registry from May 1996 through September 1998, we compared patients who developed cryptosporidiosis to those who did not. Cases were individually matched to controls based on age, sex, race/ethnicity, $CD4^+$ T lymphocyte count, date of $CD4^+$ count, and date of case diagnosis. Population attributable fractions (PAFs) were calculated.

Results: The study consisted of 49 cases and 99 matched controls. In the multivariable analysis with adjustments for confounders, tap water consumption inside and outside the home at the highest exposure categories was associated with the occurrence of cryptosporidiosis (inside the home: odds ratio (OR), 6.76; 95% CI 1.37–33.5, and outside the home: OR 3.16; 95% CI 1.23–8.13). The PAF was 85%; that is, the proportion of cases of cryptosporidiosis in San Francisco AIDS patients attributable to tap water consumption could have been as high as 85%.

Conclusions: Although the results from this observational study cannot be considered definitive, until there is more data, we recommend persons with AIDS, especially those with compromised immune systems, consider avoiding tap water.

Background

Since human infection with *Cryptosporidium parvum* was first documented in 1976 [1], this protozoan parasite has been recognized worldwide as a major cause of diarrheal disease in humans [2]. In healthy, immunocompetent persons, *C. parvum* causes a self-limited diarrheal illness (cryptosporidiosis); however, in persons with severe immunosuppression, particularly those infected with the human immunodeficiency virus (HIV) and who have developed acquired immunodeficiency syndrome (AIDS), the diarrhea can be prolonged, severe, and life-threatening [3,4]. Currently there are no effective chemotherapeutic agents against cryptosporidiosis [5]. *Cryptosporidium* oocysts are found in the feces of infected humans, livestock, and wild animals [6]. Humans acquire the infection through person-to-person or animal-to-person contact, ingestion of fecally-contaminated water or food, or contact with fecally-contaminated environmental surfaces [7].

Cryptosporidium oocysts have an ubiquitous geographic distribution and can be detected in most surface drinking water sources [8]. The oocysts are resistant to environmental degradation [9], survive chlorination water treatment, and are too small (4 to 6 microns) to be removed by conventional water filters [6]. Risk factors for acquiring cryptosporidiosis have been determined primarily in studies of community-wide outbreaks, and drinking water has been implicated as the source of these outbreaks [9–14]. Case-control studies in AIDS patients have also been conducted during outbreaks [12,15], but levels of endemic risk in the United States remain uncertain, even though there is great concern for diarrheal disease associated with drinking water in this population [16,17]. Because defining the risk associated with drinking tap water is particularly important for counseling immunocompromised patients on reducing their risk of cryptosporidiosis, we conducted a case-control study among persons with AIDS in San Francisco to test the hypothesis that the pattern of tap water consumption is associated with the development of endemic cryptosporidiosis.

Methods

Study design

We conducted a matched case-control study. Among patients reported to the San Francisco AIDS Registry from May 1996 through September 1998, we compared patients who developed cryptosporidiosis to those who did not. We evaluated the hypothesis that cryptosporidiosis among AIDS patients would be associated with the pattern of tap water consumption after adjusting for potential confounders in a multivariable conditional logistic regression model. The study was not designed to assess whether point of use filtering, boiling, or other tap water processing among tap water consumers was protective. Therefore, for this study, tap water was defined as municipal water from the faucet whether or not it was filtered, boiled or processed further.

The Committee on Human Research and the Biosafety Committee of the University of California at San Francisco approved this study protocol.

Study subjects

The study population consisted of individuals with an AIDS-defining diagnosis living in San Francisco, California. The San Francisco Department of Public Health (SFDPH) maintains a reporting system on cases of HIV/AIDS residing in San Francisco. Records are regularly updated with $CD4^+$ T lymphocyte count and diagnosis of conditions associated with HIV/AIDS, such as cryptosporidiosis. The completeness of reporting AIDS cases in San Francisco has been 97% overall: 100% from hospitals, 96% from clinics, and 70% from private physicians [18].

A case was defined as a resident of San Francisco with AIDS who was reported to the San Francisco Department of Public Health with a laboratory-confirmed, positive stool test for *Cryptosporidium parvum* from May 1996 through September 1998. Cases could have cryptosporidiosis diagnosed as an initial AIDS-defining opportunistic infection or as a subsequent opportunistic infection. A control was defined as any resident of San Francisco who was reported with AIDS to the San Francisco Department of Public Health and did not have a laboratory-confirmed diagnosis of cryptosporidiosis. For cases and controls we collected information on date of birth, race/ethnicity, gender, month and year of the diagnosis of cryptosporidiosis, all $CD4^+$ T lymphocyte counts recorded and the date of each test. For each case, we determined the $CD4^+$ count closest to the date of cryptosporidiosis diagnosis.

Cases and controls were matched based on five criteria: age (within 5 years), sex, race/ethnicity, $CD4^+$ T lymphocyte count (+/- 25 points) and date of $CD4^+$ count (within 2 months of the case's $CD4^+$ count that was closest to the date of diagnosis), and date of case diagnosis. Controls who were participating in other studies conducted by the San Francisco Department of Public Health were not eligible for this study. In addition, we excluded eligible controls who had a history of psychiatric illness or psychosis. Controls were tested for subclinical disease by testing stool for *Cryptosporidium*. Three documented negative stool samples defined a potential control for this study. No potential controls were positive on stool testing. One to three controls were matched to each case.

The primary health care providers of the cases and controls were asked for permission to solicit the participation of their patients in this study. Cases and controls were initially contacted by phone at home between 9:00 am and 8:00 pm. If three calls were unsuccessful, up to two written solicitations were sent. The questionnaire was administered by telephone in English or Spanish after verbal consent was obtained. Controls were sent a package containing stool collection vials and instructions for collection and mailing of samples. Controls received a payment of $50 after SFDPH received written consent. Cases received a payment of $25 for participation in this study.

Exposure measurement

The questionnaire was designed to assess the relative importance of several risk factors for cryptosporidiosis in the recent past. Cases were asked about water exposures in the four-week period before the onset of diarrhea. Controls were asked about water exposures in the four-week period before the interview. The interviewer requested information about sources of exposure to water. Respondents were asked whether they always, sometimes, or never drank tap water inside and outside the home (such as workplace or restaurants). They were asked to reply (yes or no) to the use of tap water for brushing teeth, washing vegetables, consuming beverages containing ice made from tap water both inside and outside the home. Respondents were asked the type of drinking water consumed while traveling outside San Francisco, whether they used hot tubs, swam in lakes or streams, or had other recreational exposure in the four weeks prior to diarrhea (for cases) or interview (for controls). Our primary exposure variable was the pattern of tap water consumption (always, sometimes, never) whether or not the water was processed further.

We asked about the pattern of bottled water consumption inside and outside the home. Responses to cleaning vegetables with tap water (yes, no) and consumption of unpasteurized milk (yes, no) were also obtained. Other sources of cryptosporidiosis infection were assessed, such as potential exposure to fecal material from sexual behavior, diapers, patient care, or animals. Subjects were asked about recent travel outside of San Francisco.

San Francisco's municipal water system distributes water that is either filtered or unfiltered at the treatment facilities. The water distribution varies both geographically and temporally depending on the operational requirements of the water system. Respondents' residential address was used to determine whether, 4 weeks prior to the case's illness, their residence received municipal water that was either filtered, mixed, or unfiltered. Addresses and interview dates were provided to the San Francisco Public Utilities Commission Water Quality Bureau to classify this exposure. This analysis was added after study completion and was not a primary hypothesis.

Statistical analysis

For the sample size calculations we estimated that our study would have required 200 cases and 400 controls to detect an odds ratio of 3 with a Type I error of 0.05% and 80% power. However, because the number of cases occurring decreased dramatically we extended our study period to accrue more study subjects. At the end of the study we had 49 cases and 99 matched controls.

Bivariate analyses of associations with cryptosporidiosis infection were performed for water exposure variables, fecal exposure variables, and other possible exposures using conditional logistic regression. The matched odds ratios (ORs) and 95% confidence intervals (CIs) are reported.

Risk factors for cryptosporidiosis were determined a priori. Composite variables were developed for three major exposure routes (tap water, bottled water, fecal matter). For each we constructed three levels of exposure: lowest, intermediate, and highest. For example, subjects who answered "never" to drinking tap water at home and also answered "never" to drinking tap water outside the home were categorized as "lowest" exposure for the tap water composite variable. Subjects who responded "always" to both questions were classified as "highest" exposure, and a mixed response resulted in an intermediate exposure classification. A similar composite variable was created from bottled water consumed at home and outside the home. A fecal exposure composite variable was created from two questions: sex partner with diarrhea, and touching anything soiled with feces or helping someone with toileting. If respondents answered "yes" to having either exposure, they were classified as having been exposed to fecal material.

A composite variable was created for recreational water exposure, i.e., exposure to pools, lakes, rivers, streams, or oceans. If respondents ingested water from any of these bodies of water or submerged their heads under the water, then they were classified as having been exposed to a recreational body of water that could have put them at risk for cryptosporidiosis.

To examine the independent association between the pattern of tap water consumption and cryptosporidiosis infection, while adjusting for other potential sources of cryptosporidial infection, adjusted, matched odds ratios and 95% confidence intervals were calculated using multivariable conditional logistic regression models.

Population attributable fraction

The population attributable fraction (PAF) is the theoretical proportion of disease cases that would have been prevented had a specific exposure never occurred, assuming the exposure is causal [19]. We calculated the proportion of cryptosporidiosis cases theoretically attributable to various water exposures from the results of the multivariable

Table 1: Characteristics of cryptosporidiosis cases and matched controls

	Cases (*n* = 49)		Controls (*n* = 99)		
Characteristic	*N*	(%)	*N*	(%)	Total
Age (years)					
20 to 29	7	(14)	9	(9)	16
30 to 39	22	(45)	53	(54)	75
40 to 49	16	(33)	31	(31)	47
50 to 59	4	(8)	6	(6)	10
Gender					
Males	48	(98)	97	(98)	145
Females	1	(2)	2	(2)	3
Race/ethnicity					
White	34	(69)	70	(71)	104
African-American	6	(12)	11	(11)	17
Latino	9	(18)	8	(18)	27
Other	0	(0)	0	(0)	0
Sexual orientation					
Gay/Bisexual	45	(92)	93	(94)	138
Heterosexual	1	(2)	6	(6)	7
Unknown	3	(6)	0	(0)	3

conditional logistic regression models using PAF methods for case-control studies [20].

All analyses were conducted in S-Plus [21]. For one bivariate analysis where cells contained zero, unmatched, median-unbiased odds ratios and exact 95% confidence intervals were calculated from the mid-p function as described by Rothman [22].

Results

During the study period, 72 cases from the AIDS Registry were identified for possible inclusion in the study; of these, 3 persons moved out of jurisdiction, 1 was deceased at the time of contact, 5 were ineligible for the study (2 did not have AIDS, 2 did not have cryptosporidiosis, and 1 was diagnosed with cryptosporidiosis outside the study period), 1 was lost to follow-up, 11 did not respond to repeated attempts for recruitment, and 2 individuals refused. The remaining 49 cases constituted the case sample.

Using pairwise matching criteria, 168 eligible controls were identified from the AIDS registry. From these, 10 individuals were not contacted because the primary care provider did not grant permission, 14 individuals moved out of jurisdiction, 1 was deceased, 14 were ineligible, 7 were lost to follow-up, 16 did not respond to repeated attempts to be contacted, 5 were not needed for the study because we had a sufficient number of controls per case, and 2 individuals refused. The remaining 99 controls constituted the control sample.

The demographic characteristics of the cases and controls are shown in Table 1. The study population consisted of 49 cases, each matched by date of case diagnosis, $CD4^+$ count, age, ethnicity, and gender to 1 to 3 controls for a total of 99 controls. Seventy-eight percent of cases and 85% of controls were between the ages 30 to 49. Ninety-eight percent of subjects were male, 70% were white, 11% were African American, and 18% were Latino. Ninety-two percent of cases and 94% of controls were gay/bisexual.

The unadjusted, matched odds ratios for the occurrence of cryptosporidiosis according to exposure to water consumption sources are shown in Table 2. Compared to "never" drinking tap water inside or outside the home (lowest exposure), cryptosporidiosis was associated with the intermediate exposure category of tap water consumption (OR, 7.1; 95% CI, 1.59–31.4) and strongly associated with the highest category of tap water consumption (OR, 24.3; 95% CI, 4.21–139). Exposure to tap water consumption at home accounted for most of this effect (sometimes category: OR, 9.54; 95% CI, 2.06–44.1) and (always category: OR, 9.78; 95% CI, 2.14–44.7). The pattern of always drinking bottled water in the home had a strong negative association with cryptosporidiosis (always category: OR, 0.09; 95% CI, 0.03–0.37). Always drinking bottled water was strongly correlated with not drinking tap water: Of 21 responses of always drinking bottled water in the home, only 6 (9.2%) reported sometimes drinking tap water and 0 (0%) reported always drinking tap water in the home. Of 65 responses of always drinking bottled water outside the home, only 1 (1.5%) reported sometimes drinking tap water and 0 (0%) reported always drinking tap water outside the home.

Table 2: Unadjusted, matched odds ratios for the occurrence of cryptosporidiosis among patients with AIDS according to exposure to drinking water sources

	Cases (*n* = 49)		Controls (*n* = 99)			
Variable	*N*	(%)	*N*	(%)	Odds Ratio	95% CI
Tap water at home						
Never	2	(4)	31	(31)	1.00	Reference
Sometimes	20	(41)	30	(30)	9.54	2.06, 44.1
Always	27	(55)	38	(38)	9.78	2.14, 44.7
Tap water outside home						
Never	29	(59)	81	(82)	1.00	Reference
Sometimes	4	(8)	8	(8)	2.00	0.53, 7.50
Always	16	(33)	10	(10)	4.20	1.76, 10.0
Tap water composite[a]						
Lowest exposure	2	(4)	29	(29)	1.00	Reference
Intermediate exposure	35	(71)	64	(65)	7.08	1.59, 31.4
Highest exposure	12	(24)	6	(6)	24.3	4.21, 139
Bottled water at home						
Never	25	(51)	38	(38)	1.00	Reference
Sometimes	24	(49)	40	(40)	0.81	0.37, 1.76
Always	0	(0)	21	(21)	0.09[c]	0.03, 0.37
Bottled water outside home						
Never	17	(35)	36	(36)	1.00	Reference
Sometimes	10	(20)	20	(20)	0.97	0.28, 3.40
Always	22	(45)	43	(43)	0.75	0.28, 2.06
Bottled water composite[b]						
Lowest exposure	11	(22)	17	(17)	1.00	Reference
Intermediate exposure	38	(78)	70	(71)	0.66	0.26, 1.68
Highest exposure	0	(0)	12	(12)	0.17[c]	0.06, 0.83
Filtered municipal water						
Filtered	27	(55)	51	(52)	1.00	Reference
Mixed	14	(29)	37	(37)	0.75	0.35, 1.58
Unfiltered	8	(16)	11	(11)	1.36	0.44, 4.16

[a]Lowest = answered *never* consumed tap water both inside and outside the home; Highest = answered *always* consumed tap water both inside and outside the home; Intermediate = all other responses [b]Lowest = answered *never* consumed bottled water both inside and outside the home; Highest = answered *always* consumed bottled water both inside and outside the home; Intermediate = all other responses [c]Unmatched, median-unbiased odds ratio estimate and exact 95% confidence intervals calculated directly from the mid-p function based on the hypergeometric model (see methods)

The unadjusted, matched odds ratios for the occurrence of cryptosporidiosis according to exposure to non-drinking water sources are shown in Table 3. Neither sexual activity, sex with a partner with diarrhea, nor travel outside of San Francisco were associated with the development of cryptosporidiosis. Sex with a partner with diarrhea had an elevated, but not statistically significant, measure of association with cryptosporidiosis (OR, 2.00; 95% CI, 0.61–3.30). Having touched anything soiled with feces or helping someone with toileting were not associated with cryptosporidiosis.

Two multivariable conditional logistic regression models are shown in Table 4. Model 1 tested the hypothesis of whether the pattern of tap water consumption inside the home and outside the home were separately associated with cryptosporidiosis after adjusting for potential exposure to fecal material (had sex with partner who had diarrhea, cared for person with diarrhea, or touched something soiled with feces from person with diarrhea) and living in a residence supplied with filtered or unfiltered municipal water. In this model the pattern of tap water consumption inside the home was associated with cryptosporidiosis (sometimes category: OR, 7.70; 95% CI, 1.63–36.3, always category: OR, 6.76; 95% CI, 1.37–33.5) as was the pattern of tap water consumption outside the home (always category: OR, 3.16; 95% CI, 1.23–8.13). In model 2, the overall pattern of tap water consumption was strongly associated with cryptosporidiosis with a dose-response relationship (intermediate exposure: OR, 6.92; 95% CI, 1.55–30.9, highest exposure: OR, 23.6; 95% CI, 4.08–137). In both models, cryptosporidiosis was not associated with whether the residence was supplied with filtered or unfiltered municipal tap water.

Table 3: Unadjusted, matched odds ratios for the occurrence of cryptosporidiosis among patients with AIDS according to exposure to non-tap water sources

	Cases (*n* = 49)		Controls (*n* = 99)			
Variable	*N*	(%)	*N*	(%)	Odds Ratio	95% CI
Sex partner						
No	14	(29)	31	(31)	1.00	Reference
Yes	35	(71)	68	(69)	1.07	0.48, 2.38
Sex partner with diarrhea						
No	47	(96)	91	(92)	1.00	Reference
Yes	2	(4)	8	(8)	2.00	0.61, 3.30
Touched anything soiled with feces or help someone with toileting						
No	44	(90)	94	(95)	1.00	Reference
Yes	5	(10)	5	(5)	1.89	0.54, 6.66
Fecal exposure composite[a]						
No	42	(86)	87	(88	1.00	Reference
Yes	7	(14)	12	(12)	1.23	0.44, 3.43
Ingested water or submerged head in a body of water						
No	42	(86)	83	(84)	1.00	Reference
Yes	7	(14)	16	(16)	1.00	0.36, 2.76
Exposed to any animals						
No	25	(51)	37	(37)	1.00	Reference
Yes	24	(49)	62	(63)	0.63	0.31, 1.29
Traveled outside of San Francisco						
No	40	(82)	74	(75)	1.00	Reference
Yes	9	(18)	25	(25)	0.45	0.11, 1.93

[a]Had sex with partner who had diarrhea, cared for person with diarrhea, or touched something soiled with feces from person with diarrhea

Assuming a causal relationship between tap water consumption and the development of cryptosporidiosis in persons with AIDS, the PAF was 85%; that is, the proportion of cases in San Francisco AIDS patients attributable to tap water consumption could have been as high as 85%. The PAF from other potential factors, such as exposure to feces or living at a residence supplied with unfiltered water, was below 1%.

Discussion

This is the first population-based case-control study enrolling incident cases of cryptosporidiosis to evaluate and detect a strong association between an increasing pattern of tap water consumption and the development of cryptosporidiosis among AIDS patients in the United States. Prior studies of cryptosporidiosis in the US among AIDS patients did not interview incident cases, and therefore, often did not have information on individual-level waterborne exposures [3,23–25]. We also detected a strong negative association between the pattern of always drinking bottled water at home and cryptosporidiosis. This can be explained by the finding that persons who reported always drinking bottled water rarely drank tap water. Additionally, this result suggests drinking bottled water may be a safer alternative to drinking tap water.

San Francisco's municipal water is derived from several sources. Some of these sources filter the water before distribution to city residences [26]. No waterborne outbreak of cryptosporidiosis has ever been detected. This study did not find an association between developing cryptosporidiosis and living in a residence that received filtered compared to unfiltered water, even after adjusting for the pattern of tap water consumption (Table 4). Although this result is consistent with a previous ecologic study [27], suggesting that filtering at the level of a municipal system may not be successful in decreasing cases of cryptosporidiosis, this negative finding must be viewed with caution since our study was not specifically designed nor statistically powered to assess this exposure.

Because this was an observational study, our results do not prove that tap water was the source of cryptosporidial infection. However, the dose-response relationship between the pattern of tap water consumption and cryptosporidiosis makes a causal relationship more likely. Nonetheless, it is possible that residual confounding due

Table 4: Multivariable conditional logistic regression models of cryptosporidiosis among patients with AIDS according to pattern of tap water consumption and adjusted for potential confounders

	Cases (*n* = 49)		Controls (*n* = 99)			
Models and variables	*N*	(%)	*N*	(%)	Odds Ratio	95% CI
Model 1						
Tap water at home						
Never	2	(4)	31	(31)	1.00	Reference
Sometimes	20	(41)	30	(30)	7.70	1.63, 36.3
Always	27	(55)	38	(38)	6.76	1.37, 33.5
Tap water outside home						
Never	29	(59)	81	(82)	1.00	Reference
Sometimes	4	(8)	8	(8)	1.59	0.38, 6.73
Always	16	(33)	10	(10)	3.16	1.23, 8.13
Exposure to fecal material[a]						
No	42	(86)	87	(88)	1.00	Reference
Yes	7	(14)	12	(12)	1.03	0.32, 3.36
Filtered municipal water						
Filtered	27	(55)	51	(52)	1.00	Reference
Mixed	14	(29)	37	(37)	0.77	0.35, 1.74
Unfiltered	11	(16)	8	(11)	1.19	0.34, 4.20
Model 2: Composite water variable						
Tap water exposure[b]						
Lowest exposure	2	(4)	29	(29)	1.00	Reference
Intermediate exposure	35	(71)	64	(65)	6.92	1.55, 30.9
Highest exposure	12	(24)	6	(6)	23.6	4.08, 137
Exposure to fecal material[a]						
No	42	(86)	87	(88)	1.00	Reference
Yes	7	(14)	12	(12)	0.96	0.30, 3.06
Filtered municipal water						
Filtered	27	(55)	51	(52)	1.00	Reference
Mixed	14	(29)	37	(37)	0.81	0.37, 1.77
Unfiltered	11	(16)	8	(11)	1.23	0.38, 4.02

[a]Had sex with partner who had diarrhea, cared for person with diarrhea, or touched something soiled with feces from person with diarrhea [b]Model 2 tap water composite exposure variable (Lowest = *never* consumed tap water both inside and outside the home; Highest = *always* consumed tap water both inside and outside the home)

to measured or unmeasured factors may explain the results. However, statistical adjustment for known confounders did not weaken the association between the pattern of tap water consumption and cryptosporidiosis. The strength of this association would require that unknown or unmeasured confounders have very strong effects [28], which is unlikely given that adjustment for the likely confounders did not change our results.

We also considered the possibility that our finding is due to bias from cases having differential recall of specific water exposures. However, during this period there was a general awareness in the AIDS community of tap water as a potential source of cryptosporidial infection [29]. We believe this prior awareness would have influenced the recall of both cases and controls, thereby reducing any differential recall. Also, there does not appear to be differential recall with respect to sexual and other potential fecal exposures. Therefore, we believe that even if such a recall bias was operating, it would not account for the large association we detected.

Other routes of fecal contamination were not associated with cryptosporidiosis in the bivariate and multivariable analyses. Sex with a partner with diarrhea was moderately associated in the bivariate analysis (OR, 2.00) but was not statistically significant. Because the incubation period between exposure to *Cryptosporidium* oocysts and symptoms is not well understood in persons with AIDS, it is possible that contact with fecal material which occurred long before the incident diagnosis might be the source of these infections. In favor of this hypothesis is the observation that cryptosporidiosis is more common among gay and bisexual men with AIDS than among other groups with AIDS [30]. Nonetheless, prior sexual practices are unlikely to be associated with current water consumption patterns [29].

The methods we used to calculate the attributable fractions depend on two assumptions: the incidence of disease in the base population is sufficiently small so that the odds ratio provides a satisfactory estimate of the relative risk; and the cases in this study are representative of all cases in the population, thus allowing us to calculate the proportion of cases in each stratum of exposure categories [20]. The annual risk of a cryptosporidiosis diagnosis among AIDS patients during this study period was less than 1% [31,32], sufficiently low so that the odds ratio approximates the relative risk. The study base population, the San Francisco AIDS registry, is representative of AIDS cases in San Francisco [18].

There were several limitations to this study. First, the annual number of cryptosporidiosis cases dropped dramatically during the study period resulting in a much smaller study population than initially planned. The number of cryptosporidiosis cases decreased annually: 126 cases were reported in 1995, 69 in 1996, 38 in 1997, and 32 in 1998 [31]. In the year 2001, only 13 cases of cryptosporidiosis were recorded in the AIDS Registry [33]. Because of the small study size, our ability to more precisely calculate matched adjusted odds ratios for the multivariable model were limited. However, for our primary hypothesis, the association of the pattern of tap water consumption and cryptosporidiosis, the sample size was sufficient to detect the observed large and statistically significant dose-response relationship. Second, cases were asked about potential exposures in the four weeks prior to their illness onset, whereas controls (whose stools tested negative for *Cryptosporidium*) were asked about potential exposures in the four weeks prior to their interview. Because of the lag time between selecting a eligible control and interviewing them, an intercurrent illness could have caused them to lower or increase their tap water consumption in the four weeks prior to their interview, thereby inflating or deflating the association the between the pattern of tap water consumption and cryptosporidiosis.

Third, when this study was designed the use of highly active anti-retroviral therapy (HAART) was uncommon (about 5%) and this information was not collected on subjects; however, from 1995 to 1999 the use of HAART increased from 5% to 60% among persons living with AIDS in San Francisco [31]. Although cases and controls were matched on $CD4^+$ T lymphocyte count, the exposure to HAART may have been a potential confounder if this exposure was protective against cryptosporidiosis independent of $CD4^+$ count and if HAART exposure was correlated with decreased tap water consumption. Fourth, we did not actually measure tap water consumption but rather we asked about the pattern of use (never, sometimes, always) in the four weeks preceding illness (cases) or interview (controls). This assumes that these pattern of use categories have the same meaning to cases and controls with respect to quantity of water consumed, which may not be the true.

Finally, our matched case-control study was designed to assess the first-level effect of tap water exposure and not the effect of boiling or filtering (although this information was collected from subjects that answered "yes" to consuming tap water). To assess the effects of filtering or boiling would require a case-control analysis among only those that consumed tap water; this was not possible with the pairwise matching and small study size. Additionally, our study underestimates the association between the pattern of tap water consumption and cryptosporidiosis because among those that consumed tap water, some of them also filtered or boiled their tap water which would have mitigated the risk of tap water exposure. Among those that consumed tap water at home sometimes or always (47/49 [96%] of cases and 68/99 [69%] of controls), 20/47 (42%) of cases and 32/68 (47%) of controls filtered their water sometimes or always, and 5/47 (11%) of cases and 10/68 (15%%) of controls boiled their water sometimes or always.

In spite of its limitations, our study suggests that the relative risk of cryptosporidiosis among AIDS patients from drinking tap water is high (adjusted OR, 23.6 for highest exposure category). A similar study conducted among immunocompetent persons in the same geographic region found that cryptosporidiosis was only associated with foreign travel but not tap water consumption [34]. This discordance in results supports the observation that host susceptibility, i.e., immune status, is the primary determinant of developing cryptosporidiosis among AIDS patients. Because the relative importance of the risk factors for cryptosporidiosis is different among immunocompetent and immunocompromised persons in the San Francisco Bay Area, public health prevention messages to the two groups must be tailored accordingly.

Conclusions

The public health significance of our study, i.e. a population attributable fraction of 85%, is noteworthy, especially since there are no effective chemotherapeutic agents against cryptosporidiosis [5]. The only effective way to combat cryptosporidiosis among AIDS patients is treatment with HAART [35] because this raises $CD4^+$ T lymphocyte count, and AIDS patients with $CD4^+$ counts over 200 cells/ml are better able to resist cryptosporidial infection [36]. Although our results cannot be considered definitive, until there is more data, we would recommend persons with AIDS in the San Francisco area, especially those with compromised immune systems, avoid tap water. AIDS patients in other geographic areas may consider avoiding tap water. This is consistent with current Centers for Disease Control and Prevention (CDC) prevention Guidelines that, for a non-outbreak setting, people with HIV disease may consider tap water avoidance or boiling water prior to drinking to reduce the risk of infection with *Cryptosporidium* [17]. Whether it would be better to drink boiled water or bottled water is unknown at this time, although our results suggest that appropriately bottled water may be effective. Prevention of infection, either by avoidance of risky exposures or by improving immune function or both, is critical in this vulnerable population.

Competing interests
None declared.

Authors' contribution
TJA directed the study, and prepared, revised, and finalized the manuscript. SN directed data entry, data cleaning, and preliminary data analyses. AK directed the literature review, and drafted sections of the discussion. WE carried out quality control, procedural documentation, statistical modeling, and PAF calculations under the guidance of TJA. MHK and DJV conceived and designed the study. All authors extensively contributed to manuscript editing and revisions.

All authors read and approved the final manuscript.

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