A pilot randomized, controlled trial of an in-home drinking water intervention among HIV + persons

John M. Colford Jr, Sona R. Saha, Timothy J. Wade, Catherine C. Wright, Mai Vu, Sandra Charles, Peter Jensen, Alan Hubbard, Deborah A. Levy and Joseph N. S. Eisenberg

ABSTRACT

Although immunocompromised persons may be at increased risk for gastrointestinal illnesses, no trials investigating drinking water treatment and gastrointestinal illness in such patients have been published. Earlier results from San Francisco suggested an association (OR 6.76) between tap water and cryptosporidiosis among HIV + persons. The authors conducted a randomized, triple-blinded intervention trial of home water treatment in San Francisco, California, from April 2000 to May 2001. Fifty HIV-positive patients were randomized to externally identical active (N = 24) or sham (N = 26) treatment devices. The active device contained a filter and UV light; the sham provided no treatment. Forty-five (90%) of the participants completed the study and were successfully blinded. Illness was measured using 'highly credible gastrointestinal illness' (HCGI), a previously published measure. There were 31 episodes of HCGI during 1,797 person-days in the sham group and 16 episodes during 1,478 person-days in the active group. The adjusted relative risk was 3.34 (95% CI: 0.99–11.21) times greater in those with the sham device. The magnitude of the point estimate of the risk, its consistency with recently published observational data, and its relevance for drinking water choices by immunocompromised individuals support the need for larger trials.

Key words | drinking water quality, gastroenteritis, HIV, randomized trial, triple blinding

John M. Colford Jr (corresponding author)
Sona R. Saha
Catherine C. Wright
Alan Hubbard
Joseph N. S. Eisenberg
University of California, Berkeley,
School of Public Health,
Divisions of Epidemiology and Environmental Health Sciences,
140 Warren Hall #7360, Berkeley, CA 94720,
USA
E-mail: *jcolford@berkeley.edu*

Timothy J. Wade
United States Environmental Protection Agency,
Human Studies Division,
Mail Drop 58C, Research Triangle Park, NC 27711,
USA

Mai Vu
Sandra Charles
Peter Jensen
University of California,
San Francisco Veterans' Affairs Medical Center,
4150 Clement Street, Mail Stop 111W,
San Francisco, CA 94121,
USA

Deborah A. Levy
Centers for Disease Control and Prevention,
Division of Healthcare Quality Promotion,
1600 Clifton Road NE,
Mail stop E-68,
Atlanta, GA 30341
USA

INTRODUCTION

A recent case control study in San Francisco reported an elevated risk (OR 6.76, 95% confidence interval: 1.37, 33.5) for cryptosporidiosis among HIV-positive persons consuming tap water (Aragon *et al.* 2003). No randomized trials have been published evaluating the benefits, if any, of supplemental in-home drinking water treatment among HIV-positive persons. Randomized trials evaluating in-home drinking water treatment among immunocompetent persons have been published and reached conflicting results. For example, two studies by Payment and colleagues in Canada suggested a significant reduction in gastrointestinal illness arising from the use of in-home drinking water treatment (Payment *et al.* 1991, 1997). A study by Hellard *et al.* (2001) in Australia and a study by our group in California (Colford *et al.* 2002), found no significant reduction in gastrointestinal illness from the use of in-home drinking water treatment devices. These studies differed with respect to several important features. The Payment studies were not blinded (i.e. individuals knew the group to which they were assigned in the trial)

*Portions of this manuscript were presented at the USEPA National Science Forum on 6 May 2003 in Washington, DC.

and the source water was challenged (subject to industrial and human contaminants). The Hellard study was a blinded trial and was conducted in a system with a reportedly pristine surface water source. A blinded study in California was conducted in a system with a challenged surface water source (Colford *et al.* 2002). Another blinded trial in Davenport, Iowa enrolled 1,296 participants and found no benefit to an in-home drinking water intervention (Colford *et al.* 2005).

The present study was designed as a pilot to apply the randomized trial design to the issue of tap water consumption and gastrointestinal illness in HIV-positive persons. Our principal objectives were: 1) to confirm that enrolment and participation rates among this population would be high; 2) to replicate our earlier results suggesting that blinding can be achieved in drinking water trials; and 3) to develop a preliminary estimate of the relative rates of gastrointestinal illness between groups of HIV-positive persons receiving tap water with or without supplementary in-home treatment. Such an estimate, reliably obtained in a randomized trial, was felt to be necessary before the design and conduct of a large-scale trial in an immunocompromised population.

METHODS

The study and the informed consent process were reviewed, approved and monitored throughout by four Institutional Review Boards at the University of California, Berkeley, the University of California, San Francisco, the Centers for Disease Control and Prevention (CDC) and the San Francisco Veterans' Affairs Research and Development Committee.

Preliminary work: cross-sectional survey

In preparation for the intervention trial, we conducted and published a cross-sectional survey to analyse the prevalence of gastrointestinal illness and drinking water patterns in our potential study population (Eisenberg *et al.* 2002). Between October 1998 and January 2000, the survey was administered to 226 patients at the same Infectious Diseases Clinic at the San Francisco Veterans' Affairs Medical Center from which trial participants would later be recruited. Forty-seven per cent of respondents reported diarrhoea in the 7 days prior to being surveyed. Eighty-one per cent of respondents were unaware of CDC drinking water guidelines for HIV-infected individuals, though 34% reported being very concerned about the health effects of their drinking water.

Study area, water supply and water distribution system

The trial was performed primarily within the city of San Francisco, California. Forty-nine (98%) of the 50 participants were residents of San Francisco and one participant was a resident of Daly City, California. San Francisco receives its water from the largest unfiltered water supply on the West Coast, the Hetch Hetchy Water and Power Project (SFPUC 2002). Although all of the water supply is chlorinated only a small proportion of the water supply is fully filtered. Consumers receive either filtered, primarily unfiltered (approximately 82% unfiltered) or a mixed water supply depending on their location. The Hetch Hetchy watershed is a 1188.8 sq km (459 square mile) area located in Yosemite National Park at the headwaters of the Tuolumne River. Although the consistently high quality of surface source water has resulted in filtration exemption status, *Cryptosporidium* has been found in low levels in both the source and treated water (SFPUC 2002). A more detailed water characterization is available at www.sfwater.org. This is one of several unfiltered city water supplies in the US (others include New York, Boston and Seattle).

Recruitment, enrolment and compensation of participants

Participants for this trial were recruited from patients enrolled in the Infectious Diseases Clinic at the San Francisco Veterans Affairs Medical Center from April through December 2000. The first device was installed in May 2000 and the last participant completed the trial in May 2001. Our proposed sample size was 64 participants, estimated to be sufficiently large to detect successful blinding (blinding index >0.50, see Methods) (Colford *et al.* 2002). Initial contact was made by a research nurse or

pharmacist during scheduled or drop-in clinic visits, from patient response to a mailed flyer, or by telephone. The inclusion criteria required that each participant: has a confirmed diagnosis of HIV; routinely (75% or more of the time) uses municipal (tap) water at home with neither home filtration devices nor bottled water; confirms that all household members were aware of the HIV status of the participant and were willing to give consent to have the study device installed; and has no children residing at home.

Research staff reviewed the health diary with each participant. The first section consisted of a daily log of gastrointestinal symptoms. Two weeks of responses could be entered in each health diary. The second section contained questions on water consumption, blinding and potential risk factors for gastrointestinal illness. Participants were to complete the log every day and the second section at the end of the 2-week period. Participants received US$50 upon completion of the enrolment questionnaire and US$15 for each of the eight diaries submitted during the 16-week study.

All participants received a study binder containing contact information for study staff, instructions for use of the device and the collection of a stool sample, and the current CDC safe drinking water guidelines for immunocompromised persons regardless of their treatment assignment (CDC 1999*a*, *b*). We believed that, given the existence of published CDC recommendations about drinking water safety for immunocompromised persons, it would not have been ethical to conduct the study without making participants aware of these guidelines.

Randomization and (triple) blinding

Participants were randomized 50:50 to receive either an active or sham water treatment device in blocks of ten. Random allocation within each block was accomplished using computer-generated random numbers. The manufacturer provided a list of device serial numbers and their corresponding active/sham status to facilitate device assignment. All study participants, the study investigators (including clinic personnel and those performing data analysis) and the device installer were blinded throughout the trial as to device assignment.

Active and sham water treatment devices and installation

The device chosen for this study was a countertop unit custom manufactured for the study by Tri H2O (San Leandro, California) and based on their commercially available 'Ultimate II' water filtration device. A tamper-proof seal prevented the filter casing from being opened. We chose an active device that selectively removes microorganisms from the water without affecting other water quality parameters that could lead to unblinding of participants. Our active device used a 1-micron filter followed by ultraviolet radiation to maximize the microbiological disinfection and physical removal capabilities of the treatment device without significantly affecting the taste and odour of the treated water. The specification of a 1-micron absolute filter was chosen in order to enable the device to remove *Cryptosporidium* oocysts, a waterborne pathogen of great concern for HIV + populations.

The ultraviolet lamp was designed to emit wavelength at 254 nm, the optimum for disinfection, and a total minimum dose of 26,000 μwatt-sec cm^{-2}. This dosage inactivates 99.99% of bacteria and viruses and conforms to 'Class B' standards for ultraviolet treatment devices as specified by the National Sanitation Foundation (USEPA 1996). The sham device consisted of an empty filter casing, and an ultraviolet lamp secured within a glass sleeve in order to block ultraviolet light, without unblinding the device by having significant weight disparities between the active and sham devices.

Following consent by all household members, the study technician came to the participant's residence to install the device. The device was attached to the main faucet used for accessing drinking water in the home using a connector hose and a diverter valve that allowed for water to either be directed to the device or into the sink. If a device could not be adjusted or repaired without opening the casing of the device, the study technician was instructed to replace the device to ensure that he and the participants remained blinded as to device type.

Statistical methods: Blinding index

One goal of the study was to examine the feasibility of blinding of participants in such a trial among HIV-positive

persons. For this goal, we used the 'blinding index' (BI) of James *et al.* (1996) in which scores above 0.5 are viewed as evidence of effective blinding. At the end of every 2 weeks, participants answered questions on which device, active or sham, they believed was installed. Colford *et al.* (2002) reported the use of this same index in an earlier drinking water trial. With this index (analogous to the kappa statistic) a score of 0.0 suggests all participants accurately identified device assignment, a score of 0.5 suggests random guessing by participants, and a score of 1.0 suggests all participants guessed assignment incorrectly or answered 'don't know'.

Health outcomes

Participants recorded daily occurrences of diarrhoea, nausea, vomiting, abdominal cramps and fever in their health diaries. Diarrhoea was defined as the occurrence of two or more loose stools in one day. The principal health outcome measured in the trial was episodes of 'highly credible gastrointestinal illness' (HCGI), a measure based on that reported in several prior drinking water intervention trials (Payment *et al.* 1991, 1997; Hellard *et al.* 2001; Colford *et al.* 2002). A new episode was defined as any of the following four conditions, preceded by at least 6 symptom-free days: 1) vomiting, 2) watery diarrhoea, 3) soft diarrhoea and abdominal cramps, or 4) nausea and abdominal cramps. Days with missing data were not counted as 'disease-free'. The requirement for 6 disease-free days was first used by others to increase the likelihood that separate episodes truly represented distinct infections (rather than a prolonged course of one infection) (Payment *et al.* 1991, 1997; Hellard *et al.* 2001).

HCGI data were analysed using logistic regression with the outcome being either HCGI (1) or no-HCGI (0) for every day at risk (see above). Poisson regression provided a poor fit to the summary counts per subject, as HCGI rates varied widely between subjects in the same treatment group. Therefore, logistic regression with a generalized estimating equation (GEE) – robust variance estimation approach was used on the daily data. When calculating standard errors, this approach both adjusts for residual correlation of the repeated (daily) outcome measurements within a subject and allows for different underlying rates between subjects within treatment groups (Liang K 1986). The attributable risk from drinking water was calculated as (OR − 1)/(OR) where OR is the estimated odds ratios of HCGI in the sham group compared with that in the active group (Hennekens & Buring 1987). In addition to simple bivariate analyses, we also examined whether the direct effect of the device differed by baseline gastrointestinal symptoms.

In addition to the primary health outcome (*episodes* of HCGI), we calculated the total *days* of HCGI experienced by each participant. This measure is an attempt to quantify the total burden of gastrointestinal disease experienced by the two groups. For example, although a prolonged episode of HCGI could last for many days, it would only be recorded as one episode in the primary analysis. With respect to the principal analysis of the causal relationship between use of the water treatment device and HCGI, the analysis of *episodes* of HCGI, as stated above, was the *a priori* defined analysis. Participant medical records were reviewed to obtain CD4 count count (a measure of the current immune status of an individual), viral load and current medications.

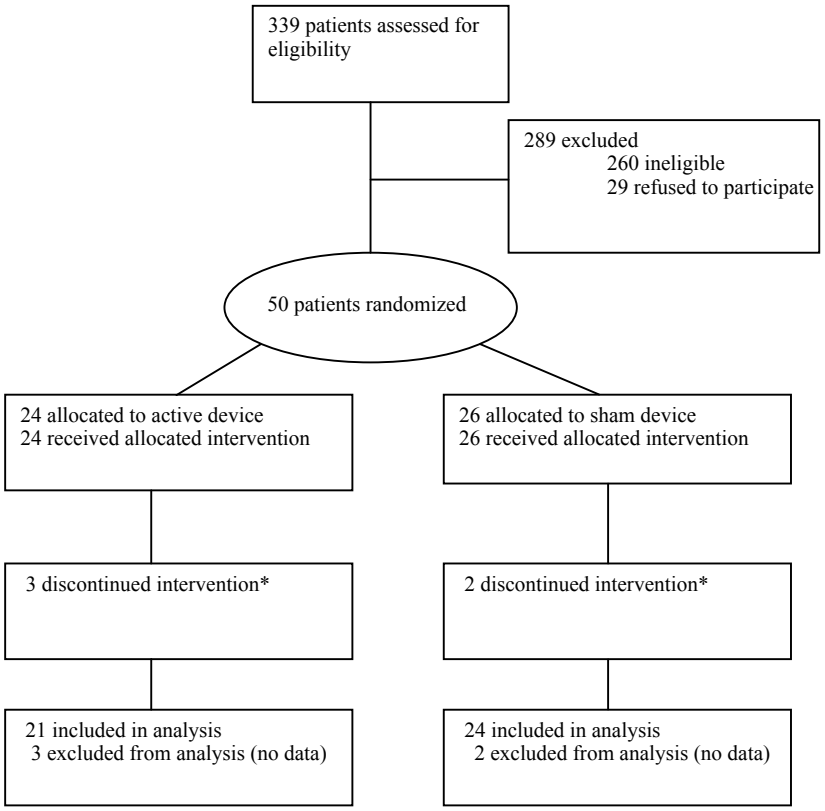
Water consumption

Water consumption was self-reported using questions inserted into the health diary at 2-week intervals. Participants estimated (in numbers of 240 ml (eight ounce) glasses) their daily consumption of drinking water at home (separately through the study device and through all other sources at home) and outside the home. Participants were provided with water bottles and encouraged to carry water from the home device for use when outside the home. Mean water consumption was compared by study group using the two-sample t-test.

RESULTS

Recruitment, enrolment, randomization and adverse events

We began recruitment in April 2000. As shown in Figure 1, 339 potential participants were screened and 50 were enrolled and randomized (24 active, 26 sham). The principal reasons for non-eligibility were: residence outside of the study area (45%) or use of bottled water as a primary source of drinking water (11%). Five (10%, 3 active, 2 sham)



** Reasons for withdrawal were as follows: declined marital status (1 participant), objections from room mate on device appearance (1 participant), taste of the water from device (1 participant), no longer interested in participating (2 participants).*

Figure 1 | HIVWET screening and enrolment flow diagram.

of the 50 randomized participants dropped out of the study before any blinding or health data were collected. The remaining 45 participants are the source of data for all analyses. The first device was installed in May 2000 and the last participant completed the trial in May 2001. No adverse events were attributed to trial participation. One consented participant committed suicide before device installation. A second participant (assigned to sham group) expired with *Pneumocystis carinii* pneumonia.

Baseline characteristics of participants and completeness of data collection (Table 1)

Forty-four (98%) of the 45 participants were HIV-positive males, reflecting the demographic composition of our clinic. The median age was 51.9 years in the active and 52.1 in the sham group. Randomization appeared to successfully balance the baseline characteristics of the two groups with respect to age, race, education, income, CD4 count, viral load, HIV medication usage and water consumption patterns. Recent symptoms of gastrointestinal illness (e.g. cramps, diarrhoea, nausea, vomiting, fever), however, were 2–3 times more common in the participants randomized to the active group ($p = 0.028$). The 45 participants completed health diaries with 4,682 days of total observation time (2,087 active and 2,595 sham). This represents diary completion rates of 89.3% for the active group and 97.4% for the sham group.

Effectiveness of blinding of participants (Table 2)

Responses from the final health diary (week 16) were evaluated using the blinding index. Thirty-nine (87%) of the 45 participants completed the week 16 health diary. The most frequent guess about treatment assignment in both the active (59%) and sham (50%) groups was

Table 1 | Participant baseline characteristics (n = 45)

Characteristic	Active device (n = 21)	Sham device (n = 24)
Age (years)	**n (%)**	**n (%)**
30–39	2 (9.5)	3 (12.5)
40–49	5 (23.8)	6 (25)
50–59	10 (47.6)	11 (45.8)
60–69	4 (19)	3 (12.5)
70 +	0 (0)	1 (4.2)
Gender		
Male	20 (95.2)	24 (100)
Female	1 (4.8)	0 (0)
Race		
White	12 (57.1)	14 (58.3)
African–American	5 (23.8)	6 (25)
Latino	3 (14.3)	2 (8.3)
Other	1 (4.8)	1 (4.2)
Not available	0 (0)	1 (4.2)
Highest level of education		
2–3 years high school	1 (4.8)	2 (8.3)
High school graduate	6 (28.6)	7 (29.2)
1–3 years college	8 (38.1)	7 (29.2)
College graduate	3 (14.3)	5 (20.8)
1–2 years post-graduate	3 (14.3)	2 (8.3)
Not available	0 (0)	1 (4.2)
Annual income		
< US$20,000	13 (61.9)	14 (58.3)
US$20,000–30,000	1 (4.8)	3 (12.5)
US$30,000–40,000	2 (9.5)	4 (16.7)
US$40,000–50,000	3 (14.3)	2 (8.3)
US$50,000–100,000	2 (9.5)	1 (4.2)
Gastrointestinal symptoms (prior 7 days)		
Any GI symptom	13 (61.9)	7 (29.2)
Cramps	5 (23.8)	2 (8.3)
Diarrhoea	11 (52.4)	6 (25)
Nausea	6 (28.6)	2 (8.3)
Vomiting	1 (4.8)	1(4.2)
Fever	1 (4.8)	1 (4.2)
HIV indicators		
Mean viral load (log copies ml^{-1})	4.2	3.5
Mean CD4 count (cells mm^{-3})	402 cells mm^{-3}	376 cells mm^{-3}
CD4 count (cells mm^{-3}) by category		
CD4 < 50	0 (0)	0 (0)
CD4 50–200	2 (9.5)	7 (29.17)
CD4 201–500	14 (66.7)	11 (45.8)
CD4 > 500	5 (23.8)	6 (25.0)
HIV medications		
Any nuceleoside reverse transcriptase inhibitor	20 (95.2)	19 (79.2)
Any non-nucleoside reverse transcriptase inhibitor	10 (47.6)	11 (45.8)
Any protease inhibitor	11 (52.4)	12 (50.0)
Sulfamethoxasole-trimethoprim	5 (23.8)	6 (25.0)
Potential exposures (prior month)		
Swam in a pool	1 (4.8)	2 (8.3)

Table 1 | *(continued)*

Characteristic	Active device (n = 21) n (%)	Sham device (n = 24) n (%)
Changed a diaper	1 (4.8)	0 (0)
Shared a cup	0 (0)	0 (0)
Farm animal contact	0 (0)	0 (0)
Pet at home	10 (47.6)	9 (37.5)
Swam in a lake	0 (0)	0 (0)
Drank from a lake	0 (0)	0 (0)
Ate at a restaurant	17 (80.9)	18 (75)
Had sexual contact	10 (47.6)	9 (37.5)
Sexual contact with men	9 (42.9)	8 (33.4)
Sexual contact with women	1 (4.8)	1 (4.2)
Concerned about drinking water		
Very concerned	5 (23.8)	9 (37.5)
A little concerned	8 (38.1)	8 (33.4)
Not concerned	8 (38.1)	7 (29.2)
Heard of CDC guidelines	3 (14.3)	2 (8.3)
Bottled water consumption		
Always	0 (0)	0 (0)
Often	2 (9.5)	3 (12.5)
Sometimes	5 (23.8)	8 (33.4)
Rarely	9 (42.9)	10 (41.7)
Never	2 (9.5)	3 (12.5)
Not available	3 (14.3)	1 (4.2)
Filtered water consumption		
Always	2 (9.5)	2 (8.3)
Often	2 (9.5)	2 (8.3)
Sometimes	0 (0)	1 (4.2)
Rarely	2 (9.5)	4 (16.7)
Never	14 (66.7)	13 (54.2)
Not available	1 (4.8)	2 (8.3)
Boiled water consumption		
Always	2 (9.5)	0 (0)
Often	1 (4.8)	0 (0)
Sometimes	0 (0)	0 (0)
Rarely	4 (19)	3 (12.5)
Never	13 (61.9)	19 (79.2)
Not available	1 (4.8)	2 (8.3)

assignment to the active device. The blinding index was 0.67 (95% CI: 0.53, 0.82) suggesting that participants were successfully blinded.

Analysis of gastrointestinal illnesses

Participants randomized to the active device experienced 16 episodes of HCGI; those in the sham group experienced 31 episodes (Table 3). Because of the baseline imbalance in the frequency of gastrointestinal symptoms, we examined the data to determine if there was any interaction present between the presence of GI symptoms at baseline and treatment group assignment. No evidence of an interaction was found. Because the presence of gastrointestinal symptoms at baseline was strongly predictive of HCGI during the trial and was not balanced in the two treatment groups, this factor did appear to confound the relationship between device assignment and the incidence of HCGI. Because confounding factors not balanced at baseline by randomization should be adjusted in any analyses of data from randomized trials (Freidman *et al.* 1998), we adjusted for the presence of GI symptoms at baseline in our analysis. The adjusted odds of disease in the sham group were 3.34 (95% CI: 0.99–11.21) times higher in the sham group than in the group receiving treated water. The attributable risk associated with such an odds ratio would be 0.70 (95% CI: 0.00–0.91).

Table 2 | Final (week 16) device blinding questionnaire

All participants who completed blinding questionnaire at 16 weeks (n = 39)

Guess	Active device	Sham device	Total
Active	10	11	21
Sham	1	2	3
Don't know	6	9	15
Total	17	22	39

Blinding index = 0.67 (95% CI, 0.53–0.82).

In addition to this adjustment for the difference in baseline symptoms, we also stratified the participants directly (Table 4) by the presence of these symptoms. These stratified results were qualitatively consistent with those found in the multivariate model (Table 3) in that the rates of HCGI were higher in the sham group. Because of the small sample sizes in these strata, formal statistical testing was not undertaken within stratified groups.

Participants randomized to the active device reported 253 *days* of HCGI; those in the sham group reported 322 *days* of HCGI. Adjusted for the baseline imbalance in GI symptoms, the odds ratio for the two groups with respect to *days* of HCGI was 2.27 (95% CI, 0.64, 8.01). Further analysis (Table 5) did not suggest that the difference in HCGI between the two groups was caused by individuals experiencing numerous (i.e. >5) episodes during the study.

Water consumption (exposure) patterns during the trial (Table 6)

There was no significant difference between the two groups with respect to water consumption patterns. There were

Table 3 | Episodes* of highly credible gastrointestinal illness (HCGI) and days of illness

	Active device (n = 21)	Sham device (n = 24)	Total (n = 45)	Odds ratio (adjusted)**
Total *episodes*+ of HCGI defined by:	16	31	47	3.34 (0.99–11.21)
Vomiting	2	9	11	
Watery diarrhoea	11	17	28	
Soft diarrhoea with abdominal cramps	0	0	0	
Nausea with abdominal cramps	6	6	12	
Total days at risk for HCGI episodes	1,478	1,797	3,275	
Total *days* of HCGI defined by:+	253	322	575	2.27 (0.64, 8.02)
Vomiting	15	22	37	
Watery diarrhoea	234	284	518	
Soft diarrhoea with abdominal cramps	0	2	2	
Nausea with abdominal cramps	30	35	65	
Total days of observation	2,087	2,595	4,682	

*A new episode of HCGI was defined as the presence of any of the four definitions of HCGI preceded by 6 HCGI-free days. The difference in total episodes of HCGI was the principal *a priori* health outcome measure for the study.

+Because individual participants could report multiple symptoms of HCGI on the same day, the total episodes of HCGI (and total days of HCGI) are less than the sums of the individual definitions.

** Adjusted for baseline differences in the presence of GI symptoms (diarrhoea, vomiting, nausea or cramps) in the prior 7 days using logistic regression with generalized estimating equations.

Table 4 | Episodes* of highly credible gastrointestinal illness (HCGI) and days of illness stratified by baseline GI symptoms

	Active device (n = 21)	Sham device (n = 24)
Episodes of highly credible gastrointestinal illness (HCGI)		
Participants with baseline GI symptoms		
Total episodes of HCGI	15	17
Total days at risk for HCGI episodes	790	310
Crude rate	0.019	0.055
Participants without baseline GI symptoms		
Total episodes of HCGI	1	14
Total days at risk for HCGI episodes	688	1,487
Crude rate	0.001	0.009
Days of HCGI		
Participants with baseline GI symptoms		
Total days of HCGI	246	262
Total days of observation	1,313	784
Crude rate	0.187	0.334
Participants without baseline GI symptoms		
Total *days* of HCGI	7	60
Total days of observation	774	1,811
Crude rate	0.009	0.033

*A new episode of HCGI was defined as the presence of any of the four definitions of HCGI preceded by 6 HCGI-free days.

Table 5 | Distribution of highly credible gastrointestinal illness episodes and days

	Number of participants experiencing listed number in active device group (n = 21)	Number of participants experiencing listed number in sham device group (n = 24)
Number of episodes of HCGI		
0	10	10
1	5	4
2	2	2
3	1	5
4	1	1
5	0	1
6–10	2	1
Number of days of HCGI		
0	10	10
1–5	5	5
6–10	1	1
11–20	1	3
21–50	2	3
51–112	2	2

insufficient data with which to evaluate the presence of any dose-response trend based on amount of drinking water consumed.

DISCUSSION

This study is the first randomized controlled trial of a drinking water intervention among HIV-positive persons, a group potentially at risk both for increased susceptibility to waterborne infections as well as to increased clinical severity once infected (Gerba *et al.* 1996). Our findings suggest that a randomized controlled trial of an in-home drinking water intervention in HIV-positive persons is feasible with respect to recruitment and enrolment. Additionally, the increased point estimate of risk of gastrointestinal illness (of borderline statistical significance) in the sham treatment group in this small trial, combined with a recent case control investigation suggesting an elevated risk (Aragon *et al.* 2003) raises issues about what recommendations should be given to HIV-positive individuals about tap water treatment.

Table 6 | Water consumption patterns

	Mean number of 240 ml (8 oz) glasses of water consumed per day (95% CI)		
	Active group (n = 21)	**Sham group (n = 24)**	**Total (n = 45)**
Bottled water	2.98 [2.44, 3.52]	3.40 [2.85, 3.96]	3.21 [2.83, 3.60]
Unheated tap water at home	2.73 [2.08, 3.39]	3.40 [2.88, 3.92]	3.10 [2.68, 3.51]
Unheated tap water away from home	1.98 [1.32, 2.63]	1.63 [1.32, 1.96]	1.79 [1.45, 2.13]

Blinding of participants

There are few published approaches to the measurement of blinding and we chose to evaluate blinding in a method suggested by James *et al.* (1996) which uses a summary statistic analogous to the kappa statistic and has been used in other studies (Noseworthy *et al.* 1994; James *et al.* 1996; Colford *et al.* 2002). Inability to properly blind the participants in drinking water trials could lessen the credibility of reported results (Noseworthy *et al.* 1994). It is interesting to note that there is a tendency for participants (in this study and others) in both the active and sham groups to more frequently believe that they are in the active group than is true (Hellard *et al.* 2001; Colford *et al.* 2002). We speculate that this may arise from a desire of participants for assignment to the active arm.

Gastrointestinal illness

There is no doubt, in light of the reports of numerous outbreak investigations, that waterborne transmission of pathogens resulting in gastrointestinal illness is possible among both immunocompetent and immunocompromised individuals. It is not clear what proportion of gastrointestinal illnesses in the United States (if any) is attributable to the consumption of tap water that is treated and delivered according to all regulatory standards (in distinction to drinking water that is accidentally contaminated in distribution systems or homes). It is this latter question that is the motivation for drinking water intervention trials such as this. While it is recognized that, when feasible, a randomized, controlled intervention trial is desirable for studying health questions, few such trials have been completed in this area. The experimental evaluation of a drinking water intervention is tractable, however, because of the short latency between exposure to waterborne pathogens and the onset of gastrointestinal illness, the existence of powerful but affordable in-home water treatment devices, and the frequency of occurrence of gastrointestinal illness in the population. This is in contrast to many types of drinking water risks, such as cancers arising from waterborne chemicals, in which the latency period could be years.

Our study design was similar to that of the trial reported by Australian investigators (Hellard *et al.* 2001). Like the Australian study, our investigation was blinded and conducted in a municipality believed to have excellent source water. This is in contrast to the Canadian studies (Payment *et al.* 1991, 1997) which were not blinded and were conducted in the setting of challenged source water. Both the Canadian and Australian studies were conducted among immunocompetent participants. Whether or not the differences between these studies and our trial are due to differences in the source water, the treatment device, the immune status of the participants, or differences in the distribution systems cannot be answered using the existing data. It is important to note that both groups in our study (but not in the earlier studies) received a form of intervention: for the ethical reasons described in the Methods section, all participants in our trial (regardless of their randomization assignment) received counselling at the start of the trial about current federal recommendations for drinking water safety for immunocompromised persons (CDC 1999*a*, *b*). Theoretically, this could lead to an underestimation of the effect in our study.

Our estimate of an attributable fraction of 0.70 (CI 0.00–0.91) of cases of HCGI attributable to tap water consumption is consistent with that estimated by Aragon

et al. (2003) for the attributable fraction of cryptosporidiosis cases in San Francisco attributable to tap water consumption.

Limitations

Even though our trial was randomized and triple-blinded there are limitations. First, its limited sample size and the borderline statistical significance of the primary health outcome, HCGI, make the precise risk (if any) of tap water consumption for immunocompromised individuals uncertain. Based on the strength of the point estimate we observed, we estimate that a minimum of 50 participants would need to be enrolled in each arm (sham and active) of a larger trial in order to detect a relative risk of 3.0 (sham vs. active) with 90% power; detection of a relative risk of 2.0 with 90% power would require 170 participants in each arm.

Second, although a number of baseline characteristics were balanced between the two groups, suggesting proper randomization, there was a difference at baseline in the number of participants with recent gastrointestinal symptoms which is itself strongly associated with HCGI. Because the presence of gastrointestinal symptoms was associated with both the exposure variable (the device assignment) and the outcome variable (HCGI) it confounded the crude relationship between device assignment and HCGI and we adjusted for this baseline GI illness and included it in our final model.

Our principal health outcome, HCGI, has been used repeatedly in prior studies (Payment *et al.* 1991, 1997; Hellard *et al.* 2001; Colford *et al.* 2002). However, such use does not ensure validity and validation studies of the measure itself. Such validation would require expensive, close observation of each participant's actual bowel habits compared with their reports of illness. Unless there was a systematic difference in reporting of HCGI, the use of randomization in the trial design should minimize the introduction of bias into the results.

One theoretical cause for a difference between the two groups would be degradation of the water by the sham device. We conducted a limited water sampling programme and found no evidence of such degradation. A larger water sampling programme should be a part of future trials to confirm these findings.

We do not believe that a firm conclusion can be drawn from this trial about the risk of HCGI from the consumption of tap water among HIV + individuals. Future studies must be larger to further reduce the potential for any chance baseline imbalance in important covariates.

An additional limitation of our study is that the generalizability of our findings to other municipalities (with differing water systems) or to other participants (with differing forms of immune compromise and demographic composition, including age) is unclear. Such risk estimation must await further research in those geographic and participant communities. Recruitment for such a study in other, younger or gender-balanced HIV participant groups could differ from that which we experienced.

CONCLUSIONS

Our findings suggest that it is feasible to conduct randomized controlled trials among HIV + persons to investigate the risk of gastrointestinal illness from the consumption of drinking water. The presence of very large numbers of immunocompromised persons in the United States implies that even a slight elevation of risk from infection due to waterborne pathogens would carry a significant public health impact (USEPA 2000). Despite the borderline statistical significance of the findings in this small trial, the magnitude of the relative risk (OR 3.34, 95% CI: 0.99–11.21), its consistency with recently published data on cryptosporidiosis and tap water in San Francisco (Aragon *et al.* 2003), and the potential public health impact all support the need for larger trials of optimal drinking water treatment for immunocompromised persons.

ACKNOWLEDGEMENTS

Funding for this work was provided entirely through the University of California University-wide AIDS Research Program Award No. M98-B-1300 and Cooperative Agreement No. UR2/CCU916252-02-2 from the Centers for Disease Control and Prevention. The authors acknowledge the following individuals without whose contributions this project could not have been completed: Sherline Lee,

Dr Judy Rees, Julie Hsieh, Jane Jang, Dr David Schnurr, Vern St Peter, Dr Madhukar Pai and Dr Allen Hightower.

REFERENCES

Aragon, T. J., Novotony, S., Enanoria, W., Vugia, D. J., Khalakdina, A. & Katz, M. 2003 Endemic cryptosporidiosis and exposure to municipal tap water in persons with acquired immunodeficiency syndrome (AIDS): A case-control study. *BMC Public Health* **2**(3) 10.1186/1471-2458-3-2.

CDC, DoHAP 1999a You can prevent Cryptosporidiosis: A Guide for People with HIV Infection, Report 578001, Centers for Disease Control and Prevention, Atlanta, GA, USA.

CDC, DoHAP 1999b Safe Food and Water: A Guide for People with HIV Infection, Centers for Disease Control and Prevention, Atlanta, GA, USA.

Colford, J. M., Jr, Rees, J. R., Wade, T. J., Khalakdina, A., Hilton, J. F., Ergas, I. J., Burns, S., Benker, A., Ma, C., Bowen, C., Mills, D. C., Vugia, D. J., Juranek, D. D. & Levy, D. A. 2002 Participant blinding and gastrointestinal illness in a randomized, controlled trial of an in-home drinking water intervention. *Emerg. Infect. Dis.* **8**(1), 29–36.

Colford, J. M., Jr, Wade, T. J., Sandhu, S. K., Wright, C. C., Lee, S., Shaw, S., Fox, K., Burns, S., Benker, A., Brookhart, M. A., van der Laan, M. & Levy, D. A. 2005 A randomized, controlled trial of in-home drinking water intervention to reduce gastrointestinal illness. *Am J Epidemiol.* **161**(5), 472–482.

Eisenberg, J. N. S., Wade, T. J., Charles, S., Vu, M., Hubbard, A., Wright, C. C., Levy, D., Jensen, P. & Colford, J. M., Jr 2002 Risk factors in HIV-associated diarrhoeal disease: the role of drinking water, medication and immune status. *Epidemiol. Infect.* **128**(1), 73–81.

Freidman, L. M., Furberg, C. D. & DeMets, D. L. 1998 *Fundamentals of Clinical Trials*. Springer-Verlag, New York.

Gerba, C. P., Rose, J. B. & Haas, C. N. 1996 Sensitive populations: who is at greatest risk? *Int. J. Food Microbiol.* **30**(1–2), 113–123.

Hellard, M. E., Sinclair, M. I., Forbes, A. B. & Fairley, C. K. 2001 A randomized, blinded controlled trial investigating the gastrointestinal health effects of drinking water quality. *Environ. Health Perspect.* **108**(8), 773–778.

Hennekens, C. H. & Buring, J. E. 1987 *Epidemiology in Medicine*. Little, Brown and Company, Boston, Massachusetts.

James, K. E., Bloch, D. A., Lee, K. K., Kraemer, H. C. & Fuller, R. K. 1996An index for assessing blindness in a multi-centre clinical trial: Disulfiram for alcohol cessation – A VA cooperative study. *Statists Med.* **15**, 1421–1434.

Liang, K. Z. S. 1986 Longitudinal data analysis using generalized linear models. *Biometrika* **73**(1), 12–22.

Noseworthy, J. H., Ebers, G. C., Vandervoort, M. K., Farquhar, R. E., Yetisir, E. & Roberts, R. 1994 The impact of blinding on the results of a randomized, placebo-controlled multiple sclerosis clinical trial. *Neurology* **44**, 16–20.

Payment, P., Richardson, L., Siemiatycki, J., Dewar, R., Edwardes, M. & Franco, M. 1991 A randomized trial to evaluate the risk of gastrointestinal disease due to consumption of drinking water meeting current microbiological standards. *Am. J. Public Health* **81**(6), 703–708.

Payment, P., Siemiatycki, J., Richardson, L., Gilles, R., Franco, M. & Prevost, M. 1997 A prospective epidemiological study of gastrointestinal health effects due to consumption of drinking water. *Int. J. Environ. Health Res.* **7**, 5–31.

SFPUC 2002 2001 Water Quality Report. Consumer Confidence Report, San Francisco Public Utilities Commission, San Francisco, California.

USEPA 1996 Ultraviolet light disinfection technology in drinking water application: An overview. Report EPA 811-R-96-02. United States Environmental Protection Agency, Office of Water, Washington, DC.

USEPA 2000 Report to Congress: EPA studies on sensitive subpopulations and drinking water contaminants. Report EPA 815-R-00-015. United States Environmental Protection Agency, Office of Water, Washington, DC.