Patient-Delivered Partner Treatment With Azithromycin to Prevent Repeated Chlamydia trachomatis *Infection Among Women*

A Randomized, Controlled Trial

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Background: **Repeated infection with *Chlamydia trachomatis* increases the risk for serious sequelae: pelvic inflammatory disease, ectopic pregnancy, infertility, and chronic pelvic pain. A substantial proportion of women treated for *C trachomatis* infection are reinfected by an untreated male sex partner in the first several months after treatment. Effective strategies to ensure partner treatment are needed.**

Goal: **The goal of the study was to determine whether repeated infections with *C trachomatis* can be reduced by giving women doses of azithromycin to deliver to male sex partners.**

Study Design: **A multicenter randomized controlled trial was conducted among 1787 women aged 14 to 34 years with uncomplicated *C trachomatis* genital infection diagnosed at family planning, adolescent, sexually transmitted disease, and primary care clinics or emergency or other hospital departments in five US cities. Women treated for infection were randomized to one of two groups: patient-delivered partner treatment (in which they were given a dose of azithromycin to deliver to each sex partner) or self-referral (in which they were asked to refer their sex partners for treatment). The main outcome measure was *C trachomatis* DNA detected by urine ligase chain reaction (LCR) or polymerase chain reaction (PCR) by 4 months after treatment.**

Results: **The characteristics of study participants enrolled in each arm were similar except for a small difference in the age distribution. Risk of reinfection was 20% lower among women in the patient-delivered partner treatment arm (87/728; 12%) than among those in the self-referral arm (106/726; 15%); however, this difference was not statistically significant (odds ratio, 0.80; 95% confidence interval, 0.62–1.05; $P = 0.102$). Women in the patient-delivered partner treatment arm reported high compliance with the intervention (82%).**

Conclusion: **Patient-delivered partner treatment for prevention of repeated *C trachomatis* infection among women is comparable to self-referral and may be an appropriate option for some patients.**

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GENITAL INFECTION with *Chlamydia trachomatis* is endemic in the United States,[1] where each year an estimated 3 million infections occur among persons aged 15 to 44 years.[2] Repeated chlamydial infection poses a significant public health problem. In the first 6 months after treatment for an initial infection, between 6% and 21% of adolescent females have another chlamydial infection diagnosed.[3–6] Both human and animal studies have shown that repeated chlamydial infection increases risk of pelvic inflammatory disease and its sequelae: infertility, ectopic pregnancy, and chronic pelvic pain.[7–10] In the United States in 1998, these conditions resulted in an estimated $1.9 billion in direct medical costs.[11] Successful strategies to prevent repeated chlamydial infection in women would have a substantial impact on the morbidity and economic burden associated with this infection.

A minority of chlamydial infections detected in the months after treatment represent persistent rather than new infections and may be attributable to antibiotic treatment failure or noncompliance with the full treatment regimen.[4,12] However, most infections diagnosed in women in the first several months after treatment are the result of reexposure to infected male sex partners who were not treated after the women's initial infections were detected.[4,6] Strat-

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egies aimed at preventing reinfection and interrupting disease transmission therefore must provide timely treatment to all potentially infected sex partners. In the United States, the number of chlamydial infections far exceeds the capacity of most public health departments to assist in locating and treating sex partners. As a result, health departments commonly rely on a process known as self-referral, in which persons with chlamydial infection are asked to take responsibility for contacting sex partners themselves, notifying partners of exposure to infection, and encouraging them to seek treatment.[13]

Self-referral is a suboptimal strategy for ensuring partner treatment. In one study of adolescent women with chlamydial infection, self-referral was estimated to result in treatment for only 36% of male partners.[14]

Patient-delivered partner treatment is a strategy wherein persons with a sexually transmitted disease (STD) notify their sex partners of exposure to an STD and provide treatment, using medication they have been given to deliver to each sex partner. There is evidence that the practice of prescribing or dispensing medication to treat sex partners without prior examination occurs in the public sector,[15,16] and it may be common among providers in the private sector,[17] where the majority of STD services are delivered.[18] However, the efficacy of this intervention in preventing reinfection is unknown. Two retrospective studies of patient-delivered partner treatment for chlamydia have shown reduced rates of chlamydial infection among treated women who are provided with medication to give to their partners.[16,20] We report the results of a multicenter randomized controlled trial that compared patient-delivered partner treatment for chlamydial infection to self-referral, the standard practice in the United States for notifying the partners of women with chlamydial infections.

Methods

Study Design

A randomized controlled trial was conducted at research centers in Seattle, Southern and Northern California (the California research center recruited study participants from clinics in the cities of Long Beach, Torrance, Los Angeles [Southern California], and San Francisco [Northern California]), New Orleans, Birmingham, and Indianapolis. The Division of STD Prevention at the Centers for Disease Control and Prevention (CDC), in Atlanta, Georgia, functioned as the study coordination center.

Study Population

Women aged 14 to 34 years (the lower age limit for recruitment differed at some sites: Indianapolis, 15 years; San Francisco, Los Angeles, and Long Beach, 16 years; and Torrance, 18 years) were recruited for study participation at the time of treatment for a laboratory-confirmed uncomplicated urogenital chlamydial infection diagnosed at family planning (Southern California, Seattle, and New Orleans), adolescent (Birmingham, Indianapolis, Northern California, and Seattle), primary care (Indianapolis), and STD clinics (Birmingham, Indianapolis, New Orleans, Southern and Northern California, and Seattle) or emergency and other hospital departments (Birmingham). Women were excluded from participating if they had already been treated for their chlamydial infection, had not had intercourse in the 60 days before enrollment, reported that their male sex partners had already been treated for exposure to chlamydial infection, were pregnant, had HIV infection, were coinfected with *Neisseria gonorrhoeae*, *Treponema pallidum*, or *Trichomonas vaginalis* at the time of the visit for chlamydial infection treatment, or had a history of an adverse reaction to macrolide antibiotics.

Randomization and Blinding

Study allocations were made with use of randomly sized blocks.[21] Study arm assignments were printed on cards and placed in sequentially numbered, opaque envelopes and sealed at the CDC before being sent to each of the research centers. Once an envelope was opened at the research center, neither the study staff nor the study participants were masked to the assigned intervention. A computer file relating study arm assignment to study number was retained by a single staff member at the CDC.

Study Procedures

Study endpoint. The study endpoint was detection of *C trachomatis* DNA in urine specimens collected 21 days or more after treatment for the initial infection. A minimum interval of 21 days was chosen because *C trachomatis* DNA can be detected in urine as many as 21 days after treatment with an antibiotic effective against *Chlamydia*.[22] Urine specimens were tested for *C trachomatis* DNA with a nucleic acid amplification test, either the ligase chain reaction (LCR; Abbott Diagnostics, North Chicago, IL) or the polymerase chain reaction (PCR; Roche Diagnostics, Indianapolis, IN).

Enrollment. At the enrollment visit, women in both arms were treated for chlamydial infection with a directly observed single oral dose of 1.0 g azithromycin (Pfizer, NY) in sachet (powder) form and were advised to abstain from intercourse with sex partners until 7 days after each partner's treatment. By means of a standard questionnaire, women were asked detailed questions about as many as four partners (identified by first name or initials) during the past 60 days. Questions included whether the participants considered each sex partner to be "steady" or "casual," whether they lived with the partner, about the perceived likelihood of contacting each partner to tell him about the infection, whether they expected that each partner would follow treatment instructions, and whether they had any concerns that telling their partner of the chlamydial infection could result in violence or a change in the relationship.

Intervention

Patient-delivered partner treatment. Study participants were provided with as many as four doses of 1.0 g oral azithromycin in sachet form (one dose for each male partner named) and were instructed to tell each of their partners that he had been exposed to a chlamydial infection, to encourage him to seek treatment, and to offer him the azithromycin as treatment for possible infection. Each azithromycin dose was individually packaged and labeled with the drug name and dose and with the name and phone number for a health care provider who could be contacted with questions. The package also included instructions for reconstituting the powdered drug, warnings about contraindications and possible adverse effects from azithromycin therapy, advice to abstain from intercourse until 7 days after treatment, and a fact sheet on chlamydial infection.

Self-referral. Study participants were instructed to tell each of their sex partners that he had been exposed to a chlamydial infection and to recommend that he seek treatment. Women were given an information sheet for each of their partners, stating that he had been exposed to an STD and listing clinics where he could receive free care. All but one of the enrolling clinics (a family

planning clinic) provided STD care to men. Men who identified themselves as the sex partner of a study patient were seen in an expedited fashion (i.e., before other patients) at some of the enrolling clinics.

Follow-Up

A follow-up visit was scheduled for 1 month after enrollment. At that visit women in both arms were asked about use of antibiotics, diagnosis of chlamydial infection, and new sex partners since the last study visit. Women were asked detailed questions about each sex partner reported at the baseline visit, including whether they had spoken to each partner about his need for treatment and whether they had resumed sex with each partner. Women in the patient-delivered partner treatment arm were asked whether they had given each partner the 1.0-g dose of azithromycin. Women in the self-referral arm were asked whether they had given each partner the information sheet listing the clinics where he could receive free treatment. A urine specimen was collected for chlamydial testing by LCR/PCR.

Women who were positive for chlamydial infection at the first follow-up visit were not followed-up further. Women who were negative for chlamydial infection were asked to return for a second follow-up visit, scheduled 3 months later (women who returned for a second follow-up visit any time in the 6 months after enrollment were evaluated). At the second visit, questions likewise focused on behaviors, including the acquisition of new sex partners since the previous study visit.

At each follow-up visit, women were compensated with $20 to $50 for their time. The study protocol was approved by the investigational review boards at each of the participating institutions and the CDC.

Data Management

Each research center entered locally collected data into standard Epi Info (CDC) databases; bimonthly, data were submitted electronically to the study coordination center. At the study coordination center, data were aggregated and checked for accuracy and completeness. Study policies and procedures were discussed during monthly conference calls and during annual site visits conducted by the CDC.

Analysis

Sample size. The null hypothesis was that there would be no difference in the proportion of women in the self-referral and patient-delivered partner treatment arms with chlamydial infection diagnosed by 4 months after treatment for an initial infection. The estimate of sample size was based on the assumption that 12% of women in the self-referral arm would be infected during the follow-up interval. A total of 2330 women were needed for the study to have 80% power to detect a 30% increase or decrease in infection among women in the patient-delivered partner treatment arm with 95% confidence (two-sided α, 0.05). Anticipating that a third of enrolling women would be lost to follow-up, we specified in the protocol that 3600 women were to be enrolled.

Interim data analysis. Three years after study initiation, a data safety and monitoring committee reviewed study findings to consider whether the study should be continued for an additional year because of lower-than-expected enrollment and higher-than-anticipated loss to follow-up. The committee used a stopping rule for large effect, corresponding to a two-sided P value of <0.001, and a futility stopping rule, which stated that the trial would be stopped if an additional year of enrollment at current enrollment and event rates would not provide a 40% reduction in the width of the confidence interval around the estimate of effect. The committee recommended that the trial be continued. Neither overall infection rates nor any data presented by arm were released to investigators at the enrolling research centers.

Final analysis. Data were analyzed with an intention-to-treat strategy. (Women were analyzed with the arm to which they had been randomly assigned, regardless of which intervention they actually received or whether they reported that they adhered to the assigned intervention.) Women who did not return for a follow-up visit or for whom follow-up urine test results were unavailable were considered nonevaluable and excluded from analysis. The characteristics of enrolled and analyzed study participants were compared by arm. The number of chlamydial infections detected at first and second follow-up visits was summed and divided by the number of women with one or more follow-up visits to calculate cumulative infection. The main comparative analysis was overall infection by study arm; risk for infection was calculated and adjusted for age and enrolling research center by means of logistic regression. Infection rates at "early" visits (21–44 days after enrollment) and "late" visits (45 or more days after enrollment) were also calculated for each arm. Data are presented, by arm, for the number and percentage of women with infection in certain subgroups (e.g., by age and number of baseline sex partners); however, the associated odds ratios and P values are not presented because the study was designed to measure only overall efficacy. Data were analyzed with use of SAS software (version 6.12). Because of the multicenter study design, all statistical tests were adjusted for enrolling research center.

Results

Disposition of Enrolled Patients

Between September 1996 and June 2000, 1889 women were enrolled; 946 (50%) were randomly assigned to patient-delivered partner treatment and 943 to self-referral (Figure 1). A small number of women in each arm (one in the patient-delivered partner treatment arm and five in the self-referral arm) received the intervention alternative to the one to which they were randomized. After randomization it was determined that 94 (5%) of enrolled women had not met inclusion criteria (almost half of women determined to be ineligible after enrollment [45/94, or 48%] were enrolled at a single site due to a laboratory error that resulted in false-positive test reports). A total of 8 women withdrew from the study. Overall, 1454 (81%) of 1787 eligible women returned for at least 1 follow-up visit (patient-delivered partner treatment, 728/887 [82%]; self-referral, 726/900 [81%]).

Characteristics of Enrolled and Analyzed Women, by Study Arm

The characteristics of enrolled study participants and those analyzed were very similar across arms, with the exception of a small difference in the age distribution (Table 1). Women in both treatment arms who were lost to follow-up did not differ meaningfully from those retained in the study (Table 1)

Most analyzed women were aged 14 to 24 years and reported 1 sex partner in the 60 days before enrollment (Table 1). Among women with 1 partner, almost 90% of those in each arm characterized their single partner as "steady," and 24% of women in each arm reported that they were living with the partner. Among women with one partner, 97% expected they would be able to contact that partner (patient-delivered partner treatment, 95%; self-referral, 98%), and 26% were somewhat or very concerned that their

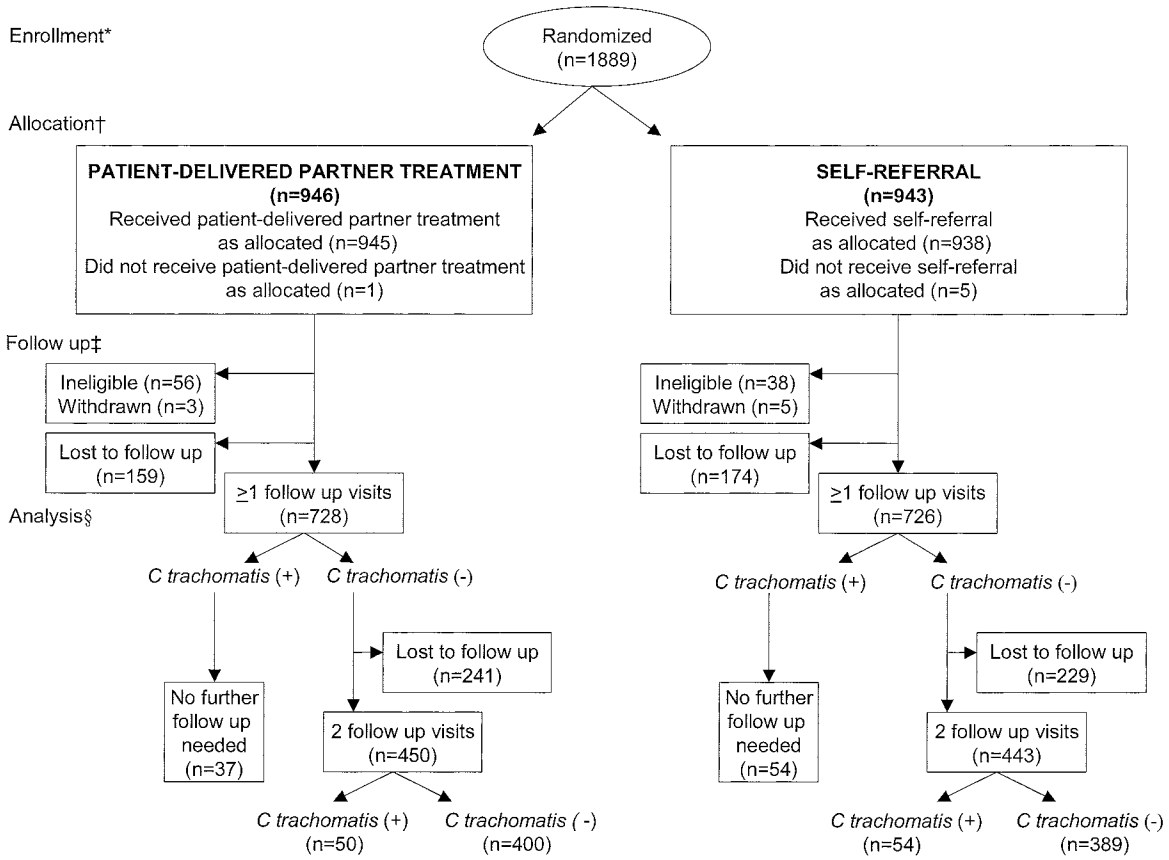

Fig. 1. Flow diagram showing disposition of study participants entering the trial (n = 1884). *Not all study sites maintained records of the number of women eligible for enrollment; all women recruited to the study and randomized reported here. †A total of 6 women were given the incorrect intervention; 1 randomized to patient-delivered partner treatment was given self-referral, and 5 randomized to self-referral were given patient-delivered partner treatment. ‡A total of 94 women were determined to be ineligible after randomization for one or more of the following reasons: negative chlamydia test or positive gonorrhea test at enrollment, age <14 or >34, no sex partners reported for the 60 days before enrollment, or refusal to answer any questions on study instrument; a total of 333 women completed an enrollment visit but did not return for a follow-up visit. §Study participants with one or more follow-up visits were included in the analysis (N = 1454).

relationship would change as a result of the diagnosis of an STD (patient-delivered partner treatment, 26%; self-referral, 25%). Among women with more than one partner, 97% expected they could reach at least one partner (patient-delivered partner treatment, 96%; self-referral, 97%), and 52% were somewhat or very concerned that at least one of their relationships would change (patient-delivered partner treatment, 48%; self-referral, 55%). Overall, 6% of the women in the patient-delivered partner treatment arm (44/728) and 8% of the women in the self-referral arm (49/726) reported being somewhat or very concerned that at least one sex partner would hurt or hit her if she told him that she had an STD.

Women in the patient-delivered partner treatment arm reported higher compliance with the intervention. Among women with one partner, 85% of women in the patient-delivered partner treatment arm reported compliance, compared to 75% of women in the self-referral arm ($P < 0.01$). Among women with more than one partner, 81% of women in the patient-delivered treatment arm reported giving the medication to at least one of their partners and 47% reported giving the medication to all of their partners. Seventy-one percent of women in the self-referral arm reported complying with the intervention with at least one of their partners, but only 25% percent reported giving the intervention to all of their partners. Women in the patient-delivered partner treatment arm were more likely to report that they had resumed intercourse by the time of their first follow-up visit (patient-delivered partner treatment, 82%; self-referral, 75%), although the number of the days waited before resuming intercourse appeared similar across arms (data not shown). A small number of women in each arm reported that they had been treated for chlamydial infection (patient-delivered partner treatment, 1%; self-referral, 2%) or had taken an antibiotic in the interval between enrollment and follow-up visits (patient-delivered partner treatment, 7%; self-referral, 9%). No adverse events or instances of violence were reported by study participants.

Chlamydial Infections

The cumulative rate of chlamydial infection was 12% (87/728) in the patient-delivered partner treatment arm, compared to 15% (108/726) in the self-referral arm, yielding a relative risk for infection of 0.80 with a 95% confidence interval (95% CI) of 0.62 to 1.05 ($P = 0.102$) (Table 2). Adjustment for age and enrolling research center did not meaningfully change the risk estimate.

At the first follow-up visit, 37 (5%) of 728 women in the patient-delivered partner treatment arm and 54 (7%) of 726 women

TABLE 1. Characteristics of Eligible Enrolled Women and Analyzed Women, by Arm

Characteristic*	No. (%) of Enrolled Women			No. (%) of Analyzed Women		
	Patient-Delivered Partner Treatment (n = 887)	Self-Referral (n = 900)	*P* Value‖	Patient-Delivered Partner Treatment (n = 728)	Self-Referral (n = 726)	*P* Value‖
Age (y)						
14–19	474 (53)	430 (48)		391 (54)	338 (47)	
20–24	271 (31)	304 (34)		222 (30)	252 (35)	
25–29	112 (13)	113 (13)		90 (12)	93 (13)	
30–34	30 (3)	50 (6)	0.025	25 (3)	41 (6)	0.015
Race†						
White	197 (22)	209 (23)		163 (22)	183 (25)	
Black	555 (63)	545 (61)		447 (61)	417 (57)	
American Indian	16 (2)	32 (4)		15 (2)	27 (4)	
Asian Pacific Islander	41 (5)	46 (5)		36 (5)	41 (6)	
Other	46 (5)	45 (5)		40 (6)	38 (5)	
Unknown	31 (3)	23 (3)	0.08	26 (4)	20 (3)	0.103
Hispanic ethnicity						
Yes	125 (14)	133 (15)		117 (16)	118 (16)	
No	761 (86)	767 (85)	0.62	610 (84)	608 (84)	0.95
No. of named sex partners in previous 2 months						
1	723 (82)	731 (81)		591 (81)	576 (79)	
2	140 (16)	126 (14)		118 (16)	110 (15)	
3	17 (2)	29 (3)		13 (2)	28 (4)	
≥ 4	7 (1)	14 (2)	0.09	6 (1)	12 (2)	0.05
Research Center						
Birmingham	118 (13)	124 (14)		82 (11)	83 (11)	
Indianapolis	93 (10)	84 (9)		74 (10)	72 (10)	
Southern/Northern California	203 (23)	206 (23)		189 (26)	189 (26)	
New Orleans	282 (32)	299 (33)		231 (32)	225 (31)	
Seattle	191 (22)	187 (21)	0.90	152 (21)	157 (22)	0.99
Considers partner to be steady partner‡						
Yes	—** —	— —		522 (88)	515 (89)	
No	— —	— —		69 (12)	61 (11)	0.55
Lives with partner‡						
Yes	— —	— —		142 (24)	139 (24)	
No	— —	— —		449 (76)	437 (76)	0.97
Adherence to the intervention‡						
Yes	— —	— —		505 (85)	431 (75)	
No	— —	— —		86 (15)	145 (25)	<0.01
New sex partner reported at a follow-up visit§						
Yes	— —	— —		167 (23)	201 (28)	
No	— —	— —		561 (77)	525 (72)	0.043

*Because of missing data, for certain variables the number of participants may not total number of women randomized to that arm.
†American Indian, Asian Pacific Islander, and Others grouped together for statistical testing.
‡Among 1167 women reporting only one partner at baseline.
§Ascertained at each follow-up visit.
‖All *P* values adjusted for research center (Cochran-Mantel-Haenszel chi-square), except *P* value for research center (Pearson chi-square).
**Dashes indicate data collected only at follow-up visits.

in the self-referral arm were *Chlamydia*-positive (Figure 1). The median time to follow-up was similar for both groups (patient-delivered partner treatment, 34 days; self-referral, 33 days). Of 691 women in the patient-delivered partner treatment arm who were *Chlamydia*-negative at the first follow-up visit, 65% returned for a second visit (median time to follow-up, 126 days) and 11% were found to be infected. Among 672 women in the self-referral arm who were *Chlamydia*-negative at a first follow-up visit, 66% returned for a second follow-up (median time to follow-up, 125 days), and 12% of these women were infected. When study visits were categorized as "early" and "late," infection rates were 4% (patient-delivered partner treatment) and 5% (self-referral) for the early visit and 12% (patient-delivered partner treatment) and 14% (self-referral arm) for the late visit.

Infection rates were lower among women in the patient-delivered partner treatment arm for almost all subgroups examined. Infection rates at the enrolling centers varied (range for patient-delivered partner treatment, 9–16%; range for self-referral, 11–21%); one of the centers (Birmingham) had the same infection rate in both arms (12%). Within each study arm, infection rates among women who reported compliance and noncompliance with the intervention did not differ. Among women who did not report a new sex partner, differences in infection between study arms were similar to those in the overall trial (patient-delivered partner treat-

TABLE 2. Chlamydial Infections Detected at Follow-Up Visits, by Baseline Characteristics and Study Arm

	Chlamydial Infections Detected at Follow-Up, Per Group					
	Patient-Delivered Partner Treatment			Self-Referral		
Characteristic	N	n	(%)	N	n	(%)
Total	728	87	(12)	726	108	(15)*
Age (y)						
14–19	391	50	(13)	338	58	(17)
20–24	222	30	(14)	252	32	(13)
25–29	90	4	(4)	93	10	(11)
30–34	25	3	(12)	41	8	(20)
Race						
White	163	18	(11)	183	23	(13)
Black	447	54	(12)	417	63	(15)
American Indian	15	1	(7)	27	3	(11)
Asian Pacific Islander	36	9	(25)	41	6	(15)
Other	40	5	(13)	38	7	(18)
Unknown	26	0	(0)	20	6	(30)
Hispanic ethnicity						
Yes	117	9	(8)	118	21	(18)
No	610	78	(13)	608	87	(14)
No. of named sex partners in previous 2 months						
1	591	65	(11)	576	80	(14)
2	118	20	(17)	110	19	(17)
3	13	1	(8)	28	5	(18)
≥ 4	6	1	(17)	12	4	(33)
Research center						
Birmingham	82	10	(12)	83	10	(12)
Indianapolis	74	12	(16)	72	15	(21)
New Orleans	231	21	(9)	225	26	(12)
Southern/Northern California	189	20	(11)	189	28	(15)
Seattle	152	24	(16)	157	29	(18)
One partner, considered “steady”	522	59	(11)	515	70	(14)
All other women†	206	28	(14)	211	38	(18)
Lives with partner‡						
Yes	142	13	(9)	139	19	(14)
No	449	52	(12)	437	61	(14)
Adherence to the intervention‡						
Gave partner medication/referral sheet	505	56	(11)	432	62	(14)
Did not give medication/referral sheet	86	9	(10)	144	18	(13)
New sex partner reported at follow-up visit§						
Yes	167	24	(14)	201	22	(11)
No	561	63	(11)	525	86	(16)

*Relative risk = 0.80, 95% CI = 0.62–1.05; $P = 0.102$.
†Includes women with one partner who is not characterized as steady and all women with more than one partner.
‡Among 1167 women with one partner only.
§As reported at follow-up visits after treatment.

ment, 11%, versus self-referral, 16%). Since women who had a single sex partner they characterized as “steady” constituted the majority of participants in our study, we examined infection rates in that group. Infection rates in this group were similar to those in the overall trial (patient-delivered partner treatment, 11%, versus self-referral, 14%).

Discussion

This is the first randomized controlled trial of patient-delivered partner treatment. Our findings suggest that patient-delivered partner treatment may be slightly more efficacious than the standard practice of self-referral and at worst could result in a 5% increase in the risk for infection. The intervention was well accepted by women, who reported a high level of compliance. Our study findings are consistent with those of the two previous observational studies of patient-delivered partner treatment, which demonstrated lower chlamydial infection rates among women provided medication or a prescription to give to their partners than among those in a self-referral group.[16,20] However, the results of this randomized trial do not provide conclusive evidence that giving women azithromycin to provide to their sex partners is either more or less efficacious for reducing early repeated chlamydial infection than is the well accepted strategy of self-referral.

Chlamydial infection rates were high in both arms of the study. The 12% infection rate observed in the patient-delivered partner treatment arm was almost as high as that observed in a cohort study of persistent and recurrent chlamydial infection conducted at many of the same venues in the years leading up to this trial, which included no intervention.[4] The high infection rates in this trial cannot be attributed to the acquisition of disease from new sex partners because infection rates greater than 10% were observed among women who did not acquire a new sex partner, and only 25% of women reported a new partner during follow-up. These

findings suggest that both patient-delivered partner treatment and self-referral have limited efficacy in preventing early repeated infection and that self-referral may be particularly ineffective.

There are many reasons to expect that patient-delivered partner treatment would be an effective strategy for preventing repeated infection. First, at the time of treatment for their own chlamydial infection, a majority of women have a partner who remains untreated.[23] Second, most patients with an STD prefer to notify partners themselves rather than accepting assistance from public health department staff members.[23] Third, studies exploring reasons for delays in seeking care have suggested that men perceive practical obstacles to obtaining treatment.[24] Many patients prescribed a 7-day course of doxycycline do not complete the full course.[25] Azithromycin was chosen as the medication for both index treatment and patient delivery because (1) it is highly effective in treating chlamydial infection,[12] (2) therapy can be directly observed for the index patient, and (3) sex partners might be more likely to comply with single-dose therapy. Thus, we expected that giving women the opportunity to deliver a single oral dose of medication to male partners would be acceptable to women and would potentially eliminate practical barriers to care-seeking by male partners.

Patient-delivered partner treatment may be more effective if selectively offered as part of a "menu" of choices for women. Studies comparing strategies for partner treatment suggest that a woman's preference for how partners are contacted may be influenced by her age or other factors[14] and that once undertaken, the success of referral may be dependent on the nature of her relationship with her partners.[26,27] Often, patients will not notify a partner they do not consider their main or steady partner.[23,26] Therefore, patient-delivered partner treatment may be a good choice for some but not all of a woman's partners.

This study had several limitations. First, a substantial number of women were lost to follow-up after enrollment, and it is possible that the risk of infection was different for those women. This seems unlikely, however, given that women retained in the study were similar to those lost to follow-up and that there were no substantial differences in follow-up losses by study arm. Second, there was limited power to detect a difference between the two study arms. Using a 0.05 significance level, the study had only 62% power to detect a 30% reduction in infection, with 1454 women completing the study. For a 20% difference in infection rate (as was observed in this study), there was only 37% power to detect a significant difference between the two interventions. In order to have 80% power to detect a 20% reduction in infection rate (15% and 12%), 2035 women would have been needed in each arm.

Third, among women who were *Chlamydia*-positive at the first follow-up visit, we cannot differentiate between infections that were not eradicated by treatment (persistent infection) and those that were introduced by a new or preexisting sex partner (repeat infection). However, the similarity between the 4% to 5% infection rates observed at early visits and those measured in efficacy trials of azithromycin suggest that infections detected at early visits in our trial may be those that persist despite treatment. Differences in the number of infections detected in each arm at late follow-up visits may be considered more indicative of the intervention effect; in our study this difference (patient-delivered partner treatment, 12%; self-referral, 14%) was very similar to the overall study effect. Finally, use of the powder form of azithromycin for treating partners in the patient-delivered partner treatment arm may have resulted in a minimal estimate of intervention efficacy. Although the powder and tablet forms of azithromycin have equivalent pharmacodynamics (Pfizer, unpublished data), the powder formulation may have been perceived by male partners as inconvenient to take or unpalatable. If male partners' compliance with treatment could be increased by using the tablet form, lower infection rates could be observed for women providing patient-delivered treatment.

As with other partner treatment strategies, the success of patient-delivered partner treatment is contingent on the behaviors of both the index patient and his or her partners. In this study, women who reported that they complied with the intervention had infection rates similar to those among women who reported that they did not comply. While self-reported compliance probably overestimates actual compliance, even full compliance by women cannot ensure that men will take medication offered to them or seek clinical evaluation. Men who do take the medication may still become reinfected by other (untreated) female partners, with subsequent reintroduction of chlamydial infection into a previously treated partnership. Further studies are needed to determine whether women deliver medication to their partners and to elucidate factors influencing men's decisions to accept treatment. Additional work should also be done to determine which patients might be best suited to patient-delivered partner treatment. In the absence of a strong intervention effect, a cost-effectiveness analysis could be a useful guide to clinicians and STD control program administrators considering patient-delivered partner treatment. Such an analysis should compare the cost-effectiveness of patient-delivered partner treatment to self-referral, as well as other partner treatment strategies.

The largely asymptomatic nature of chlamydial infection and the vast number of infections detected by screening pose a special challenge to disease control efforts, and multiple, varied approaches are warranted. Although we did not conclusively show that patient-delivered partner treatment is more effective than self-referral, the ease and acceptability of this intervention may make it a desirable approach for some patients.

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