

ORIGINAL ARTICLE

Effect of Expedited Treatment of Sex Partners on Recurrent or Persistent Gonorrhea or Chlamydial Infection

Matthew R. Golden, M.D., M.P.H., William L.H. Whittington, A.B., H. Hunter Handsfield, M.D., James P. Hughes, Ph.D., Walter E. Stamm, M.D., Matthew Hogben, Ph.D., Agnes Clark, B.S., Cheryl Malinski, B.S., Jennifer R.L. Helmers, B.S., Katherine K. Thomas, M.S., and King K. Holmes, M.D., Ph.D.

ABSTRACT

BACKGROUND

Many sex partners of persons with gonorrhea or chlamydial infections are not treated, which leads to frequent reinfections and further transmission.

METHODS

We randomly assigned women and heterosexual men with gonorrhea or chlamydial infection to have their partners receive expedited treatment or standard referral. Patients in the expedited-treatment group were offered medication to give to their sex partners, or if they preferred, study staff members contacted partners and provided them with medication without a clinical examination. Patients assigned to standard partner referral were advised to refer their partners for treatment and were offered assistance notifying partners. The primary outcome was persistent or recurrent gonorrhea or chlamydial infection in patients 3 to 19 weeks after treatment.

RESULTS

Persistent or recurrent gonorrhea or chlamydial infection occurred in 121 of 931 patients (13 percent) assigned to standard partner referral and 92 of 929 (10 percent) assigned to expedited treatment of sexual partners (relative risk, 0.76; 95 percent confidence interval, 0.59 to 0.98). Expedited treatment was more effective than standard referral of partners in reducing persistent or recurrent infection among patients with gonorrhea (3 percent vs. 11 percent, $P=0.01$) than in those with chlamydial infection (11 percent vs. 13 percent, $P=0.17$) ($P=0.05$ for the comparison of treatment effects) and remained independently associated with a reduced risk of persistent or recurrent infection after adjustment for other predictors of infection at follow-up (relative risk, 0.75; 95 percent confidence interval, 0.57 to 0.97). Patients assigned to expedited treatment of sexual partners were significantly more likely than those assigned to standard referral of partners to report that all of their partners were treated and significantly less likely to report having sex with an untreated partner.

CONCLUSIONS

Expedited treatment of sex partners reduces the rates of persistent or recurrent gonorrhea or chlamydial infection.

From the Division of Infectious Diseases and the Center for AIDS and Sexually Transmitted Diseases (M.R.G., W.L.H.W., H.H.H., J.P.H., W.E.S., K.K.T., K.K.H.) and the Department of Biostatistics (J.P.H.), University of Washington, Seattle; Public Health—Seattle and King County, Seattle (M.R.G., H.H.H., A.C., C.M., J.R.L.H.); and the Division of Sexually Transmitted Diseases Prevention, Center for Human Immunodeficiency Virus, Sexually Transmitted Diseases, and Tuberculosis Prevention, Centers for Disease Control and Prevention, Atlanta (M.H.).

N Engl J Med 2005;352:676-85.

Copyright © 2005 Massachusetts Medical Society.

PARTNER NOTIFICATION, THE PROCESS of informing and treating the sex partners of patients with sexually transmitted infections, has been a centerpiece of U.S. efforts to control sexually transmitted infections since the 1940s.¹ However, in areas with the highest rates of sexually transmitted infections in the United States, public health departments provide partner-notification services for less than 20 percent of patients with gonorrhea or chlamydial infection, leaving most patients to arrange their partners' treatment without assistance.^{2,3} Many, and perhaps most, such partners do not receive treatment after their partner's diagnosis,⁴⁻⁸ and reinfection and further transmission are common.^{6,9-13}

A more effective approach to partner notification could substantially reduce the prevalence of bacterial sexually transmitted infections.^{14,15} However, few studies have rigorously evaluated partner-notification strategies.¹⁶ Many clinicians and several health departments offer patients antimicrobial agents to give to their sex partners,^{3,17,18} a practice called patient-delivered partner therapy. Observational studies suggest that this approach may decrease the rate of recurrent or persistent chlamydial infection in women,^{19,20} but the practice remains controversial. The only published randomized, controlled trial to assess the effect of a partner-notification intervention on morbidity from sexually transmitted infections demonstrated a nonsignificant reduction in the rate of persistent or recurrent chlamydial infections among women who were given medication to treat their partners, as compared with women advised to refer their partners for treatment.¹² We performed the present study to test the hypothesis that expedited treatment of partners with the use of patient-delivered partner therapy and by other methods could reduce the rate of persistent or recurrent gonorrhea or chlamydial infections among women and heterosexual men.

METHODS

STUDY POPULATION

The study population included women and heterosexual men who received a diagnosis of gonorrhea or genital chlamydial infection in King County, Washington, between September 29, 1998, and March 7, 2003. Patients were identified through laboratory reporting (71 percent), case reports from health care providers (26 percent), and on-site case ascertainment (3 percent). We contacted clinicians

who diagnosed the infections to seek permission to contact their patients and then contacted potential participants by telephone or mail. Members of the study staff interviewed participants in person who were enrolled at the Public Health–Seattle and King County (PHSKC) Sexually Transmitted Diseases (STD) Clinic and one other PHSKC clinic. To minimize the likelihood of reinfection of index patients before randomization, we excluded patients who could not be contacted within 14 days after treatment. Figure 1 shows the number of cases reported, the numbers of patients who were ineligible, the number enrolled, and the number who completed the study. After contacting potential participants, we read them a description of the study and sought oral informed consent. Participants were interviewed about each of their sex partners during the 60 days preceding the diagnosis of STD; those who denied having sex during that interval were questioned about their most recent partner. Patients describing at least one untreated partner for whom they had some contact information were randomly assigned to receive either standard referral for their sex partners or expedited treatment for their partners.

PARTNER-TREATMENT STRATEGIES

Before randomization, we offered to contact partners whom participants were unable or unwilling to contact themselves. In the expedited-treatment group, patients were offered medication to give to up to three partners; study staff members offered medication to partners they contacted themselves. In the standard-referral group, patients were advised to tell their partners to seek care and that care was available at no cost at the STD clinic. Study staff members similarly counseled partners they contacted directly.

DISTRIBUTION OF MEDICATION IN THE EXPEDITED-TREATMENT GROUP

Partner packets were distributed to patients or their partners through commercial pharmacies, the PHSKC STD Clinic, or direct mailing. Packets for partners of patients with gonorrhea contained a single 400-mg dose of cefixime and 1-g sachet of azithromycin; packets for partners of patients with chlamydial infection contained only azithromycin. Packets also contained condoms; information about the medications, including a warning about adverse effects; instructions to telephone study staff members with questions or concerns; and a brochure about preventing sexually transmitted infec-

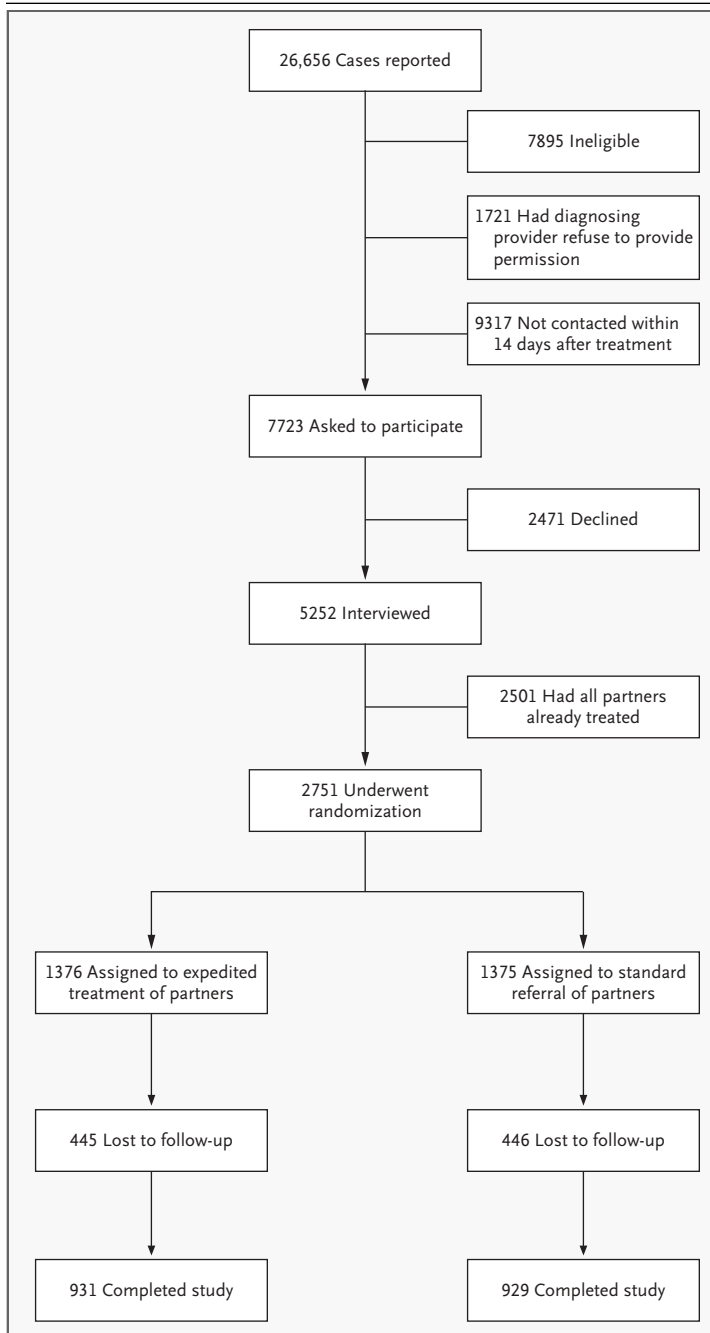


Figure 1. Enrollment and Outcomes.

Of the 7895 ineligible patients, 1949 were incarcerated, 1711 were men who had sex with men, 1184 were in a nonparticipating clinic, 873 did not speak English, 873 lived outside King County, 722 were previously enrolled in the study, 277 were homeless or institutionalized, 119 received the diagnosis in the context of a sexual assault, 100 were younger than 14 years of age, 52 were unable to give informed consent, 25 were contacts of another study participant, and 10 had only partners who were jailed or institutionalized. The 9317 patients who were not contacted within 14 days after treatment include 307 patients with incomplete case reports, 148 enrolled in an alternative partner-notification study, and 380 for whom the reason was not recorded.

tions describing free care available at the STD clinic. Twelve commercial pharmacies, chosen to ensure wide geographic access to treatment, distributed partner packets. We called the pharmacies one week after medications were prescribed to determine whether the patients had obtained the packets; patients or partners who failed to pick up medication within one week were reminded to do so once by telephone. We gave packets directly to patients in the expedited-treatment group who were interviewed in person.

OUTCOMES

We attempted to interview all patients 10 to 18 weeks after treatment, testing urine samples for *Chlamydia trachomatis* and, for those who originally received a diagnosis of gonorrhea, for *Neisseria gonorrhoeae*, using LCx ligase chain reaction (Abbott Diagnostics) or Aptima Combo 2 (Gen-Probe). The primary outcome specified by the protocol was persistent or recurrent gonorrhea or chlamydial infection, defined as chlamydial infection in patients who originally received a diagnosis of chlamydial infection, gonorrhea in those originally given a diagnosis of gonorrhea, or either infection in those originally given a diagnosis of both infections. The original protocol defined persistent or recurrent infections to include a positive culture or nucleic acid–amplification test for the patient’s initial infection 21 to 126 days after treatment. Patients were considered to be free of persistent or recurrent infection if they had a negative test for their initial infection 70 to 126 days after treatment. The earlier period for defining a positive end point was adopted to ensure that patients in whom infections were diagnosed in the 21 to 69 days after treatment were not classified as being free of infection. Before unblinding or viewing results stratified according to study group, the investigators reviewed the distribution of times of follow-up testing and decided to maximize the numbers of patients for whom data on the end point were available by expanding the definition of the primary outcome to include all test results obtained 21 to 133 days after the patient’s initial treatment.

The protocol specified behavioral outcomes and subgroup analyses. If a patient reported not telling a partner about his or her diagnosis of a sexually transmitted infection, refused to contact a partner or allow study staff members to do so, or claimed to have no information on how to contact a partner, that partner was classified as not “very likely” to have been treated.

Study staff members notified the lead investiga-

tor of adverse events associated with medication or partner notification when patients or partners volunteered such information during interviews or telephone calls. However, specific questions regarding adverse events were not asked of all patients.

The institutional review boards of the University of Washington and Group Health Cooperative approved the study procedures. The Washington State Pharmacy Board approved the pharmacy procedures.

STATISTICAL ANALYSIS

On the basis of a previous study,¹¹ the trial was designed to have 80 percent power (two-tailed $\alpha=0.05$) to detect a 4 percentage point reduction in the rate of persistent or recurrent gonorrhea or chlamydial infection, assuming a 12 percent prevalence of infection at follow-up in the standard-referral group and balanced randomization. The resulting sample size of 1667 patients was increased by 10 percent to 1834 to accommodate imprecision in these estimates.

We used Fisher's exact test to compare the rates of persistent or recurrent infection between groups. Bivariate and multivariate relative risks and associated confidence intervals comparing partner-notification outcomes or infection outcomes were estimated with the use of a generalized linear model with a binary outcome and log link and robust standard errors, where appropriate.²¹ Adjusted relative risks were reported for variables remaining statistically significant ($P\leq 0.05$) after adjustment for randomization and one another.

RESULTS

ENROLLMENT AND STUDY POPULATION

Of 26,656 cases of gonorrhea or chlamydial infection reported to PHSKC during the study period, 7723 eligible patients were asked to participate and 5252 (68 percent) were enrolled (Fig. 1). As compared with those who declined participation, enrollees were younger (mean age, 23.2 vs. 25.2 years; $P<0.001$), less likely to be male (26 percent vs. 36 percent, $P<0.001$), less likely to have gonorrhea alone (13 percent vs. 18 percent, $P<0.001$), more likely to have received the diagnosis in an emergency room (10 percent vs. 6 percent, $P<0.001$), and less likely to have received the diagnosis in a family-planning or community clinic (16 percent vs. 18 percent, $P=0.009$).

At enrollment, 2751 patients reported having un-

treated partners they could contact and underwent randomization. Factors significantly associated with having untreated partners included female sex; black race; having more than one sex partner in the preceding 60 days, a casual or one-time partner, and sex with a partner the patient did not anticipate having sex with again; shorter time from treatment to interview; and diagnosis in an emergency room. Patients treated in community health centers or family-planning clinics were less likely than those who were treated in other venues to have untreated partners. A published analysis of the first 1693 patients enrolled in the study reported similar findings.⁷

Patients in the two groups had similar characteristics (Table 1). Of 2751 randomized patients, 1860 (68 percent) were retested for infection and 1833 (67 percent) were both retested and reinterviewed. As compared with those who were not retested, the 1860 who were retested were more likely to be women (79 percent vs. 72 percent, $P<0.001$), to have received an initial diagnosis of chlamydial infection alone (86 percent vs. 79 percent, $P<0.001$), and to be Asian, Hawaiian, or Pacific Islander (14 percent vs. 11 percent, $P=0.04$) and less likely to have received the initial diagnosis in an emergency room (10 percent vs. 15 percent, $P=0.005$). Patients who were successfully retested did not differ significantly from those who were not retested with respect to the presence of symptoms, numbers of sex partners, or pattern of condom use at enrollment.

Similar proportions of patients in each group completed the study. For the 1860 patients who completed the study, patients whose partners received expedited care did not differ significantly in any of the characteristics presented in Table 1 from patients whose partners received a standard referral (data not shown) or in the mean (\pm SD) time to follow-up testing (90.0 ± 19.4 vs. 89.8 ± 19.4 days).

ADHERENCE TO TREATMENT, SUCCESS OF PARTNER NOTIFICATION, AND SEXUAL BEHAVIORS AFTER INITIAL TREATMENT

Among the 912 patients assigned to expedited treatment who were retested and reinterviewed, 647 (71 percent) had agreed to give medication to at least one partner. This included 169 provided medication at the clinic or through the mail, 9 given a prescription, and 469 who agreed to obtain medication through a commercial pharmacy, 376 (80 percent) of whom successfully did so. Of the 647 patients who agreed to provide treatment to at least one partner, 93 percent of those originally given a diagnosis

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Expedited Treatment of Partner (N=1375)	Standard Referral of Partner (N=1376)
STI diagnosis — no. (%)		
Chlamydial infection only	1074 (78)	1088 (79)
Gonorrhea only	237 (17)	213 (15)
Both chlamydial infection and gonorrhea	64 (5)	75 (5)
Male sex — no. (%)	317 (23)	329 (24)
Age — yr	23.1±7.3	22.8±7.1
Race or ethnic group — no. (%)†		
White	655 (50)	677 (52)
Black	456 (35)	484 (37)
Native American or Alaskan Native	82 (6)	70 (5)
Asian, Hawaiian, or Pacific Islander	176 (13)	164 (13)
Other	78 (6)	66 (5)
Unknown	9 (1)	10 (1)
Hispanic	122 (9)	134 (10)
Place of STI diagnosis — no. (%)		
STD clinic	254 (18)	255 (19)
Other public health clinic	325 (24)	319 (23)
Emergency room	168 (12)	164 (12)
Family-planning or community clinic	171 (12)	183 (13)
Private-sector clinician	457 (33)	455 (33)
Symptoms prompted diagnosis — no. (%)	423 (31)	419 (30)
No. of sex partners in 60 days before diagnosis	1.5±1.1	1.6±1.3
Proportion of sex acts involving condoms in previous 60 days	0.29±0.36	0.30±0.35
Completed follow-up — no. (%)	929 (68)	931 (68)

* Plus-minus values are means ±SD. There were no significant differences between groups. Chi-square and t-tests were used for categorical and continuous outcomes, respectively, except for the number of sex partners in the previous 60 days and the proportion of sex acts with condoms, for which the Wilcoxon rank-sum test was used because data were not normally distributed. STI denotes sexually transmitted infection.

† Data on race or ethnic group were obtained from 2614 patients. Some patients are listed in more than one category.

of gonorrhea or both gonorrhea and chlamydial infection, as compared with 90 percent of those given a diagnosis of chlamydial infection alone, obtained medications for partners ($P=0.32$). The mean interval from treatment of the index patient to dispensing of the medications for partners was shorter for patients with gonorrhea or both gonorrhea and chlamydial infection than for those with chlamydial infection alone (3.1 ± 8.7 vs. 6.1 ± 9.2 days, $P<0.01$).

Patients in the expedited-treatment group reported having 1367 partners; 114 (12 percent) asked study staff members to notify 125 (9 percent) of their partners; 114 (91 percent) of these partners were successfully notified, of whom 62 (54 percent) obtained medication from a pharmacy and 14 (12 percent) were evaluated and treated at the STD clinic. The 921 patients in the standard-referral group who were retested and reinterviewed reported having 1409 partners; 95 participants (10 percent) requested assistance notifying 116 partners (8 percent), of whom 97 (84 percent) were notified.

Patients in the two study groups reported notifying similar proportions of their sex partners (Table 2). However, patients in the expedited-treatment group were significantly more likely than those in the standard-referral group to report that all their partners were very likely to have been treated or tested negative for sexually transmitted infections and significantly less likely to report having had sex with an untreated partner after their own treatment for gonorrhea or chlamydial infection.

GONORRHEA AND CHLAMYDIAL INFECTION AT FOLLOW-UP

Gonorrhea or chlamydial infection was significantly less common at follow-up among patients in the expedited-treatment group than among patients in the standard-referral group (relative risk, 0.76; 95 percent confidence interval, 0.59 to 0.98) (Table 3). Expedited treatment of partners was associated with a 73 percent reduction in the presence of gonorrhea (3 percent vs. 11 percent, $P=0.01$) but only a 15 percent reduction in the presence of chlamydial infection at follow-up (11 percent vs. 13 percent, $P=0.17$) ($P=0.05$ for the comparison of treatment effects). The reduction in the presence of infection at follow-up associated with expedited treatment of partners was somewhat greater among male patients (7 percent vs. 12 percent; relative risk, 0.56; 95 percent confidence interval, 0.30 to 1.08) than among female patients (11 percent vs. 13 percent; relative risk, 0.81; 95 percent confidence interval, 0.61 to 1.07), though this difference in treatment effect was not significant and was limited to patients with chlamydial infection. Among 94 patients who originally received a diagnosis of both gonorrhea and chlamydial infection, 16 (17 percent) tested positive for *C. trachomatis* and 10 (11 percent) tested positive for *N. gonorrhoeae* at follow-up.

Regardless of randomization assignment, among female patients who reported no sexual in-

Table 2. Outcomes of Partner Notification and Exposure to Untreated Partners, as Reported by Study Participants.*

Variable	Expedited Treatment of Partner	Standard Referral of Partner	Relative Risk (95% CI)
	<i>no. with response/total no. (%)</i>		
Patients			
All partners "very likely" to have been treated or tested negative for STI†	519/850 (61)	435/888 (49)	1.2 (1.1–1.4)
Sex with any partner not believed to be "very likely" either to have been treated or to have tested negative for STI†	51/886 (6)	110/902 (12)	0.5 (0.3–0.6)
Partners			
Partner notified by patient, tested negative or treated	1025/1335 (77)	1098/1403 (78)	1.0 (0.9–1.0)
Partner "very likely" to have been treated or tested negative for STI†	816/1268 (64)	732/1354 (52)	1.2 (1.1–1.3)

* Data on the following categories were missing: all partners "very likely" to have been treated, 33 patients in the standard-referral group and 62 patients in the expedited-treatment group; sex with any partner not believed to be "very likely" to have been treated, 19 and 26, respectively; partner notified by patient, tested negative or treated, 6 and 32 partners, respectively; partners "very likely" to have been treated, 55 and 99 partners, respectively. CI denotes confidence interval, and STI sexually transmitted infection.

† Differences between groups remained significant with a change of less than 10 percent in the relative risks if results were restricted to the last two years of study enrollment, for which data were more than 99 percent complete in both study groups.

tercourse after initial treatment, 1 of 38 originally treated for gonorrhea (3 percent; 95 percent confidence interval, 0 to 8 percent) and 22 of 289 originally treated for chlamydial infection (8 percent; 95 percent confidence interval, 5 to 11 percent) had persistent infections at follow-up. Among male patients who reported no intercourse after treatment, none of the 30 originally treated for gonorrhea or of the 57 originally treated for chlamydial infection tested positive for gonorrhea or chlamydial infection at follow-up.

MULTIVARIATE ANALYSIS OF RISK FACTORS FOR GONORRHEA OR CHLAMYDIAL INFECTION AT FOLLOW-UP

In multivariate analysis, an elevated risk of infection at follow-up was significantly associated with standard referral of partners as well as with younger age, initial chlamydial infection or both gonorrhea and chlamydial infection (vs. gonorrhea alone), diagnosis at a public health clinic other than the STD clinic, non-Hispanic ethnicity, any sex since treatment, and greater numbers of sex partners since treatment with whom the patient had any unprotected vaginal sex (Table 4). An increased risk of gonorrhea or chlamydial infection at follow-up was also associ-

Table 3. Persistent or Recurrent Gonorrhea and Chlamydial Infection.

Variable	Expedited Treatment of Partner	Standard Referral of Partner	Unadjusted Relative Risk (95% CI)*
	<i>no./total no. (%)</i>		
Either gonorrhea or chlamydial infection†	92/929 (10)	121/931 (13)	0.76 (0.59–0.98)
Men	13/194 (7)	24/202 (12)	0.56 (0.30–1.08)
Women	79/735 (11)	97/729 (13)	0.81 (0.61–1.07)
Gonorrhea‡	6/179 (3)	19/179 (11)	0.32 (0.13–0.77)
Men	3/72 (4)	8/85 (9)	0.44 (0.12–1.61)
Women	3/107 (3)	11/94 (12)	0.25 (0.07–0.83)
Chlamydial infection‡	86/797 (11)	105/798 (13)	0.82 (0.62–1.07)
Men	10/132 (8)	17/135 (13)	0.60 (0.29–1.27)
Women	76/665 (11)	88/663 (13)	0.86 (0.65–1.15)

* CI denotes confidence interval.

† Three patients had both gonorrhea and chlamydial infection at follow-up.

‡ The treatment effect (relative risk) was greater for gonorrhea than for chlamydial infection ($P=0.05$) with the use of a general linear model with a binary outcome and log link and robust SEs to account for the presence of more than one rescreening test per subject (in cases in which a subject had both diseases at baseline).

Table 4. Demographic, Clinical, and Behavioral Factors Associated with Persistent or Recurrent Gonorrhea or Chlamydial Infection.*

Factor	Persistent or Recurrent STI†	Relative Risk (95% CI)	
		Unadjusted	Adjusted
	no./total no. (%)		
Age		0.7 (0.6–0.8)‡	0.8 (0.7–0.9)‡
<20 yr	109/714 (15)		
20–24 yr	68/639 (11)		
25–29 yr	22/255 (9)		
≥30 yr	14/252 (6)		
Sex			
Male	37/396 (9)	0.8 (0.6–1.1)	
Female	176/1464 (12)	1.0	
Initial diagnosis			
Gonorrhea only§	15/265 (6)	1.0	1.0
Chlamydial infection only	175/1501 (12)	2.1 (1.2–3.4)	1.7 (0.9–2.9)
Both gonorrhea and chlamydial infection	23/94 (24)	4.3 (2.4–7.9)	3.4 (1.8–6.4)
Source of STI diagnosis			
STD clinic	33/341 (10)	1.1 (0.7–1.6)	
Other public health clinic	73/435 (17)	1.8 (1.3–2.5)	1.4 (1.1–1.9)
Emergency room	22/195 (11)	1.2 (0.8–2.0)	
Community clinic	27/253 (11)	1.2 (0.8–1.8)	
Other§	58/636 (9)	1.0	
Race or ethnic group¶			
White	93/862 (11)	0.9 (0.7–1.2)	
Black	75/619 (12)	1.1 (0.8–1.4)	
Native American or Alaskan Native	10/107 (9)	0.8 (0.4–1.5)	
Asian, Hawaiian, or Pacific Islander	34/245 (14)	1.3 (0.9–1.8)	
Other	12/89 (13)	1.2 (0.7–1.2)	
Hispanic	13/174 (7)	0.6 (0.4–1.1)	0.5 (0.3–1.0)
No. of sex partners at baseline (past 60 days)			
0–1§	126/1188 (11)	1.0	
2	56/474 (12)	1.1 (0.8–1.5)	
≥3	31/196 (16)	1.5 (0.9–1.9)	
Any sex since treatment			
Yes	182/1436 (13)	2.2 (1.5–3.4)	1.9 (1.1–3.2)
No	22/391 (6)	1.0	1.0

ated with having sex with a partner whom the patient believed was not very likely either to have been treated or to have tested negative for sexually transmitted infections and with reporting that not all of one's partners had been treated. Treatment effects did not vary significantly according to age.

Among patients assigned to expedited treatment of partners, infection at follow-up was somewhat

more common among those who did not obtain medication for partners after agreeing to do so than among those who did obtain such medication (17 percent vs. 10 percent, $P=0.06$) and among those who notified partners more than seven days after their own treatment than among those who notified partners within seven days after their own treatment (23 percent vs. 9 percent, $P=0.03$). Four of six gono-

Table 4. (Continued.)*

Factor	Persistent or Recurrent STI†	Relative Risk (95% CI)	
		Unadjusted	Adjusted
	no. (%)		
New sex partner since treatment‡			
Yes	70 (14)	1.2 (0.9–1.6)	
No	112 (12)	1.0	
No. of sex partners since treatment with whom condom not used for all vaginal sex		1.7 (1.4–2.2)‡	1.5 (1.2–2.0)‡
0	66 (8)		
1	122 (14)		
≥2	14 (20)		
Reexposure to sex partner patient believes had other partners			
Yes	73 (14)	1.4 (1.1–1.8)	
No	130 (10)	1.0	
Sex with any partner not believed to be “very likely” either to have been treated or to have tested negative for STI¶			
Yes	40 (25)	2.6 (1.9–3.5)	
No	156 (10)	1.0	
All partners “very likely” to have been treated or to have tested negative for STI¶			
Yes	87 (9)	0.7 (0.5–0.9)	
No	106 (14)	1.0	
Study group			
Expedited treatment	92 (10)	0.8 (0.6–1.0)	0.75 (0.57–0.97)
Standard referral	121 (13)	1.0	1.0

* Rates of recurrent chlamydial infection did not differ significantly between index patients treated with azithromycin and those treated with doxycycline (13 percent and 11 percent, respectively) (relative risk, 1.2; 95 percent confidence interval, 0.8 to 1.6). STI denotes sexually transmitted infection.

† Persistent or recurrent infection was defined as chlamydial infection at follow-up in patients originally given a diagnosis of chlamydial infection, gonorrhea in those originally given a diagnosis of gonorrhea, or either infection in those originally given a diagnosis of infection with both pathogens.

‡ The relative risk is per category change, with the first category as the reference group.

§ The analysis excludes patients who had had no sex partners since treatment.

¶ The variable was significant in the multivariate model. Inclusion in the model results in the study assignment's not being significantly associated with persistent or recurrent infection. These variables were not included in the final multivariate model because of their role in the presumed causal pathway between the trial's intervention and the outcome of persistent or recurrent STI. Relative risks for multivariate model were generated by means of a generalized linear model with binary outcomes and log link.

coccal infections detected at follow-up among patients in the expedited-treatment group occurred in patients who refused medication for partners.

DISCUSSION

As compared with standard referral of partners, providing medication for the sexual partners of patients with gonorrhea or chlamydial infection without re-

quiring the partners' prior medical evaluation significantly reduced persistent or recurrent infections among participants. Patients offered expedited treatment of their partners more often reported that their partners had been treated and less often reported having sex with untreated partners. Failure to treat sex partners and sex with an untreated partner were both associated with an elevated risk of infection at follow-up and represent a direct causal

link between the intervention and the study's primary, biologic outcome.

Expedited treatment of partners was more effective in reducing persistent or recurrent gonorrhea than persistent or recurrent chlamydial infection. Differences in the risk of reexposure, reinfection after reexposure, or the frequency of repeated self-treatment do not explain this differential effect. The reduction in the percentage of patients reexposed to an untreated partner was similar among patients originally treated for chlamydial infection (11 percent for standard referral and 6 percent for expedited treatment; $P=0.006$) and those treated for gonorrhea (12 percent and 9 percent, respectively; $P=0.10$). Among patients who reported having sex with untreated partners, 34 of 135 treated for chlamydial infection (25 percent) and 7 of 34 treated for gonorrhea (21 percent) were infected at follow-up. All patients were asked whether they repeated their treatment using medication intended for a partner; only one person acknowledged doing so.

Our data suggest that infections detected at follow-up may have represented treatment failure more often for chlamydial infection than for gonorrhea. Regardless of study-group assignment, women, but not men, who denied having intercourse between treatment and follow-up had a surprising 8 percent prevalence of chlamydial infection at follow-up. Previous trials of doxycycline and azithromycin for chlamydial infection in women reported treatment-failure rates of only 0 to 3 percent but, unlike this study, defined failure on the basis of culture results, not nucleic acid–amplification tests, and followed patients for only 35 days.^{22,23}

Although expedited treatment of partners increases the proportion of partners treated and decreases persistent or recurrent infections among index patients, this benefit must be weighed against the potential deleterious effects of treating partners without clinically evaluating them. First, some partners may have allergic reactions or other drug-related adverse effects. We used drugs with a low risk of anaphylaxis and dispensed all medications with instructions about adverse effects. No drug-related adverse effects were reported, nor was this a substantial problem in a previous study.¹² Second, partners treated without a clinical evaluation may have concurrent sexually transmitted infections identifiable only if they seek medical care. We have separately studied this possibility in four U.S. STD clinics and found that heterosexuals evaluated for exposure to gonorrhea or chlamydial infection infrequently had

human immunodeficiency virus infection or other bacterial sexually transmitted infections that would be unresponsive to the regimens of patient-delivered partner therapy that we used (unpublished data). Third, with the use of patient-delivered partner therapy, an opportunity may be lost to counsel sex partners to refer their other partners for evaluation and treatment. However, partner notification assistance is infrequently provided by health departments in the United States to patients with gonorrhea or chlamydial infection, and when assistance is provided, the process has been relatively inefficient when extended to second-generation sexual contacts.^{24,25}

Beyond the potential deleterious effects of patient-delivered partner therapy, legal barriers and the uncertain availability of cefixime may inhibit its use. Although commonly used,¹⁷ the legality of patient-delivered partner therapy remains ill-defined in most states, and more widespread use of it or other approaches to expedited treatment of partners may require new laws or administrative rulings. Cefixime tablets, which we used to treat the partners of participants with gonorrhea, are not currently available in the United States but should be available later this year. PHSKC currently uses a 400-mg tablet of cefpodoxime for patient-delivered partner therapy for gonorrhea.²⁶

Our study has two main limitations. The external validity of our findings may be limited by the fact that we interviewed only 31 percent of potentially eligible persons in King County during the study period. In addition, those enrolled differed from those who declined enrollment. However, the study was large and population-based and enrolled patients reported by 541 clinical providers. The internal validity of our findings could have been compromised by the fact that only 68 percent of participants completed the study. However, follow-up rates and baseline characteristics among those completing the study were similar in the two study groups.

In summary, expedited treatment of sex partners of patients who received a diagnosis of gonorrhea or chlamydial infection reduced the rate of persistent or recurrent infection in participants and increased the proportion of partners treated. This reduction was greater for gonorrhea than for chlamydial infection. Although the safety and opportunity costs of this approach warrant further study, we believe that the inadequacies of current approaches to partner notification and the persistence of unacceptably high levels of morbidity from sexually transmitted infections in the United States should

motivate both clinicians and public health authorities to incorporate patient-delivered partner therapy and other approaches to expedited care of partners into clinical and public health policies.

Supported by a grant (K23 AI01846) from the National Institutes of Health, a grant (AI31448) from the University of Washington National Institutes of Health STD Cooperative Research Center, and the Division of STD Prevention, National Center for HIV, STD, and Tuberculosis Prevention, Centers for Disease Control and Prevention.

Mr. Whittington and Drs. Golden, Stamm, and Holmes report having received research support from Roche Molecular Diagnostics and Gen-Probe. Dr. Stamm reports having received consulting

and lecture fees from Abbott Laboratories, Corixa, Activbiotics, and Gen-Probe. Drs. Hughes and Handsfield report having received research support from Gen-Probe. Mr. Whittington reports having received research support from Therocycler-Biostar Diagnostics and Biomed Diagnostics.

We are indebted to Harborview, Rite-Aid, and Bartell pharmacies for distributing study medication; to Barbara Krekeler for administrative oversight; to Marjorie Boyd for assistance organizing the study; to Tim Tyree and Fred Koch for assistance with data management; to the Public Health–Seattle and King County Disease Intervention Specialists and Jill Langdon for work recruiting some participants; to clinical providers throughout King County for allowing us to enroll their patients in the trial; and to Wyeth Pharmaceuticals for donating cefixime.

REFERENCES

- Parran T. Shadow on the land: syphilis. New York: Reynal & Hitchcock, 1937.
- St Lawrence JS, Montano DE, Kasprzyk D, Phillips WR, Armstrong K, Leichter JS. STD screening, testing, case reporting, and clinical and partner notification practices: a national survey of US physicians. *Am J Public Health* 2002;92:1784-8.
- Golden MR, Hogben M, Handsfield HH, St Lawrence JS, Potterat JJ, Holmes KK. Partner notification for HIV and STD in the United States: low coverage for gonorrhea, chlamydial infection, and HIV. *Sex Transm Dis* 2003;30:490-6.
- Potterat JJ, Rothenberg R. The case-finding effectiveness of self-referral system for gonorrhea: a preliminary report. *Am J Public Health* 1977;67:174-6.
- Woodhouse DE, Potterat JJ, Muth JB, Pratts CI, Rothenberg RB, Fogle JS II. A civilian-military partnership to reduce the incidence of gonorrhea. *Public Health Rep* 1985;100:61-5.
- Oh MK, Boker JR, Genuardi FJ, Cloud GA, Reynolds J, Hodgins JB. Sexual contact tracing outcome in adolescent chlamydial and gonococcal cervicitis cases. *J Adolesc Health* 1996;18:4-9.
- Golden MR, Whittington WL, Handsfield HH, et al. Partner management for gonococcal and chlamydial infection: expansion of public health services to the private sector and expedited sex partner treatment through a partnership with commercial pharmacies. *Sex Transm Dis* 2001;28:658-65.
- Fortenberry JD, Brizendine EJ, Katz BP, Orr DP. The role of self-efficacy and relationship quality in partner notification by adolescents with sexually transmitted infections. *Arch Pediatr Adolesc Med* 2002;156:1133-7.
- Orr DP, Langefeld CD, Katz BP, Caine VA. Behavioral intervention to increase condom use among high-risk female adolescents. *J Pediatr* 1996;128:288-95.
- Kjaer HO, Dimcevski G, Hoff G, Olesen F, Ostergaard L. Recurrence of urogenital *Chlamydia trachomatis* infection evaluated by mailed samples obtained at home: 24 weeks' prospective follow up study. *Sex Transm Infect* 2000;76:169-72.
- Whittington WL, Kent C, Kissinger P, et al. Determinants of persistent and recurrent *Chlamydia trachomatis* infection in young women: results of a multicenter cohort study. *Sex Transm Dis* 2001;28:117-23.
- Schillinger JA, Kissinger P, Calvet H, et al. Patient-delivered partner treatment with azithromycin to prevent repeated *Chlamydia trachomatis* infection among women: a randomized, controlled trial. *Sex Transm Dis* 2003;30:49-56.
- Fortenberry JD, Brizendine EJ, Katz BP, Wools KK, Blythe MJ, Orr DP. Subsequent sexually transmitted infections among adolescent women with genital infection due to *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or *Trichomonas vaginalis*. *Sex Transm Dis* 1999;26:26-32.
- Hethcote HW, York JA. Gonorrhea transmission dynamics and control. New York: Springer-Verlag, 1984.
- Kretzschmar M, van Duynhoven YT, Severijnen AJ. Modeling prevention strategies for gonorrhea and Chlamydia using stochastic network simulations. *Am J Epidemiol* 1996;144:306-17.
- Macke BA, Maher JE. Partner notification in the United States: an evidence-based review. *Am J Prev Med* 1999;17:230-42.
- Golden MR, Whittington WL, Gorbach PM, Coronado N, Boyd MA, Holmes KK. Partner notification for chlamydial infections among private sector clinicians in Seattle-King County: a clinician and patient survey. *Sex Transm Dis* 1999;26:543-7.
- Klausner JD, Chaw JK. Patient-delivered therapy for chlamydia: putting research into practice. *Sex Transm Dis* 2003;30:509-11.
- Ramstedt K, Forssman L, Johannisson G. Contact tracing in the control of genital *Chlamydia trachomatis* infection. *Int J STD AIDS* 1991;2:116-8.
- Kissinger P, Brown R, Reed K, et al. Effectiveness of patient delivered partner medication for preventing recurrent *Chlamydia trachomatis*. *Sex Transm Infect* 1998;74:331-3.
- Wacholder S. Binomial regression in GLIM: estimating risk ratios and risk differences. *Am J Epidemiol* 1986;123:174-84.
- Martin DH, Mroczkowski TF, Dalu ZA, et al. A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. *N Engl J Med* 1992;327:921-5.
- McCormack WM, Dalu ZA, Martin DH, et al. Double-blind comparison of trovafloxacin and doxycycline in the treatment of uncomplicated Chlamydial urethritis and cervicitis. *Sex Transm Dis* 1999;26:531-6.
- Ruden AK, Jonsson A, Lidbrink P, Allebeck P, Bygdeman SM. Endemic versus non-endemic gonorrhoea in Stockholm: results of contact tracing. *Int J STD AIDS* 1993;4:284-92.
- David LM, Wade AA, Natin D, Radcliffe KW. Gonorrhoea in Coventry 1991-1994: epidemiology, coinfection and evaluation of partner notification in the STD clinic. *Int J STD AIDS* 1997;8:311-6.
- Oral alternatives to cefixime for the treatment of uncomplicated *Neisseria gonorrhoeae* urogenital infections. Atlanta: Centers for Disease Control and Prevention, 2004. (Accessed January 21, 2005, at <http://www.cdc.gov/STD/treatment/Cefixime.htm>.)

Copyright © 2005 Massachusetts Medical Society.