Expedited Partner Therapy in the Management of Sexually Transmitted Diseases

Review and Guidance

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EXPEDITED PARTNER THERAPY IN THE MANAGEMENT OF SEXUALLY TRANSMITTED DISEASES

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PREFACE

This report was prepared at the direction of John M. Douglas, Jr., M.D., Director, Division of STD Prevention, NCHSTP, CDC. It summarizes the available literature on expedited partner therapy (EPT) for the management of the partners of persons with STD and interprets the results. It also incorporates perspectives gained from two expert consultations, one that predominantly addressed the scientific evidence related to EPT and a second that emphasized operational issues that will affect implementation of EPT. The report serves as background on EPT and provides the evidence in support of anticipated guidelines for the selective use of EPT. It is intended as a reference document for use by CDC and by public health agencies, other organizations, interested individuals, and other partners in the public and private sector.

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EXECUTIVE SUMMARY

Overview

Expedited partner therapy (EPT) is the practice of treating the sex partners of persons with sexually transmitted diseases (STD) without an intervening medical evaluation or professional prevention counseling. The usual implementation of EPT is through patient-delivered partner therapy (PDPT), although other methods may be employed. The available literature and selected unpublished studies were systematically reviewed, and this report provides background for the development of guidance on use of EPT as an option for partner management for selected STDs and patients.

Evidence

For STDs other than syphilis, partner management based on patient referral or provider referral has had only modest success in assuring partner treatment, largely attributable to limitations of available financial and personnel resources. EPT is believed to have been widely employed in women with trichomoniasis. Recent surveys document occasional use by many primary care providers in the management of patients with gonorrhea and chlamydial infection, and consistent use by a few. A retrospective case control study and two process-oriented analyses suggested that EPT holds promise as a partner management option. These studies contributed to CDC decisions to fund 4 randomized controlled trials (RCTs) designed to compare EPT with standard partner management approaches in men and women with gonorrhea, chlamydial infection, or trichomoniasis; and to assess behavioral predictors of treatment and reinfection.

Persistent or Recurrent Infection

The first RCT of EPT followed 1,787 women in 6 cities after treatment for chlamydial infection. Recurrent infection was documented at follow-up visits 1 months and 4 months later in 12% of women randomized to EPT and 15% of those managed by patient referral (odds ratio [OR] 0.80, 95% confidence interval [CI] 0.62-1.05). The second RCT enrolled 2,751 men and women with gonorrhea or chlamydial infection from both public and private care settings in a single metropolitan area. Persistent or recurrent infection with either disease was found in 9.9% of subjects randomized to EPT and 13.0% of those who had standard patient-referral or provider-referral of their partners (OR 0.76, 95% CI 0.59-0.98). EPT was more effective in preventing gonorrhea at follow-up (OR 0.32, 95% CI 0.13-0.77) than chlamydial infection (OR 0.82, 95% CI 0.62-1.07). Chlamydial infection was present at follow-up in 7.6% of women who denied all sex since treatment, suggesting that a higher than expected rate of treatment failure accounted for some infections at follow-up. In the third available RCT, 977 men with symptomatic urethritis (principally gonorrhea and chlamydial infection) were randomized to EPT, patient referral, or patient referral enhanced by written education materials. Follow-up testing for gonorrhea and chlamydial infection 4-8 weeks later was accomplished in 37.5% of patients. Persistent or recurrent infection was found in 43% of subjects in the patient referral group (referent), 14% of men randomized to enhanced patient referral (OR 0.22, 95% CI 0.11-0.44, P<0.001), and 23% of men randomized to EPT (OR 0.38, 95% CI 0.19-0.74, P<0.001). For trichomoniasis, in an as yet unpublished RCT of 463 women randomized to the same interventions as the male

urethritis trial, with 80% follow-up, the prevalences of infection 3-7 weeks later were not significantly different for patient referral (6%), enhanced patient referral (9%), or EPT (9%).

Behavioral Outcomes

The 4 available RCTs evaluated the association of EPT with index cases' reports of success in partner notification, confidence that their partners were treated, and sexual behaviors likely to predict reinfection. In 2 trials that enrolled male index cases, men randomized to EPT were equally or more likely to notify their partners than those randomized to the control strategies. Female index cases with chlamydial infection or gonorrhea who were randomized to EPT had either equivalent success or enhanced success in notifying partners compared with women randomized to standard partner management. In all 3 trials of gonorrhea or chlamydial infection, EPT was associated with at least equivalent and typically increased confidence by both male and female index cases that their partners had received treatment, including direct observation that their partners took medication. Two trials that addressed both gonorrhea and chlamydial infection found EPT to be associated with significantly reduced rates of sex with untreated partners at follow-up. The trichomoniasis trial showed general equivalence of EPT with desirable behavioral outcomes compared with standard patient referral.

Cost Effectiveness

Preliminary economic analyses suggest that EPT is a cost-saving and cost effective partner management strategy.

Limitations

The data available to support EPT for chlamydial infection were derived in larger and geographically more diverse samples of patients than those for gonorrhea. Nevertheless, the evidence in favor of EPT, as measured by the rate of persistent or recurrent infection at follow-up, is stronger for gonorrhea than for chlamydial infection, perhaps due to a higher than expected rate of persistent chlamydial infection in women. This finding confounds the assessment of EPT in women with chlamydial infection. Assuring the treatment of infected men's female partners is a high priority to prevent ongoing transmission and community spread.

As for all RCTs, the extent to which the results of the available trials can be safely generalized to other populations and settings is not certain. Owing to modest sample sizes in some disease-specific patient groups, and varying effect sizes, not all outcomes of interest have been shown to be statistically significant. For example, further data are desirable on the use of EPT in male index cases. The available data do not support the routine use of EPT in the management of trichomoniasis, and no published data support the use of EPT for chlamydial infection or gonorrhea in men who have sex with men (MSM). Although substantial numbers of adolescents were included in the available trials, there is little experience in patients <18 years old.

Issues in Implementation of EPT

Among several pragmatic issues that will influence implementation of EPT as an STD prevention strategy, a dominant one is the possibility of undetected STD in partners. The potential for undiagnosed pelvic inflammatory disease (PID) is of concern when EPT is used to treat the female partners of men with gonorrhea or chlamydial infection. Therefore, EPT intended for female partners should be accompanied by warnings about the symptoms of PID and advice that women seek medical attention in addition to accepting treatment. Undiagnosed gonorrhea and chlamydial infection are common in the partners of women with trichomoniasis, and undiagnosed HIV infection and other morbidities have been found in many partners of STD-infected MSM.

The legality of EPT is uncertain in some states and overt statutory impediments exist in others; the practice is clearly legal only in a few states. The medicolegal ramifications may be uncertain in the event of adverse outcomes in the recipients of EPT. Other barriers include direct and indirect costs, including limitations on third-party insurance coverage; missed opportunities for prevention counseling of partners; risks of allergic reactions and other adverse drug effects; administrative barriers; privacy issues; and the attitudes and beliefs of health care providers and agencies about the practice.

Conclusions

Both clinical and behavioral outcomes of the available studies indicate that EPT is a useful option to facilitate partner management among heterosexual men and women with chlamydial infection or gonorrhea. The evidence indicates that EPT should be available to clinicians as an option for partner management, although ongoing evaluation will be needed to define when and how EPT can be best utilized. EPT represents an additional strategy for partner management that does not replace other strategies, such as standard patient referral or provider-assisted referral, when available. Along with medication, EPT should be accompanied by information that advises recipients to seek personal health care in addition to EPT. This is particularly important when EPT is provided to male patients for their female partners, and for male partners with symptoms. Existing data suggest that EPT has a limited role in partner management for trichomoniasis. No data support its use in the routine management of syphilis, and there is no experience with EPT for gonorrhea or chlamydial infection among MSM.

INTRODUCTION

Assuring treatment of infected persons' sex partners has been a central component of prevention and control of bacterial STDs in the United States for six decades, since the concept was introduced in the United States by Thomas Parran and systematic efforts were implemented for the prevention of syphilis under Parran's leadership of the U.S. Public Health Service in the 1940s.[1] In general, treatment has been recommended for all partners sexually exposed to the infected index case within a specified time interval in order to prevent morbidity in the partners and curtail transmission. Usually treatment was preceded by clinical evaluation, diagnostic testing, and education or formal counseling, and attendance at traditional clinical facilities was required. Initially developed as a strategy for control of syphilis, such partner management came to be widely recommended for gonorrhea, chlamydial infection and, most recently, human immunodeficiency virus (HIV) infection.[2,3]

Several strategies have been employed to facilitate clinical assessment and treatment of partners, as indicated in the Centers for Disease Control and Prevention's Program Operations Guidelines.[2] With *provider referral*, partners are directly contacted, usually by telephone or in person, by the index patient's health care provider or by a disease intervention specialist (DIS) or other outreach worker on behalf of the provider. Under *patient referral*, also called *self referral*, the index patient assumes primary responsibility to notify and refer his or her partners at risk. These approaches may be combined. For example, *conditional referral*, also called *contract referral*, describes patient referral supplemented by provider referral, such as a telephone reminder, for partners who do not respond within a specified time. The term *dual referral* also has been used, particularly in the context of HIV partner management, to describe joint referral by the patient and a public health professional.[3] Patient referral also can be supplemented by various mechanisms to assist the index patient in notifying his or her partners; for example, *card referral* means providing patients with appointment cards to deliver to partners.

Despite extensive use, the contribution of partner management to overall STD prevention and control has been difficult to ascertain. Success has been evaluated largely by analysis of process indicators, such as numbers of partners elicited and the number brought to treatment. By these measures, provider referral strategies generally have been most effective.[4-6] Provider referral is widely considered to have contributed significantly to control of syphilis, with a 1990s trial providing estimates of process effectiveness,[7] but the efficacy of traditional partner management in assuring treatment of the partners of persons with gonorrhea or chlamydial infection remains problematical and their contribution to prevention and control uncertain. Social network approaches for management of the partners of persons with syphilis or HIV infection have shown substantial promise in retrospective evaluations,[8,9] but have not been studied for chlamydial infection, and may be too costly for routine use in most settings. A single prospective evaluation of network techniques to enhance interviews and analyze data uncovered more syphilis cases than would have resulted from contacting only the sex partners of infected persons.[10]

Most STD cases in the United States are diagnosed and treated in the private sector by primary care providers,[11] but the available data on partner management are dominated by analyses in patients attending STD clinics or other public health clinics who often may not

be representative of most infected persons. Except for syphilis, most health departments make little direct effort in partner management for persons with STDs treated in the private sector.[12,13] The Institute of Medicine described STD partner management in the United States as inadequate, inefficient, and in need of redesign.[14]

Anecdotal reports have long suggested that some clinicians selectively arrange for treatment of partners without referral or examination, typically by providing the index patient medication for his or her partner(s) or by writing a prescription to be delivered by the patient to the partner. This practice is generally believed to have been particularly widely used for the treatment of the male partners of women with vaginal trichomoniasis.[*] Nevertheless, public health and prevention experts have typically insisted that treatment for partners of persons with gonorrhea, chlamydial infection or syphilis be administered only through direct clinical intervention. However, as the inadequacy of resources for provider referral and the modest success rate of patient referral in assuring notification and treatment of partners became apparent, streamlined approaches to partner management became the subject of increasing attention.

This document reviews the evidence for use of *expedited partner therapy* (EPT), defined as treatment of partners without an intervening personal assessment by a health care provider. EPT may be implemented by any of several methods. The usual method in many settings, and the one used predominantly to date, is *patient-delivered partner therapy* (PDPT), wherein clinicians provide their patients with drugs intended for the partners, prescribe extra doses of medication in the index patients' names, or write prescriptions in the partners' names. Other potential means to achieve EPT include non-prescriptive arrangements with cooperating pharmacies, retrieval of medication by partners at public health clinics or other venues, or delivery of medication to partners in non-clinical settings by public health workers.

[*] There are several possible reasons that the practice gained currency for trichomoniasis in particular. For many years trichomoniasis probably was not widely understood by many clinicians to be an STD, despite the conflict of that perception with the practice itself. Until the 1980s, gonorrhea typically required penicillin by injection and chlamydial infection was virtually unknown, so that trichomoniasis was the only commonly diagnosed STD that could be managed with single doses or short courses of oral antibiotic. Further, some clinicians may have believed that local or state health departments would assure treatment of the partners of patients with reportable STDs, but not trichomoniasis.

CURRENT PRACTICES

Traditional Partner Management

To estimate the scope of attempted provider referral for common STDs by public health departments, Golden et al. surveyed 78 metropolitan health departments that collectively represented the 50 cities in the United States with the highest rates of at least one reportable bacterial STD (gonorrhea, chlamydial infection, syphilis) and the 50 metropolitan areas with the highest reported rates of AIDS.[12,13] Sixty health departments (77%) submitted usable responses. Of 8,492 cases of infectious syphilis reported to these health departments, in 7,583 cases (89%) public health authorities attempted to assure treatment of the patients' sex partners. By contrast, the responding health departments attempted to identify and contact the partners of 17% of 139,287 reported cases of gonorrhea and 12% of 228,210 persons with chlamydial infection. When partner management was attempted for persons with gonorrhea or chlamydial infection, patient referral was the predominant model employed. Forty-one health departments (68%) made no attempt to notify or contact the partners of patients treated for gonorrhea outside public health clinics, and 46 (77%) made no such attempt for the partners of persons with chlamydial infection. The survey respondents cited lack of sufficient personnel and other resources as the dominant reason for low partner management coverage.[12]

Most health care providers advise their patients with STD to notify their sex partners. St. Lawrence et al. reported on the practices of a national probability sample of 4,223 physicians in 5 specialties that report most STD morbidity in the United States (general or family practice, internal medicine, pediatrics, gynecology-obstetrics, emergency medicine).[15] Eighty-eight percent of the respondents were in private practice and the survey had a 70% response rate. Almost 82% of respondents reported that they advised their infected patients to notify partners of exposure to gonorrhea or chlamydial infection and 9-11% collected partner information to send to a health department; only 4% attempted provider referral. In another analysis of the same national probability sample, Hogben et al.[16] found that most physicians in the U.S. were willing to report STD cases to their local health departments, but most respondents believed that provider referral is no more useful than patient referral in assuring partner treatment and were less supportive of provider referral by health departments than of other partner management strategies. Among 150 private sector providers in King County, Washington who had reported $\geq$1 case of chlamydial infection in the preceding year, 135 (90%) said they told their patients that their sex partners required treatment, and 72 (95%) of 76 patients acknowledged that they had been so informed.[17] Twenty-six providers (17%) were confident that all partners at risk had been treated.

Thus, patient referral is the dominant mechanism employed in the U.S. to assure treatment of the partners of persons with chlamydial infection or gonorrhea. The proportion of partners who actually receive treatment or other direct clinical services is difficult to ascertain. Table 1 summarizes the results of 7 studies conducted in the United States and western Europe that reported the success of various patient referral strategies conducted by public health personnel to achieve treatment of partners exposed to gonorrhea or chlamydial infection.[18-24] One study reported that 29% of partners were successfully treated; the

remaining studies reported success rates from 49% to 59%. The proportion of partners who respond to patient referral as practiced by most providers, without the involvement of public health personnel, is unknown. However, the available data suggest that roughly half of all partners of persons with gonorrhea or chlamydial infection receive treatment.

Expedited Partner Therapy

Emerging data indicate that many providers in the United States selectively employ EPT for gonorrhea and chlamydial infection and that some do so routinely. Hogben et al.[25] analyzed the responses of the national sample of physicians described above[15] to questions about the providers' partner management practices (Figure 1). Among 2,538 physicians who reported treating at least one patient for chlamydial infection in the preceding 12 months, 56% had managed at least one partner by PDPT and 15% "usually" or "always" did so. The results were similar for gonorrhea, with 50% of providers reporting use of PDPT and 11% reporting PDPT as their usual or universal approach to partner management. The investigators estimated that PDPT had been employed in the management of 9% to 15% of the respondents' patients with gonorrhea and 13% to 20% of those with chlamydial infection.

Four geographically limited surveys also have addressed the practice of EPT. Among 111 Connecticut and Rhode Island physicians, 48% indicated favorable attitudes toward PDPT, 50% had employed the practice, and 6% reported using PDPT "frequently".[26] Of 150 providers surveyed in King County, Washington, 57% had employed EPT for chlamydial infection in the preceding year and 21% reported doing so at least half the time, although only 5% of the providers had done so for their most recently diagnosed cases.[17] In a stratified random sample of 708 physicians and 805 nurse practitioners in California undertaken soon after legislation was adopted to legalize EPT for chlamydial infection, EPT was reported substantially more frequently than in the preceding studies; about half the respondents reported "usually" or "always" using EPT for their patients with chlamydial infection, primarily by providing index patients with prescriptions for their partners.[27] Finally, according to preliminary analysis of a survey of providers in New York City,[28] approximately half the respondents had ever used PDPT and 27% reported doing so "frequently." In the New York survey, an atypically high proportion of providers (24%) reported that they directly contacted their patients' partners (provider referral).[28]

Collectively, the national survey and two of the regional ones suggest that roughly half of U.S. clinicians who treat STD cases use EPT selectively and that 5% to 10% do so frequently or as their standard approach to partner management. EPT may be used more frequently in California than elsewhere, perhaps because the survey was conducted amid publicity about recent legalization of the practice for chlamydial infection. New York City providers apparently use EPT more frequently than in most regions but less frequently than those in California.

RESEARCH IN EXPEDITED PARTNER THERAPY

Preliminary Studies

The first published study with data on EPT was a retrospective analysis of the prevalence of *Chlamydia trachomatis* within 12 weeks of treatment for chlamydial infection in Swedish women (Figure 2).[29] Among 372 women in whom no effort was made to identify or treat partners, 38 (10.2%) had recurrent or persistent infection. Infection was present in 84 (8.4%) of 997 women told to refer their partners without further follow-up (patient referral), and in 31 (4.5%) of 645 women who were told to refer partners followed by reminders when partners failed to appear (conditional referral). Among 167 women managed with PDPT, 3 (1.8%) had persistent or recurrent infection. Although the partner management strategies were not randomly assigned and provider selection probably influenced the results, this report offered the first evidence that EPT might hold promise for partner management in women with chlamydial infection.

Kissinger et al. analyzed reinfection rates in 256 women with chlamydial infection treated at an urban STD clinic, of whom 178 were re-tested a mean of 17.7 $\pm$ 7.7 months later.[30] The annualized rate of reinfection was 12% among 43 women managed with PDPT, compared with 22% of 135 managed by card-enhanced patient referral (odds ratio [OR] 0.37, 95% confidence interval [CI] 0.15-0.97, P <0.05). In Uganda, Nuwaha et al. undertook a randomized controlled trial (RCT) of PDPT compared with card-enhanced patient referral in STD clinic patients given syndromic management for urethral or vaginal discharge.[31] After 2 weeks follow-up, index patients managed with PDPT reported that 176 (74%) of 237 identified partners had received treatment, whereas 79 (34%) of the 234 partners identified by control patients attended the clinic to be treated. Although the investigators reported these outcomes as significant in favor of PDPT (OR 2.44, 95% CI 1.95-3.07), the differences in ascertainment of partner therapy—index case report vs. partner attendance at a clinic—make comparison difficult and the validity of the outcome uncertain.

Randomized Controlled Trials: Biomedical Outcomes

Four RCTs comparing EPT with traditional partner referral strategies, funded wholly or in part by CDC, have been conducted in the United States among patients with gonorrhea, chlamydial infection or trichomoniasis.[32-35] The prevalences of persistent or recurrent infection in index cases at follow-up are summarized in Table 2.

Multicenter Study of Chlamydial Infection in Women

Schillinger et al.[32] conducted a trial of PDPT compared with patient referral in women with uncomplicated chlamydial infection from 1996 to 2000 in 6 metropolitan areas, including San Francisco, California; Seattle, Washington; New Orleans, Louisiana; Birmingham, Alabama; Indianapolis, Indiana; and urban southern California (Long Beach, Torrance and Los Angeles). Patients were diagnosed in family planning, teen health, primary care, and STD clinics, and emergency departments. Initial chlamydial infections were diagnosed by various tests in routine use at the participating clinics, and follow-up infections were

determined by nucleic acid amplification tests (NAAT) (specifically, ligase chain reaction [LCR] or polymerase chain reaction [PCR]) testing of urine specimens. A total of 1,787 eligible subjects were randomly assigned either to partner management by PDPT with single doses of 1.0 g azithromycin (for up to 4 partners) or to patient referral. In both groups the subjects were counseled to tell their partners about exposure and to encourage the partners to seek treatment. Those in the PDPT arm were provided with packets for delivery to their partners that contained powdered azithromycin, instructions on drug reconstitution and administration, advice about possible adverse effects and to abstain from sexual intercourse until 7 days after treatment, and a fact sheet about chlamydial infection. Control subjects, but not those in the PDPT arm, were provided with a list of clinics where their partners could obtain cost-free care.

Follow-up visits were scheduled 1 month and 4 months after enrollment. At least 1 follow-up visit was completed $\geq$3 weeks after treatment in 728 (82%) of 887 patients assigned to PDPT and 726 (81%) of 900 controls.[32] The control and intervention groups were similar demographically and in several behavioral measures. Women found to be infected at the first follow-up visit were not followed thereafter. At the first follow-up visit, *C. trachomatis* was identified in 37 women (5.1%) in the PDPT group and 54 (7.4%) of those in the patient referral arm. Among women who were chlamydia-negative at the first follow-up and were followed again a median of 13 weeks after treatment, *C. trachomatis* was identified in 50 (11.1%) of 450 women in the PDPT arm and 54 (12.2%) of 443 controls. Thus, the cumulative prevalences of persistent or recurrent infection were 87 (12.0%) of women in the PDPT arm and 108 (14.9%) of controls (OR 0.80, 95% CI 0.62-1.05, P = 0.102). (The analysis assumed that women who tested negative at 1 month and were not followed further remained uninfected.) This effect remained after adjusting for patient age and study center, and the risk of reinfection was not correlated with compliance with the intervention within each study arm. Among women who reported a new sex partner after treatment and before follow-up, those the PDPT arm were more likely to be reinfected than women in the patient referral arm.

Gonorrhea and Chlamydial Infection in Men and Women, King County, Washington

From 1998 to 2003, Golden et al.[33] contacted 7,723 patients with reported gonorrhea or chlamydial infection (among 26,656 reported cases). After excluding 2,471 persons who declined study participation and 2,501 who believed all partners at risk had already been treated, the investigators randomized 2,751 subjects to EPT (N = 1,376) or standard partner management (N = 1,375). Nineteen percent of enrolled subjects were diagnosed in public STD clinics, 23% in other public health clinics, 13% in community or family planning clinics, 12% in hospital emergency departments, and 33% by other clinicians in the private sector. Statistically significant differences between participants and those who declined participation were found in age (mean 23.2 and 25.2 years old, respectively, P<0.001), gender (74% and 64% female, P<0.001), diagnosis with gonorrhea without chlamydial infection (13% and 18%, P<0.001), diagnosis in emergency departments (10% and 6%, P<0.001), and diagnosis in family planning or community clinics (16% and 18%, P = 0.009).

For patients with gonorrhea, EPT consisted of cefixime 400 mg plus azithromycin 1.0 g; azithromycin alone was administered for chlamydial infection. The medications were delivered in “partner packs” that contained drug and written materials with instructions on

drug administration, warnings about possible side effects and allergic reactions, fact sheets about gonorrhea and/or chlamydial infection, and a list of clinics where cost-free STD care was available. In the EPT arm, index patients enrolled in the STD clinic who were able and willing to contact their partners were given partner packs for up to 3 partners. Participants randomized to EPT who were enrolled by telephone retrieved partner packs at pharmacies that had agreed to collaborate in the project. When index patients were unable or unwilling to contact their partners, study personnel contacted the partners and arranged for the partners to retrieve partner packs from the cooperating pharmacies. The standard arm was patient referral for subjects who were willing and able to contact their partners and provider referral by study personnel for others. Index patients or study personnel advised the partners to attend the STD clinic or to visit their own health care providers for treatment, and were provided written materials as in the EPT arm, without the medication-specific information. Index patients in both study arms were followed for interview and for urine NAAT testing for *C. trachomatis* and *Neisseria gonorrhoeae* by NAAT (LCR or transcription mediated amplification [TMA]). There were no significant differences between study arms in the distribution of gonorrhea or chlamydial infection, gender, age, race, ethnicity, type of health care facility where the diagnosis was made, symptoms, number of sex partners, or frequency of condom use in the 60 days before enrollment.

The prevalences of persistent or recurrent infection at follow-up are summarized in Figure 3. Follow-up 3-19 weeks after enrollment was 68% in each arm. The protocol-defined primary outcome of persistent or recurrent infection with either *N. gonorrhoeae* or *C. trachomatis* was found in 92 (9.9%) of 929 patients in the EPT group and 121 (13.0%) of 931 controls (OR 0.76, 95% CI 0.59-0.98, P = 0.04). The reduction in persistent or recurrent infection was greater for gonorrhea (OR 0.32, 95% CI 0.13-0.77, P <0.01) than for chlamydial infection (OR 0.82, 95% CI 0.62-1.07, P = 0.17). Table 3 summarizes the prevalence of infection at follow-up separately for men and women and for each infection. EPT remained independently associated with a lower prevalence of infection with either organism at follow-up (OR 0.7, 95% CI 0.6-1.0) after adjustment for gonorrhea versus chlamydial infection, index patient age, the clinical setting where the diagnosis was made, race/ethnicity, resumption of sex following treatment, and number of partners with whom index patients had unprotected sex since treatment (Table 4). (Factors associated with the outcome on univariate analysis but which were believed to be in the causal pathway for the effects of EPT, such as the index cases' belief that all partners at risk had been treated, were excluded from the final multivariate model.)

Golden et al offered 4 hypotheses to explain the weaker association with chlamydial infection than gonorrhea at follow-up.[33] Three of these (differences between patients with gonorrhea or chlamydial infection in successful delivery of therapy to partners; differences in resumption of sex with untreated partners; and differences in receipt of antibiotic therapy in addition to the initial treatment) were not supported by data from the index case interviews at follow-up. The fourth hypothesis was that chlamydial infections in women may persist following therapy more frequently than do gonococcal infections. Among women with chlamydial infection, 289 (21.8%) of 1,328 who returned for follow-up denied sex with any partner since treatment, as did 38 (18.9%) of 201 women with gonorrhea who were followed. *C. trachomatis* was identified at follow-up in 22 (7.6%) of the 289 subjects who denied sexual exposure since treatment, whereas *N. gonorrhoeae* was found in 1 (3%)

of the 38 female gonorrhea patients who denied sex after treatment (Figure 4). None of 87 men who denied sex after treatment was infected with either organism.

Urethritis in Men, New Orleans

From December 2001 to March 2004, Kissinger et al.[34] enrolled 977 male STD clinic patients with symptomatic urethritis into a 3-arm RCT of PDPT, patient referral, or booklet-enhanced partner referral (BEPR), i.e. patient referral supplemented with a booklet that provided information about gonorrhea and chlamydial infection. Patients were enrolled on the day of presentation, before the diagnosis was bacteriologically confirmed, and the EPT regimen for all patients was azithromycin 1.0 g plus either cefixime 400 mg or ciprofloxacin 500 mg. Subsequent diagnostic testing documented gonorrhea alone at enrollment in 54.5% of subjects, chlamydial infection alone in 15.0%, and both infections in 5.9%; neither infection was found in the remaining 25%. Seven hundred seventy men (79%) returned for follow-up 2-8 weeks after enrollment, but testing for *N. gonorrhoeae* and *C. trachomatis* was available for only 289 men (37.5%), attributed by the authors to multiple factors, including patients' fears that testing for illicit drugs would be conducted on urine. The subjects tested were similar to those not tested in all demographic and behavioral characteristics measured at baseline and in the proportion who had sex with a new partner since treatment (14% of those who permitted testing and 13% of those who did not). Follow-up tests were permitted by 43% of men randomized to BEPR compared with 33% of those managed with EPT or standard partner referral ($P < 0.05$). Testing at follow-up was accomplished by the strand displacement NAAT of urine in 242 subjects, and in 47 men by non-amplified DNA probe test on urethral swab specimens.

The results are summarized in Table 2. For subjects with either chlamydial infection, gonorrhea or both, infection was present at follow-up in 35 (43%) of 82 men in the patient referral arm (referent), 20 (23%) of 87 managed with PDPT (adjusted OR 0.38, 95% CI 0.19-0.74), and 16 (14%) of 112 in the BEPR arm (adjusted OR 0.22, 95% CI 0.11-0.44). Compared with patient referral, the reduction in infection prevalence at follow-up in the PDPT arm was similar for gonorrhea (OR 0.34, 95% CI 0.13-0.86) and chlamydial infection (OR 0.46, 95% CI 0.13-0.87). Using an intention-to-treat mode, reinfection rates for subjects in both the PDPT and BEPR conditions remained significantly lower than in the control condition. In an analytic model in which all untested men were assumed to be uninfected at follow-up, the prevalences of persistent infection were 5.8% for PDPT, 4.6% for BEPR, and 12.3% for subjects managed with standard patient referral ($P<0.01$).[34]

Trichomoniasis in Women, New Orleans

From 2001 to 2004, Kissinger et al.[35] conducted a trial of PDPT in 463 women with vaginal trichomoniasis in an STD clinic. PDPT with single doses of metronidazole 2.0 g was compared with patient referral and BEPR, as described above. Infection at baseline and follow-up was diagnosed by culture of *Trichomonas vaginalis*. The prevalences of infection at follow-up are summarized in Table 2. Among 376 women followed 3-7 weeks after enrollment, persistent or recurrent trichomoniasis was documented in 8 (6%) of 126 women in the patient referral group (referent), 12 (9%) of 128 patients randomized to PDPT, and 11 (9%) of 122 in the BEPR arm ($P = 0.6$). The results were not substantially different when controlled for several demographic and behavioral variables. The investigators hypothesized that the absence of measurable differences in treatment

Table 2

Randomized Controlled Trials in the United States: Persistent/Recurrent Infection

Trial	Setting and Study Population	Study Design	Intervention and Control	Persistent/Recurrent Infection Rate
CDC Project 455, B2 Schillinger et al. *Sex Transm Dis* 2003;30:49-56	• Multi-center (6 cities) • 1996- 2000 • N=1,787, 81% followed • Women age 14-34 • Primary care, FP, teen, STD, ED	• **Uncomplicated CT** (without GC) • 1.0g azithromycin DOT • 21 days – 3 months • Urine PCR/LCR	• PDPT to maximum 4 partners • Control = patient-referral (verbal and written)	• Control 108/726 (14.9%) • EPT 87/728 (12.0%) **OR = 0.80 (0.62 – 1.05)** ^{2} = 2.67, p = .102
Seattle Golden et al. *NEJM* 2005;.352:676-685.	• Seattle-King Co., WA • 1998 - 2003 • N=2,751, 68% follow-up • Male 23%, Female 77%, age ≥14 yr (mean 23 yr) • All reporting sites: STD, FP, private, ED	• **Uncomplicated CT** (N=2162), **GC** (450), or **both** (139) • AZM 1.0 g ± CFX 400 mg for CT, GC • Follow-up 3-19 wk • Urine NAAT (LCR or TMA)	• Patient or partner pick-up of drug at 1 of 12 pharmacies • Control = patient-referral • DIS assistance (both arms) if patient unable/unwilling to contact partner	• Control 121/931 (13.0%) • EPT 92/929 (9.9%) **RR = 0.76 (0.59 – 0.98)** ^{2} = 4.39, p = .04 See supplemental tables for separate CT/GC outcomes
New Orleans Urethritis Trial Kissinger et al. *Clin Inf Dis* 2005;41:623-9.	• New Orleans, LA • 2002 - 2004 • N=629, 80% behavioral FU, 30% biological FU • Male age ≥16, median 24 yr • STD clinic	• **Symptomatic urethritis** (61% **GC**, 21% **CT**, 6% **both**) • AZM 1.0 g ± CFX 400mg or cipro 500 mg • GenProbe(enrollment) Urine PCR (follow-up)	• PDPT • Control = patient-referral with brief counseling • Third arm "Booklet Referral"	• Control 35/82 (43%) • EPT 20/87 (23%) • Booklet 16/112 (14%) **EPT v control:** **OR = 0.38 (0.19 – 0.74)** **BEPR v control:** **OR = 0.22 (0.11 – 0.44)**

New Orleans Trichomoniasis Trial Kissinger et al. *Sex Transm Dis* In press.	• New Orleans, LA • 2001 – 2004 • N=282, 87% behavioral FU, 80% biological • Women age 16-44 yr • STD clinic	• **Trichomonal vaginitis** • Metronidazole 2.0 g • Follow-up 21-56 d • Wet mount at enrollment, culture (InPouch) at follow-up	• PDPT to maximum 4 partners • Control = patient-referral with brief counseling • Third arm "Booklet Referral"	• Control = 7/111 = 6.3% • EPT = 11/114 = 9.6% • Booklet = 11/122 (9.0%) **EPT v control:** **OR = 1.58 (0.61 – 4.12)** **BEPR v control:** **OR = 1.47 (0.57 – 3.82)**

Table 5

Variations in Sex Partner Notification as a Function of EPT versus Control Condition among RCTs

Notification Behavior	EPT	Control	RR (95% CI)	P
6-city trial				
Talked to partner and delivered fact sheet (and medications in EPT)	85%	75%	1.14 (1.08 – 1.21)	.01
Seattle trial				
Notified partner of exposure or knew of negative test	77%	78%	0.92 (0.77 – 1.10)	ns
New Orleans (urethritis)[1]				
Talked to partner about infection	71%	48%	--	.001
Gave intervention to partner	70%	48%	--	.001
New Orleans (trichomoniasis)[1]				
Talked to partner about infection	90%	88%	--	ns
Gave intervention to partner	82%	88%	--	ns

[1]Percentages for this study are based on proportion of partnerships, not proportion of cases. Significance levels are based on GEE.

Table 6

Variations in Sex Partner Treatment as a Function of EPT versus Control Condition

Treatment Behavior		EPT	Control	RR (95% CI)	P
6-city trial					
	Reported "very likely" partner took medication[1]	86%	57%	1.50 (1.40 – 1.59)	.001
Seattle trial					
	Reported all partners "very likely treated" or tested negative	61%	49%	1.25 (1.14 – 1.36)	.001
	Reported partner "very likely" treated or tested negative	64%	52%	1.19 (1.12 – 1.27)	.001
New Orleans (urethritis)[2]					
	Reported seeing patient take medication	48%	26%	--	.001
	Partner reported taking medication	56%	34%	--	.001
	Checked partner was treated	64%	42%	--	.001
New Orleans (trichomoniasis)[2]					
	Reported seeing patient take medication	63%	18%	--	.001
	Partner reported taking medication	77%	70%	--	ns
	Checked partner was treated	78%	76%	--	ns

[1]Analysis limited to women with one partner. [2]Percentages for this study are based on proportion of partnerships, not proportion of cases. Significance levels are based on GEE.

Table 7

Variations in Sexual Behaviors as a Function of EPT versus Control Condition

Sexual Behavior	EPT	Control	RR (95% CI)	P
6-city trial				
Reported acquisition of new sex partner	23%	28%	0.83 (0.69 – 0.99)	.05
Seattle trial				
Reported sex with an untreated partner	6%	12%	0.47 (0.34 – 0.65)	.001
New Orleans (urethritis)				
Reported unprotected sex before partner took medication[1]	8%	13%	0.63 (0.40 – 0.99)	.05
Reported unprotected sex with any partner	29%	34%	0.85 (0.66 – 1.10)	ns
New Orleans (trichomoniasis)				
Reported unprotected sex before partner took medication[1]	8%	5%	1.55 (0.62 – 3.88)	ns
Reported unprotected sex with any partner	26%	13%	1.99 (1.20 – 3.34)	.01

[1]Percentages for this analysis are based on proportion of partnerships, not proportion of cases. Significance levels are based on GEE; the effect size is a prevalence odds ratio, not a relative risk.