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.

TABLE OF CONTENTS

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 The available literature and selected unpublished studies were systematically reviewed, and this report provides background for the development of guidance on use of EPT as an option for partner management for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

outcomes may reflect a higher-than-expected treatment failure with single-dose metronidazole in index patients, partners, or both. In addition, the 73% compliance rate for the patient referral (control) arm was substantially higher than expected, requiring a larger than anticipated sample size to document possible differences.

Randomized Controlled Trials: Behavioral Outcomes

The 4 RCTs[32-35] included self-reported behavioral outcomes derived from interviewing subjects who returned for follow-up, and many measures were similar across these studies in both design and procedure. Because of these similarities, and because desirable behaviors of patients and partners are common to all three STDs studied (gonorrhea, chlamydial infection, trichomoniasis), the results in three domains—partner notification behaviors, patients' perceptions that their partners were treated, and sexual behaviors following treatment—were combined.

Partner Notification

In 3 RCTs,[33-35] index patients were directly asked at follow-up whether they had notified their partners. In the other trial, Schillinger et al.[32] asked trial participants whether they complied with the intervention, which required women in both arms to notify their partners that they had been exposed and recommend they be evaluated and treated, and for women in the PDPT arm to deliver medication to their partners. The results from all 4 trials are summarized in Table 5. For PDPT, 505 (85%) of 591 women responded affirmatively, compared with 431 (75%) of 576 controls ($P<0.01$). In the New Orleans urethritis trial,[34] participants were directly asked whether they notified their partners: 500 (71%) of 705 men randomized to PDPT reported that they did so, compared with 280 (48%) of 579 in the patient referral arm ($P<0.001$) and 375 (53%) of 707 men managed with booklet-enhanced partner referral (BEPR) ($P<0.001$).

In the King County study[33] and the New Orleans trichomoniasis trial,[35] the rates of reported partner notification were virtually identical for EPT and standard partner management: 77% of 1,335 EPT patients versus 78% of 1,403 controls in King County; and 90% of 176 for EPT versus 88% of 173 patients in the patient referral arm in New Orleans (Table 5). The rate was 84% of 172 New Orleans women in the BEPR group. None of the observed differences was statistically significant. The especially high rates of partner notification observed in New Orleans (84 – 90%) may have resulted from enhanced counseling in all trial conditions; all participants received expanded instructions and education about the importance of notification that were not routine in the authors' clinic.

Partner Treatment

The participants in all 4 RCTs were asked if they believed their partners were treated, and in two trials they were asked whether they observed their partners take medication (Table 6). Among women with a single partner at enrollment in the 6-city trial, 518 (86%) of 602 subjects in the PDPT arm thought it "very likely" that their partners took the medication, compared with 392 (57%) of 681 women in the patient referral arm who stated it was "very likely" that the partners had been treated ($P<0.001$). In King County,[33] 816 (64%) of 1,268 participants in the EPT group and 732 (52%) of 1,354 persons randomized to standard management reported that their partners "very likely" were treated ($P<0.001$); and 519

(61%) of 850 EPT patients versus 435 (49%) of 888 controls reported that all partners at risk had been treated (P<0.001).

In the New Orleans urethritis trial[34] the subjects managed with PDPT reported compliance with the intervention for 70% of their partners, compared with 48% of the partners of men in the patient referral arm (P<0.001) and 58% of those in the BEPR arm (P<0.01). The index cases in the PDPT arm reported that 56% of their partners said they took medication, compared with 34% for patient referral and (P<0.001) and 44% for BEPR (P<0.01).[34] Among women with trichomoniasis studied in New Orleans,[35] the patients randomized to PDPT observed 63% of their partners take the drug, compared with 18% for patient referral (P<0.001) and 20% in the BEPR arm (P<0.001). However, in the same trial women randomized to PDPT were no more likely than those in the standard management group to report that their partners said they took medication (77% vs. 70%, P = NS). Women in the BEPR condition reported that only 58% of their partners said they took their medications (P<0.01 compared with PDPT).[35]

Sexual Behavior Following Treatment

Schillinger et al.[32] asked their study subjects whether they had acquired new sex partners between treatment and follow-up; 167 (23%) of 728 women in the PDPT arm had done so, compared with 201 (28%) of 726 randomized to patient referral (P<0.05) (Table 7). In the King County study,[33] 51 (5.8%) of 886 participants randomized to EPT had sex following treatment with ≥1 partner who had neither been treated nor tested and found to be negative for STDs, compared with 110 (12.2%) of 902 controls (OR 0.5, 95% CI 0.3-0.6, P<0.01) (Table 7).

Although the two New Orleans trials studied the same interventions, significantly different sexual behavior outcomes were observed for men with urethritis and women with trichomoniasis (Table 7).[34,35] Men managed with PDPT reported unprotected sex before partner treatment with 28% of their partners, compared with 37% of partners of men in the patient referral arm (P<0.05), and 35% of partners of men in the BEPR arm (P = NS).[34] Among women with trichomoniasis, the comparable outcomes were 8% for PDPT, versus 5% for the patient referral arm (P = NS) and 6% for BEPR (P = NS).[35] After treatment, 29% of men managed with PDPT reported unprotected sex during the follow-up period with their partners, compared with 34% of men in the patient referral arm and 37% of men in the BEPR arm (P = NS). By contrast, 26% of women with trichomoniasis randomized to PDPT reported unprotected sex during follow-up with their partners, versus 13% of women managed with patient referral (P<0.01) and 16% of women managed with BEPR (P<0.05).

Randomized Controlled Trials: Cost Effectiveness

A retrospective cost effectiveness analysis[36] was conducted based on the results of the 6-city trial.[32] Providing PDPT for all partners, which was the most effective method of treating the male partners of women enrolled in the study, was the model that resulted in the fewest number of cases of PID in the index women. When the costs of averted sequelae were considered, PDPT was cost-saving compared either to standard patient referral, or to a modeled strategy of selective PDPT in which medication was assumed to be provided for delivery to only those partners women believed unlikely to seek care. When considering

only program costs, i.e. excluding the costs of sequelae, PDPT was slightly more expensive than either patient referral or the selective PDPT strategy, because an individual clinic or program typically does not realize the cost savings that result from preventing sequelae. The program cost of PDPT per index patient was higher per index patient ($32) than the alternative of standard patient referral ($28) or the modeled option of selective EPT ($28). However, because treatment rates were higher, EPT was less costly per infected partner treated ($82 versus $137 and $130, respectively). EPT was cost-saving compared to the alternatives when costs of averted sequelae were included in the analysis.[36]

Cost effectiveness analyses[37] were incorporated prospectively into the King County and New Orleans trials of EPT for chlamydial infection and gonorrhea.[32,33] Literature estimates were used for the costs of sequelae, the proportions of other partners likely to be infected, and the costs of unobserved patient visits to health care providers. Cost effectiveness was analyzed from programmatic and health care systems perspectives. In the King County trial.[33] Personnel costs were derived from prospective records of the time spent by study personnel in contacting providers, patients and pharmacies, and for related administrative work; these variables were designed to mimic those anticipated in implementation of partner management in a typical health department. EPT was found to be cost-saving compared to standard partner management as practiced in the trial (patient referral or provider referral, depending on the subjects' willingness and ability to personally contact their partners), and remained cost-saving whether or not the costs of sequelae averted were included in the analysis. Because public health personnel or resources are not involved in partner management for most patients with gonorrhea or chlamydial infection treated in U.S. health departments,[12] the analysis was repeated without these expenditures. The programmatic cost of EPT was $200 more per additional infected partner treated than for standard patient referral or provider referral. When the costs of sequelae averted were included in the analysis, EPT was cost-saving compared to the low-cost referral model that had been adjusted for public health expenditures for male index patients, but not for female index patients. In any particular program, the latter figure would be highly sensitive to the proportion of patients managed by patient referral, provider referral, conditional referral, or other mechanisms.[37]

In the New Orleans urethritis trial,[34] the program cost of EPT per index patient ($60) was found to be lower than the equivalent costs for standard patient referral ($81) or booklet-enhanced partner referral (BEPR) ($79).[37] The cost per infected partner treated was $86 for EPT, compared with $193 for standard referral and $176 for BEPR. The difference was primarily the result of reduced numbers of health care visits by partners managed by EPT. EPT remained substantially less costly than the control interventions after adjustment for the costs of averted sequelae.[37]

IMPLEMENTATION ISSUES

Numerous practical issues will influence implementation of EPT and its priority compared with traditional partner management strategies. Except where indicated, this discussion addresses EPT for chlamydial infection and gonorrhea.

Special Populations

The 4 available RCTs and other evaluation studies are largely limited to heterosexual adult men and women, whereas EPT may be used for other populations diagnosed with STD, such as men who have sex with men (MSM), pregnant women, and adolescents. No data are known to exist on EPT for gonorrhea or chlamydial infection among MSM. The rates of syphilis, gonorrhea and probably of chlamydial infection in MSM are substantially higher than in most heterosexual populations and have been rising rapidly in all industrialized countries.[38] All partner management strategies have variable success in this population because of high rates of partner change and anonymous partnerships, which would challenge the efficacy of EPT. Further, it is likely that high prevalences of co-morbidities, including HIV infection, other STDs, substance use, and psychological impairment favor traditional partner management over EPT in MSM.

Pregnant women were not separately analyzed in the available trials of EPT. Because of potential adverse effects of gonococcal or chlamydial infection on the course of pregnancy and neonatal health, preventing reinfection may be a higher priority than in nonpregnant women. On the other hand, most pregnant women have ready access to health care and many are highly motivated to protect the health of the fetus, factors that are likely to enhance the success of traditional partner management and might reduce the role of EPT.

Improved partner management is a high priority among heterosexual adolescents,[39,40] among whom the rates of gonorrhea and chlamydial infection in females outstrip those of all other age groups.[41] Recent data on partner notification in teens assessed dispositional correlates of success, such as self-efficacy and relationship quality.[24] No studies have explicitly addressed EPT in predominantly adolescent populations. Slightly over half the patients in the 6-city RCT of women with chlamydial infection were aged 14-19 years, and the results were not materially different than in the study population as a whole, with prevalences of infection at follow-up of 13% of in the EPT arm and 17% of controls (P = 0.09).[32] However, few subjects were $\leq$16 years old, and useful data are lacking on the efficacy of EPT in young teens.

Other Sexually Transmitted Diseases

In many settings, EPT may be a consideration in partner management for STDs other than those studied to date. Partners of patients with NGU, MPC, or PID often are treated before the results of diagnostic tests are available, and some providers likely will use EPT without knowledge of microbiologic etiology. The utility of partner treatment in reducing morbidity in partners or preventing reinfection has not been established for nonchlamydial NGU or MPC. Uncertainty about how to manage partners is an important reason clinicians are encouraged to test all patients with NGU, MPC, or PID for *N. gonorrhoeae* and *C.*

trachomatis. Syphilis requires injection therapy with benzathine penicillin G, precluding PDPT and most other EPT strategies. Azithromycin may have promise as a single-dose or two-dose oral option for treatment of persons with infectious syphilis and their partners,[42,43] and was transiently used by some health departments as PDPT for MSM with syphilis.[44] However, high and rising rates of azithromycin-resistant strains of *Treponema pallidum* and substantial rates of treatment failure following azithromycin therapy preclude EPT with azithromycin unless and until expanded research establishes the safety and efficacy of such treatment.[45,46] It seems likely that some providers now use EPT in the management of some patients with scabies, pediculosis pubis, and perhaps genital herpes or other STDs, but no data are known to exist on these practices.

STD Co-morbidity in Partners

If partners receiving EPT do not seek evaluation, EPT may incur missed opportunities for diagnosis and therapy of STDs that would be detected by personal evaluation of the partners. Stekler et al.[47] reviewed the medical records of 4 urban STD clinics (Baltimore, Birmingham, Denver and Seattle) to determine the prevalence of STDs in persons named as partners of persons who gave their reason for clinic attendance as sexual contact with persons who had gonorrhea, chlamydial infection, NGU or trichomoniasis (Table 8). The STD contact histories were self-reported, without corroboration by record review or by other methods. Among 8,623 patients, 28 (0.3%) had infectious syphilis; 24 of these were in a single clinic (Baltimore), where the 1.1% prevalence of syphilis was substantially higher than in the other clinics. Infectious syphilis was present in 8 (1.7%) of 473 MSM. Among female partners of men with gonorrhea, chlamydial infection or NGU, acute PID and trichomoniasis were diagnosed in 3.8% in 4.9%, respectively. Previously undiagnosed HIV infection was present in 19 (0.4%) of 4,716 heterosexual men and women and 13 (6%) of 207 MSM. Among 785 male partners of women with trichomoniasis, 81 men (10.3%) had gonorrhea or chlamydial infection; in Birmingham the prevalence was 15%.

STD contact was self-reported, and the clinics' databases do not systematically record patients' histories of contact with multiple STDs, factors that limit the interpretation of this study. Another important limitation is that patients who attend STD clinics as partners of persons diagnosed with STD probably are not representative of partners who do not seek care, or partners who seek care in venues other than STD clinics.

Effects on Bacterial Ecology and Antimicrobial Resistance

The recipients of EPT have indications for antimicrobial therapy. Nevertheless, a substantial increase in relatively unsupervised antibiotic usage might raise concerns about the effects on bacterial ecology and antimicrobial resistance. However, the incremental effect of EPT on overall antibiotic use likely would be small. For example, about 55 million prescriptions for azithromycin and other macrolide antibiotics are written in the US annually.[48] Even if azithromycin could be successfully administered through EPT and other means to one sex partner for each of 3 million estimated annual cases of incident chlamydial infection, the increment in macrolide prescriptions would approximate 5%; the actual increment in macrolide use would be much smaller. Similar considerations apply to

single-dose treatment with fluoroquinolones and cephalosporins. Use of doxycycline probably carries a greater risk of adverse ecological outcomes than the other options, because unused medication from multiple-dose regimens undoubtedly increases the potential for unsupervised later use.

Adverse Effects of Drugs

Drug toxicity and allergic reactions in partners treated without direct medical supervision are potential problems for all drugs likely to be used for EPT in managing patients with chlamydial infection, gonorrhea or trichomoniasis. Less serious but more frequent adverse outcomes consist primarily of transient gastrointestinal intolerance. Delivery of dual therapy active against both gonorrhea and chlamydial infection increases the risk of adverse reactions and drug intolerance. Doxycycline and the fluoroquinolones carry theoretical risks for adverse effects in pregnant women or the fetus, but the actual frequencies of fetal and pregnancy-related morbidity are low. Metronidazole carries risks of gastrointestinal intolerance, allergic reactions, and disulfiram-like reactions in association with alcohol ingestion. The potential for reducing the frequency of adverse effects represents a particular advantage of EPT strategies that depend on delivery of drug by pharmacies, whether by written prescription or other means.[49]

Missed Opportunities for Prevention Counseling

Compared with personal evaluation in a health care setting, treatment by EPT represents a missed opportunity for professional counseling of patients' sex partners, and there is broad consensus that partners who are willing and able to attend for personal care should be encouraged to do so. However, few data are available to judge the prevention efficacy of such counseling, especially when provided by typical primary care providers, or to document that its prevention benefit outweighs that which might accrue through educational literature that might accompany EPT or counseling by a pharmacist; or the relative efficacies, on a population level, of such counseling compared with overall enhanced partner treatment. McCree et al. encouraged pharmacists to embrace counseling and educational responsibilities related to EPT, as an initial interface between sex partners and the health care system.[49] One facet of pharmacy-based counseling would be to encourage recipients of EPT to seek medical evaluation. An expanded role of pharmacies in STD partner management is consistent with increasing involvement by pharmacists in preventive medicine through blood pressure monitoring, immunization, provision of emergency contraception, and other initiatives.

Legal Status of EPT

Providing a prescriptive drug to a patient with whom the clinician lacks an established provider-patient relationship is not legal in some states, and elsewhere may be incorrectly perceived by providers as illegal. Golden et al. surveyed the directors of medical practice boards and pharmacy boards in 2003 in order to assess the legal status of EPT in the 50 states.[50] Usable responses were received from either or both sources from 47 states. In 4 states (Washington, California, Colorado, Tennessee), both respondents stated that EPT is

legal. The practice was classified by both respondents as illegal in 30 states, but many of the respondents expressed uncertainty and stated that the issue had never been directly addressed in their states. The medical and pharmacy board representatives in 3 states (Arizona, Oregon and North Carolina) gave conflicting responses. In 42 states where EPT was not known to be legal, most respondents expressed uncertainty as to whether enforcement action would be taken against providers who pursued the practice.[50]

Medicolegal Concerns

The risk of litigation in the event of adverse outcomes may be elevated (or perceived by practitioners to be elevated) when a practice has uncertain legal status or is outside formally accepted community practice standards. Guidance from authoritative bodies may help determine community standards of care and thereby influence the assessment of medicolegal impediments to EPT.

Funding

When clinicians simply integrate EPT into their existing practices, the primary increased cost may be that of drug therapy per se, which often will be absorbed by index cases or their partners. The importance of this obstacle will vary widely between patients and in various settings. Increasingly comprehensive programs by public health departments, health maintenance organizations, or other agencies will incur additional costs, including expenses incurred in counseling index patients, purchasing drugs, development of educational literature, packaging drugs and counseling aids, administrative expenses incurred by arrangements with pharmacies, personnel time when medications are delivered to patients by public health workers, and others. The cost effectiveness studies undertaken in connection with 3 RCTs of EPT had promising outcomes, suggesting that institutionalized EPT in health department settings likely is cost-saving and probably is a cost effective partner management strategy.[36,37] The expenses of EPT may be modest in relation to the total costs incurred in diagnosis and management of patients with treatable STDs, and in relation to the potential to prevent complications and curtail the spread of infection.[37] Nevertheless, even small incremental costs may cause difficulties for under-funded public health departments, especially those that now expend few resources on partner management for STDs other than syphilis and HIV infection.

The same cost effectiveness considerations are relevant to patients treated in institutionalized settings other than health departments, such as health maintenance organizations and managed care plans. Partner management strategies that reduce risk of persistent or recurrent gonorrhea and chlamydial infection may influence some such agencies and health insurers to finance EPT for their enrollees' sex partners. Others undoubtedly will demur for logistical and administrative reasons or because of medicolegal considerations, in particular perceived liability for adverse effects in non-enrolled patients. Further, there are regulatory impediments to use of patients' third party coverage for partner treatment.

Privacy

Pharmacy laws or policies may require that identifying information be recorded for persons receiving prescription drugs. At the same time, stipulations of the Health Information Portability and Accountability Act (HIPAA), as well as historic concerns for patient confidentiality, may preclude documenting a partner's identity in an index patient's medical record. To surmount this obstacle, some programs have established pharmacy records that are separate from patient records. Recent legislation in Tennessee permits EPT for unnamed partners, presumably facilitating recording of all necessary information in index patients' medical or pharmacy records. In many jurisdictions providers and health care agencies are likely to require guidance on implementation of EPT while guarding the privacy of both index patients and partners and to comply with HIPAA.

Drug Delivery and Packaging

PDPT, either of medications per se or of prescriptions, undoubtedly will be the usual mechanism for EPT, especially in the private sector. Acceptance of PDPT for chlamydial infection in San Francisco initially was low,[51] but qualitative research among recipients of PDPT with azithromycin for syphilis in the same setting revealed that professional-appearing (and therefore more costly) packaging enhanced patient acceptance.[44] However, some patients will be unwilling or unable to assist in contacting or treating one or more partners, and optimal use of EPT may depend on partners retrieving drug at pharmacies, health department clinics, or other facilities, or delivery of medications DIS or other outreach workers. There is broad consensus that EPT should be accompanied by written materials that include descriptions of the STD of concern, symptoms of infection, advice that personal evaluation is preferable to self-treatment, sources of STD-related health care, and information about potential adverse effects and allergic reactions. In some settings, packaging and delivery of drugs and accompanying materials may carry significant administrative and financial costs.

Providers' and Health Agencies' Attitudes and Beliefs

It is likely that multilayered attitudinal differences have long existed between most public health agencies' recommendations, some providers' practices, and providers' beliefs about the appropriateness or utility of EPT. Historically, public health experts and agencies have overtly or tacitly condemned EPT, yet some providers employed it frequently and at least half did so sporadically for chlamydial infection or gonorrhea.[25-28] These attitudes and beliefs undoubtedly will influence the acceptance and implementation of EPT. There are other precedents for EPT-like uses of anti-infective drugs for prevention of communicable diseases, as when antibiotics are distributed to persons exposed to invasive meningococcal disease; when entire families are treated for pediculosis or pinworm infestation diagnosed in one member of the household; and when patients and employees of extended health care facilities are treated after diagnosis of a single case of scabies. Nevertheless, some providers may not view these practices as precedents for EPT for STDs. The California experience suggests that many providers who employ EPT for gonorrhea or chlamydial infection do so despite believing it to be suboptimal health care.[27] Endorsement of EPT by

professional societies and organizations may be anticipated in the future, perhaps facilitating provider acceptance.

Administrative Barriers and Organization of EPT

Although EPT is presently in use by some providers at little apparent administrative cost, substantial barriers may exist at the institutional level. To reach large numbers of persons diagnosed with gonorrhea or chlamydial infection, the King County trial of EPT[33] depended on substantial cooperation and coordination between public health and the private sector, involving the health department, numerous health care providers and clinics, the local medical society, and pharmacies.[23] This collaboration itself has been cited as a useful outcome of the study.[52] A demonstration project designed to implement a similar system statewide, and to assess the impact of routine use of EPT on gonorrhea on the incidence and prevalence of infection at a population level, will soon be underway in the state of Washington (Golden MR, personal communication).

Provider Education

Few public health agencies currently employ EPT, and there is great variability in the frequency of use by private health care providers.[17,25-27] It is likely that most providers have not systematically considered the advantages, disadvantages, costs, and barriers associated with various partner management strategies for particular STDs and in various populations at risk. These facts imply a need for a concerted and focused effort to educate providers on all partner management strategies.

Interaction with Other Partner Management Strategies

The resources available and index patient willingness to bring or refer his or her partners for personal evaluation and the availability and expected effectiveness of provider referral will influence implementation of EPT. Some patients will be willing and able to refer their partners for traditional care, with confidence the partners will comply, and in other settings effective provider referral may be available. EPT may have a lesser role in partner management in such settings. Most health departments have insufficient resources to attempt to provide partner services for persons with gonorrhea, but 6 jurisdictions (each with <2,500 annual cases of gonorrhea) of 60 surveyed reported that they attempted to initiate partner services for >80% of persons with gonorrhea.[12] Data are generally not available from those jurisdictions to judge overall effectiveness of partner management, but EPT may have a lesser role for gonorrhea management in those settings than others. Similar data are not available for chlamydial infection.

Retesting for Chlamydial Infection and Gonorrhea

Retesting of women, also called rescreening, is emerging as an important strategy for control of chlamydial infection.[53-55] Some providers might believe that enhanced assurance that partners received treatment reduces the need for retesting, but the results of 3 RCTs of

EPT reviewed in this report reconfirm the importance of retesting women following treatment of chlamydial infection, regardless of the partner management strategy employed, and highlight its probable importance for men with chlamydial infection and both men and women following treatment of gonorrhea.[32-34]

DISCUSSION

Summary and Interpretation of the Randomized Controlled Trials

Persistent and Recurrent Infection Following EPT

In 4 RCTs, the frequency of persistent and recurrent infection following EPT compared to standard partner management was assessed among persons with gonorrhea, chlamydial infection, or trichomoniasis. The effects were largely consistent across the trials, but varied according to disease and gender. In two RCTs that evaluated men with gonorrhea or chlamydial infection to assess treatment of their female partners,[33,34] EPT was associated with reduced rates of reinfection compared with patient referral and/or provider referral. However, the combined sample size of males available for biomedical follow-up is modest. In the King County trial,[33] this information is available for 157 men with gonorrhea and 267 men with chlamydial infection. In New Orleans,[34] persistent or recurrent infection was measured in 289 men with either infection.

In women, the association of EPT with a reduced prevalence of infection at follow-up was weaker for chlamydial infection[32,33] than gonorrhea.[33] In the King County trial, 7.6% of female index cases with chlamydial infection who were treated with azithromycin and denied all sexual exposure after treatment nevertheless were infected at follow-up.[33] By contrast, among patients who denied sex following treatment, only one woman had gonorrhea at follow-up and no man had either infection. Analysis of the determinants of persistent or recurrent chlamydial infection in 5 of the centers (and most of the same clinics) where the 6-city trial[32] was subsequently conducted also suggested a higher than expected rate of persistent infection in women who denied sexual reexposure.[53] Thus, the apparent efficacy of both EPT and the control strategies in preventing reinfection with *C. trachomatis* may have been reduced by a higher-than-expected rate of persistent infection at follow-up. Highly sensitive NAATs were used to detect chlamydial infection in the EPT trials[32-35] and the 5-city cohort study of reinfection that preceded it,[53] whereas culture was employed in most published studies designed to determine the efficacy of azithromycin against *C. trachomatis*.[56] In addition, the therapeutic trials typically followed patients at 3-6 weeks,[56] compared with 6-20 weeks follow-up in the EPT-related studies.[32-35,53] Other evidence also suggests that persistent *C. trachomatis* following treatment with azithromycin may be more common than previously believed.[57]

The single available RCT of EPT for trichomoniasis in women did not demonstrate a significant difference in the prevalence of persistent or recurrent infection compared with either standard or booklet-enhanced patient referral, and mixed results were observed for desirable behavioral outcomes.[35] The trial is limited in its generalizability because the population studied, almost exclusively minority patients of low socioeconomic status in a southern, inner city STD clinic, is poorly representative of many women with trichomoniasis. Further, the control subjects displayed an unexpectedly high success rate of 73% in referring their partners for treatment, perhaps challenging the ability of the study to document differences in outcomes between the study arms. Finally, higher than expected rates of persistent or recurrent infection might have contributed to the outcome. The recommended 2.0 g metronidazole regimen used in the trial cures 90-95% of cases,[58,59]

compared with ≥96% cure rates for the recommended gonorrhea and chlamydial regimens. No studies have assessed the efficacy of metronidazole using maximally sensitive tests of cure such as PCR for *T. vaginalis*,[60] raising the possibility that the actual cure rate is <90% in men, women, or both. Tinidazole may be more effective than metronidazole.[59,61]

Behavioral Outcomes Associated with EPT

All 4 RCTs reviewed incorporated assessment of behavioral outcomes in addition to the primary outcome of persistent or recurrent infection.[32-35] Across the 4 trials, according to interviews of the index cases at follow-up, EPT resulted in higher or equivalent frequencies of partner notification and partner treatment. In 3 of the trials,[32-34] EPT was associated with lower frequencies of behaviors that would risk reinfection, including sexual re-exposure to untreated partners and unprotected sex with new partners. In the trichomoniasis RCT, however, EPT was associated with a greater likelihood of unprotected sex compared with standard management.[35] The generally favorable outcomes associated with EPT were based on self-report by subjects who might have overtly or unwittingly provided desirable responses, but there is no particular reason to believe that this potential bias was systematically associated with EPT compared with the control strategies. Some of the behavioral outcomes, such as patients' reports that they observed their partners ingest the medication and reduced frequency of post-therapeutic sex with untreated partners, undoubtedly are involved in the causal pathway for reduced prevalence of infection at follow-up. These findings give promise that behavioral outcomes may serve as surrogate markers for partner treatment success in less costly future studies that do not rely on prolonged follow-up to measure persistent or recurrent infection.

Generalizability

With rare exceptions, all RCTs raise questions of generalizability: to what extent are the patient populations, interventions and outcomes pertinent to settings other than those represented in the trials? The geographic distribution of the patients studied by Schillinger et al is an important strength of the 6-city trial, especially since PDPT was associated with similarly reduced rates of recurrent or persistent infection in 5 of the 6 study centers and across most subgroups analyzed.[32] Data are not available on the proportion of potentially eligible subjects who were enrolled, how those persons compared with those not enrolled, and how the study population compares with other women infected with *C. trachomatis*. Golden et al.[33] enrolled subjects diagnosed at a broad and well-documented range of clinical settings, with predominant representation from private practices and other non-public clinics, and carefully characterized the study population, demonstrating substantial comparability to subjects who declined participation or were ineligible. However, the trial was undertaken in a single metropolitan area that may not be representative of many jurisdictions where EPT might be employed. For example, although racial and ethnic minorities were well represented in relation to the population of King County, the numbers and population proportions of minorities were small in comparison to those in many geographic areas.

The design of both trials necessarily excluded subjects whose partners already had received treatment, i.e. patients in whom partner management (probably almost exclusively through patient referral) already was successful. This is a particular issue for the King County trial, in which about half the potential subjects were excluded because the index cases believed

all partners at risk had been treated. Thus, the study population probably was biased toward a subset of patients less likely than others to facilitate partner treatment, which might have reduced the apparent efficacy of both EPT and the control strategies. It is likely that fewer patients enrolled in the 6-city trial[32] had an opportunity to inform and arrange for treatment of their partners before enrollment, but the available data do not permit definitive assessment of this possibility.

The New Orleans trials of EPT for urethritis in men[34] and trichomoniasis in women[35] enrolled most patients at the time of diagnosis, before any effort had been made to assure referral and treatment of the subjects' partners. In this respect, the studies may more accurately reflect the implementation of EPT in settings where index case treatment and partner management are undertaken simultaneously, such as public STD clinics. However, both New Orleans patient populations were composed almost entirely of African Americans attending an inner city STD clinic. These patients may be more socioeconomically disadvantaged than many patients who may be offered EPT, especially in the private sector. The failure of many male subjects in New Orleans to provide urine specimens at follow-up, ostensibly because of fears that the specimens would be tested for illicit drugs, may have introduced undetected biases in the analysis of persistent or recurrent infection, and further may suggest particularly high rates of substance use that might challenge the generalizability of the findings.

The 4 RCTs also had limited power to draw conclusions about efficacy for some combinations of disease, gender, and patient characteristics. The available data do not permit definitive evaluation of disease-specific or gender-specific EPT outcomes in relation to potentially important confounders, such as age, socioeconomic status, education, clinical setting, and a variety of sexual behaviors. On the other hand, the consistency of both biological and behavioral outcomes for chlamydial infection and gonorrhea across 3 trials, despite substantial differences in population and study design, provides a measure of assurance that the results are robust and broadly applicable.

Implementation Issues

Of the numerous issues pertinent to systematic implementation of EPT as a partner management strategy, the potential for missed morbidity in partners, the legal status of EPT, and concerns about adverse effects of antibiotics probably are the dominant potential obstacles in most settings.

Missed Morbidity

There is particular concern that EPT in male index cases might foster underdiagnosis and undertreatment of complicated infections in their female partners, especially if women with overt or incipient PID forego medical evaluation. Stekler et al.[47] found that PID was diagnosed in almost 4% of women who gave their reason for attending STD clinics as exposure to men with STD, including but not limited to men with gonorrhea or chlamydial infection. The clinics in the study use clinical criteria for PID similar to those recommended by CDC for presumptive treatment, which are designed to maximize sensitivity and are relatively nonspecific.[54] Therefore, the analysis might have overestimated the prevalence of symptomatic PID. However, it is not known whether a higher or lower proportion of

women who attend STD clinics as contacts of infected men may have complications compared with women who have not yet sought clinical services. Thus, special caution is warranted in use of EPT in men for delivery to their female partners. On the other hand, the potential for missed PID is partly balanced (and may be exceeded) by an overall reduction in PID and its complications that might accrue from improved overall partner management. Similar but less urgent considerations apply to symptomatic male recipients of EPT, who should be encouraged to seek care in addition to (or instead of) accepting treatment.

High prevalences of STD co-morbidity also can be expected in women with trichomoniasis and their partners,[47,62] contributing to caution in use of EPT for trichomoniasis. The reverse observation, a high likelihood of undiagnosed trichomoniasis in the partners of persons with gonorrhea or chlamydial infection,[62] is less relevant to the use of EPT or other partner management strategies. Sensitive diagnostic tests for *T. vaginalis*, such as PCR, are not yet widely available, and most cases of trichomoniasis in partners (and many cases in index patients with gonorrhea or chlamydial infection) will not be diagnosed regardless of the partner management strategy employed. Stekler et al also found a 6% prevalence of undiagnosed HIV infection in MSM who gave STD exposure as their reason for visiting STD clinics,[47] a significant issue in considering use of EPT in this population. Finally, no data are available on the prevalence of non-STD morbidities in partners, such as substance abuse and mental health problems, although it is not clear that other partner management strategies are any more effective in detecting or preventing them.

Legal Issues

The legal status of EPT, whether real or perceived, will affect implementation. Some clinicians apparently use EPT without obvious inhibition based on legal status,[25] but most public health departments and many health care institutions, such as health maintenance organizations and managed care plans, will be constrained from formal institution of EPT until the legal status of EPT has been addressed in their jurisdictions. Health officers in most or all states possess statutory powers to protect and maintain the public's health, and in some states these powers may override laws or policies that apparently conflict with EPT. In others, administrative or judicial rulings may nullify apparent legal barriers, as occurred in the state of Washington (Klopfenstein L, personal communication). However, new legislation may be necessary to establish the legality of EPT, as undertaken recently in California and Tennessee[63,64] and currently under consideration elsewhere. Pharmacy laws may also influence the utilization of EPT. For example, legislation to regulate or curtail online access to prescription drugs may unwittingly place limits on EPT.

Adverse Effects of Antimicrobial Therapy

Although individualized use of EPT for selected STDs apparently has been common for many years, systematic use as a public health recommendation represents a new paradigm for STD prevention. The risk of serious adverse intolerance, toxicity, or allergic reactions is low for the regimens recommended for treatment of gonorrhea and chlamydial infections, and for the drugs that might be contemplated for treatment of other STDs. However, even low risk may influence the acceptance of EPT as a routine procedure by some providers, health maintenance organizations, and public health agencies, largely because of the possible medicolegal implications of adverse events. Development and implementation of guidelines by public health agencies, professional societies, and health care institutions

should influence community standards of clinical care and help to reduce such risks or providers' perceptions of the risks. The success of EPT as an STD prevention strategy also will depend in part on the development and implementation of methods to reduce the risk of adverse effects. Therefore, EPT should routinely be accompanied by information that warns potentially allergic recipients to defer treatment and seek medical attention, and advises partners of the potential side effects of therapy and sources of care in the event of adverse events. At the same time, the likely population-level benefits of improved STD partner management dictate that the risk of adverse events should not in itself preclude use of EPT.

Research Agenda

Review of the available data on EPT revealed numerous gaps in knowledge that must be filled to optimize recommendations and implementation of EPT as a routine partner management strategy. The following list is not comprehensive, and the sequence does not denote priority. Each of the implementation issues implies one or more research needs, as do all the limitations of the existing data cited above.

Therapeutic Efficacy of Regimens Employed for EPT

Systematic research is indicated to confirm and explain the observation of higher-than-expected rates of persistent *C. trachomatis* infection in women. Studies should include extended follow-up of treated patients, treatment with alternate antibiotics, variable regimens of azithromycin and perhaps doxycycline, and associated laboratory-based research. Research also is indicated to elucidate the possible contribution of suboptimal efficacy of single-dose treatment recommendations for trichomoniasis as a factor that may have contributed to the apparent failure of EPT in one trial to modify the frequency of persistent or recurrent infection. Scant data document the efficacy of single-dose metronidazole against trichomoniasis in men, and no studies of therapeutic efficacy in men have used sensitive diagnostic methods, such as PCR, to document cure. Knowledge of the efficacy of the regimens recommended for uncomplicated gonorrhea and chlamydial infection against subclinical or incipient PID would inform strategies to help prevent PID and its complications in the female recipients of EPT.

Organization and Systems for EPT

EPT will continue to be employed by individual practitioners and clinics, but optimal use to maximize prevention efficacy will require coordinated, systematic approaches involving the public health sector, private sector clinicians and agencies, pharmacies, health insurers, and community-based organizations. Organization of such collaborative efforts is the logical domain of state and local health departments. Research is indicated into systematic approaches and organization, including expanded cost effectiveness research. Such a study is soon to be initiated in Washington State (Golden MR, personal communication).

Therapeutic Compliance

Research is indicated on compliance with various models of EPT, including patient delivery of drugs, patient delivery of prescriptions, treatment by public health personnel away from clinical facilities, pharmacy-facilitated treatment and, for each of these circumstances, the influence of direct observation of treatment by the index patient, pharmacist or other

provider. Although most EPT probably will be accomplished primarily with single-dose regimens, compliance with multiple-dose regimens (e.g., doxycycline for chlamydial infection) also is of interest.

EPT for Trichomoniasis

Despite the challenges to successful and safe EPT in partner management for women with trichomoniasis, it is likely that many providers will continue to employ the practice, and further research on the efficacy of EPT is a high priority. Studies should include confirmation of the efficacy of single-dose and short-course therapy with metronidazole or tinidazole in women with vaginal trichomoniasis, as well as assessment of co-morbidities, and should be conducted in broadly representative populations. Expanded information is needed on the efficacy of single-dose metronidazole or tinidazole against *T. vaginalis* infection or carriage in men.

EPT for Etiologically Undefined STDs

Study is indicated on use of EPT for partners of patients with NGU, MPC, PID and perhaps scabies and pediculosis pubis. An important component will include qualitative research among health care providers and patients about the role and implementation of EPT in persons with NGU or cervicitis in the absence of diagnostic tests for *N. gonorrhoeae* and *C. trachomatis*, or while awaiting the results of such tests. In some settings, studies are indicated for use of EPT in chancroid, although this presently is a low priority in the U.S.

Behavioral Research and Surrogate Markers of EPT Success

Substantial behavioral research is indicated to enhance the efficacy and evaluate the performance of EPT as a partner management strategy. Currently available data demonstrate the value of behavioral outcomes and suggest that behavioral markers, perhaps especially those in the causal pathway that results in reduced prevalence of infection at follow-up, might serve as surrogates for prediction of rates of index case reinfection, facilitating the design of future trials with shorter follow-up and at considerably less expense than studies dependent on biomedical outcomes. Future behavioral research also should address the association of various partner management strategies with resumption of sex with treated versus untreated partners, with new partners, and with condom use.

Additional Populations

The high rates and potentially serious consequences of gonorrhea and chlamydial infection in teens <18 years old, pregnant women, and MSM dictate the need for studies of EPT implementation and outcomes in these populations. Studies among MSM may be a particularly high priority, in view of resurgent sexual risks and STD rates and the poor outcomes of standard partner management practices. Research in MSM should incorporate methods to assess the prevalence of previously undiagnosed HIV infection in the recipients of EPT and the response to accompanying advice to seek health care, including HIV testing and counseling.

STD Co-morbidity in Recipients of EPT

The available data on co-morbidity in the sex partners of infected patients were derived from retrospective analysis of patients attending STD clinics with self-described STD exposures. Studies of partners who are offered EPT are indicated to determine the

prevalences of the index STD, other STDs, and other co-morbidities. A particularly high priority is to elucidate the prevalence of overt PID, and ideally of subclinical salpingitis, in female recipients of EPT for chlamydial infection or gonorrhea. Information also is desirable on non-STD co-morbidities, such as substance abuse and psychological impairment.

Development of Patient Education Materials and Counseling Strategies

Systematic research is needed on the formulation and context of written materials to accompany EPT, counseling strategies to enhance communication between index cases with their partners, and the roles of ancillary health personnel and agencies, such as pharmacies and community based organizations. Such research should emphasize not only the development of such counseling and educational materials, but the recipients' immediate and long-term behavioral responses to them.

Effect of EPT on Health Care-seeking Behavior

Studies are indicated to determine the compliance of intended recipients of EPT with treatment and to accompanying advice to seek health care. There should be particular emphasis on women, especially those with symptoms consistent with salpingitis, but such knowledge is needed for the entire range of intended recipients, including heterosexual men, MSM, teens, and women with and without symptoms of complicated infection.

Health Care Providers' Perceptions, Beliefs, and Attitudes

Although several recent surveys document considerable use of EPT by some providers, no systematic data have addressed the determinants of providers' decisions about EPT or other partner management strategies. Similarly, providers' beliefs about what partner services are and are not offered by their local or state health departments might influence their utilization of EPT and the development of local policies, strategies, and options.

Other Research Issues

Most of the EPT implementation issues carry their own implications for research. For example, the only available data on the legality of EPT is based on the personal opinions of survey respondents, and refinement is desirable. The frequency of adverse drug effects in recipients of EPT may be worthy of formal study. Systematic understanding of the attitudes and responses of health insurers would facilitate implementation. Assessment of programs' responses to the cost of EPT, and other experiences in implementation, will inform program development in other jurisdictions. Further research is needed to determine optimal packaging of drugs and counseling materials, and qualitative research is indicated to assess providers' and health agencies' attitudes, beliefs and practices with respect to EPT in particular and STD partner management in general.

CONCLUSIONS

Three RCTs available for analysis and other supporting data indicate that EPT is a useful option to facilitate partner management in heterosexual men and women with chlamydial infection or gonorrhea. This support derives from documented prevention of persistent or recurrent infection one month to 4 months after treatment, and from favorable associations of EPT with the study subjects' reported success in notifying their partners, beliefs that their partners were treated, and reductions in post-treatment sexual behaviors that risk reinfection. Reducing reinfection is particularly important in women because of the risk of PID and its sequelae, and serious outcomes of chlamydial infection and gonorrhea are uncommon in men. Thus, from a clinical perspective, preventing reinfection may be less important in men than women. However, at a population level men generally are more efficient STD transmitters than women, and preventing recurrent infections in men may be important in reducing continued transmission in the community.

Ongoing assessment will be needed to evaluate all partner management strategies. However, the available evidence indicates that EPT is at least equivalent in efficacy to standard partner management for gonorrhea and chlamydial infection; that traditional partner management by public health agencies and health care providers for these STDs is limited in scope; and that the benefits of EPT outweigh the risks. Therefore, EPT should be available to clinicians as an option for partner management for gonorrhea and chlamydial infection. EPT represents an additional strategy for partner management of persons with gonorrhea or chlamydial infection that does not replace other strategies such as standard patient referral and provider-assisted partner referral, when available. Along with medication, recipients of EPT should also receive written advice (and, when possible, personal counseling, such as by a pharmacist) that clinical evaluation is desirable in addition to EPT. This is particularly important when EPT is provided for female partners and for male partners with symptoms. EPT also should be accompanied by information warning recipients not to accept treatment if allergic to the drug or to related compounds, and about common side effects and the appropriate responses to them.

At present, recommendations to employ EPT are not feasible in many settings because of pragmatic issues in implementation, including the uncertain legal status of EPT in some states. The legal and other barriers to implementation of EPT will need to be addressed and resolved at the local or state level by collaboration between individuals, local and state health departments, and other organizations interested in STD prevention. Substantial operational research is indicated to optimize the use of EPT.

The available data do not support routine employment of EPT in the management of women with trichomoniasis, despite its historically frequent use. However, only a single trial of modest size and uncertain generalizability has been conducted. Drug intolerance may be more frequent in treating trichomoniasis than with the regimens used for gonorrhea or chlamydial infection, and STD co-morbidities are especially prevalent in persons with trichomoniasis, further challenging the utility of EPT. Therefore, pending additional data, EPT should be used with caution in managing women with trichomoniasis, but it should remain an option when treatment of partners cannot otherwise be assured.

No data support the use of EPT in the routine management of syphilis, which typically requires injection therapy and for which direct assistance with partner management is

generally available from local or state public health departments. No available data address the efficacy or role of EPT in the management of any STD in MSM, many of whose partners are likely to have undiagnosed HIV infection or other STDs. Experience also is lacking in the use of EPT in the management of patients with etiologically undefined clinical syndromes such as NGU, MPC, and PID.

The available RCTs reinforce existing recommendations for retesting women with chlamydial infection approximately 3 months after treatment, and provide support for extension of routine retesting to men following chlamydial infection and to both men and women with gonorrhea.

GUIDANCE FOR USE OF EXPEDITED PARTNER THERAPY

EPT is at least equivalent to patient referral in preventing persistent or recurrent gonorrhea or chlamydial infection in heterosexual men and women, and in its association with several desirable behavioral outcomes. These conclusions support the following recommendations:

- **Gonorrhea and chlamydial infection in women:** EPT can be used to treat partners as an option when other management strategies are impractical or unsuccessful. Symptomatic male partners should be encouraged to seek medical attention, in addition to accepting therapy by EPT, through counseling of the index case, written materials, and/or personal counseling by a pharmacist or other personnel.
- **Gonorrhea and chlamydial infection in men:** EPT can be used to treat partners as an option when other management strategies are impractical or unsuccessful. Female recipients of EPT should be strongly encouraged to seek medical attention, in addition to accepting therapy. This should be accomplished through written materials that accompany medication, by counseling of the index case and, when practical, through personal counseling by a pharmacist or other personnel. It is particularly important that female recipients of EPT who have symptoms that suggest acute PID, such as abdominal or pelvic pain, seek medical attention.
- **Gonorrhea and chlamydial infection in men who have sex with men:** EPT should not be considered a routine partner management strategy, because data are lacking on the efficacy in this population, and because of a high risk of co-morbidity, especially undiagnosed HIV infection, in partners. EPT should only be used selectively, and with caution, when other partner management strategies are impractical or unsuccessful.
- **Women with trichomoniasis:** EPT is not recommended for routine use in the management of women with trichomoniasis, because of a high risk of STD co-morbidity in partners, especially gonorrhea and chlamydial infection. EPT should only be used selectively, and with caution, when other partner management strategies are impractical or unsuccessful.
- **Syphilis:** EPT is not recommended for routine use in the management of patients with infectious syphilis.

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Table 1

Outcomes of Partner Notification for Gonorrhea and Chlamydial Infection by Patient Referral

Location (year)	Number Index Patients Studied	STI	% Partners Treated	PN procedures and outcome ascertainment
Colorado Springs (1977)[18]	93	GC	54	All patients received a routine follow-up call. Partner treatment status based on confirmed treatment in STD clinic
Colorado Springs (1985)[19]	975	GC	29	"Perfunctory" PN interviewing performed with no follow-up. Partner treatment status based on confirmed treatment or evaluation
London (1994)[20]	254	CT	53	Index patients had ocular CT infection. Treatment status based on confirmed treatment.
Amsterdam (1997)[21]	440	GC/CT	49	Patients given referral cards. Partner treatment status based on confirmed treatment in STD clinic or elsewhere
Houston (2000)[22]	54	GC/CT	55	Partner treatment status based on index patient report. Percentage reflects any partner having been treated
Seattle (2001)[23]	698	GC/CT	51	Partner treatment status based on index patient report
Indianapolis (2002)[24]	241	GC/CT/NGU/TV	59	Partner notification status based on index patient report (treatment outcome not reported)

GC=gonorrhea, CT=*C. trachomatis*, NGU=nongonococcal urethritis, TV=trichomoniasis.

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 3

Persistent or Recurrent Gonorrhea and Chlamydial Infection in the Seattle RCT

Index Case Dx	EPT (%)	Standard (%)	RR (95% CI)
GC or CT	92/929 (10)	121/931 (13)	0.76 (0.59 – 0.98)
Male	13/194 (7)	24/202 (12)	0.56 (0.30 – 1.08)
Female	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)
Male	3/72 (4)	8/85 (9)	0.44 (0.12 – 1.61)
Female	3/107 (3)	11/94 (12)	0.25 (0.07 – 0.83)
Chlamydial Inf.	86/797 (11)	105/798 (13)	0.82 (0.62 – 1.07)
Male	10/132 (8)	17/135 (13)	0.60 (0.29 – 1.27)
Female	76/665 (11)	88/663 (13)	0.86 (0.65 – 1.15)

Note. Table is a reproduction from Golden et al. *NEJM* 2005;352:676-685, with permission from the *New England Journal of Medicine*.

Table 4

Demographic, clinical and behavioral factors associated with persistent or recurrent gonorrhea or chlamydial infection

	Persistent or recurrent STI* N (%)		Unadjusted RR	Adjusted RR
Age:				
< 20	109	(15)	0.7 (0.6-0.8)	0.8 (0.7-0.9)
20-24	68	(11)	per category change	per category change
24-29	22	(9)		
30+	14	(6)		
Gender:				
Male	37	(9)	0.8 (0.6-1.1)	
Female	176	(12)		
Initial diagnosis:				
Gonorrhea only	15	(6)	1.0	1.0
Chlamydial infection only	175	(12)	2.1 (1.2-3.4)	1.7 (0.9-2.9)
Both gonorrhea & chlamydial infection	23	(24)	4.3 (2.4-7.9)	3.4 (1.8-6.4)
Source of STI diagnosis:				
STD clinic	33	(10)	1.1 (0.7-1.6)	
Other public health clinic	73	(17)	1.8 (1.3-2.5)	1.4 (1.1-1.9)
Emergency room	22	(11)	1.2 (0.8-2.0)	
Community Clinic	27	(11)	1.2 (0.8-1.8)	
Other	58	(9)	1.0	
Race/ethnicity:				
White	93	(11)	0.9 (0.7-1.2)	
Black race	75	(12)	1.1 (0.8-1.4)	
Native American / Alaskan Native	10	(9)	0.8 (0.4-1.5)	
Asian / Hawaiian / Pacific Islander	34	(14)	1.3 (0.9-1.8)	
Other race	12	(13)	1.2 (0.7-1.2)	
Hispanic	13	(7)	0.6 (0.4-1.1)	0.5 (0.3-1.0)
Number of sex partners at baseline (last 60 days)				
0-1	126	(11)	1.0	
2	56	(12)	1.1 (0.8-1.5)	
3+	31	(16)	1.5 (0.9-1.9)	
Any sex since treatment				
Yes	182	(13)	2.2 (1.5-3.4)	1.9 (1.1-3.2)
No	22	(6)		

New sex partner since treatment**				
Yes	70	(14)	1.2 (0.9-1.6)	
No	112	(12)		
Number of sex partners since treatment with whom condom not used for all vaginal sex				
0	66	(8)	1.7 (1.4-2.2)	1.5 (1.2-2.0)
1	122	(14)	per category change	per category change
2+	14	(20)		
Reexposure to sex partner patient believes had other partners				
Yes	73	(14)	1.4 (1.1-1.8)	
No	130	(10)		
Sex with any partner not believed to be "very likely" treated or tested STI negative				
Yes	40	(25)	2.6 (1.9-3.5)	†
No	156	(10)		
All partners "very likely" treated or tested STI negative				
Yes	87	(9)	0.7 (0.5-0.9)	†
No	106	(14)		
Study arm				
Expedited partner treatment	92	(10)	0.8 (0.6-1.0)	0.7 (0.6-1.0)
Standard partner care	121	(13)		

Rates of recurrent chlamydial infection did not differ between index patients treated with azithromycin (13%) and those treated with doxycycline (11%) (RR=1.2 95% CI 0.8-1.6).

* Persistent or recurrent infection defined as chlamydial infection at follow-up in persons originally diagnosed with chlamydial infections, gonorrhea in those originally diagnosed with gonorrhea, or either infection in those originally diagnosed with both pathogens.

**Excludes those with no sex partners since treatment

†Variable statistically significant in multivariate model. Inclusion in model results in study randomization assignment 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. RRs for multivariate model generated via generalized linear model with binary outcomes and log link

Note. Table is a reproduction from Golden et al. *NEJM* 2005;352;676-685, with permission from the *New England Journal of Medicine.*

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.

Table 8

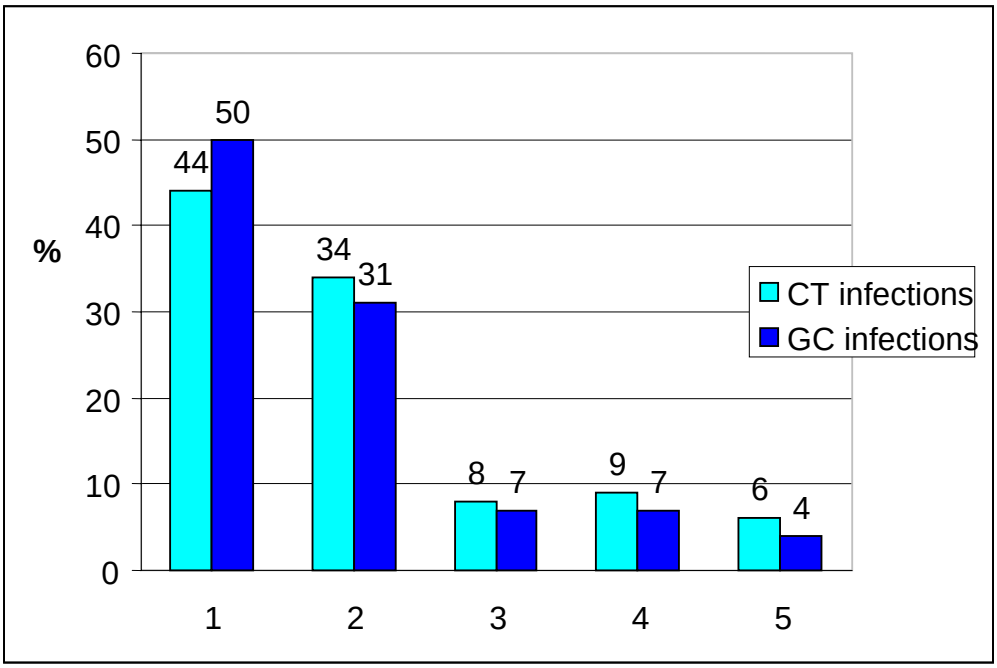
STD in Contacts to GC, CT, NGU, or MPC in Seattle, Baltimore, Birmingham and Denver

STD	Women (N = 2507)	Heterosex. men (N = 3511)	MSM (N = 460)
GC (non-GC contacts only)	3.9%	3.1%	6.1%
PID	3.7%	n/a	n/a
New HIV	0	0.2%	5.5%
Early syphilis	0.1%	0	0.4%
Trichomoniasis	4.9%	n/a	n/a
GC/CT (partners of women with TV)	--	10.3%	--

Note. Data drawn from Stekler et al. *Clin Inf Dis* 2005;40:787-793.

Figure 1

Percentages of Physicians Giving Patients Medications to Take to Sex Partners in a National Survey

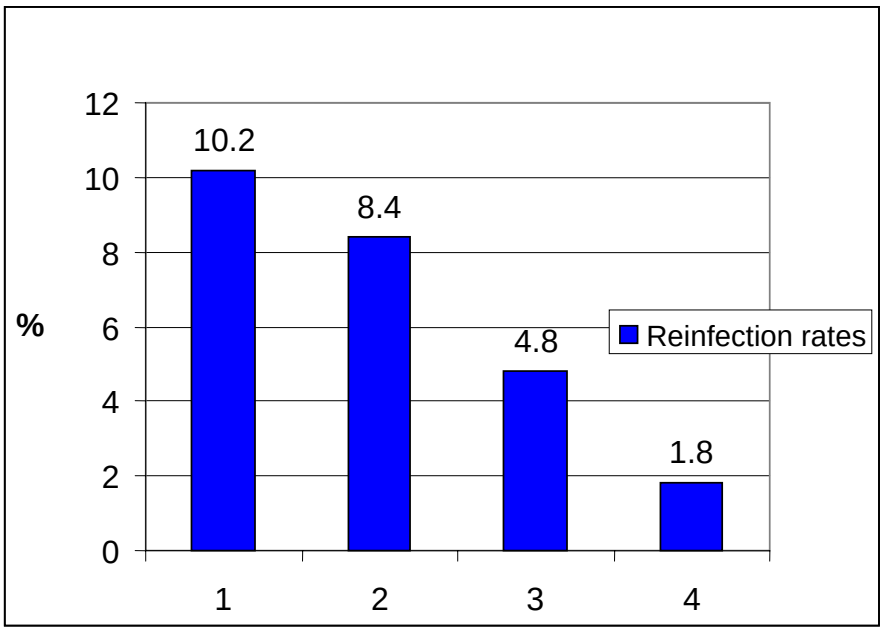


Note. Data drawn from Hogben, et al. *Sex Transm Dis* 2005;32:101-105.

1 = Never; 2 = Sometimes; 3 = About half the time; 4 = Usually; 5 = Always.

Figure 2

Chlamydial Reinfection Rates In Sweden By Partner Management Strategy According to Retrospective Chart Review, 1979 – 1980 and 1983 – 1984

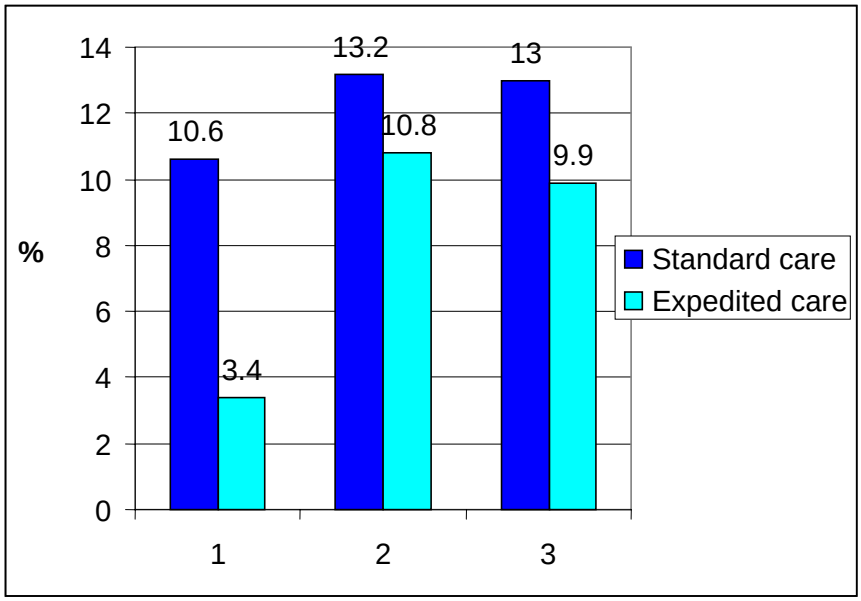


Note. Data are drawn from Ramstedt, et al. *Int J STD AIDS* 1991;2:116-118.

1 = No partner management (N = 372); 2 = Patient couseled to refer partner(s) (N = 997); 3 = Patient counseled to refer partner(s), compliance monitored (N = 645); 4 = Patient-delivered partner therapy (N = 167).

Figure 3

Infection Rates at Follow-up in Seattle Randomized, Controlled Trial of Expedited Partner Therapy

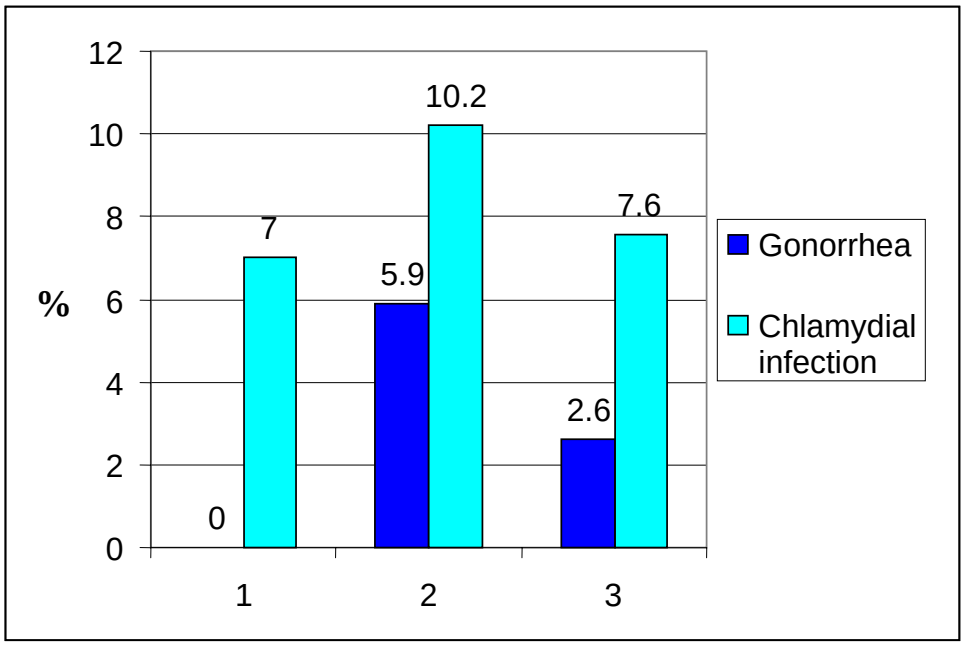


Note. Data are drawn from Golden, et al. *NEJM* 2005;352:676-685.

1 = GC infections only, P = .02 (N = 358); 2 = CT infections only, P = .17 (N = 1595); 3 = GC or CT infections, P = .04 (N = 1860).

Figure 4

Differential Infection at Follow-up Among Women Who Reported any Sex Since Treatment in Seattle Randomized, Controlled Trial of Expedited Partner Therapy



Note. Data are drawn from Golden, et al. *NEJM* 2005;352:676-685.

1 = Expedited care; 2 = Standard care; 3 = Total.