

# Developing a Public Health Response to *Mycoplasma genitalium*

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Although *Mycoplasma genitalium* is increasingly recognized as a sexually transmitted pathogen, at present there is no defined public health response to this relatively newly identified sexually transmitted infection. Currently available data are insufficient to justify routinely screening any defined population for *M. genitalium* infection. More effective therapies, data on acceptability of screening and its impact on clinical outcomes, and better information on the natural history of infection will likely be required before the value of potential screening programs can be adequately assessed. Insofar as diagnostic tests are available or become available in the near future, clinicians and public health agencies should consider integrating *M. genitalium* testing into the management of persons with sexually transmitted infection (STI) syndromes associated with the infection (ie urethritis, cervicitis, and pelvic inflammatory disease) and their sex partners. Antimicrobial-resistant *M. genitalium* is a significant problem and may require clinicians and public health authorities to reconsider the management of STI syndromes in an effort to prevent the emergence of ever more resistant *M. genitalium* infections.

**Keywords.** *Mycoplasma genitalium*; public health; prevention.

*Mycoplasma genitalium* was originally described as a sexually transmitted infection (STI) in 1981 [1] and, over the last 2 decades, has become an infection of increasing concern as mounting evidence has documented the organism's association with diverse STI syndromes, its potential to cause significant reproductive tract sequelae, and the rapid selection for antimicrobial resistance following treatment [2–4]. In this article, we discuss the public health implications of *M. genitalium*, including whether a screening program is justified, how *M. genitalium* laboratory tests might best be used, and the treatment of the infection. We highlight some of the challenges inherent to developing public health policy for STIs caused by an organism that can rapidly develop resistance and for which the natural history of infection remains ill-defined.

## SCREENING FOR *M. GENITALIUM*: CRITERIA FOR INSTITUTING A SCREENING PROGRAM AND ADDRESSING THE NEED FOR *M. GENITALIUM* SCREENING

Screening is the testing of asymptomatic persons to find those with an infection, disease, or disorder. However, principles of screening are often misunderstood in clinical practice [5]. Criteria for determining if a screening test is warranted include the following: (1) the prevalence of infection is well defined and

the severity of the morbidity associated with the infection justifies action; (2) the natural history of the infection is established and earlier diagnosis and treatment prevents symptoms or disease and improves quality of life or survival; (3) patients will adhere to the course of antimicrobials or any other known effective prevention interventions in the absence of symptoms; and (4) the accuracy, predictive values, safety, and cost of the screening test are acceptable [6]. In addition, any screening program should be cost-effective, be accessible to those who would benefit, and be potentially available in healthcare facilities that have the expertise and resources to diagnose and treat. Furthermore, the follow-up after a positive result should be agreeable and acceptable to those screened [7].

The criteria for instituting a screening program are similar to those used in public health to prioritize diseases and conditions of public health importance, establish which diseases should be nationally notifiable by law in the United States, and implement national public health prevention and control programs. In general, public health uses 7 criteria to determine if infections, diseases, or other conditions are of public health importance: frequency or burden, severity in terms of morbidity or mortality, communicability, preventability, disparities or inequities associated with the health event, costs associated with the health event, and public interest. As an example, most recently, these criteria were used to develop the Centers for Disease Control and Prevention (CDC) antibiotic-resistant bacteria threat report [8]. Table 1 summarizes the status of *M. genitalium* in meeting criteria to establish a screening program of public health importance. Of the 7 criteria listed, current evidence is insufficient for establishing a *M. genitalium* screening program as only 3

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The Journal of Infectious Diseases® 2017;216(S2):S420–6

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**Table 1. Status of *Mycoplasma genitalium* in Meeting Criteria to Establish a Screening Program of Public Health Importance**

Criteria	Criteria Met	Some but Insufficient Evidence to Meet Criteria	No Evidence or Evidence Does Not Support Criteria	Comments
Infection is common	✓ [25, 48–50]			
Infection causes significant morbidity		✓ [3]		Uncertain how often infection causes PID, TFI, or other major sequelae
Condition is communicable	✓ [51, 52]			
Morbidity is preventable			✓	Treatment not consistently effective
Infection has disparate impact on different populations	✓ [25, 50, 53]			Prevalence is higher in African Americans
Infection is associated with significant costs			✓	Few data exist on the potential medical costs and population-level morbidity associated with infection
Condition associated with significant public interest			✓	

Abbreviations: PID, pelvic inflammatory disease; TFI, tubal factor infertility.

conditions are met: this infection is common, communicable, and has disparate impact on different populations. Further evidence is needed regarding the morbidity, costs, preventability, and public interest associated with *M. genitalium* infection.

In the United States, the United States Preventive Services Task Force (USPSTF) makes evidence-based recommendations for clinical preventive services to be used by the primary care community, including screening along with counseling and preventive medications, which apply to adults and children with no recognized signs or symptoms. Recommendations are based on rigorous review of existing peer-reviewed evidence and evaluation of benefits and harms of each preventive service. While many of the screening program indices above are included in the USPSTF process, the cost of the health event, screening, and intervention are not included.

Based on current US criteria for defining when a screening program is justified, available data do not currently support the institution of widespread *M. genitalium* screening among young women and/or men or other populations sometimes screened for STI (eg, pregnant women).

Ideally, the decision to institute a *M. genitalium* screening program would be informed by 1 or more randomized controlled trials evaluating the impact of screening on major reproductive health morbidity in women and associated cost-effectiveness analyses. Prevention of tubal factor infertility (TFI), the most morbid and costly sequelae of bacterial STIs in women [9], would be the ideal outcome, perhaps with population-level trials evaluating the impact of serial rounds of screening on *M. genitalium* incidence or prevalence and *M. genitalium*-related TFI. Studies undertaken in the United States and some other nations suggest that chlamydia screening decreases the risk of pelvic inflammatory disease (PID) [10–13] and are the basis for the USPSTF recommendation for annual chlamydia screening of females <26 years of age [14]. However, the impact of chlamydia screening on infertility remains uncertain. This uncertainty has prompted some experts to question the value of chlamydia screening and

suggest the need for much higher evidentiary standards to justify prevention programs [15]. However, it is not clear that any STI screening program could be definitively shown to affect an outcome like TFI, and more feasible approaches for defining the potential impact of screening are needed. TFI is a rare event and a randomized trial would need to be extremely large and involve many years of follow-up to demonstrate an effect. If 2.5% of women screened have *M. genitalium* infection, PID develops in 10% of women with *M. genitalium* infection, TFI occurs in 10% of women with PID (similar to estimates for *Chlamydia trachomatis* [16]; ie, 0.25 women per 1000 women screened TFI from *M. genitalium*), and screening averts 50% of cases of TFI, one would need >400 000 persons in a randomized trial to demonstrate a benefit. Such a trial is not realistic. A *M. genitalium* screening trial with a PID outcome similar to the previously conducted chlamydia studies would be more feasible and could provide valuable information on the impact of *M. genitalium* screening. At the same time, such a trial would be subject to a number of limitations as the clinical diagnosis of PID is relatively subjective, the histologic diagnosis of endometritis is difficult to make and not consistently associated with disease in the fallopian tubes [17, 18], and biologic markers of STI-related TFI are not available. In addition, a trial with a PID outcome would leave unanswered the question of how often *M. genitalium* causes TFI or what proportion of TFI cases screening could avert.

The difficulties inherent in trying to establish the value of screening for *M. genitalium* infection requires careful consideration of how much evidence is needed to advocate for screening, a topic that affects a wide array of medical problems, not just *M. genitalium* or STIs. A first step related to screening for *M. genitalium* might be to define under what circumstances screening would be cost-effective. This would require defining a range of parameters related to the natural history of *M. genitalium*, the effectiveness of screening, and the costs associated with TFI and other sequelae of PID. Results of such a study could help inform decisions on whether a trial looking at a

PID outcome would be worthwhile. If efficacy in averting PID was cost-effective in preventing infertility across a wide range of assumptions regarding how often PID results in TFI, a trial with a PID outcome might be sufficient to justify widespread screening.

In considering a way to determine the cost-effectiveness of a *M. genitalium* screening program, the subject of how to value infertility merits particular attention. Studies assessing how much infertility affects health have produced widely variable estimates [19, 20]. Health economists typically express the value of an intervention in terms of cost per quality-adjusted life year (QALY) gained. The number of QALYs associated with infertility (or the number gained by averting infertility) depends on factors such as the time horizon used and discount rates; QALYs lost per case of TFI vary from 1 to approximately 6.5 (Thomas Gift, January 2017). From a population perspective, the impact of screening is further influenced by whether one assumes that infertility has a cost for all or almost all affected women independent of treatment costs. Many cost-effectiveness analyses of chlamydial screening have focused only on the medical costs associated with infertility treatment among women seeking such treatment, essentially ignoring the morbidity associated with the condition among those not seeking treatment [21]. Better defining the cost of infertility beyond medical treatment will be critical in defining the potential impact of *M. genitalium* screening, and could also lead to a reappraisal of the cost-effectiveness of other STI screening programs that impact reproductive health.

## DIAGNOSTIC TESTING FOR *M. GENITALIUM*

Although the available data are insufficient to support population-level programs to prevent *M. genitalium*, clinicians are frequently required to make testing and treatment decisions for patients presenting with *M. genitalium*-associated syndromes and their sex partners. This need is particularly acute in public

health sexually transmitted disease (STD) clinics, which see large numbers of patients with STD syndromes, and which are ideally centers where patients can seek expert care for STIs. The following discussion reviews recent efforts to provide clinical guidelines for the medical management of *M. genitalium*.

There are currently no laboratory tests for *M. genitalium* approved by the US Food and Drug Administration (FDA), and it is uncertain when an FDA-approved test will be available. However, commercial assays are available outside the United States (including a test that includes detection of macrolide resistance), some laboratories in the United States offer locally developed tests, and analyte-specific *M. genitalium* reagents are available in the United States that laboratories can use for clinical testing following internal validation of the test's performance [22]. The expanding availability of non-FDA-approved tests and potential future availability of FDA-approved tests should prompt the development of guidance on the indications for *M. genitalium* testing. Specific guidance on the use of these tests should reflect an effort to minimize the morbidity associated with *M. genitalium*, preserve the reservoir of antimicrobial susceptibility, and limit cost. Such an approach will be particularly important in health departments or medical facilities that operate STD specialty clinics, venues that should ideally be early adopters of *M. genitalium* testing, and where antimicrobial resistance monitoring and research can be conducted, similar to current prevention efforts for *Neisseria gonorrhoeae*.

Table 2 summarizes recently developed European guidelines and provisional local Public Health–Seattle & King County (PHSKC) guidelines for *M. genitalium* testing [23]. Development of these guidelines was prompted by the recognition that *M. genitalium* is a relatively common cause of urethritis, and that azithromycin therapy is not consistently effective in treating *M. genitalium* and contributes to the development of antimicrobial resistance [2, 24]. In the absence of a consistently effective treatment and stronger evidence supporting routine

**Table 2. Potential Indications for *Mycoplasma genitalium* Testing<sup>a</sup>**

Indication	European Guidelines [23]	Provisional PHSKC Guidelines	Comment
Persons failing treatment for urethritis, PID, or cervicitis	Recommended	Recommended	- Diagnosis helps inform counseling and treatment - Affects small numbers of persons
Persons presenting with urethritis, PID, cervicitis, or epididymitis-orchitis	Recommended	Recommended	- Allows earlier diagnosis (ie, does not require treatment failure) - Might be useful as part of effort to use doxycycline (not azithromycin) for NGU, PID, and cervicitis, and limit azithromycin to treatment of <i>M. genitalium</i> known to be susceptible
Sex partners of persons diagnosed with <i>M. genitalium</i>	Recommended	Recommended	- Help avert reinfection and clinically inapparent morbidity
Women presenting with vaginal discharge	Recommended	Not recommended	- Uncertain how often <i>M. genitalium</i> causes vaginal discharge in the absence of MPC
Women being screening for chlamydial infection	Not recommended	Not recommended	- Insufficient evidence to justify screening
MSM being screening for STI	Not recommended	Not recommended	- Insufficient evidence to justify screening

Abbreviations: MPC, mucopurulent cervicitis; MSM, men who have sex with men; NGU, nongonococcal urethritis; PHSKC, Public Health–Seattle & King County; PID, pelvic inflammatory disease; STI, sexually transmitted infection.

<sup>a</sup>Testing ideally includes testing for macrolide resistance.

screening, use of *M. genitalium* assays should initially be used for diagnostic testing only in certain clinical situations. A limited role for a new assay might include testing persons with persistent or recurrent urethritis, PID, or cervicitis following receipt of recommended therapy, and perhaps testing the sex partners of persons with diagnosed *M. genitalium* infections. (Persistent urethritis does not resolve following recommended therapy, while recurrent urethritis recurs following initial improvement in the absence of likely reexposure to infection.) This approach would confine testing to persons who would likely benefit most and minimize costs, but would delay patients' *M. genitalium* microbiologic diagnosis and result in some infected persons not being optimally treated if they did not return for reevaluation.

An alternative approach would be to perform testing on all men with nongonococcal urethritis (NGU) (or urethritis if Gram stain testing is not performed), and women with PID or cervicitis. This may increase costs, but would identify a larger number of *M. genitalium*-infected persons and might avoid some clinical visits as those persons with persistent symptoms would have test results available to guide treatment decisions prior to seeking reevaluation. In addition, if coupled with a decision to adopt doxycycline, not azithromycin, as the standard therapy (or part of standard therapy) for NGU, PID, and cervicitis, such an approach might decrease antibiotic pressure that promotes the selection and dissemination of azithromycin-resistant *M. genitalium* [24], though recent data suggest that azithromycin resistance is already very widespread in many areas [25, 26]. European guidelines also suggest testing women for *M. genitalium* with vaginal discharge if they have risk factors for STI [23]. While some women with vaginal discharge have cervical infections, a proportion of which are due to *M. genitalium*, vaginal discharge has not been consistently associated with *M. genitalium* [27, 28], and most women presenting for evaluation of vaginal discharge have vaginitis, not cervicitis. Because of this and until additional data are available on the association of vaginal discharge with *M. genitalium* in the United States, testing all women with vaginal discharge is a lower priority than testing persons with STI syndromes more closely linked to *M. genitalium* infection.

#### **TREATMENT OF *M. GENITALIUM* INFECTION AND IMPACT OF *M. GENITALIUM* ON STI TREATMENT**

The recognition of *M. genitalium* as a sexually transmitted pathogen requires guidance on the optimal treatment for confirmed infection, and has implications for syndromic treatment of NGU, PID, and cervicitis in the absence of microbiologic data. The CDC 2015 STD treatment guidelines do not make specific recommendations related to the treatment of *M. genitalium*, but suggest clinicians consider *M. genitalium* as a potential pathogen in those with persistent urethritis, and recommend azithromycin 1 g orally once in men who did not receive azithromycin for initial NGU therapy, and moxifloxacin 400 mg orally daily for

7 days in those who were initially treated with azithromycin [29]. European guidelines recommend *M. genitalium* testing of persons with STI syndromes (Table 2), including macrolide resistance testing [23, 30], and recommend azithromycin (500 mg orally once, then 250 mg once daily for 4 days) to treat macrolide-susceptible infections and moxifloxacin (400 mg orally once daily for 7–10 days) to treat macrolide-resistant infections.

Both of the above-mentioned approaches are likely to cure many, and in areas where macrolide resistance is rare, most *M. genitalium* infections. However, approximately 10% of persons initially infected with azithromycin-susceptible organisms develop persistent, azithromycin-resistant infections following azithromycin treatment [4, 24, 26, 31–33]. Some evidence suggests that 5-day courses of azithromycin are less likely to select for resistance than single-dose therapy [24, 34, 35], though this finding has not been consistently observed [36, 37], and recent data suggest that approximately 50% of *M. genitalium* infections in the United States are already resistant to azithromycin [25]. How often moxifloxacin treatment selects for persistent, resistant infections is not known, but recent data suggest that fluoroquinolone resistance is increasing. Mutations associated with quinolone resistance have been identified in 15%–33% of infections in studies from Australia and Asia [33, 38–41] and occur at least occasionally among infections in Europe [39, 42], though in some instances these mutations may not be sufficient to cause treatment failure.

Developing treatment recommendations for *M. genitalium* presents several dilemmas. First, to what extent should treatment regimens incorporate considerations related to antimicrobial resistance, particularly in the absence of data demonstrating a differential impact of different regimens on the development of resistance? Second, should treatment recommendations incorporate efforts to contain the development of resistance at the population level and what, if any, risks is it reasonable for individual patients to assume as part of an effort to contain population-level antimicrobial resistance? Finally, how much evidence do we need to develop guidelines that incorporate an effort to prevent antimicrobial resistance at both the individual and population levels?

Evidence that *M. genitalium* is responsible for 15%–20% of cases of NGU, that azithromycin selects for macrolide-resistant *M. genitalium*, and that this selective pressure could play an important role in fostering *M. genitalium* resistance at the population level has led European authorities and at least 1 US health department (PHSKC) to change standard treatment recommendations for NGU to move away from the use of azithromycin and toward routine use of doxycycline 100 mg orally twice daily for 7 days [29, 43]. Multiple observational studies suggest that doxycycline may be more effective than azithromycin in the treatment of rectal chlamydial infection, and some evidence exists that doxycycline may be slightly more effective than azithromycin in treating chlamydia-associated NGU [44, 45].

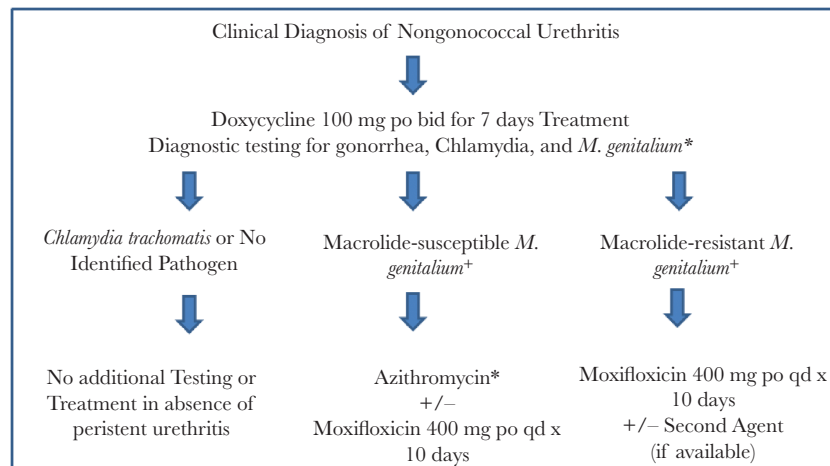
Findings from these studies, in addition to concerns related to *M. genitalium* resistance, may justify some reconsideration of standard NGU and chlamydia treatment recommendations.

The more difficult problem relates to treatment of urethritis diagnosed without the aid of a urethral Gram stain. In many settings in the United States, clinicians do not perform Gram stains and treat urethritis syndromically with ceftriaxone and azithromycin [29]. This approach is designed to treat chlamydial infection and ensure that gonorrhea therapy includes 2 active antimicrobial agents, a strategy thought to be effective in diminishing the emergence of antimicrobial-resistant gonorrhea. However, dual therapy for urethritis that includes azithromycin may help foster the selection and dissemination of macrolide-resistant *M. genitalium*. How clinicians should balance the potentially competing treatment issues related to gonorrhea, chlamydia, and *M. genitalium* infection when empirically treating men with urethritis presents a number of dilemmas that may also merit reconsideration of how urethritis is managed.

Given the risk of resistance, one could argue for treating *M. genitalium* with combination therapy. The rationale for this approach, like the rationale for using combination therapy to treat gonorrhea, is that dual therapy might raise the genetic barrier to resistance by limiting treatment failures to organisms with resistance to 2 classes of drug with separate mechanisms of action. While there is no direct evidence supporting this approach to mitigate emerging *M. genitalium* or gonorrhea resistance, the paucity of treatment options for both infections necessitates measures to preserve the efficacy of the drugs we currently have.

Figure 1 presents a suggested approach to testing and treatment of NGU developed, but not yet implemented, for use in the PHSKC STD clinic. Men with NGU will initially be treated with doxycycline while being tested for *M. genitalium* using an assay that can detect macrolide resistance. Subsequent

treatment is then restricted to persons with diagnosed *M. genitalium* infections. European guidelines suggest that men with macrolide-susceptible infections be treated with azithromycin and those men with macrolide-resistant infections be treated with moxifloxacin. The theoretical rationale for this approach, which involves either sequential or partially concurrent 2-drug therapy depending on laboratory result turnaround time, is that doxycycline, though not a highly effective treatment for *M. genitalium*, may decrease the *M. genitalium* bacterial load, thereby facilitating the success of treatment with azithromycin or moxifloxacin. An alternative approach, presented in the figure, would involve concurrent dual therapy. Potential regimens might include azithromycin plus moxifloxacin in persons with macrolide-susceptible infections, and moxifloxacin plus a second drug in persons with macrolide-resistant infections. Unfortunately, at present, in the United States there is no other drug available that is consistently effective in the treatment of *M. genitalium*. This alternative approach always includes moxifloxacin, which is more costly than azithromycin alone and involves a 0.08%–0.2% risk of tendon injury, though this risk may be lower in patients with *M. genitalium*-related sexually transmitted syndromes, which involve a relatively short course of therapy among persons who typically lack risk factors for tendinopathy (older age, corticosteroid use, and comorbid conditions) [46]. The rationale for treating with combination therapy following initial doxycycline treatment reflects uncertainty about the benefit associated with doxycycline given its poor efficacy as a single therapy for *M. genitalium*, and an effort to more aggressively avoid promoting resistance. It should be noted that much of the approach outlined here is how one clinic proposes to integrate *M. genitalium* testing into routine clinical management of NGU. It will require rigorous evaluation and perhaps modifications based on experience.



**Figure 1.** Proposed Public Health–Seattle & King County testing and treatment algorithm for nongonococcal urethritis. Abbreviations: bid, twice daily; po, oral; qd, once daily.

## PARTNER NOTIFICATION AND TREATMENT

At present, there are very few data related to the role of partner notification for *M. genitalium*, and the appropriate contact period for defining at-risk partners is undefined. Given that uncertainty, medical providers performing *M. genitalium* testing could consider adopting an approach that is somewhat similar to that employed for chlamydia and gonorrhea; sex partners from the 60 days prior to diagnosis (or last partner) of persons diagnosed with *M. genitalium* infection should be notified, clinically evaluated, and tested for infection, with partner treatment guided by the results of testing. In the absence of *M. genitalium* testing, some clinicians may empirically treat the sex partners of persons with persistent or recurrent NGU for *M. genitalium*. However, only 19%–41% of men with persistent or recurrent urethritis have *M. genitalium* infection [47], highlighting the desirability of microbiologic testing when possible. The ideal approach for managing the sex partners of persons with *M. genitalium* infection merits future study.

## SURVEILLANCE

Unlike gonorrhea or chlamydial infection, *M. genitalium* is not legally reportable in any area of the United States, and it seems unlikely that many health departments will make it reportable in the absence of a larger control program. At the same time, insofar as specialized STD clinics begin testing for *M. genitalium*, sentinel surveillance in such sites could be useful in defining the prevalence of infection and, if possible, levels of antimicrobial resistance to macrolides and quinolones. Such surveillance, coupled with rigorous program evaluation, could also be useful in refining clinical management algorithms.

## CONCLUSIONS

The public health response to *M. genitalium* is in its infancy. Current evidence is insufficient to justify a *M. genitalium* screening program. On the other hand, insofar as accurate assays are available or become available, there is at least a limited role for *M. genitalium* testing in persons with STI syndromes associated with the microorganism and the sex partners of persons with diagnosed *M. genitalium* infections. Barriers to defining an appropriate public health response to *M. genitalium* include the absence of a widely available FDA-approved test, the lack of consistently effective treatments, and uncertainty about the natural history of infections in women. Addressing these gaps, along with the development of effective screening and treatment programs that are acceptable and accessible for persons at risk of *M. genitalium* infection, will be critical to the success of developing an appropriate clinical and public health response to this increasingly recognized STI pathogen.

## Notes

**Disclaimer.** The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC.

**Financial support.** This work is an outcome of a *Mycoplasma genitalium* Experts Technical Consultation that was supported by the Division of Microbiology and Infectious Diseases of the National Institute of Allergy and Infectious Diseases (contract number HHSN272201300012I), with the University of Alabama at Birmingham Sexually Transmitted Infections Clinical Trials Group.

**Supplement sponsorship.** This work is part of a supplement sponsored by the University of Alabama at Birmingham Sexually Transmitted Infections Clinical Trials Unit and the National Institute of Allergy and Infectious Diseases.

**Potential conflicts of interest.** M. R. G. has received research support from Hologic. All other authors report no potential conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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