PELVIC INFLAMMATORY DISEASE

Moxifloxacin versus ofloxacin plus metronidazole in uncomplicated pelvic inflammatory disease: results of a multicentre, double blind, randomised trial

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There is an appendix and a figure on the STI website (www.stijournal.com/supplemental).

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Accepted for publication 11 May 2006

Sex Transm Infect 2006;**82**:446–451. doi: 10.1136/sti.2005.019109

Objective: This multinational, multicentre, prospective, randomised, double blind, parallel group, non-inferiority study compared the efficacy and safety of moxifloxacin monotherapy with ofloxacin plus metronidazole in women with uncomplicated pelvic inflammatory disease.

Methods: Women from hospitals throughout 13 countries received a 14 day course of either oral moxifloxacin, 400 mg once daily (n = 384), or oral ofloxacin, 400 mg twice daily plus oral metronidazole, 500 mg twice daily (n = 365).

Results: Of the 741 patients in the intent to treat (ITT) population, 564 (74.2%) were valid for the per protocol (PP) analyses; 112 (19.9%) of these were included in the microbiologically valid population (MBV). Clinical resolution rates in the PP population at the test of cure visit (TOC, 5–24 days post-therapy, primary efficacy end point) were 90.2% (248/275) for moxifloxacin and 90.7% (262/289) for ofloxacin plus metronidazole (95% CI: –5.7% to 4.0%). At follow up (28–42 days post-therapy), resolution rates in the PP population were 85.8% (236/275) and 87.9% (254/289) for moxifloxacin and comparator, respectively (95% CI: –8.0% to 3.1%). Bacteriological success rates in the MBV population at TOC were 87.5% (49/56) for moxifloxacin and 82.1% (46/56) for comparator (95% CI: –8.3% to 18.8%). Against *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, bacteriological success rates with moxifloxacin were 88.5% (23/26) and 100% (13/13) and for comparator 85.7% (18/21) and 81.8% (18/22), respectively. Drug related adverse events occurred less frequently with moxifloxacin (22.5% (85/378)) versus the comparator (30.9% (112/363)) (p = 0.01).

Conclusion: In uncomplicated PID, once daily moxifloxacin monotherapy was clinically and bacteriologically as efficacious as twice daily ofloxacin plus metronidazole therapy and was associated with fewer drug related adverse events.

Pelvic inflammatory disease (PID) is common among women of reproductive age although its incidence is unknown as it cannot be diagnosed reliably from clinical signs and symptoms.¹ Nevertheless, Simms *et al* reported that in the United Kingdom diagnoses of PID were made at 1.7% of GP attendances among women between the ages of 16 years and 46 years.² Risk factors for PID include young age, multiple sexual partners, a previous history of sexually transmitted disease (STD), insertion of an intrauterine device (IUD) within the previous 6 weeks, reduced socioeconomic circumstances, and recent new sexual partner.^{1–3} In the long term, PID can have serious clinical consequences, including an increased risk of infertility, ectopic pregnancy, chronic pelvic pain, and recurrence of acute episodes of the disease.¹ Westrom *et al* showed that each repeated episode of PID increased the rate of tubal factor infertility approximately twofold.⁴

Most cases of PID result from ascending infection from the cervix. *Neisseria gonorrhoeae* and *Chlamydia trachomatis* have both been identified as causative agents, while micro-organisms that comprise the vaginal flora (for example, anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae*, enteric Gram negative rods, and *Streptococcus* spp) have also been implicated.³ Additionally, cytomegalovirus (CMV), *Mycoplasma genitalium*, and *Ureaplasma urealyticum* may be the aetiological agents in some cases.⁵

The objective of antimicrobial therapy in PID is to control acute symptoms and prevent late sequelae, and early diagnosis and broad spectrum antibacterial therapy are

recommended.^{3–6} Although the impact of antibiotic therapy on long term reproductive health is not entirely clear, several studies, including the PEACH study, provide evidence to support their prompt use to improve outcomes.^{7–9} In the PEACH study, those women with uncomplicated PID, treated with cefoxitin and doxycycline, had pregnancy rates after 3 years that were similar to or higher than the national rates in the United States.⁹

Because of the diverse microflora implicated in PID, combination antibiotic therapies are considered the standard regimen for this condition. In both the United Kingdom and United States, oral ofloxacin, 400 mg twice daily, plus oral metronidazole, 400–500 mg twice daily, for 14 days is recommended as an appropriate first line regimen for the outpatient setting.^{5–6} The addition of metronidazole improves anaerobic coverage. There are also some data showing that levofloxacin may be as effective as ofloxacin and may be substituted, although no clinical trials for PID have been undertaken with this agent.¹⁰

Moxifloxacin is an 8-methoxy-fluoroquinolone, characterised by a broad spectrum of antibacterial activity and bactericidal action, with good in vitro activity against Gram positive and Gram negative aerobic organisms, anaerobes,

Abbreviations: CMV, cytomegalovirus; ITT, intent to treat; IUD, intrauterine device; MBV, microbiologically valid population; PCR, polymerase chain reaction; PID, pelvic inflammatory disease; PP, per protocol; STD, sexually transmitted diseases; TOC, test of cure

Table 1 Baseline and demographic characteristics for the intention to treat (ITT) populations in the two treatment groups (mean (SD) or frequency (%))

Characteristic	Moxifloxacin (n = 378)	Ofloxacin plus metronidazole (n = 363)	p Value*
Race			
White	230 (61%)	212 (58%)	0.646
Black	114 (30%)	109 (30%)	
Asian	2 (1%)	4 (1%)	
Hispanic	1 (<1%)	0 (0%)	
Uncodable†	31 (8%)	38 (10%)	
Age (years; mean (SD))	30.1 (8.4)	30.5 (8.5)	0.408
Body mass index	24.3 (5.0)	24.1 (5.0)	0.389
Previous pregnancies	240 (63%)	255 (70%)	0.066
Previous abortions	98 (26%)	108 (30%)	0.900‡
Use of birth control	322 (85%)	323 (89%)	0.153
Regular vaginal douching	20 (5%)	19 (5%)	0.948
Syphilis test§			
Negative	348 (92%)	323 (89%)	0.195
Positive	29 (8%)	39 (11%)	

*From Cochran-Mantel-Haenszel test (categorical values) or ANOVA (continuous variables) stratified by region.

†Patients from South Africa of mixed race.

‡Test based on all possible outcomes.

§Missing information in one patient of each group; 62/68 positive syphilis test findings were from South Africa.

and atypicals.^{11–13} Moxifloxacin provides improved activity over existing fluoroquinolones against *C. trachomatis* and greater coverage of anaerobic bacteria.^{11–14} Preliminary clinical data in women with PID suggested that moxifloxacin could represent a significant improvement over currently available treatments and be of value in empirically based therapeutic regimens.¹⁵ Additionally, the pharmacokinetics of moxifloxacin permit once daily dosing, with rapid absorption and high bioavailability after oral administration.^{16, 17}

This paper describes the findings of a study comparing the efficacy and safety of once daily oral moxifloxacin monotherapy with a combination of twice daily oral ofloxacin plus oral metronidazole in women with uncomplicated PID.

METHODS

See appendix on the STI website (www.stijournal.com/supplemental).

RESULTS

Patients

The numbers of patients who were recruited and randomised into the study and eligible for the analyses are summarised in figure 1 (on STI website (www.stijournal.com/supplemental)). Overall, demographic and baseline characteristics were similar between the treatment groups (table 1).

Almost 30% of women in both treatment groups reported one or more previous episodes of PID. There were no differences in clinical presentation between groups (for example, onset of PID, previous symptoms, total pelvic pain scores; data not shown), and the incidences of the various signs and symptoms of PID (for example, abnormal vaginal discharge, discharge colour and odour, dyspareunia) were similar in each treatment arm (data not shown). Thirty patients receiving moxifloxacin and 27 receiving the comparator regimen were hospitalised before or on day 1. Six

Table 2 Summary of clinical response rates for the per protocol population (n = 564) and supporting intent to treat analyses at test of cure (days 5–24 post-therapy) and at follow up (days 28–42 post-therapy) (for calculation of 95% CI, missing information and “indeterminate” cases were treated as non-successes)

Clinical response	Intent to treat (n = 741)		Per protocol (n = 564)	
	Moxifloxacin (n = 378)	Ofloxacin plus metronidazole (n = 363)	Moxifloxacin (n = 275)	Ofloxacin plus metronidazole (n = 289)
Test of cure (TOC)				
Clinical resolution	286 (75.7%)	300 (82.6%)	248 (90.2%)	262 (90.7%)
Clinical failure or <70% improvement	46 (12.2%)	41 (11.3%)	27 (9.8%)	27 (9.3%)
Indeterminate/missing*	46 (12.2%)	22 (6.1%)	0	0
Treatment difference (95% CI)	−6.9% (−12.3% to −0.9%)		−0.5% (−5.7% to 4.0%)	
Indeterminates/missing considered non-successes	−6.9% (−12.3% to −0.9%)		−0.5% (−5.7% to 4.0%)	
Indeterminates/missing excluded	−1.8% (−6.9% to 3.2%)			
Follow up				
Continued resolution	284 (75.1%)	294 (81.0%)	236 (85.8%)	254 (87.9%)
Clinical relapse	12 (3.2%)	15 (4.1%)	10 (3.6%)	11 (3.8%)
Failures carried forward from TOC†	36 (9.5%)	22 (6.1%)	22 (8.0%)	16 (5.5%)
Indeterminate/missing*	46 (12.2%)	32 (8.8%)	7 (2.5%)	8 (2.8%)
Treatment difference (95% CI)	−5.9% (−11.5% to 0.3%)		−2.1% (−8.0% to 3.1%)	
Indeterminates/missing considered non-successes	−5.9% (−11.5% to 0.3%)		−2.1% (−8.0% to 3.1%)	
Indeterminates/missing excluded	−3.3% (−8.3% to 1.8%)		−2.3% (−7.8% to 2.6%)	

*Reasons for indeterminate/missing given in figure 1 (on STI website (www.stijournal.com/supplemental)).

†Only clinical failures were carried forward from TOC, improvements were re-assessed by the investigator at the follow up visit.

patients in the moxifloxacin group and six in the comparator group underwent laparoscopy.

Clinical response

Based on the clinical success criteria, moxifloxacin monotherapy was clinically comparable with ofloxacin plus metronidazole combination therapy. Clinical resolution rates at the primary efficacy end point (per protocol (PP) population at the test of cure (TOC) assessment) were statistically similar in the two treatment groups: 90.2% (248/275) for moxifloxacin and 90.7% (262/289) for ofloxacin plus metronidazole (difference 0.5%; 95% CI: -5.7% to 4.0%) (table 2). At the subsequent follow up visit, with clinical failures at TOC carried forward (missing and indeterminates treated as non-successes), resolution rates in the PP population were 85.8% (236/275) for moxifloxacin and 87.9% (254/289) for ofloxacin plus metronidazole (difference 2.1%; 95% CI: -8.0% to 3.1%) (table 2). Clinical resolution rates for the intent to treat (ITT) population were consistent with the PP analyses (table 2). Clinical resolution rates in patient subgroups (defined by age, race, PID severity score, duration of symptoms before entry, concomitant analgesic use, positive syphilis test, and condom use) were consistent with the main clinical efficacy results (data not shown).

Bacteriological response

All patients had a culture and/or polymerase chain reaction (PCR) sample taken from the cervix/endocervix, while 101/275 moxifloxacin patients (37%) and 111/289 ofloxacin plus metronidazole patients (38%) had a sample taken for culture/PCR from the endometrium. In the microbiologically valid population (MBV) population, 158 causative organisms were identified from 112 patients. The most common organisms identified were *C trachomatis* (n = 47) and *N gonorrhoeae* (n = 35) (table 3). Overall, there were no major differences in the distribution of causative organisms between treatment groups.

At TOC, bacteriological success rates in the MBV were 87.5% of patients (49/56) for moxifloxacin and 82.1% of patients (46/56) for ofloxacin plus metronidazole (95% CI: -8.3% to 18.8%). At follow up, with bacteriological failures at TOC carried forward (missing and indeterminates excluded), bacteriological success rates in the MBV population were 81.1% of patients (43/53) for moxifloxacin and 77.8% of patients (42/54) for ofloxacin plus metronidazole (95% CI: -12.6% to 18.6%). Against *C trachomatis* and *N gonorrhoeae*, the bacteriological success rates with moxifloxacin were 88.5% (23/26) and 100% (13/13), respectively. Corresponding success rates for ofloxacin plus metronidazole were 85.7% (18/21) and 81.8% (18/22), respectively (table 3).

With regard to susceptibility against *N gonorrhoeae*, moxifloxacin minimum inhibitory concentration (MIC) values

(n = 7) were 0.004–2 mg/l, and for ofloxacin (n = 7), the corresponding values were 0.008–4.0 mg/l.

Pain scores

Before treatment, the mean pain score for the PP population, as assessed using a visual analogue scale, was 63.8 (20.3) mm and 64.9 (20.6) mm in moxifloxacin versus ofloxacin plus metronidazole treated patients, respectively. At TOC, pain severity had fallen in both treatment groups, down to a mean score of 8.3 (15.6) mm for the moxifloxacin group and 7.3 (15.0) mm for those in the comparator group.

Safety

In the safety population, significantly more patients in the ofloxacin plus metronidazole group experienced adverse events during the study (200/363 (55.1%)) compared with the moxifloxacin group (179/378 (47.4%)) (p = 0.035). Most events were mild to moderate in intensity and resolved or improved by the end of the study.

Similarly, significantly fewer patients in the moxifloxacin group (85 (22.5%)) had a study drug related adverse event versus the comparator group (112 (30.9%)), p = 0.01 (table 4). Gastrointestinal events (particularly nausea, diarrhoea, and vomiting) were the most common drug related events, leading to the greatest number of premature discontinuations (14.3% versus 19.6% for moxifloxacin and comparator, respectively, p = 0.057) (table 4). Of 42 patients (5.7%) who discontinued prematurely because of an adverse event, 24/378 (6.3%) were in the moxifloxacin group, whereas 18/363 (5.0%) were randomised to ofloxacin plus metronidazole (p = 0.41). There were 11 patients experiencing serious adverse events in the moxifloxacin group (2.9%) compared with eight in the ofloxacin plus metronidazole group (2.2%). There were no deaths during the study. One patient in the ofloxacin plus metronidazole group died from AIDS 3 months after the end of the study. There were no differences between groups in relation to changes in laboratory parameters, with the exception of an increase in alanine transaminase levels (moxifloxacin, 2.6% versus ofloxacin plus metronidazole, 8.8%, p = 0.0003).

DISCUSSION

The aims of this study were to compare the efficacy and safety of moxifloxacin, a new fluoroquinolone, used as monotherapy, with a first line dual combination of ofloxacin plus metronidazole. This is the first study in women with PID to compare these two regimens.

Only women with uncomplicated PID were recruited into this study. The low percentage of women requiring hospitalisation for treatment (57/741, 4%) and relatively low pelvic/abdominal tenderness scores (mean of 16.6 points out of a possible 36) reflected the exclusion of women with more severe disease. Diagnosis was based on clinical and laboratory

Table 3 Bacteriological success at test of cure by major diagnosed (culture/PCR) organisms (microbiologically valid population, n = 112)

Organism, No/n patients (%)	Moxifloxacin (n = 56)	Ofloxacin plus metronidazole (n = 56)
<i>Chlamydia trachomatis</i>	23/26* (88.5%)	18/21 (85.7%)
<i>Mycoplasma hominis</i>	11/11 (100%)	16/16 (100%)
<i>Mycoplasma genitalium</i>	3/3 (100%)	1/1 (100%)
<i>Neisseria gonorrhoeae</i>	13/13 (100%)	18/22 (81.8%)
<i>Escherichia coli</i>	5/5 (100%)	4/4 (100%)
Other Gram negatives	3/3 (100%)	1/2 (50%)
<i>Streptococcus agalactiae</i>	3/4 (75.0%)	0/3 (0%)
Other Gram positives	5/8 (62.5%)	5/5 (100%)

*This includes one indeterminate case. Indeterminate was assigned by causative organisms found in endocervix/cervix samples where no repeated sample at test of cure was taken.

Table 4 Number of women with drug related adverse events occurring in at least 1% of patients in either treatment group (intent to treat/safety population)

Adverse event	Moxifloxacin (n = 378)	Ofloxacin plus metronidazole (n = 363)
	No (%)	No (%)
No of women with an event	85 (22.5)	112 (30.9)
Gastrointestinal disorder	54 (14.3)	71 (19.6)
Nausea	31 (8.2)	51 (14.0)
Diarrhoea	9 (2.4)	6 (1.7)
Vomiting	9 (2.4)	6 (1.7)
Abdominal pain (upper)	4 (1.1)	5 (1.4)
Abdominal pain	4 (1.1)	4 (1.1)
Dyspepsia	4 (1.1)	2 (0.6)
Dry mouth	1 (0.3)	4 (1.1)
Flatulence	4 (1.1)	—
General and administration site conditions	13 (3.4)	7 (1.9)
Asthenia	7 (1.9)	4 (1.1)
Infections and infestations	11 (2.9)	17 (4.7)
Vaginal candidiasis	5 (1.3)	9 (2.5)
Vaginal mycosis	4 (1.1)	7 (1.9)
Nervous system disorders	18 (4.8)	32 (8.8)
Headache	6 (1.6)	17 (4.7)
Dizziness	9 (2.4)	9 (2.5)
Taste disturbance	3 (0.8)	14 (3.9)
Psychiatric disorders	2 (0.5)	5 (1.4)
Reproductive system and breast disorders	3 (0.8)	6 (1.7)
Genital pruritus	2 (0.5)	4 (1.1)
Skin and subcutaneous tissue disorders	6 (1.6)	8 (2.2)

criteria, but supported by laparoscopic evidence if laparoscopy was performed.

Moxifloxacin and ofloxacin plus metronidazole were found to have comparable clinical efficacy. Clinical resolution rates were 90.2% for moxifloxacin and 90.7% for ofloxacin plus metronidazole. Both moxifloxacin and the comparator regimen also provided excellent bacteriological efficacy—87.5% for moxifloxacin and 82.1% for ofloxacin plus metronidazole. One point of note is that there were more missing/indeterminate results in the moxifloxacin than the ofloxacin plus metronidazole group (46 v 22, respectively). Essentially, the reasons for patients being categorised as missing/indeterminate were very similar between the moxifloxacin and the ofloxacin plus metronidazole groups for the ITT population: missing information at TOC visit, 15 (33%) v 7 (32%); missing TOC visit, 12 (26%) v 5 (23%); and treatment duration too short, 13 (28%) v 7 (32%). (All other reasons for missing and indeterminate status occurred in ≤ 2 patients per group.) Thus, it seems unlikely that the difference in missing/indeterminate numbers biased the results.

As in other published studies, *C trachomatis* and *N gonorrhoeae* were the most frequently isolated causative organisms and both moxifloxacin and the comparator regimen were highly effective against both of these pathogens, with success rates at TOC of 88.5% and 85.7% (*C trachomatis*) and 100% and 81.8% (*N gonorrhoeae*), respectively. A total of 112 (19.9%) patients out of 564 comprising the PP population were microbiologically valid. This low frequency of isolation can be explained by the fact that only *C trachomatis* and *N gonorrhoeae* were considered causative when identified from cervix/endocervix samples and all other organisms, such as *E coli*, when isolated from these sites were considered to be normal flora.

There are increasing reports of quinolone resistant gonococcal infection throughout the world.^{18–19} Elevated ciprofloxacin MICs have been associated with mutations of the *gyrA* and *parC* genes and high level resistance (MICs 8–64 mg/l) is associated with double mutations in the *parC* gene.^{20–21} In this study, the overall incidence of *N gonorrhoeae* (with or without another causative organism) from any site (cervix, endocervix, or

endometrium) was 5.1% (14/275 patients) for the moxifloxacin group and 7.6% (22/289 patients) for the comparator group. Given this relatively low incidence and the limited number of *N gonorrhoeae* isolates with MIC testing (n = 7), the resulting MIC values of moxifloxacin do not allow any definitive conclusions to be drawn with regard to moxifloxacin's coverage of drug resistant strains. Further studies designed to explore this problem would be of interest and would allow more definitive conclusions to be drawn on this topic. Nevertheless, eradication rate at TOC for isolates exposed to moxifloxacin (n = 13 in the MBV population) and the overall clinical outcome do not suggest any potential limitation in eradicating *N gonorrhoeae*. The proportion of women in the study infected with chlamydia or gonorrhoea is similar to that found in other PID studies: 17%,¹⁵ 30%,²² and 39%.⁸ Studies with higher rates of isolation of *C trachomatis* and *N gonorrhoeae* were typically undertaken on populations with a higher proportion of patients at risk for sexually transmitted infections; for example, in the PEACH study 75% of subjects were African-American versus 34% of patients with black ethnicity in the current study.⁹

There has been one previous study of oral moxifloxacin in uncomplicated PID. In this study, moxifloxacin, 400 mg once daily, was compared with doxycycline, 100 mg twice daily, plus metronidazole, 400 mg three times daily, for 14 days.¹⁵ The combination group also received a single dose of ciprofloxacin, 500 mg, on the first day of therapy. Here, too, the clinical and bacteriological success rates for moxifloxacin were high: 96.6% (224/232 patients) and 92.5% (37/40 patients) at 2–14 days post-therapy, respectively. For comparison, clinical and bacteriological success rates in the combination group were 98.0% (198/202 patients) and 88.2% (30/34 patients), respectively.¹⁵ Aggregated data of outpatient antibiotic regimens, currently used for acute uncomplicated PID, indicate short term clinical and bacteriological success rates of at least 70%, with some regimens providing bacteriological success rates above 90%. Hence, moxifloxacin appears to provide at least comparable efficacy to regimens in current use.¹

From a safety perspective, both treatments appeared to be well tolerated, though there was a significantly lower

incidence of all adverse events and drug related events in the moxifloxacin group compared with ofloxacin plus metronidazole. In particular, there was a trend for lower rates of gastrointestinal tract adverse events (14% versus 20%), such as nausea and diarrhoea, and nervous system events (5% versus 9%), such as headache and dizziness with moxifloxacin versus the comparator. Heystek *et al* also found that moxifloxacin was well tolerated and associated with fewer gastrointestinal events than ciprofloxacin plus doxycycline plus metronidazole.¹⁵ The type and incidence of adverse events with moxifloxacin did not differ from those previously reported for this agent—cumulative data from clinical trials and post-marketing studies from over 50 000 patients also support the favourable safety profile of moxifloxacin.^{15 23}

Compliance with recommended regimens for PID is a well recognised concern in clinical practice,²⁴ which may relate to the complexity of regimens and frequency of side effects. A recent study in PID by Dunbar-Jacob *et al* (part of the PEACH study) found low adherence to a twice daily regimen of oral doxycycline in an outpatient setting, suggesting the need to determine the effectiveness of antibiotic regimens involving longer dosing intervals.²⁵ The investigators found that the study participants took an average of only 70% of prescribed doses with an unscheduled drug holiday for around 25% of their outpatient days. From a compliance perspective, it is possible that the once daily dose regimen and good gastrointestinal tolerability of moxifloxacin may improve patient adherence to therapy.

Reviewing the study design, the randomised, double blind approach and large numbers of patients (more than 200 in each treatment arm for the PP population) represented strengths, helping to avoid any bias and ensuring an even distribution of baseline characteristics among each treatment group. An established scoring system (modified McCormack score)²⁶ for assessing abdominal and pelvic tenderness permitted an objective evaluation of severity and clinical response to treatment. Diagnosing women using accepted clinical criteria for PID, knowing that not all women have microbiological evidence of PID, enabled the results to be extrapolated to typical clinical practice. Furthermore, as all patients in the present study were systematically screened for *N gonorrhoeae* and *C trachomatis*, this large, multinational, PID study, with a population representative of the overall population with PID, may reflect the true incidence of these organisms in acute PID. Indeed, the incidences are rather low. One reason for this could be that the role of the endogenous vaginal flora in causing PID is commonly underestimated.

In conclusion, this study showed that 14 days of monotherapy with oral moxifloxacin, 400 mg once daily, is clinically and bacteriologically comparable to 14 days' combination therapy with oral ofloxacin, 400 mg twice daily, plus oral metronidazole, 500 mg twice daily, in women with uncomplicated PID and was associated with fewer adverse events and drug related adverse events. Because of similar efficacy, better safety, and potential for improved compliance, moxifloxacin may be considered one of the first line antibiotic regimens for PID.

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This study was supported by a grant from Bayer HealthCare.

Competing interests: No competing interests are declared for HC, TP, IR, or DV. JR has received payment as a consultant and lecturer, and sponsorship to attend medical conferences from Bayer HealthCare. JR is an associate editor of *Sexually Transmitted Infections*. AK, MA, PA, and PR are employees of Bayer HealthCare.

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