Doxycycline versus azithromycin for the treatment of anorectal *Chlamydia trachomatis* infection in women concurrent with vaginal infection (CHLAZIDOXY study): a multicentre, open-label, randomised, controlled, superiority trial

*Olivia Peuchant, Edouard Lhomme, Pervenche Martinet, Anne Grob, Dounia Baïta, Claire Bernier, Sophie Anne Gibaud, Isabelle Le Hen, Erwan Le Naour, Nathalie Trignol-Viguier, Philippe Lanotte, Philippe Lefebvre, Anne Vachée, Thomas Girard, Julien Loubinoux, Cécile Bébéar, Bellabes Ghezzoul, Caroline Roussillon, Marion Kret, Bertille de Barbeyrac, and the CHLAZIDOXY Study Group**

Summary

Background Anorectal infections with *Chlamydia trachomatis* are commonly found in women. Although the efficacy of doxycycline and azithromycin is comparable in the treatment of urogenital infection, their efficacies toward anorectal infection remain unclear. We therefore aimed to compare a single dose of azithromycin with a 7-day course of doxycycline for the treatment of anorectal *C trachomatis* infection in women with concurrent vaginal infection.

Methods We did a multicentre, open-label, randomised, controlled, superiority trial involving four sexually transmitted infection screening centres and three pregnancy termination centres in France. We included sexually active adult women (≥18 years) with a positive *C trachomatis* vaginal swab who agreed to provide self-collected anorectal swabs for *C trachomatis* detection. Participants were randomly assigned (1:1), using block sizes of six and eight and stratification by each investigating centre, to orally receive either azithromycin (a single 1-g dose, with or without food) or doxycycline (100 mg in the morning and evening at mealtimes for 7 days [ie, 100 mg of doxycycline twice per day for 7 days]). All laboratory staff who did the bacteriological analyses, but not the participants and the investigators, were masked to the treatment groups. The primary outcome was the microbiological anorectal cure rate defined as a *C trachomatis*-negative nucleic acid amplification test (NAAT) result in anorectal specimens 6 weeks after treatment initiation among women who had a baseline *C trachomatis*-positive anorectal NAAT result. The primary analysis was done in the modified intention-to-treat population, with multiple imputation, which included all women who underwent randomisation and had a *C trachomatis*-positive vaginal and anorectal NAAT result at baseline. Adverse events were reported in all women who underwent randomisation. This study is registered with ClinicalTrials.gov, number NCT03532464.

Findings Between Oct 19, 2018, and April 17, 2020, we randomly assigned a total of 460 participants to either the doxycycline group (n=230) or the azithromycin group (n=230). Four (1%) of 460 participants were excluded because they refused to take doxycycline or were found to be ineligible after randomisation. Among the 456 participants, 357 (78%) had a concurrent *C trachomatis*-positive anorectal NAAT result at baseline; 184 (52%) of 357 were in the doxycycline group and 173 (48%) were in the azithromycin group (ie, the modified intention-to-treat population). Microbiological anorectal cure occurred in 147 (94%) of 156 participants in the doxycycline group (28 missing values) versus 120 (85%) of 142 in the azithromycin group (31 missing values; adjusted odds ratio with imputation of missing values 0·43 [95% CI 0·21–0·91]; p=0·0274). Reported adverse events possibly related to treatment were notified in 53 (12%) of 456 women: 24 (11%) of 228 in the doxycycline group and 29 (13%) of 228 in the azithromycin group. Gastrointestinal disorders were the most frequently occurring, in 43 (9%) of 456 women: 17 (8%) of 228 in the doxycycline group and 26 (11%) of 228 in the azithromycin group.

Interpretation The microbiological anorectal cure rate was significantly lower among women who received a single dose of azithromycin than among those who received a 1-week course of doxycycline. This finding suggests that doxycycline should be the first-line therapy for *C trachomatis* infection in women.

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For the French translation of the abstract see **online** for appendix 1

*Members listed in appendix 2

Laboratoire de Bactériologie, Centre National de Référence des Infections Sexuellement Transmissibles Bactériennes (O Peuchant PharmD, Prof C Bébéar MD, B de Barbeyrac PharmD), **Pôle Santé Publique, Service d'information Médicale** (E Lhomme MD, M Kret MSc), **Centre d'Orthogénie** (D Baïta MD), **Département de Pharmacie** (B Ghezzoul MD), **and Direction de la Recherche Clinique et de l'innovation, Unité de Sécurité et Vigilance des Essais Cliniques** (C Roussillon MD), **CHU Bordeaux, Bordeaux, France; CeGIDD, Département des Bouches du Rhône, Marseille, France** (P Martinet MD, A Grob MD); **CeGIDD, Department des Maladies Infectieuses, INSERM UIC 1413** (C Bernier MD) **and Laboratoire de Bactériologie** (S A Gibaud MD), **CHU Nantes, Nantes, France; CeGIDD, Département de la Gironde, Bordeaux, France** (I Le Hen MD); **Laboratoire Exalab, Bordeaux, France** (E Le Naour PharmD); **Centre d'Orthogénie** (N Trignol-Viguier MD) **and Laboratoire de Bactériologie** (Prof P Lanotte PharmD), **CHRU Tours, Tours, France; Centre d'Orthogénie** (P Lefebvre MD) **and Laboratoire de Bactériologie** (A Vachée PharmD), **CH Roubaix,**

Introduction

Chlamydia trachomatis is the most commonly reported bacterial sexually transmitted infection (STI).[1] Screening studies showed large differences in infection rates depending on the population tested, ranging from 1–3% in the general population to 10–15% in individuals attending an STI screening centre or among women requesting an abortion.[2–5] Up to 75% of *C trachomatis*-

Roubaix, France; Espace Santé Jeunes Guy Moquet, Hôpital Hôtel-Dieu, AP-HP, Paris, France (T Girard MD); Service de Bactériologie, Hôpital Cochin, AP-HP Centre–Université de Paris, Paris, France (J Loubinoux PharmD)

Correspondence to: Assist Prof Bertille de Barbeyrac, USC EA3671 Infections Humaines à Mycoplasmes et Chlamydiae, Université de Bordeaux, 33076 Bordeaux Cedex, France
bertille.de-barbeyrac@u-bordeaux.fr

See Online for appendix 2

Research in context

Evidence before this study

We searched PubMed for articles published until Sept 8, 2021, using the terms "Chlamydia trachomatis", "rectal", "azithromycin", "doxycycline", and "trial". We reviewed 59 publications and identified 11 studies: two randomised controlled trials done in men who had sex with men and nine observational studies. The overall microbiological cure rates in the 11 studies, according to a meta-analysis of these studies, were 96·9% in the doxycycline group and 82·7% in the azithromycin group, with doxycycline having a higher microbiological cure rate than azithromycin (risk ratio 1·21 [95% CI 1·15–1·28]; p<0·05). However, the number of studies focusing on women was insufficient, and women only accounted for approximately 19% of patients in the total population analysed. More studies about women and randomised controlled trials are warranted to provide more comprehensive evidence for the effects of doxycycline and azithromycin on rectal chlamydia.

Added value of this study

The Chlazidoxy trial is the first randomised controlled trial to compare doxycycline and azithromycin for the treatment of anorectal chlamydial infection in women. Our findings add to the evidence that doxycycline is superior to azithromycin for the treatment of anorectal *C trachomatis* infection in women.

Implications of all the available evidence

Our results showed that doxycycline is more effective than azithromycin for the treatment of anorectal infection concurrent with vaginal infection in women. Together with previous evidence, the results from the Chlazidoxy trial support that doxycycline should be the preferred first-line treatment for *C trachomatis* infection.

infected women are asymptomatic. *C trachomatis* can also cause anorectal infections, which are typically asymptomatic.[6] The proportion of women having a rectal *C trachomatis* infection among those positive for urogenital *C trachomatis* ranges between 45% and 100%.[7] The anal transmission of *C trachomatis* in women might occur by autoinoculation from the vagina due to the close proximity of the vagina and the anus.[8,9] Moreover, women might become infected with *C trachomatis* orally through various sexual activities and the organisms could establish a persistent infection in the lower gastrointestinal tract where the immune response is downregulated, suggesting the potential role of autoinoculation of cervical chlamydial infection from the rectal site.[10] Such repeated urogenital infections could lead to reproductive tract morbidity.

For uncomplicated *C trachomatis* urogenital infections, the recommended treatments according to European guidelines are azithromycin 1 g orally as a single dose or doxycycline 100 mg orally twice a day for 7 days.[11] The overall efficacy of both treatments is similar in urogenital infections, with 94·3% for azithromycin and 97·4% for doxycycline.[12]

Adequate treatment for anorectal *C trachomatis* is recently under debate. A meta-analysis of observational studies found a pooled treatment efficacy of 82·9% for single-dose azithromycin and 99·6% for doxycycline twice per day for 7 days.[13] More recently, a meta-analysis including two randomised controlled trials in men who have sex with men and nine observational studies reported that the overall microbiological cure rates were 82·7% in the azithromycin group and 96·9% in the doxycycline group, with doxycycline having a higher microbiological cure rate than azithromycin (risk ratio 1·21 [95% CI 1·15–1·28]; p<0·05).[14] Nevertheless, in these rectal *C trachomatis* treatment studies, women are largely underrepresented, and no randomised controlled trials of rectal infections are available in women.

In women, if rectal *C trachomatis* is a hidden reservoir influencing transmission rates, further evidence for the need of effective rectal treatments is highly relevant, considering the potential complications of cervical infections. In this study, we aimed to compare a single dose of azithromycin with a 7-day course of doxycycline for the treatment of anorectal *C trachomatis* infection in women with concurrent vaginal infection.

Methods

Study design and participants

We did a multicentre, open-label, randomised, controlled, superiority trial involving four STI screening centres (Bordeaux, Marseille, Nantes, and Paris) and three pregnancy termination centres (Bordeaux, Roubaix, and Tours) in France. Full details about the study design can be found in the study protocol.[15]

Inclusion and exclusion criteria were described in the study protocol.[15] Briefly, those who were eligible were sexually active adult women (≥18 years) diagnosed with a urogenital *C trachomatis* infection who did not report recent (<3 weeks) use of antibiotics at enrolment or had no symptoms suggestive of pelvic inflammatory disease and were a member or beneficiary of a social security system. All eligible women were tested for urogenital *C trachomatis* infection according to the French guidelines.[16]

We obtained written informed consent from all participants. This study was done in accordance with the Declaration of Helsinki and national legislation. The study received ethics approval (CPP Sud-Est II approval number 2017-74-2) and was authorised by the French regulatory authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé, reference IDRCB 2017-002595-15).

Randomisation and masking

Eligible participants were randomly assigned (1:1) to receive orally either a single 1-g dose of azithromycin or 100 mg of doxycycline twice per day for 7 days. The randomisation list was generated before the beginning of the trial by the statistician of the central clinical trial unit. Randomisation was balanced by random block sizes of six and eight and stratified by each investigating centre. A validated web-based system (Ennov Clinical software [version 8.1.100.7]) was used to implement the random assignment to each group. Only the statisticians knew the content of the randomisation list, including block sizes. Randomisation of patients was done by the investigators in the centres using the electronic case report form at the inclusion visit. Antibiotics were dispensed in their usual packaging with a clinical trial label. Allocated treatment was not masked to participants or study investigators; however, the treatment group was masked to all laboratory technicians who did the bacteriological analyses on the primary outcome.

Procedures

Women with a vaginal *C trachomatis*-positive nucleic acid amplification test (NAAT) were approached by a study investigator who explained the trial, assessed their eligibility criteria, and obtained consent. Participants provided a self-collected anorectal swab and were randomly assigned to either the azithromycin group or the doxycycline group. In the azithromycin group, participants took four 250-mg tablets as a single dose (ie, a single 1-g dose of azithromycin), with or without food. In the doxycycline group, women were instructed to take a single 100-mg tablet in the morning and in the evening for 7 days (ie, 100 mg of doxycycline twice per day for 7 days), at mealtimes with a glass of water and at least 1 h before bedtime. The demographic characteristics, biological data, and clinical data were collected on the electronic case report form.[15] Sexual behaviour was assessed by self-reporting through anonymous completion of a paper questionnaire. The inclusion and randomisation of all women with a vaginal *C trachomatis*-positive NAAT before knowing the NAAT result of the anorectal specimen at baseline was justified for our secondary outcome concerning the prevalence of anorectal *C trachomatis* infection concomitant to a vaginal infection and to not delay treatment.

A test-of-cure appointment was scheduled 6 weeks after treatment initiation. During this follow-up visit, the study investigator looked at the result of *C trachomatis* detection for the anorectal swab done at enrolment. If the result was negative, the study ended. If the result was positive, the participant provided self-collected vaginal and anorectal swabs for *C trachomatis* detection. On the electronic case report form, the study investigator completed a questionnaire about drug adherence by counting the doxycycline tablets in the box or based on the participant's response if the box was not returned and about antibiotic tolerance by answering questions on any adverse events (ie, diarrhoea, nausea, or vomiting). Clinical data during the last 6 weeks and information about the use of other antibiotics were collected. Participants completed a self-reported questionnaire about their sexual behaviour during the last 6 weeks and their partners' treatment. At this stage, a new visit was scheduled 4 months after treatment initiation only for women with a single *C trachomatis*-positive anorectal swab. During this second follow-up visit, women again provided self-collected vaginal and anorectal swabs for *C trachomatis* detection. The study investigator collected information about taking other antibiotics, clinical data, and any adverse event since the last visit. Participants completed the same questionnaire as before about their sexual behaviour since the last follow-up visit and their partners' treatment.

Vaginal and anorectal swabs were processed and underwent NAAT for *C trachomatis* detection by the provider of laboratory analyses for each centre (appendix 2 p 3). All *C trachomatis*-positive specimens were sent to the French National Reference Center for bacterial STIs for genotyping and determination of *C trachomatis* load. DNA was extracted using the automated MagNA Pure 96 isolation and purification system (Roche Diagnostics, Meylan, France). Genovar was determined by sequencing the *omp*A gene.[17] Quantification for *C trachomatis* DNA was adapted from Stevens and colleagues' study.[18] For absolute quantification, the method was optimised as follows: the *omp*A PCR products were cloned into the pGEM-T easy vector (Promega Corporation, Charbonnieres les Bains, France) according to the manufacturer's protocol. The concentration of the plasmid was determined and converted to correspond to *C trachomatis* copies per mL. The limit of detection was determined by using ten-fold serial dilutions of the plasmid. A standard curve was generated by plotting threshold cycle values against the log-transformed DNA copy numbers. Quantitative PCR was done using a LightCycler 480 real-time PCR system (Roche Diagnostics, Meylan, France). The limit of detection was 23 copies per mL. We assigned to all samples with a load below the detection limit a load equal to half of this minimum load.

Outcomes

The primary outcome was the microbiological cure rate defined as an anorectal *C trachomatis*-negative NAAT result at the test-of-cure visit at 6 weeks after treatment initiation among women with a *C trachomatis*-positive anorectal swab at baseline. Secondary outcome measures were the prevalence of anorectal *C trachomatis* infection concurrent with urogenital infection—defined at baseline by the number of women with an anorectal *C trachomatis* infection divided by the total number of women included in the study—and the possibility of autoinoculation from

rectum to vagina using sexual behaviour data and genotyping results of anorectal-positive swabs at 6 weeks and of vaginal-positive swabs at 4 months.

Bacterial load was an exploratory post-hoc analysis; vaginal and anal load in both groups at baseline and at 6 weeks were compared and the effect of the anal bacterial load on the efficacy of both antibiotics was evaluated. Adverse events were recorded by the investigators at each visit. All adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 5.0), in which grade 1 is mild, grade 2 is moderate, grade 3 is severe, and grade 4 is potentially life-threatening. Serious adverse events were reported immediately to the safety and vigilance unit of the funder.

Statistical analysis

For the sample size calculation, we assumed a rate of successful treatment of anorectal *C trachomatis* infection of 99% for doxycycline and 83% for azithromycin, consistent with published data,[13] and a loss to follow-up of 10%. As the sample size calculation was based on a primary analysis with a hypothesis of superiority of doxycycline versus azithromycin, with a conservative replacement of missing values by a failure of the treatment, the sample size was estimated at 149 patients per group to compare 89·1% (99%×0·9=89·1%) versus 74·7% (83%×0·9=74·7%), with a two-sided type 1 error rate of 5% and a power of 90%. We made the conservative assumption of a prevalence of 65% of *C trachomatis* anorectal infection concurrent with a vaginal infection at inclusion based on our unpublished pilot study, so we had to include 230 patients per group (460 in total).

The primary analysis was done in the modified intention-to-treat population, which included all women who underwent randomisation and had a *C trachomatis*-positive vaginal and anorectal NAAT result at baseline (uninterpretable anorectal NAAT results were excluded). Secondary analyses were done in the complete case population, which included the modified intention-to-treat participants with an available and interpretable anorectal NAAT result at 6 weeks, and in the per-protocol population, which included all the participants of the complete case population except those who did not complete the self-reported questionnaire, had unprotected sex with untreated partners, took active *C trachomatis* antibiotics during follow-up, had been reinfected with a new strain, had taken fewer than ten tablets of doxycycline, or had vomited after azithromycin intake or in the 3 h following the intake of doxycycline. Contrary to what was planned in the study size calculation, all analyses of the primary outcome were done with multiple imputation by fully conditional specification to take missing values into account. This change in strategy was made when the statistical analysis plan was drafted before the analysis of the primary outcome. Multiple imputation appeared to be the most relevant strategy because the number of events was less than the number of missing values. The missing equals failure strategy was done as a sensitivity analysis. Safety analyses included all randomly assigned participants.

Baseline participant characteristics, genovars, bacterial loads, and adverse events were described: qualitative variables were expressed as proportions and quantitative variables as either means with SDs or medians with IQRs, as appropriate. For the unadjusted differences, the Wald asymptotic confidence limits based on the normal approximation to the binomial distribution was calculated. For the adjusted differences, the counterfactual principal was used, and the 95% CIs were calculated using a bootstrap resampling method. Odds ratios (ORs), confidence intervals, and p values were obtained using a mixed logistic regression model with a random effect on centre. The multiple imputation model was stratified on the treatment group and adjusted for centre; demographics (age, country of birth, marital status, education level, and professional status); history of STIs, abortion, miscarriage, and pregnancy; and clinical inclusion data (recent abnormal discharge, non-menstrual bleeding, itching, urinary pain, painful sexual intercourse, anal discharge, sensation of needing to have a bowel movement, and anal pain). Using this model, 20 complete datasets were generated, 20 independent analyses were done, and then the results of these analyses were pooled, according to Rubin's rules.

All tests were two-sided with a type 1 error of 0·05, and the prevalence of anorectal *C trachomatis* infection concurrent with urogenital infection was calculated with 95% CIs.

All analyses were done using SAS (version 9.4). The statistical analysis plan is summarised in appendix 2 (pp 16–32). This study is registered with ClinicalTrials.gov, number NCT03532464.

Role of the funding source

The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Oct 19, 2018, and April 17, 2020, 460 women with a *C trachomatis*-positive vaginal swab were enrolled and randomly assigned to either the doxycycline group (n=230) or the azithromycin group (n=230; figure). Four (1%) of 460 participants were excluded because they refused to take doxycycline or were found to be ineligible after randomisation. The median lag time between vaginal sample collection at baseline and the study enrolment visit was 7 days (IQR 5–9). A total of 357 (78%) of 456 women had an anorectal *C trachomatis* infection. Of these 357 women in the modified intention-to-treat population, 184 (52%) were included in the doxycycline group and 173 (48%) in the azithromycin group. A total of 298 participants completed the follow-up protocol at

6 weeks and were included in the complete case analysis: 156 (52%) in the doxycycline group and 142 (48%) in the azithromycin group. No protocol changes occurred during the trial.

Women evaluated at baseline (n=456), those in the modified intention-to-treat population (n=357), and those in the complete case population (n=298) did not differ regarding demographic characteristics (age, country of birth, marital status, education level, and professional status), history of STIs, and sexual behaviour, except for genital symptoms (table 1). 416 (91%) of 456 participants evaluated at baseline reported no anal symptoms and 163 (36%) reported a history of anal sex, but 393 (86%) reported oral intercourse in their lifetime. Women from STI screening centres presented higher risk factors for STI than those requesting an abortion (appendix 2 pp 4–5). Almost all patients reported good adherence to treatment (appendix 2 p 6).

Data for the primary outcome measured at week 6 were missing for 28 (15%) of 184 women in the doxycycline group and for 31 (18%) of 173 in the azithromycin group. NAAT results for the modified intention-to-treat population are summarised in appendix 2 (p 7). In this population, microbiological anorectal cure occurred in 147 (94%) of 156 women in the doxycycline group and in 120 (85%) of 142 in the azithromycin group with an adjusted OR of 0·43 (95% CI 0·21–0·91; p=0·0274) in the primary analysis with multiple imputation of missing values (table 2). This result was consistent in the planned secondary analyses in the complete case population and the per-protocol population (table 2) and in the sensitivity analysis (appendix 2 p 8).

At baseline, the chlamydial load in the vaginal and anorectal swabs was similar in the two randomised groups (appendix 2 p 13). The median chlamydial load was approximately 50 times higher in the vagina than in the anus. Successful genotyping identified the same genovar in concurrent vaginal and anorectal swabs in 230 women and a different genovar in five women (appendix 2 p 9). Genovar E was the most frequent, followed by genovars F and G. No lymphogranuloma venereum genovar was identified. No difference in *C trachomatis* load was observed between genovars (appendix 2 p 14). In both groups, the anorectal chlamydial load at baseline was approximately ten times higher in women with treatment failure than in those with microbiological cure (appendix 2 p 15).

At 6 weeks, 16 women were *C trachomatis*-negative in the vaginal swab but *C trachomatis*-positive in the anorectal swab and had a visit rescheduled at 4 months. Three women were lost to follow-up. In the doxycycline group, all four participants cleared their anorectal infection at 4 months. Among the nine participants in the azithromycin group, two (22%) cleared their anorectal infection. Five (56%) of nine women had persistent *C trachomatis* anorectal infection, with the same strain as at baseline (based on genotyping results and sexual behaviour; table 3). One (11%) of nine women had a new vaginal infection, with a different genovar at the end of the trial than the one identified at baseline. In the last case, autoinoculation from the rectum to the vagina probably occurred, as evidenced by identification of the same genovar throughout the study and the report of sexual intercourse with her regular treated partner (table 3).

Adverse events possibly related to treatment were notified in 53 (12%) of 456 women; 24 (11%) of 228 in the doxycycline group and 29 (13%) of 228 in the azithromycin group (appendix 2 pp 10–12).

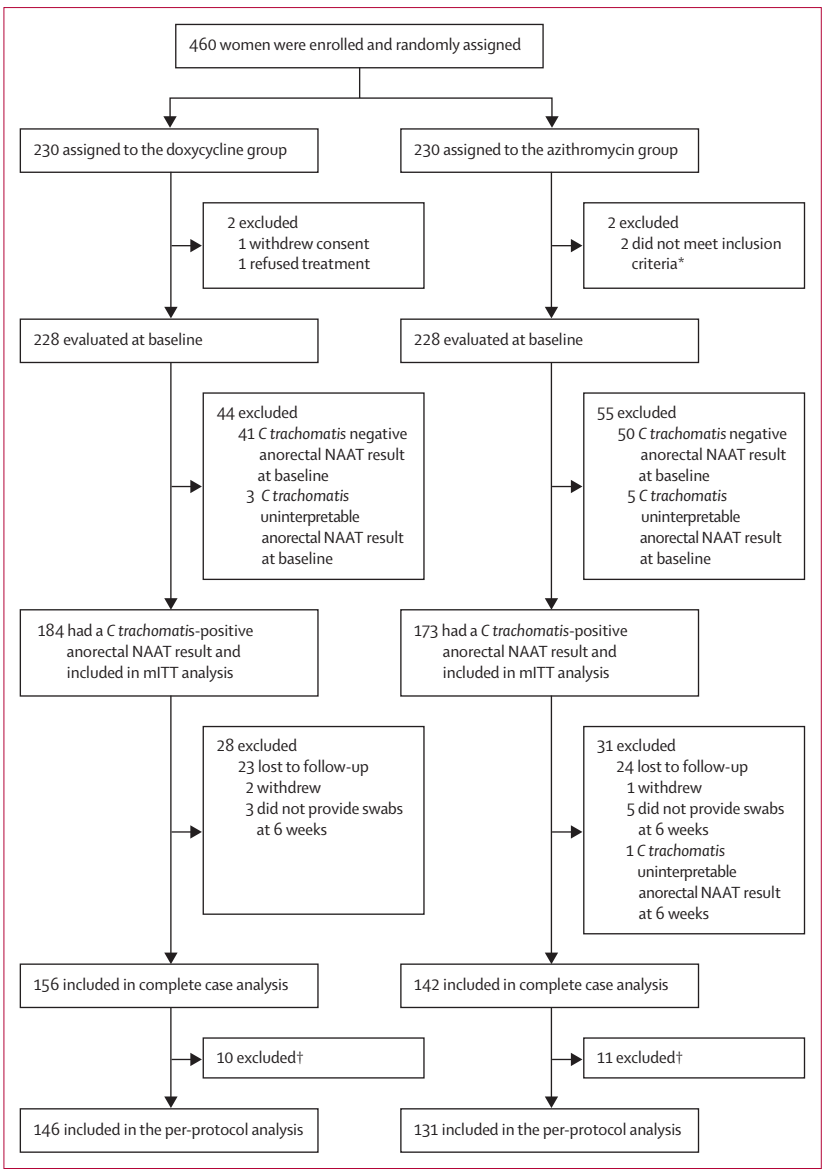

***Figure*: Trial profile**
mITT=modified intention-to-treat. *One woman was pregnant and the other had pelvic inflammatory disease. †The per-protocol population consisted of the complete case population with exclusion of women who had unprotected sex with untreated partners (n=13), did not complete the self-reported questionnaire (n=3), took active *Chlamydia trachomatis* antibiotics during follow-up (n=2), or who were reinfected with a new strain (n=3).

	Population evaluated at baseline			Modified intention-to-treat population			Complete case population		
	Total (n=456)	Doxycycline (n=228)	Azithromycin (n=228)	Total (n=357)	Doxycycline (n=184)	Azithromycin (n=173)	Total (n=298)	Doxycycline (n=156)	Azithromycin (n=142)
Age (years)	22 (19–24)	21 (20–24)	22 (19–25)	21 (19–24)	21 (19–24)	21 (19–24)	21 (19–24)	21 (19–24)	21 (19–24)
Country of birth									
France (including Overseas France)	401 (88%)	200 (88%)	201 (88%)	314 (88%)	163 (89%)	151 (87%)	266 (89%)	137 (88%)	129 (91%)
Other	55 (12%)	28 (12%)	27 (12%)	43 (12%)	21 (11%)	22 (13%)	32 (11%)	19 (12%)	13 (9%)
Marital status									
Single	305 (67%)	157 (69%)	148 (65%)	242 (68%)	129 (70%)	113 (65%)	205 (69%)	114 (73%)	91 (64%)
In a relationship	151 (33%)	71 (31%)	80 (35%)	115 (32%)	55 (30%)	60 (35%)	93 (31%)	42 (27%)	51 (36%)
Education level*									
High	323 (71%)	159 (70%)	164 (72%)	256 (72%)	124 (67%)	132 (76%)	226 (76%)	115 (74%)	111 (78%)
Low	133 (29%)	69 (30%)	64 (28%)	101 (28%)	60 (33%)	41 (24%)	72 (24%)	41 (26%)	31 (22%)
Professional status									
Employed	166 (36%)	88 (39%)	78 (34%)	131 (37%)	74 (40%)	57 (33%)	106 (36%)	60 (38%)	46 (32%)
Student	217 (48%)	104 (46%)	113 (50%)	173 (48%)	82 (45%)	91 (53%)	150 (50%)	73 (47%)	77 (54%)
Other†	73 (16%)	36 (16%)	37 (16%)	53 (15%)	28 (15%)	25 (14%)	42 (14%)	23 (15%)	19 (13%)
History of STI									
Yes	92 (20%)	42 (18%)	50 (22%)	70 (20%)	35 (19%)	35 (20%)	57 (19%)	31 (20%)	26 (18%)
No	353 (77%)	180 (79%)	173 (76%)	277 (78%)	143 (78%)	134 (77%)	233 (78%)	120 (77%)	113 (80%)
Unknown	11 (2%)	6 (3%)	5 (2%)	10 (3%)	6 (3%)	4 (2%)	8 (3%)	5 (3%)	3 (2%)
HIV serology									
Positive	0	0	0	0	0	0	0	0	0
Negative	375 (82%)	189 (83%)	186 (82%)	291 (82%)	154 (84%)	137 (79%)	250 (84%)	137 (88%)	113 (80%)
Unknown	81 (18%)	39 (17%)	42 (18%)	66 (18%)	30 (16%)	36 (21%)	48 (16%)	19 (12%)	29 (20%)
Genital and anal symptoms									
Genital symptoms									
No symptom	236 (52%)	130 (57%)	106 (46%)	173 (48%)	99 (54%)	74 (43%)	145 (49%)	85 (54%)	60 (42%)
≥1 symptoms	220 (48%)	98 (43%)	122 (54%)	184 (52%)	85 (46%)	99 (57%)	153 (51%)	71 (46%)	82 (58%)
Anal symptoms									
No symptom	416 (91%)	211 (93%)	205 (90%)	327 (92%)	171 (93%)	156 (90%)	271 (91%)	146 (94%)	125 (88%)
≥1 symptoms	40 (9%)	17 (7%)	23 (10%)	30 (8%)	13 (7%)	17 (10%)	27 (9%)	10 (6%)	17 (12%)
Sexual behaviour‡									
Age of first sexual intercourse (years)									
10–14	26 (6%)	14 (6%)	12 (5%)	20 (6%)	10 (5%)	10 (6%)	15 (5%)	8 (5%)	7 (5%)
15–19	378 (83%)	187 (82%)	191 (84%)	295 (83%)	153 (83%)	142 (82%)	247 (83%)	128 (82%)	119 (84%)
20–24	43 (9%)	24 (11%)	19 (8%)	36 (10%)	19 (10%)	17 (10%)	32 (11%)	18 (12%)	14 (10%)
≥25	8 (2%)	3 (1%)	5 (2%)	5 (1%)	2 (1%)	3 (2%)	4 (1%)	2 (1%)	2 (1%)
Sexual partner in the last 12 months									
Only regular	130 (29%)	61 (27%)	69 (30%)	100 (28%)	47 (26%)	53 (31%)	79 (27%)	35 (22%)	44 (31%)
Only occasional	137 (30%)	76 (33%)	61 (27%)	110 (31%)	63 (34%)	47 (27%)	94 (32%)	56 (36%)	38 (27%)
Occasional and regular	170 (37%)	83 (36%)	87 (38%)	132 (37%)	67 (36%)	65 (38%)	116 (39%)	60 (38%)	56 (39%)
Not documented	18 (4%)	8 (4%)	10 (4%)	14 (4%)	7 (4%)	7 (4%)	9 (3%)	5 (3%)	4 (3%)
Use condom for sex with occasional partner	307	159	148	242	130	112	210	116	94
Always	56 (18%)	32 (20%)	24 (16%)	47 (19%)	27 (21%)	20 (18%)	42 (20%)	25 (22%)	17 (18%)
Sometimes	228 (74%)	116 (73%)	112 (76%)	179 (74%)	94 (72%)	85 (76%)	153 (73%)	82 (71%)	71 (76%)
Never	23 (7%)	11 (7%)	12 (8%)	16 (7%)	9 (7%)	7 (6%)	15 (7%)	9 (8%)	6 (6%)
Number of sexual partners in lifetime									
1–5	199 (44%)	102 (45%)	97 (43%)	158 (44%)	81 (44%)	77 (45%)	128 (43%)	67 (43%)	61 (43%)
6–10	110 (24%)	54 (24%)	56 (25%)	89 (25%)	49 (27%)	40 (23%)	80 (27%)	45 (29%)	35 (25%)
≥11	146 (32%)	72 (32%)	74 (33%)	109 (31%)	54 (29%)	55 (32%)	90 (30%)	44 (28%)	46 (32%)

(Table 1 continues on next page)

	Population evaluated at baseline			Modified intention-to-treat population			Complete case population		
	Total (n=456)	Doxycycline (n=228)	Azithromycin (n=228)	Total (n=357)	Doxycycline (n=184)	Azithromycin (n=173)	Total (n=298)	Doxycycline (n=156)	Azithromycin (n=142)
(Continued from previous page)									
Anal sex in lifetime									
Yes	163 (36%)	78 (34%)	85 (37%)	132 (37%)	65 (35%)	67 (39%)	115 (39%)	57 (37%)	58 (41%)
No	292 (64%)	150 (66%)	142 (63%)	224 (63%)	119 (65%)	105 (61%)	183 (61%)	99 (63%)	84 (59%)
Oral sex in lifetime									
Yes	393 (86%)	200 (88%)	193 (85%)	308 (87%)	161 (88%)	147 (85%)	261 (88%)	137 (88%)	124 (87%)
No	62 (14%)	28 (12%)	34 (15%)	48 (13%)	23 (13%)	25 (15%)	37 (12%)	19 (12%)	18 (13%)

Data are median (IQR), n (%), or n. STI=sexually transmitted infection. *High education refers to an undergraduate degree or higher. †Other refers to people searching for employment or who are homemakers. ‡One questionnaire was not completed in the azithromycin group.

Table 1: **Baseline characteristics of participants**

Gastrointestinal disorders were the most frequently occurring, in 43 (9%) of 456 women (17 [8%] of 228 in the doxycycline group and 26 [11%] of 228 in the azithromycin group). Similar percentages of women in both groups reported vomiting (six [3%] of 228 in the doxycycline group and five [2%] of 228 in the azithromycin group), nausea (eight [4%] in the doxycycline group and 17 [7%] in the azithromycin group), and diarrhoea (four [2%] in the doxycycline group and nine [4%] in the azithromycin group). Serious adverse events were notified in nine (2%) of 456 participants and were not related to treatment (one in the doxycycline group and eight in the azithromycin group; appendix 2 pp 10–11).

Discussion

In our randomised controlled trial involving women, a 7-day course of doxycycline was significantly more efficacious than a single 1-g dose of azithromycin for the treatment of anorectal *C trachomatis* infection concurrent with vaginal infection. With analysis in the per-protocol population, we aimed to further reduce bias due to suboptimal treatment compliance and possible *C trachomatis* re-exposure. In doing so, the cure proportions for anorectal infections remained lower in the azithromycin group than in the doxycycline group. Although the difference found on the primary outcome is smaller than that defined in our sample size calculation, which was based on a meta-analysis of observational studies,[13] our finding appears clinically relevant.

Our results are consistent with two recent trials done in a population of men who have sex with men and one prospective study in women, showing a higher efficacy of doxycycline than of azithromycin in treating anorectal *C trachomatis* infections.[19–21] However, the effectiveness of azithromycin in our study (85%) was even higher than what was reported in those studies (71–78·5%). This difference could be explained by the delay of the test to evaluate microbiological cure, done at 6 weeks in our trial but at 4 weeks in the other studies.

	Doxycycline	Azithromycin	Unadjusted difference in proportion (95% CI)	Adjusted difference in proportion (95% CI)	Adjusted odds ratio (95% CI)	p value
Modified intention-to-treat population*						
Total	156	142	..	..	..	..
Number of missing values†	28	31	..	..	..	..
Microbiological anorectal cure	147 (94%)	120 (85%)	−9·7% (−16·7 to −2·7)	−9·2% (−12·8 to −5·6)	0·43 (0·21–0·91)	0·0274
Complete case population‡						
Total	156	142	..	..	..	..
Microbiological anorectal cure	147 (94%)	120 (85%)	−9·7% (−16·7 to −2·7)	−9·9% (−13·4 to −6·4)	0·33 (0·15–0·76)	0·0088
Per-protocol population§						
Total	146	131	..	..	..	..
Microbiological anorectal cure	139 (95%)	112 (85%)	−9·7% (−16·7 to −2·8)	−9·7% (−13·2 to −6·2)	0·30 (0·12–0·74)	0·0095

NAAT=nucleic acid amplification test. *The modified intention-to-treat population consisted of women with a *Chlamydia trachomatis*-positive vaginal and anorectal NAAT result at baseline; uninterpretable anorectal NAAT results were excluded. †Missing data were treated with multiple imputation. ‡The complete case population included the modified intention-to-treat population with NAAT result at 6 weeks; uninterpretable anorectal NAAT results were excluded. §The per-protocol population consisted of the complete case population with exclusion of women who had unprotected sex with untreated partners (n= 13), did not complete the self-administered questionnaire (n=3), took active *C trachomatis* antibiotics during follow-up (n= 2), and those who were reinfected with a new strain (n=3). No women were excluded for poor adherence to treatment.

Table 2: **Microbiological anorectal cure at 6 weeks by treatment group and in each analysis population**

The prevalence of concurrent urogenital and anorectal chlamydia infections was 78%, a finding that was consistent with the results of previous studies.[7,22] In women with urogenital infection, this result leads to the conclusion that testing for chlamydia in the anus is not necessary. Genotyping confirmed that concurrent anorectal and vaginal infections were caused by the same genovar strain in most women, irrespective of reporting anal intercourse. However, the low *C trachomatis* load in the anus limited the success of genotyping. Mathematical models have suggested that most infections in women start at the urogenital location through vaginal intercourse and are then transmitted to the anorectal site through autoinoculation.[23] The

	C trachomatis detection at baseline		Sexual behaviour between baseline and follow-up at 6 weeks	*C trachomatis* detection at 6-week follow-up		Sexual behaviour between follow-up at 6 weeks and at 4 months	*C trachomatis* detection at 4-month follow-up	
	Vaginal swab	Anorectal swab		Vaginal swab	Anorectal swab		Vaginal swab	Anorectal swab
Participant 1	Positive (genovar E)	Positive (genovar ND)	No intercourse	Negative	Positive (genovar E)	Intercourse with an occasional partner; no information about partner's treatment; condom use; no anorectal sex	Negative	Positive (genovar E)
Participant 2	Positive (genovar E)	Positive (genovar ND)	No intercourse	Negative	Positive (genovar E)	No intercourse	Negative	Positive (genovar E)
Participant 3	Positive (genovar G)	Positive (genovar G)	No intercourse	Negative	Positive (genovar ND)	Intercourse with her regular and untreated partner; condom use; anorectal sex	Negative	Positive (genovar G)
Participant 4	Positive (genovar F)	Positive (genovar F)	No intercourse	Negative	Positive (genovar ND)	No intercourse	Negative	Positive (genovar ND)
Participant 5	Positive (genovar F)	Positive (genovar F)	Intercourse with her regular, treated partner; no condom use; no anorectal sex	Negative	Positive (genovar F)	Intercourse with her regular partner; no condom use; no anorectal sex	Negative	Positive (genovar ND)
Participant 6	Positive (genovar F)	Positive (genovar ND)	Intercourse with an occasional partner; partner not treated; condom use; no anorectal sex	Negative	Positive (genovar ND)	Intercourse with her regular partner; no information about regular partner treatment; no condom use; no anorectal sex	Positive (genovar E)	Positive (genovar ND)
Participant 7	Positive (genovar E)	Positive (genovar E)	Intercourse with her regular, treated partner; no condom use; no anorectal sex	Negative	Positive (genovar E)	Intercourse with her regular partner; no condom use; no anorectal sex	Positive (genovar E)	Positive (genovar E)

ND=not determined.

Table 3: **Characteristics of the seven participants with anorectal *Chlamydia trachomatis*-positive results at 4 months in the azithromycin group**

likelihood of such migration might be enhanced by higher genital loads, as we observed. It is now well established that rectal *C trachomatis* is not associated with a history of anal intercourse or rectal symptoms.[7] Some investigators have hypothesised that oral acquisition of *C trachomatis*, via penile–oral sexual intercourse, might lead to rectal infection.[24] Nevertheless, a recent retrospective study did not find an association between preceding oropharyngeal chlamydia and incident anorectal chlamydia.[25]

After treatment, some women did not clear their rectal *C trachomatis* infection, which could subsequently serve as a source of recurrent urogenital *C trachomatis* infection via autoinoculation. The presence of viable strains after treatment indicated positive infectiousness and possible autoinfection from the rectum to the vagina.[26] In our trial, we investigated this hypothesis in women with a single rectal *C trachomatis* infection after treatment (microbiological anal failure). Although the number of women was small, genotyping and sexual behaviour questionnaires showed that autoinoculation occurred in only one patient in the azithromycin group and thus remained scarce. Of note, six women cleared their anal infection, one had a new infection, and five had persistent single rectal *C trachomatis* infection. O*mp*A genotyping is not sensitive enough to enable *C trachomatis* genotyping; higher resolution molecular methods such as whole-genome sequencing would be needed to determine whether the same strain exists throughout the study in each patient. Further studies are needed to provide more definitive evidence for autoinoculation.

We observed that for each randomised group, the chlamydial anal load was higher among participants with treatment failure than in those who had been cured. Similar results have been reported for patients treated with azithromycin but not with doxycycline.[21,26,27] In our study, no specific genovar was associated with treatment failure.

This study has some limitations. First, as regards to treatment, our trial was not blinded; therefore, compliance to a daily dose (as is required for doxycycline) might deter people from resuming sexual activity while undergoing treatment. We originally planned to do this trial using a doubled-blind study design, but for drug manufacturing reasons, we have done this study as an open-label, randomised controlled trial. Despite the absence of blinding, the biologists doing NAAT for *C trachomatis* detection were masked to the drugs taken by the participants. Second, whether our findings can be generalised to the general population at low risk of infection is unknown. Enrolling a low-risk population would have required a larger sample size than our funding mechanism could have supported. Third, samples were patient-collected swabs, and the risk of contamination of the samples due to the short anatomical distance between the vagina and the anus existed. In our study, this risk was ruled out at baseline because the anorectal sample was taken a few days after the vaginal sample, but it cannot be excluded at the follow-up visits. However, patients were well instructed by trained study nurses.[15] Fourth, because our NAAT did not have an internal human control, we cannot rule out the possibility that negative NAAT results were due to inadequate self-sampling.

Fifth, NAATs might detect remnant *C trachomatis* DNA from dead chlamydia. Post-treatment samples should be analysed by techniques detecting viable organisms.[28] Finally, we had 16·5% of missing data (loss to follow-up, withdrawal, or swabs not provided) at 6 weeks, which was high for the primary outcome, yet was well balanced between the two groups. Nevertheless, missing data were accounted for in the analysis by a multiple imputation strategy, which was the most relevant strategy because the event rate was less than the missing values. The results were consistent with our missing equals failure strategy.

In conclusion, our study is the first randomised controlled trial done in women, confirming the higher efficacy of doxycycline than of azithromycin for the treatment of anorectal *C trachomatis* infection. Despite the microbiological anal cure rate being lower with azithromycin treatment than with doxycycline, our results suggested that persistent rectal infection after this treatment rarely causes new urogenital infection by autoinoculation, questioning the switch to doxycycline. Nevertheless, as a 1-g single dose of azithromycin promotes macrolide resistance against *Mycoplasma genitalium* and *Neisseria gonorrhoeae,* it should no longer be used as a first-line therapy in urogenital *C trachomatis* infections in women. Doxycycline should be the recommended first-line treatment, as already proposed in some countries.[29,30]

Contributors

BdB, OP, EL, MK, BG, and CR were involved in the design, establishment, and day-to-day management and implementation of the trial. BdB and OP obtained funding for the trial. PM, DB, CBer, ILH, NT-V, PLe, and TG included participants in the trial. AG, SAG, ELN, PLa, AV, JL, and CBéb were responsible for biological analyses. EL and MK were in charge of data curation and accessed and verified the data. MK was involved in the statistical analyses. OP, BdB, EL, and MK wrote the original draft of the manuscript. All authors contributed to refinement of and approved this manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

EL has received funding from the French Ministry of Health via their institution. All other authors declare no competing interests.

Data sharing

The individual participant data underlying the results—ie, the results presented in this Article, after de-identification (text, tables, figures, and appendices)—will be shared. The data are not publicly available due to containing information that could compromise the privacy of research participants. The protocol trial is freely accessible online. Data availability will start 3 months and end 24 months after publication of the Article. To request the dataset for a meta-analysis of individual participant data, please address directly to the corresponding author (bertille.de-barbeyrac@u-bordeaux.fr) or to the sponsor's representative (recherche.interne@chu-bordeaux.fr) to obtain a data access form. All requests will be evaluated by the Trial Management Team and the sponsor. For accepted requests, data will be shared after signing a data transfer agreement with the study sponsor to be in compliance with the General Data Protection Regulation.

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References

1 Rowley J, Vander Hoorn S, Korenromp E, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. *Bull World Health Organ* 2019; **97:** 548–62P.

2 Goulet V, de Barbeyrac B, Raherison S, Prudhomme M, Semaille C, Warszawski J. Prevalence of *Chlamydia trachomatis*: results from the first national population-based survey in France. *Sex Trans Infect* 2010; **86:** 263–70.

3 Kersaudy-Rahib D, Lydie N, Leroy C, et al. Chlamyweb Study II: a randomised controlled trial (RCT) of an online offer of home-based *Chlamydia trachomatis* sampling in France. *Sex Trans Infect* 2017; **93:** 188–95.

4 Peuchant O, de Diego S, Le Roy C, et al. Comparison of three real-time PCR assays for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae* in young pregnant women. *Diagn Microbiol Infect Dis* 2015; **83:** 335–37.

5 Toyer AL, Trignol-Viguier N, Mereghetti L, et al. Interest of simultaneous *Chlamydia trachomatis* and *Neisseria gonorrhoeae* screening at the time of preabortion consultation. *Contraception* 2012; **86:** 572–76.

6 Andersson N, Boman J, Nylander E. Rectal chlamydia—should screening be recommended in women? *Int J STD AIDS* 2017; **28:** 476–79.

7 Chandra NL, Broad C, Folkard K, et al. Detection of *Chlamydia trachomatis* in rectal specimens in women and its association with anal intercourse: a systematic review and meta-analysis. *Sex Trans Infect* 2018; **94:** 320–26.

8 Ding A, Challenor R. Rectal chlamydia in heterosexual women: more questions than answers. *Int J STD AIDS* 2014; **25:** 587–92.

9 Sethupathi M, Blackwell A, Davies H. Rectal *Chlamydia trachomatis* infection in women. Is it overlooked? *Int J STD AIDS* 2010; **21:** 93–95.

10 Rank RG, Yeruva L. Hidden in plain sight: chlamydial gastrointestinal infection and its relevance to persistence in human genital infection. *Infect Immun* 2014; **82:** 1362–71.

11 Lanjouw E, Ouburg S, de Vries HJ, Stary A, Radcliffe K, Unemo M. 2015 European guideline on the management of *Chlamydia trachomatis* infections. *Int J STD AIDS* 2016; **27:** 333–48.

12 Kong FY, Tabrizi SN, Law M, et al. Azithromycin versus doxycycline for the treatment of genital chlamydia infection: a meta-analysis of randomized controlled trials. *Clin Infect Dis* 2014; **59:** 193–205.

13 Kong FY, Tabrizi SN, Fairley CK, et al. The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: a systematic review and meta-analysis. *J Antimicrob Chemother* 2015; **70:** 1290–97.

14 Chen LF, Wang TC, Chen FL, et al. Efficacy of doxycycline versus azithromycin for the treatment of rectal chlamydia: a systematic review and meta-analysis. *J Antimicrob Chemother* 2021; **76:** 3103–10.

15 Peuchant O, Lhomme E, Kret M, et al. Randomized, open-label, multicenter study of azithromycin compared with doxycycline for treating anorectal *Chlamydia trachomatis* infection concomitant to a vaginal infection (CHLAZIDOXY study). *Medicine* 2019; **98:** e14572.

16 Haute Autorité de Santé. Réévaluation de la stratégie de dépistage des infections à *Chlamydia trachomatis*. 2018. https://www.has-sante.fr/upload/docs/application/pdf/2018-10/recommandation_en_sante_publique__reevaluation_de_la_strategie_de_depistage_des_infection_a_chlamydia_trachomatis_vf.pdf (accessed Oct 24, 2018).

17 Rodriguez P, de Barbeyrac B, Persson K, Dutilh B, Bébéar C. Evaluation of molecular typing for epidemiological study of *Chlamydia trachomatis* genital infections. *J Clin Microbiol* 1993; **31:** 2238–40.

18 Stevens MP, Twin J, Fairley CK, et al. Development and evaluation of an *omp*A quantitative real-time PCR assay for *Chlamydia trachomatis* serovar determination. *J Clin Microbiol* 2010; **48:** 2060–65.

19 Dombrowski JC, Wierzbicki MR, Newman LM, et al. Doxycycline versus azithromycin for the treatment of rectal chlamydia in men who have sex with men: a randomized controlled trial. *Clin Infect Dis* 2021; **73:** 824–31.

20 Dukers-Muijrers N, Wolffs PFG, De Vries H, et al. Treatment effectiveness of azithromycin and doxycycline in uncomplicated rectal and vaginal *Chlamydia trachomatis* infections in women: a multicenter observational study (FemCure). *Clin Infect Dis* 2019; **69:** 1946–54.

For the **study protocol** see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6408020/

21 Lau A, Kong FYS, Fairley CK, et al. Azithromycin or doxycycline for asymptomatic rectal *Chlamydia trachomatis*. *N Engl J Med* 2021; **384:** 2418–27.

22 Khosropour CM, Soge OO, Suchland R, et al. Recurrent/intermittent vaginal and rectal chlamydial infection following treatment: a prospective cohort study among female sexually transmitted disease clinic patients. *J Infect Dis* 2019; **220:** 476–83.

23 Heijne JCM, van Liere G, Hoebe C, Bogaards JA, van Benthem BHB, Dukers-Muijrers N. What explains anorectal chlamydia infection in women? Implications of a mathematical model for test and treatment strategies. *Sex Trans Infect* 2017; **93:** 270–75.

24 Rank RG, Yeruva L. An alternative scenario to explain rectal positivity in chlamydia-infected individuals. *Clin Infect Dis* 2015; **60:** 1585–86.

25 Leenen J, van Liere G, Hoebe C, Hogewoning AA, de Vries HJC, Dukers-Muijrers N. A longitudinal study to investigate previous *Chlamydia trachomatis* infection as a risk factor for subsequent anorectal infection in men who have sex with men (MSM) and women visiting STI clinics in the Netherlands. *Epidemiol Infect* 2019; **147:** e214.

26 Dukers-Muijrers N, Wolffs PFG, de Vries HJC, Gotz HM, Janssen K, Hoebe C. Viable bacterial load is key to azithromycin treatment failure in rectally *Chlamydia trachomatis* infected women (FemCure). *J Infect Dis* 2019; **220:** 1389–90.

27 Kong FY, Tabrizi SN, Fairley CK, et al. Higher organism load associated with failure of azithromycin to treat rectal chlamydia. *Epidemiol Infect* 2016; **144:** 2587–96.

28 Janssen KJ, Hoebe CJ, Dukers-Muijrers NH, Eppings L, Lucchesi M, Wolffs PF. Viability-PCR shows that NAAT detects a high proportion of DNA from non-viable *Chlamydia trachomatis*. *PLoS One* 2016; **11:** e0165920.

29 Dragovic B, Nwokolo N. Update on the treatment of *Chlamydia trachomatis* (CT) infection. BASHH Clinical Effectiveness group. 2018. https://www.bashhguidelines.org/media/1191/update-on-the-treatment-of-chlamydia-trachomatis-infection-final-16-9-18.pdf (accessed Oct 17, 2020).

30 Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. Centers for Disease Control and Prevention. *MMWR Recomm Rep* 2021; **70:** 1–187.