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Azithromycin or Doxycycline for Asymptomatic Rectal *Chlamydia trachomatis*

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Background:

- regular screening for rectal chlamydia is recommended for MSM, among whom the estimated prevalence is ~9%
- increasing concern about rectal chlamydia in women and its possible role in urogenital infection through autoinoculation
- until recently most guidelines recommended treatment for rectal chlamydia with either
  - Doxycycline (100mg BID x 7 days) or
  - Azithromycin (1g single dose)

  on the assumption that both regimens are equally efficacious
- RCTs suggest that azithromycin is only slightly less effective than doxycycline for *urogenital* chlamydia infection (94% vs. 97%) [1]
- observational studies suggest that doxycycline is ~20% more effective than azithromycin for *rectal* chlamydia infection [2]
- possible explanation: chlamydial MIC for azithromycin is 4x as high in colorectal cell lines as in endocervical cell lines, whereas the chlamydial MIC for doxycycline does not vary between cell lines

1. Kong FYS, et al. Azithromycin versus doxycycline for the treatment of genital chlamydia infection: a meta-analysis of RCTs. CID 2014;59:193-205.
2. Kong FYS, et al. The efficacy of azithromycin and doxycycline for the treatment of rectal chlamydia infection: systematic review and metaanalysis. J Antimicrob Chemother 2015;70:1290-7.
3. Parnham MJ, et al. Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther 2014;143:225-45.

Study design:

- double-blind, randomized, controlled multicentre study (5 sexual health clinics in 3 Australian states [Victoria, New South Wales, South Australia])
- Study period: 08/2016 – 08/2019
- Study arms (1:1): Doxycycline (100mg BID x 7 days) & Azithromycin (1g SD)
- Inclusion criteria: MSM ≥16a with
  - history of male-to-male sexual contact in past 12 months
  - asymptomatic chlamydia infection
  - enrollment ≤7 days after routine screening by NAAT/PCR
- Exclusion criteria:
  - symptomatic chlamydia infection
  - antibiotic intake in the past 2 weeks
  - contraindication to either study drug
  - concurrent STD (syphilis, gonorrhoea, *M. genitalium*)
  - asymptomatic *Lymphogranuloma venereum* (LGV) was not detected until the end of the trial, when genotyping was performed -> patients with LGV were excluded from the analysis

- Blinding:
  - «trial drugs were identical in appearance and packed in identical bottles»
  - ∑ 14 tabl.: doxycyclin arm: First dose under observation
    (1 tabl. doxycycline + 1 placebo tablet)
    + 13 doses of doxycycline non-supervised
    azithromycin arm: First dose under observation
    (2 tabl. azithromycin)
    + 13 placebo doses non-supervised

- at recruitment, participants completed a questionnaire and provided 3 self-collected rectal swabs for testing, which included (i) confirmatory testing for *C. trachomatis*, (ii) genotyping and (iii) quantification of chlamydial load, and (iv) assaying of mRNA and genomic sequencing.

- during the first 7 days participants received a daily survey by text message to assess drug-related adverse events and medication adherence.

- at 4 weeks participants returned to the clinic and provided a rectal swab for test-of-cure assessment by NAAT and two additional rectal swabs (1 for confirmatory testing and genotyping and 1 for genomic sequencing)

- Primary outcome: microbial. cure / negative test-of-cure NAAT at week 4

- Secondary outcomes: - reported adverse events
  - chlamydial load
  - drug adherence

- Sample size determination:
  power of 90% to detect an absolute between-group difference of 6%
  at a 2-sided significance of 5% -> n=560

- Analysis: *modified intention-to-treat*:
  for prim. outcome because participants with LGV were later excluded

  per-protocol:
  exclusion of participants who
  - had taken ≤10 tablets (= greater risk for failure)
  - had ≥ 2 episodes of diarrhea or vomiting during treatment
    (= risk of low drug exposure)
  - had a negative confirmatory test for chlamydia at recruitment

LGV

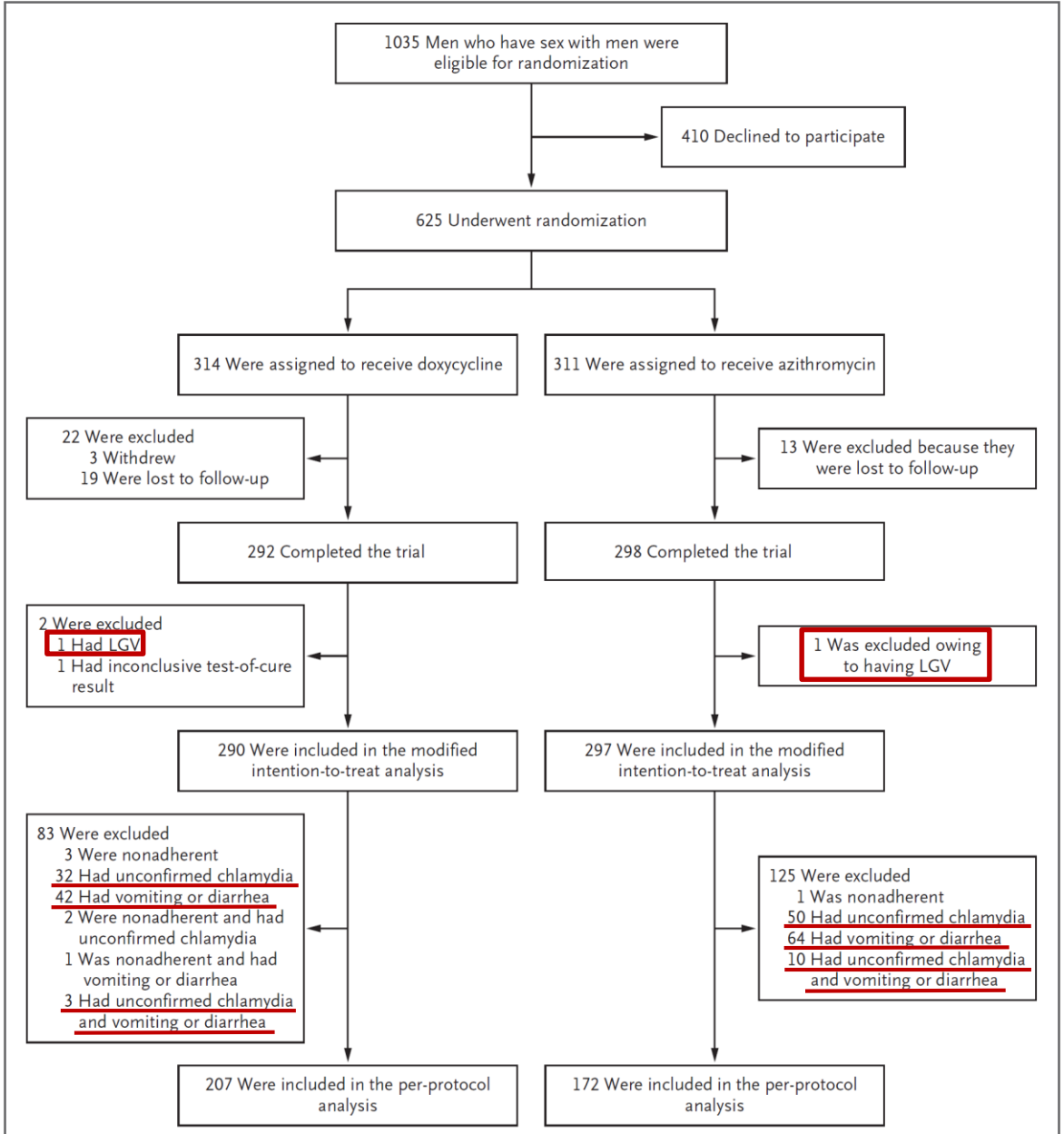

Figure 1. Enrollment and Outcomes.

After the completion of the trial, participants who were found to have asymptomatic lymphogranuloma venereum (LGV), which was not detected until the end of the trial when genotyping was performed, were excluded from the primary analysis in the modified intention-to-treat population because the treatment of LGV requires a prolonged course of doxycycline.

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Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Doxycycline (N=314)	Azithromycin (N=311)
Age — yr	32.2±9.8	32.7±10.1
Body-mass index†	24.4±7.2	24.0±3.8
Status regarding HIV and PrEP — no. (%)		
HIV negative and PrEP negative	165 (52.5)	178 (57.2)
HIV negative and PrEP positive	106 (33.8)	107 (34.4)
HIV positive	43 (13.7)	26 (8.4)
History of STI diagnosis — no. (%)		
Chlamydia	168 (53.5)	137 (44.1)
Gonorrhea	157 (50.0)	151 (48.6)
Syphilis	72 (22.9)	63 (20.3)
Median no. of sexual partners in past 3 mo (IQR)		
Any sex	5 (3–10)	5 (3–10)
Receptive anal sex	3 (2–6)	3 (1–5)
Predominant sexual position — no./total no. (%)		
Receptive	128/308 (41.6)	131/301 (43.5)
Insertive	33/308 (10.7)	28/301 (9.3)
Both	147/308 (47.7)	142/301 (47.2)
Condom use with partners for receptive anal sex past 3 mo — no. (%)		
Never	70 (22.3)	67 (21.5)
≤50% of the time	108 (34.4)	99 (31.8)
>50% of the time	75 (23.9)	86 (27.7)
100%	51 (16.2)	41 (13.2)
No receptive anal sex in past 3 mo	10 (3.2)	18 (5.8)
Douching before receptive anal sex in past 3 mo — no. (%)		
Never	48 (15.3)	50 (16.1)
≤50% of the time	48 (15.3)	62 (19.9)
>50% of the time	207 (65.9)	177 (56.9)
Rarely had receptive anal sex in past 3 mo	11 (3.5)	22 (7.1)
Chlamydia NAAT result at recruitment — no. (%)‡		
Positive	272 (86.6)	251 (80.7)
Negative	27 (8.6)	39 (12.5)
Could not be assessed§	15 (4.8)	21 (6.8)
Chlamydial load — $\log_{10}$ copies per microliter	2.1±0.7	2.1±0.9

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, PrEP preexposure prophylaxis against human immunodeficiency virus (HIV), and STI sexually transmitted infection.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ This category refers to results of Cobas 4800 nucleic acid amplification testing (NAAT) of a swab that was collected at the time of recruitment for confirmatory testing.
§ Some swabs could not be assessed because of the presence of amplification inhibitors or contamination (e.g., fecal).

Results:

Table 2. Primary Outcome.

Outcome	Doxycycline	Azithromycin	Unadjusted Risk Difference (95% CI)	P Value	Adjusted Risk Difference (95% CI)*	P Value
	no./total no. (%)		*percentage points*		*percentage points*	
Microbiologic cure: negative NAAT results						
Modified intention-to-treat analysis†	281/290 (96.9)	227/297 (76.4)	20.5 (16.4–24.6)	<0.001	19.9 (14.6–25.3)	<0.001
Per-protocol analysis‡	198/207 (95.7)	126/172 (73.3)	22.4 (13.6–31.2)		21.3 (13.3–29.4)	

Table 3. Adverse Events.*

Event	Doxycycline (N=290)	Azithromycin (N=297)	Risk Difference (95% CI)	P Value
	number of participants (%)		*percentage points*	
Any adverse event	98 (33.8)	134 (45.1)	−11.3 (−19.5 to −3.2)	0.006
Nausea	63 (21.7)	61 (20.5)	1.2 (−3.5 to 5.8)	0.62
Mild	49 (16.9)	49 (16.5)	0.4 (−3.7 to 4.5)	0.85
Moderate	11 (3.8)	9 (3.0)	0.8 (−2.3 to 3.8)	0.63
Severe	3 (1.0)	3 (1.0)	0.0 (−1.9 to 1.8)	0.98
Vomiting	3 (1.0)	3 (1.0)	0.0 (−1.9 to 1.8)	0.98
Diarrhea	74 (25.5)	118 (39.7)	−14.2 (−20.7 to −7.8)	<0.001

* Adverse events included nausea, vomiting, or diarrhea within 24 hours after the receipt of any dose of a trial drug during the first 7 days of the trial. Grading of nausea was based on the criteria of the *Medical Dictionary for Regulatory Activities* and was reported by the participants.

Chlamydia genotyping:

Those receiving azithromycin were more likely than those receiving doxycycline to have the same genovar at the end of the trial as the one identified at baseline:

Table S8: Genotype concordance between baseline and trial end for those cases which failed treatment.

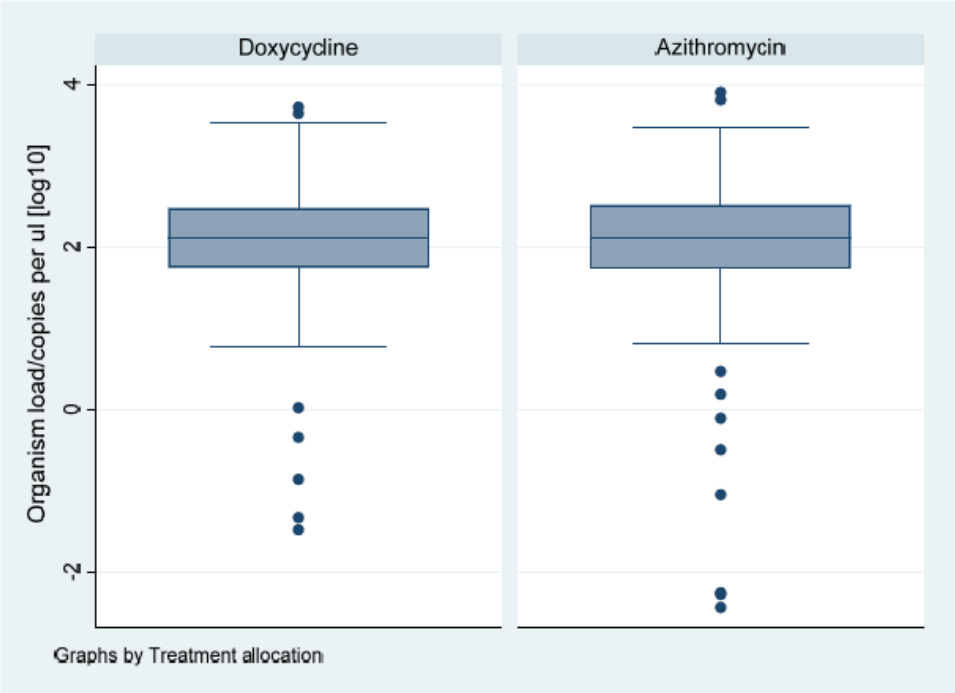
	Doxycycline	Azithromycin	Total
Same genovar	1 (11.1)	45 (64.3)	46 (58.2)
Different genovar	2 (22.2)	4 (5.7)	6 (7.6)
Uncertain*	6 (66.7)	21 (30.0)	27 (34.2)

*Unassessable genotype at either baseline (n=6) or at time of assessing cure (n=21).

Chlamydia load:

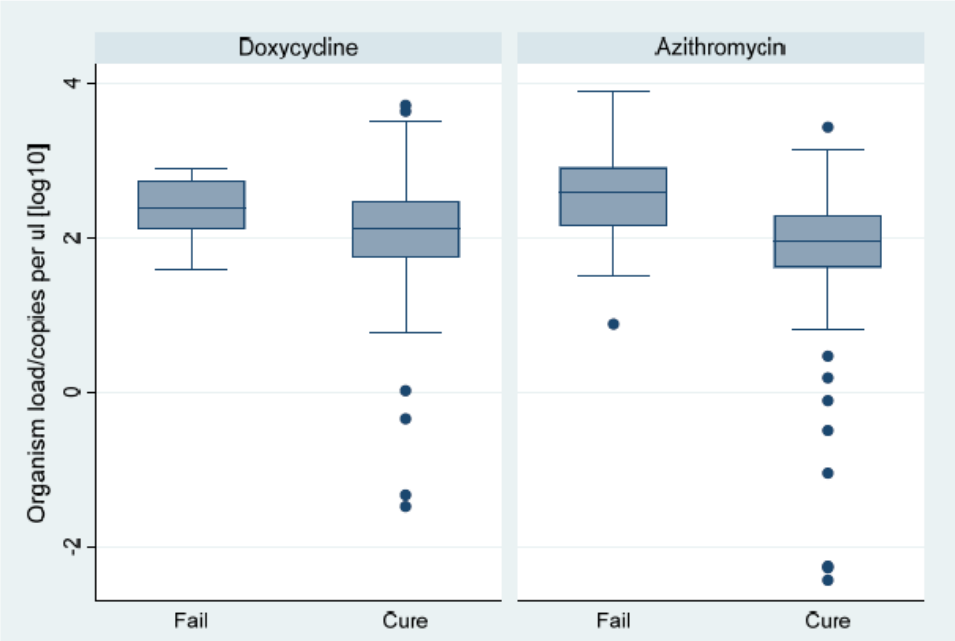
Chlamydial load at baseline according to treatment allocation

A)



Chlamydial load according to treatment and outcome

B)



Arising question: Would a higher azithromycin dose be more effective for higher-load infections?

In the azithromycin group, the chlamydial load at baseline was greater in those with treatment failure than in those with cure

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Limitations:

- limited to men
  - ↳ although data suggest that the rectal chlamydial load is similar between sexes and observational data sugget similar efficacy in males and females
- limited to asymptomatic infection
  - ↳ azithromycin efficacy may be greater in symptomatic infection as the drug is transported to the tissue mainly by inflammatory cells [1]
- not fully supervised drug intake
  - ↳ however, no evidence that non-adherence or gastrointestinal side-effects influenced treatment effect

Conclusion:

- prefer doxycycline over azithromycin for the treatment of asymptomatic rectal chlamydial infection

1. Parnham MJ, et al. Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther 2014;143:225-45.