Additional file 1 –Assessing antimicrobial prescription within the EZI-PrEP study (the Netherlands, 2021-2024)

Aim

We aimed to examine differences in antibiotic prescription between EZI-PrEP participants randomized to undergo 6-monthly versus 3-monthly monitoring.

Methods

Data on antibiotic prescriptions were available for two regions: Amsterdam and The Hague. Therefore, eligible participants for this analysis were individuals who participated in the EZI-PrEP trial and had ≥1 follow-up visit at the Center for Sexual Health in Amsterdam or The Hague. Eligible visits were enrolment visits and follow-up visits of eligible participants, up to the last monitoring visit. For each included visit, we extracted the following prescription data from participants' electronic patient files: antibiotic, route of administration, dose, frequency, and duration of treatment (e.g., doxycycline, oral, 100 milligram, twice per day, 7 days).

Based on these prescription data, we calculated antibiotic prescription as the number of defined daily doses (DDD) of antibiotics consumed per 1000 person-days, following standard WHO methodology (Table 1) (29). In short, the number of DDDs was calculated as the total grams of antibiotic *X* consumed, divided by the WHO's DDD for antibiotic *X*. This number was then divided by the number of patient-days and multiplied by 1000. Patient-days started at enrolment and continued until an individual's last monitoring visit as part of EZI-PrEP. We assumed perfect adherence to the prescribed treatment.

We calculated antibiotic prescription for the following classes of antibiotics: tetracyclines (ATC class J01AA), macrolides (ATC class J01FA), third generation cephalosporins (ATC class J01DD), and beta-lactams (ATC class J01CE). Per class, we compared the absolute difference and percentage difference in estimated DDDs consumed in the 6-monthly versus 3-monthly monitoring group. We descriptively report on prescriptions of zoliflodacin (prescribed within the context of the ZOLISTI randomized controlled trial) but excluded zoliflodacin prescriptions from further analysis due to its experimental nature (and thus, lack of assigned ATC code and DDD).

Table 1. WHO defined daily doses for antibiotics used for the treatment of gonorrhea, chlamydia, and syphilis.

Class	Name	Unit	Administration route	ATC code	WHO DDD
3rd generation cephalosporin	Ceftriaxone	gram	Parenteral	J01DD04	2
Tetracycline	Doxycycline	gram	Oral	J01AA02	0.1
Macrolide	Azithromycin	gram	Oral	J01FA10	0.3
Beta-lactam	Benzathine benzylpenicillin	gram	Parenteral	J01CE08	3.6
Spiropyrimidinetrione	Zoliflodacin	Experimental antibiotic; no ATC code or WHO DDD available.			

Abbreviations: ATC, anatomical therapeutic chemical; DDD, defined daily dose; WHO, World Health Organization;

Results

Amsterdam and The Hague accounted for 69.6% (n=314/451) of all 451 EZI-PrEP participants in this study (Amsterdam: n=244/451 (54.1%) participants; The Hague: n=70/451 (15.5%) participants). Amsterdam and The Hague accounted for 69.0% (n=536/777) of all incident STI diagnoses (Amsterdam: 418/777 (53.8%) diagnoses; The Hague: 118/777 (15.2%) diagnoses). The 536 incident STI diagnoses were made at 464 unique visits.

In total, there were 513 scheduled or unscheduled follow-up visits during which one or more course of antibiotics was prescribed. There were six visits where sampling resulted in a positive STI diagnosis but the prescribed antibiotic could not be retrieved (Table 2). There were 58 visits where sampling did not result in a diagnosis after culture or nucleic acid amplification testing (NAAT), but antibiotics were prescribed on the day of sampling (a practice named presumptive treatment; n=19 ceftriaxone, n=16 doxycycline, n=13 benzathine benzylpenicillin, and n=10 azithromycin) (Table 2). In most (82.8%, n=48/58) of these visits, participants had reported either symptoms of an STI (n=15), a partner notification for an STI (n=28), or both (n=5). The number visits with inaccurate presumptive treatment for syphilis was higher among participants receiving 6-monthly monitoring (n=13 times) than participants receiving 3-monthly monitoring (n=7 visits) (Table 2).

Table 2. Number of incident STI diagnoses with and without a relevant prescription, and number of visits with inaccurate presumptive treatment at the EZI-PrEP study sites Amsterdam and the Hague (The Netherlands, 2021-2024)

STI	Monitoring group	Number of incident diagnoses	Number of incident diagnoses with record of a relevant prescription	Number of incident diagnoses without (record of) a relevant prescription	Number of visits with presumptive treatment
Gonorrhea	3-monthly	149	145	4	11
	6-monthly	107	106	1	13
Chlamydia	3-monthly	126	125	1	18
	6-monthly	104	104	0	16
Infectious syphilis	3-monthly	24	24	0	7
	6-monthly	20	20	0	13

NB: we defined a 'relevant prescription' as ceftriaxone or zoliflodacine for gonorrhea, doxycycline or azythromycine for chlamydia, and benzathine benzylpenicillin for syphilis infections. A visit with presumptive treatment refers to a visit without a certain prescription but without a diagnosis for the relevant STI.

Ceftriaxone regimens were prescribed 274 times, doxycycline regimens 207 times, azithromycin 60 times, benzathine benzylpenicillin 64 times and zoliflodacin once during 277,486 person-days (Table 3). This equated to respectively 0.54, 15.20, 0.92, and 0.09 DDDs/1000 person-days of 3rd generation cephalosporin, tetracycline, macrolide, and beta-lactam antibiotics in the 3-monthly monitoring groups, and respectively 0.43, 13.39, 0.56, and 0.10 DDDs/1000 person-days of 3rd generation cephalosporin, tetracycline, macrolide, and beta-lactam antibiotics in the 3-monthly monitoring groups (Tables 3-4). Compared to the 3-monthly monitoring group, the 6-monthly monitoring groups consumed 0.11 fewer DDDs/1000 person-days 3rd generation cephalosporins , 1.81 fewer tetracycline antibiotics, and 0.36 fewer macrolides (Table 4). The 6-monthly monitoring group consumed 0.01 more beta-lactam antibiotics than the 3-monthly monitoring group. This corresponded to relative differences of -20.0%, -11.9%, -38.8%, and +10.4% in the prescription of 3rd generation cephalosporin, tetracycline, macrolide, and beta-lactam antibiotics, respectively.

Conclusion

Screening for STIs every 6 months (instead of every 3 months) resulted in a lower prescription of tetracycline, macrolide, and cephalosporin antibiotics.

Table 3. Frequency of antibiotic prescriptions and corresponding number of DDDs consumed in the EZI-PrEP study sites Amsterdam and the Hague (The Netherlands, 2021-2024)

Prescribed regimen	Grams per prescribed course	N. courses prescribed	Total grams consumed	WHO DDD	Number of DDDs (i.e., grams consumed / WHO DDD)
3rd generation cephalosporin					
Ceftriaxone, intramuscular, 1000 mg, once					
3-monthly monitoring	1	151	151	2	75.5
6-monthly monitoring	1	117	117	2	58.5
Ceftriaxone, intramuscular, 500 mg, once					
3-monthly monitoring	0.5	4	2	2	1.0
6-monthly monitoring	0.5	2	1	2	0.5
Tetracycline					
Doxycycline, oral, 100 mg, twice per day, 7 days					
3-monthly monitoring	1.4	90	126.0	0.1	1260.0
6-monthly monitoring	1.4	84	117.6	0.1	1176.0
Doxycycline, oral, 100 mg, twice per day, 14 days					
3-monthly monitoring	2.8	6	16.8	0.1	168.0
6-monthly monitoring	2.8	6	16.8	0.1	168.0
Doxycycline, oral, 100 mg, twice per day, 21 days					
3-monthly monitoring	4.8	15	72.0	0.1	720.0
6-monthly monitoring	4.8	10	48	0.1	480.0
Macrolide					
Azithromycin, oral, 1000 mg, once					
3-monthly monitoring	1	35	35	0.3	116.7
6-monthly monitoring	1	23	23	0.3	76.7
Azithromycin, oral, 2000 mg, once					
3-monthly monitoring	2	2	4	0.3	13.3
6-monthly monitoring	2	0	0	0.3	0
Beta-lactam					
Benzathine benzylpenicillin, intramuscular, 2.4 million units[1]					
3-monthly monitoring	1.44	31	44.6	3.6	12.4
6-monthly monitoring	1.44	33	47.5	3.6	13.2
Spiropyrimidinetrione					
Zoliflodacine, oral, 3000 mg, once[2]					
3-monthly monitoring	3	1	3	N/A	N/A
6-monthly monitoring	3	0	0	N/A	N/A

Abbreviations: ATC, anatomical therapeutic chemical; DDD, defined daily dose; WHO, World Health Organization;

1. One million units of benzathine benzylpenicillin is equal to 0.6 grams of benzathine benzylpenicillin (https://www.medicines.org.uk/emc/product/7381/smpc). As such, 2.4 million units equate to 1.44 grams.

2. Zoliflodacine was prescribed within the context of the ZOLISTI study (ZOLIFLODACINE , onderzoek naar een nieuw medicijn tegen gonorroe - openresearch.amsterdam). Since zoliflodacine is an experimental drugs, no ATC code is available.

Table 4. Difference in number of DDDs per 1000 person-days between the 6-month and 3-month monitoring arms at the study sites Amsterdam and the Hague in the EZI-PrEP study (The Netherlands, 2021-2024) (The Netherlands, 2021-2024)

	3-monthly monitoring			6-monthly monitoring				
Antibiotic class	No. DDDs	PD	DDDs / 1000 PD	No. DDDs	PD	DDDs / 1000 PD	Absolute difference in DDD / 1000 PD	Relative difference in DDD / 1000 PD
3rd generation cephalosporin	76.5	141,282	0.54	59	136,204	0.43	-0.11	-20.0%
Tetracycline	2148.0	141,282	15.20	1824.0	136,204	13.39	-1.81	-11.9%
Macrolide	130.0	141,282	0.92	76.7	136,204	0.56	-0.36	-38.8%
Beta-lactam	12.4	141,282	0.09	13.2	136,204	0.10	+0.01	+10.4%

Abbreviations: DDD, defined daily dose; No., number; PD, person-days;