DoxyPEP effectiveness: identifying dosing thresholds and high-risk contexts.

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Roberto Rossotti[1,2], Enrico Caruso[2], Camilla Muccini[2,3], Anna De Bona[2,4], Davide Moschese[2,5], Nicoletta Frattini[2], Daniele Tesoro[2,4], Alessandro Tavelli[6], Pietro Vinti[2], Giuseppe Ancona[2,4], Antonella d'Arminio Monforte[6], Massimo Cernuschi[2]

[1]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [2]Milano Checkpoint ETS, Milan Italy; [3]San Raffaele Scientific Institute, Milan, Italy; [4]ASST Santi Paolo e Carlo, Milan, Italy; [5]ASST Fatebenefratelli-Sacco, Milan, Italy; [6]ICONA Foundation, Milan, Italy

BACKGROUND

- DoxyPEP has proven to be highly effective against bacterial sexually transmitted infections (bSTI). However, in a context of increasing antimicrobial resistance (AMR) in STI, non-STI, and nonpathogenic commensal bacteria, it is essential to define the best settings where doxyPEP could be safely used with limited risk of AMR.
- Previous research demonstrated that the selection of eligible candidates may help in refining doxyPEP use.
- Additionally, it is unclear whether it should be used for each sexual contact or limited to specific settings.
- Aims of this study were (i) to describe the features of individuals who chose to use doxyPEP in our cohort of PrEP users, (ii) to assess the number of doxyPEP doses required to observe a measurable reduction in bSTI incidence, and (iii) to explore the contexts in which its use may be most appropriately targeted.

METHODS

- This retrospective analysis included all individuals who had at least two visits from January 2024 to January 2026 at Milano Checkpoint ETS, a community-based service located in northern Italy.
- All participants were counselled about doxyPEP, but the prescription was provided based on physicians risk assessment. In our setting, its use was recommended for high-risk exposures (i.e., participating to group sex; attending gay saunas or other cruising venues; chemsex practices; sex work; having more than 5 sex contacts per week).
- The analyses were performed assessing the absolute number of doxyPEP cycles taken and the percentage of sexual intercourses covered by doxyPEP.
- We used two different outcome variables represented by (i) the count of all incident bSTI episodes per observation period, allowing for recurrent infections within individuals; (ii) the count of syphilis and CT incident cases, excluding gonorrhea because of the limited efficacy of doxyPEP against NG in Europe.
- We used generalized linear models with Poisson and negative binomial distributions, including person-years as offsets, robust variance estimates clustered by individual, and inverse probability weighted (IPTW) marginal structural model (MSM) to assess the association between doxyPEP use and bSTI incidence.

DoxyPEP is effective if consistently used (more than 60-80% of the sexual contacts) and in specific sexual contexts (cruising venues, group sex).

RESULTS (1)

- The study included 975 individuals with a cumulative number of 4,187 visits; of them, 382 (32.2%) have used doxyPEP at least once (**Table 1**). Median follow up was 1.44 (IQR 0.69-1.73) years.

			Overall (N=975)	Nonuser (N=593)	Ever used (N=382)	p
Male sex at birth, n (%)			963 (98.8)	583 (98.3)	380 (99.5)	0.108
Age, years, median (IQR)			38 (32-46)	37 (31-45)	39 (33-47)	**<0.001**
Gender, n (%)	Cisgender men/women		924 (94.8)	555 (93.6)	369 (96.6)	0.142
	Transgender men		1 (0.1)	1 (0.2)	--	
	Transgender women		17 (1.7)	11 (1.8)	6 (1.6)	
	Non-binary		33 (3.4)	26 (4.4)	7 (1.8)	
Sexual behavior, n (%)		Homosexual	851 (87.3)	513 (86.5)	338 (88.5)	0.473
		Bisexual	92 (9.4)	57 (9.6)	35 (9.2)	
		Heterosexual	25 (2.6)	17 (2.9)	8 (2.1)	
		Other	7 (0.7)	6 (1.0)	1 (0.2)	
Italian born, n (%)			758 (77.7)	457 (77.1)	301 (78.8)	0.526
Ethnicity, n (%)	White		817 (83.8)	496 (83.6)	321 (84.0)	0.173
	Latinx		71 (7.3)	36 (6.1)	35 (9.2)	
	Asian		26 (2.7)	19 (3.2)	7 (1.8)	
	MENA		15 (1.5)	12 (2.0)	3 (0.8)	
	Black		12 (1.2)	7 (1.2)	5 (1.3)	
	Other		34 (3.5)	23 (3.9)	11 (2.9)	
Relationship status, single, n (%)			692 (71.0)	430 (72.5)	262 (68.6)	0.187
Employed, n (%)			849 (87.1)	507 (85.5)	342 (89.5)	0.067
Level of education, n (%)	University		714 (73.2)	436 (73.5)	278 (72.8)	0.704
	High School		230 (23.6)	138 (23.3)	92 (24.1)	
	Secondary		28 (2.9)	16 (2.7)	12 (3.1)	
	Primary		1 (0.1)	1 (0.2)	--	
	None		2 (0.2)	2 (0.3)	--	
Age of first sexual intercourse, median (IQR)			18 (16-20)	18 (16-20)	18 (16-20)	0.221
Number of lifetime sexual partners, n (%)	0-5		19 (2.0)	10 (1.7)	9 (2.3)	**0.001**
	5-10		43 (4.4)	32 (5.4)	11 (2.9)	
	10-30		171 (17.5)	123 (20.7)	48 (12.6)	
	>30		742 (76.1)	428 (72.2)	314 (82.2)	
Time on PrEP, months, median (IQR)			24.5 (10.9-37.4)	21.3 (10.2-36.2)	26.5 (14.5-39.0)	**<0.001**
Chemsex practices*, n (%)			60 (6.2)	26 (4.4)	34 (8.9)	**0.004**
Recreational drug use*, n (%)			258 (24.5)	127 (21.4)	131 (34.3)	**<0.001**
Sex worker, n (%)			28 (2.9)	16 (2.7)	12 (3.1)	0.686
Bacterial STIs°, n (%)			257 (26.3)	140 (23.6)	117 (30.6)	**0.015**
Chlamydia and/or Syphilis			154 (15.8)	83 (14.0)	71 (18.6)	0.055
N. of sexual intercourses°, median (IQR)			13 (6-25)	10 (5-22)	17 (8-31)	**<0.001**
N. of condomless sexual intercourses°, median (IQR)			7 (3-17)	6 (2-14)	10 (4-22)	**<0.001**

MENA: Middle East and Northern Africa.
* In the previous 4 weeks; ° in the previous 3 months.

- DoxyPEP has been prescribed in 1,746/3,476 visits (50.2%) but its use was reported only in 720/1,746 (41.3%). The median number of doses taken per visit was 2 (IQR 1-3). The percentage of sexual intercourses covered by doxyPEP was <20% in 83.0%, followed by ≥80% in 12.8%, whereas an intermediate use was observed in less than 2% of visits.
- The right schedule of administration was reported by 667/720 users (92.6%).

Outcome: count of all incident bSTIs				
Negative Binomial – N. doses		**IRR**	**95%CI**	**p**
Doses taken	2	0.96	0.67, 1.36	0.809
	3	1.02	0.66, 1.56	0.938
	≥4	0.80	0.63, 1.02	**0.070**
Dose-response analysis		**Coefficient**	**95%CI**	**p**
Doses taken	2	-0.06	-0.40, 0.27	0.710
	3	0.02	-0.40, 0.44	0.936
	≥4	-0.21	-0.44, 0.02	**0.073**
Negative Binomial - Contexts		**IRR**	**95%CI**	**p**
Saunas/cruising		0.96	0.77, 1.68	0.515
Group sex		0.97	0.87, 1.08	0.157
Sex work		0.85	0.66, 1.10	0.225
Chemsex		1.02	0.89, 1.18	0.751
≥5 sex contacts/week		0.26	0.07, 0.97	**0.046**
Marginal Structural Model		**IRR**	**95%CI**	**p**
Doses taken	2	0.76	0.44, 1.30	0.318
	3	0.89	0.55, 1.46	0.647
	≥4	0.88	0.63, 1.23	0.454
Saunas/cruising		1.12	0.82, 1.52	0.459
Group sex		1.06	0.83, 1.36	0.620
Sex work		0.59	0.21, 1.66	0.316
Chemsex		0.62	0.30, 1.26	0.184
≥5 sex contacts/week		0.78	0.31, 1.97	0.600

Outcome: count of incident syphilis and CT cases				
Negative Binomial – N. doses		**IRR**	**95%CI**	**p**
Doses taken	2	0.82	0.48, 1.41	0.480
	3	0.96	0.50, 1.82	0.895
	≥4	1.01	0.71, 1.43	0.951
Dose-response analysis		**Coefficient**	**95%CI**	**p**
Doses taken	2	-0.18	-0.65, 0.29	0.448
	3	-0.03	-0.64, 0.59	0.930
	≥4	0.02	-0.30, 0.34	0.898
Negative Binomial - Contexts		**IRR**	**95%CI**	**p**
Saunas/cruising		0.99	0.65, 1.01	**0.062**
Group sex		1.13	0.89, 1.45	0.307
Sex work		1.23	0.64, 2.36	0.541
Chemsex		1.23	1.01, 1.50	**0.041**
≥5 sex contacts/week		1.14	0.02, 1.35	**0.090**
Marginal Structural Model		**IRR**	**95%CI**	**p**
Doses taken	2	0.78	0.45, 1.34	0.369
	3	1.11	0.58, 2.14	0.747
	≥4	1.41	0.96, 2.07	**0.078**
Saunas/cruising		0.61	0.41, 0.91	**0.017**
Group sex		0.75	0.54, 1.03	**0.080**
Sex work		0.41	0.09, 1.84	0.248
Chemsex		0.55	0.22, 1.33	0.183
≥5 sex contacts/week		0.56	0.20, 1.52	0.255

RESULTS (2)

Outcome: count of all incident bSTIs, considering the percentage of sexual intercourses covered by doxyPEP				
Negative Binomial – Percentage		**IRR**	**95%CI**	**p**
Percentage of doses taken	20%-40%	1.19	0.84, 1.69	0.321
	40%-60%	0.32	0.10, 0.98	**0.046**
	60%-80%	0.68	0.23, 2.02	0.491
	≥80%	0.46	0.15, 1.35	0.158
Percentage (continuous)		0.70	0.44, 1.10	0.120
Marginal Structural Model		**IRR**	**95%CI**	**p**
Percentage of doses taken	20%-40%	0.73	0.46, 1.18	0.204
	40%-60%	0.79	0.19, 3.37	0.752
	60%-80%	0.76	0.27, 2.14	0.601
	≥80%	0.83	0.21, 3.31	0.794

Outcome: count of incident syphilis and CT cases, considering the percentage of sexual intercourses covered by doxyPEP				
Negative Binomial – Percentage		**IRR**	**95%CI**	**p**
Percentage of doses taken	20%-40%	0.85	0.49, 1.46	0.558
	40%-60%	0.39	0.09, 1.55	0.181
	60%-80%	0.84	0.22, 3.23	0.799
	≥80%	0.00	0.00, 0.00	**<0.001**
Percentage (continuous)		0.23	0.08, 0.70	**0.009**
Marginal Structural Model		**IRR**	**95%CI**	**p**
Percentage of doses taken	20%-40%	0.60	0.32, 1.11	0.104
	40%-60%	1.41	0.28, 7.09	0.675
	60%-80%	1.03	0.27, 3.90	0.960
	≥80%	0.00	0.00, 0.00	**<0.001**

CONCLUSIONS

- In our population, doxyPEP was used by a small proportion of individuals at major risk of exposure; additionally, those who decided to initiate doxyPEP chose to take it few times covering a small percentage of their sexual intercourses.
- Although the analyses show some differences, they demonstrate that doxyPEP works if it is used consistently (more than 4 doses, coverage of at least 60%-80% sexual contacts).
- DoxyPEP use when attending cruising venues, participating to group sex, and having more than 5 contacts per week is associated with a protective effect. Other contexts, such as chemsex practices, seem to increase the risk of acquiring bSTI probably for a risk compensation effect.
- The potency of the analyses was limited by the small utilization observed.
- Our data suggest a trend towards effectiveness with consistent doxyPEP use, especially when joining specific sexual contexts.

ADDITIONAL KEY INFORMATION

Author Contact Information: Roberto.Rossotti@ospedaleniguarda.it

Acknowledgements: the Authors wish to thank all the PrEP users who agreed to participate to this study.