Sistema Socio Sanitario

Ospedale Niguarda

Regione Lombardia

Management and trend cases of PrEP failures in Milan: the real role of Chemsex.

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Beyond HIV. Taking HIV to another level
Cerro Maggiore, 14 October 2024

IMPLEMENTATION PROJECTS

SERVICE DELIVERY SETTINGS

REGULATORY APPROVALS

VIEW

BY GEOGRAPHY

ACROSS TIME

PRODUCTS

ALL PRODUCTS

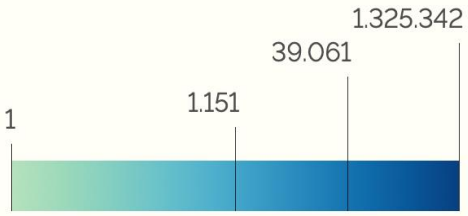
ORAL PREP TDF/XTC
(TDF PRODUCTS AND GENERIC)

ORAL PREP F/TAF
(DESCOVY)

PREP RING

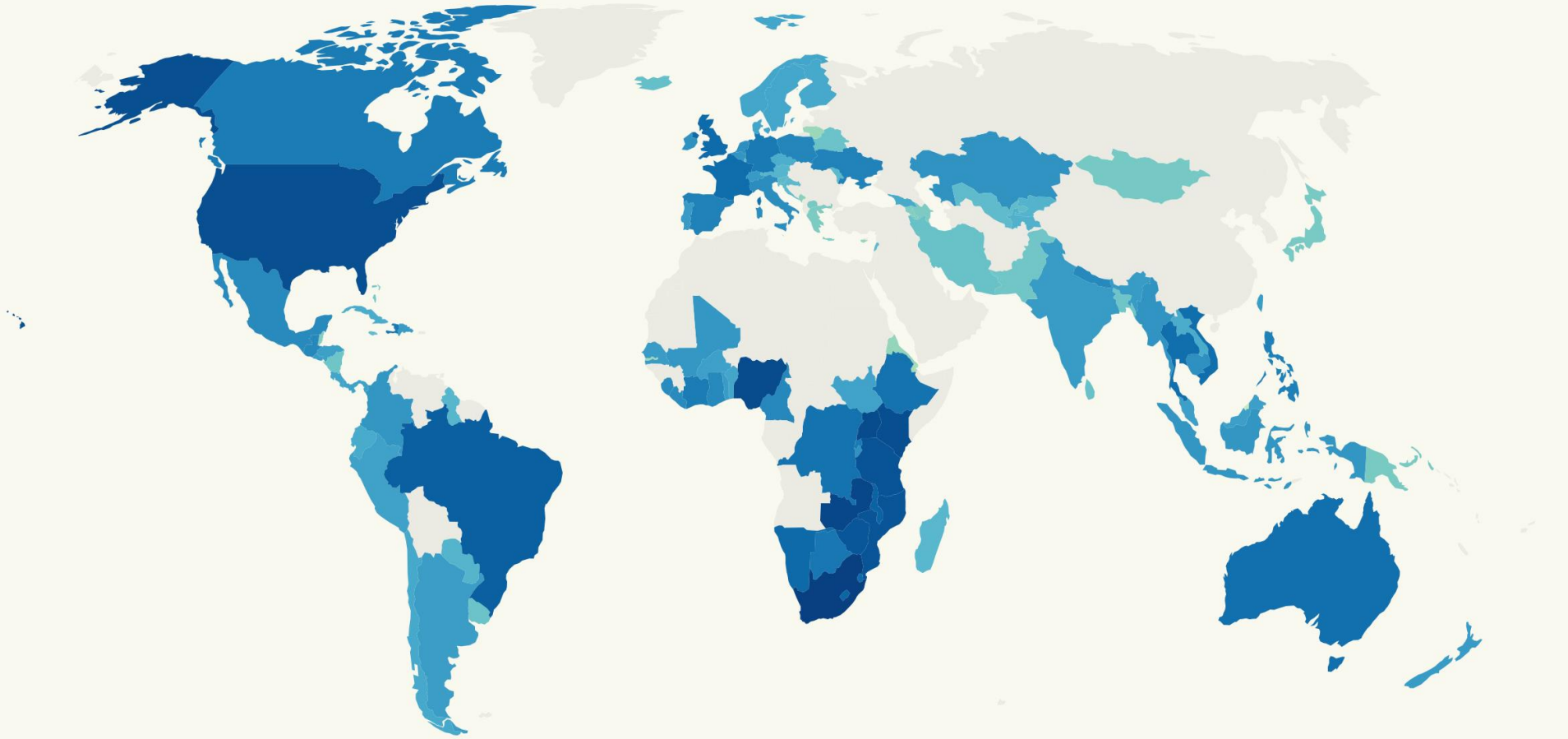
INJECTABLE PREP

Number of Initiations



Q2 2024

7.476.449 initiations



Does PrEP fail in real life?

N	Seroconversion	Sex/Age/STI	PrEP schedule and length	RAMs at diagnosis	Serologic pattern at diagnosis
1	Toronto, 2015	MSM, 43 ys, no STIs	Daily from April 2013, positive after 24 months	RT: **41L, 67G, 69D, 70R, 184V, 215E**; 181C; INSTI: 51Y, 92Q	IV generation test reactive, p24 positive, WB negative
2	New York, 2016	MSM, 26 ys, gonorrhea	Daily from December 2015, positive after 5 months	RT: **65R, 184V**, 103S, 138Q, 188L	IV generation test Ag reactive/Ab non-reactive
3	Amsterdam, 2016	MSM, 50 ys, gonorrhea and LGV	Daily from September 2015, positive after 8 months	Wild-type	IV generation test reactive, WB positive (only gp160), HIV RNA 40 copies/mL
4	North Carolina, 2017	MSM, 34 ys, anal condylomas	Daily fro February to May 2016, re-started in July 2016, positive after 9 months	RT: **65R, 184V**, 70T, 90I, V179I, 103N	IV generation test reactive, HIV RNA 27,316 copies/mL, PHI-related symptoms
5	San Francisco, 2018	MSM/W, 21 ys, Chlamydia, gonorrhea and recurrent genital herpes	Daily; 30 days of d/c between month 5 and 6, positive after 13 months	RT: **184V**, 74V, 100I, 103N	HIV RNA 559 copies/mL, followed by IV generation test reactivity, WB only p24 and gp41 positivity
6	Pattaya (Tailandia), 2018	MSM, 28 ys, SW	Daily from March 2018, positive after 8 months	RT: **184V**, 98G, 103N	HIV RNA 116,187 copies/mL, followed by IV generation test reactivity, WB negative
7	Tailandia, 2016/2017	MSM, chronic HBV hepatitis	Daily, positive after 3 months	RT: **184I**	HIV RNA 1,494 copies/mL, followed by III generation test reactivity
8	London, 2014	MSM, chronic HBV hepatitis	TDF only taken for HBV, positive after 4 years	Wild-type	IV generation test reactive, WB with 3 strings positivity, HIV RNA undetectable, PHI-related symptoms
9	London, 2014	MSM, chronic HBV hepatitis	TDF only taken for HBV, positive after 3 years	Wild-type	IV generation test Ag reactive/Ab non-reactive, HIV RNA 103,306 copies/mL, PHI-related symptoms
10	Germany, 2016	MSM, chronic HBV hepatitis, gonorrhea and Chlamydia	TDF only taken for HBV, positive after 18 months	RT: **65R**	IV generation test reactive, HIV RNA 59 copies/mL

[i] Knox DC, N Engl J Med 2017; [ii] Markowitz M, J Acquir Immune Defic Syndr 2017; [iii] Hoornenborg E, Lancet HIV 2017; [iv] Thaden JT, AIDS 2018; [v] Cohen SE, Lancet HIV 2019; [vi] Colby DJ, Clin Infect Dis 2018; [vii] Phanuphak N, Sex Health 2018; [viii] Fox J, Infect Dis Ther 2016; [ix] Davies O, J Int AIDS Soc 2014; [x] Streeck H, AIDS 2017; 31: 176–177.

HIV breakthrough infections while on PrEP

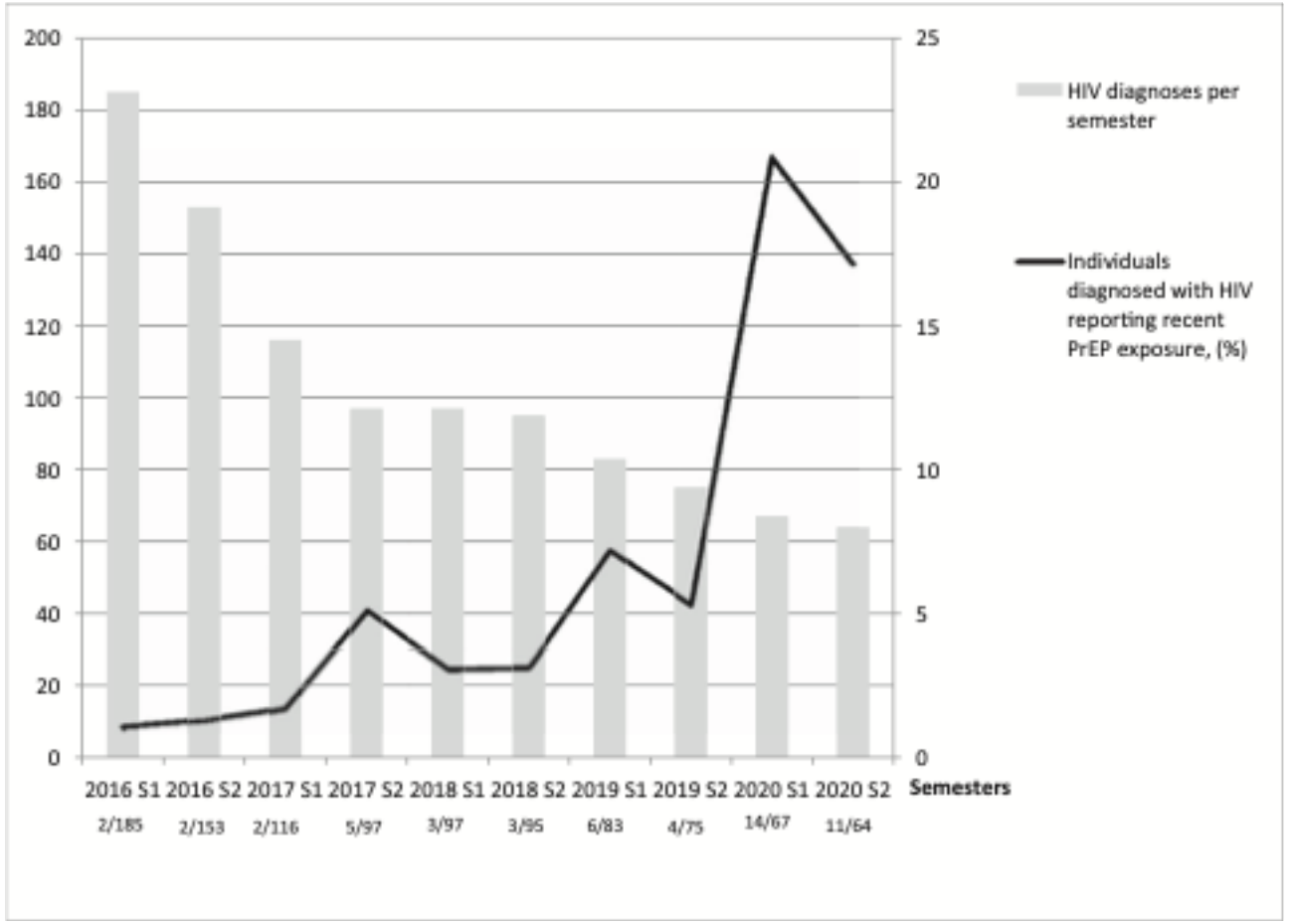


Fig. 1. Trends of HIV diagnoses in MSM at 56 Dean Street (grey bars, *n*), each semester from 2016 to 2020 and rates of MSM newly diagnosed with HIV reporting recent PrEP exposure (black line, values expressed as a %). Recent PrEP exposure was defined as a self-reported PrEP intake in the 90 days prior the HIV diagnosis. Fractions report numbers of people newly diagnosed with HIV reporting recent PrEP exposure/total number of HIV diagnoses per semester. MSM, men having sex with men; PrEP, preexposure prophylaxis.

Table 1. Baseline characteristics, immuno-virological characteristics and genotypic resistances in individuals newly diagnosed with HIV according to recent exposure to PrEP status.

Baseline characteristics	HIV+ reporting recent PrEP exposure, *n* = 52	HIV+ with no recent PrEP exposure, *n* = 978	*P*
Age, years (IQR)	34 (28–42)	32 (27–40)	0.52
MSM, *n* (%)	51 (98)[a]	935 (95)	0.42
White ethnicity, *n* (%)	34 (65)	644 (66)	0.54
UK-born, *n* (%)	18 (35)	326 (33)	0.88
Baseline HIV viral load, $\log_{10}$ *n* (IQR)	3.48 (2.56–4.88)	4.72 (4.16–5.36)	**<0.01**
Baseline CD4$^+$ cell count, mmc (IQR)	632 (468–886)	474 (347–655)	**<0.01**
Individuals with a HIV viral load <200 copies/ml at baseline, *n* (%)	10 (19)	32 (3)	**<0.01**
Genotypic resistance test at baseline, *n* (%)			**<0.01**
- Not performed	0	41 (4)	
- Unable to amplify viral DNA	9/52 (17)	27/939 (3)	
- Performed, with DNA amplification	43/52 (83)	912/939 (97)	
PrEP-related NRTI mutations, *n* (%)[b]			**<0.01**
- M184V/I	13 (30)	5 (1)	
- K65R	0	1 (<1)	
Other NRTI mutations, *n* (%)[b]			0.11
- L74V	1 (2)	0	
- M41L and/or L210W and/or T215Y/F	1 (2)	4 (<1)	
- D67N and/or K70R and/or K219Q/E/R/N	0	7 (1)	
NNRTI mutations, *n* (%)[b]			0.54
- K103N/S	3 (7)	29 (3)	
- V108V/I	1 (2)	8 (1)	
- E138A	0	26 (3)	
- G190A/S/E	1 (2)	0	
PI mutations, *n* (%)[b]			0.62
- M46I/L	0	6 (1)	
- L90M	0	18 (2)	

IQR, interquartile range; MSM, men having sex with men; NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PrEP, preexposure prophylaxis.
[a]One individual identified themselves as a trans-woman.
[b]% are calculated taking into account only individuals where viral DNA was amplified.

When reasons leading to PrEP failure were investigated, 24/52 (46%) reported inadequate adherence (11 on a daily regimen, 13 on EBD), 9/52 (17%) had issues with PrEP supply resulting in its discontinuation, 5/52 (10%) interrupted PrEP after starting a monogamous relationship, 3/52 (6%) did not plan to have sex, 3/52 (6%) chose to interrupt PrEP and 1/52 (2%) was taking an antiretroviral regimen not licensed for PrEP (raltegravir). A reason for PrEP failure could not be identified in 7/52 (13%) who reported excellent adherence to PrEP from their last HIV-negative test to the time of their HIV diagnosis. Baseline HIV viral load was significantly lower in those with recent PrEP exposure ($n = 52$) than in those not reporting recent

Girometti N, AIDS 2022

Chemsex use in a HIV pre-exposure prophylaxis (PrEP) program based in Milan

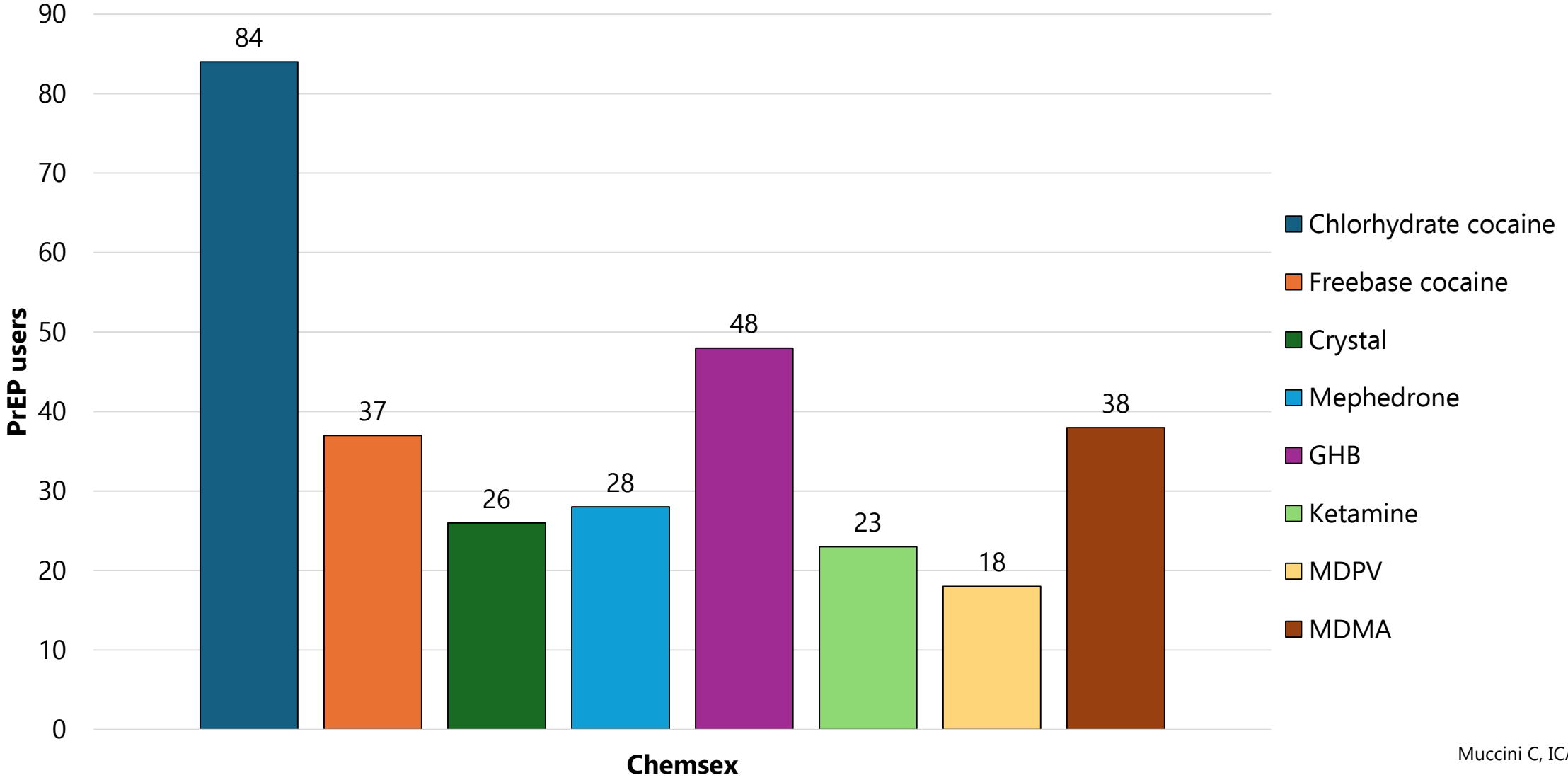
- Aims of the study:
  - To estimate prevalence of chemsex use in the Italian PrEP population of Milano Checkpoint;
  - To describe the drugs used;
  - To estimate the incidence of new chemsex use after PrEP initiation;
  - To evaluate the factors associated with chemsex use.
- Data were collected from self-administered questionnaires filled between December 2017 and July 2021 at every visit by PrEP users of Milano Checkpoint.
- PrEP users completed a questionnaire at each visit providing data on drug and alcohol use, and sexual behaviors. “Chemsex” included crystal methamphetamine, mephedrone, ecstasy, ketamine, gamma-hydroxybutyrate (GHB), methylenedioxypyrovalerone (MDPV) and cocaine (freebase and chlorhydrate).

Chemsex use in a HIV pre-exposure prophylaxis (PrEP) program based in Milan

Characteristics	Overall (n=527)	Chemsex users (n=126)	Non-Chemsex users (n=401)	p-value
Age, median (IQR)	37 (31 - 44)	36 (30 - 43)	37 (31 - 45)	0.601
Sex, n (%)	519 (98.5%)	127 (100%)	398 (98.0%)	0.134
MSM, n (%)	**505 (96.2%)**	**126 (100%)**	**379 (95%)**	**0.035**
Italian, n (%)	433 (82.2%)	100 (78.7%)	333 (83.3%)	0.247
Employed, n (%)	458 (87.2%)	112 (88.2%9	346 (86.9%)	0.712
Antidepressant, antianxiety and antipsychotic medications, n (%)	**57 (10.8%)**	**24 (18.9%)**	**33 (8.3%)**	**0.001**
Previous STI (any), n (%)	164 (31.1%)	41 (32.3%)	123 (30.8%)	0.745
Alcohol Use, n (%)	**252 (48.4%)**	**80 (63.0%)**	**172 (43.7%)**	**<0.001**
Erectile dysfunction drugs, n (%)	**89 (16.9%)**	**35 (27.6%)**	**54 (13.5%)**	**<0.001**
Kinky Sex practices (Fisting, Sex Toys, Group Sex) , n (%)	341 (64.7%)	89 (70.1%)	252 (63.0%)	0.146

Muccini C, ICAR 2021

Chemsex use in a HIV pre-exposure prophylaxis (PrEP) program based in Milan



Muccini C, ICAR 2021

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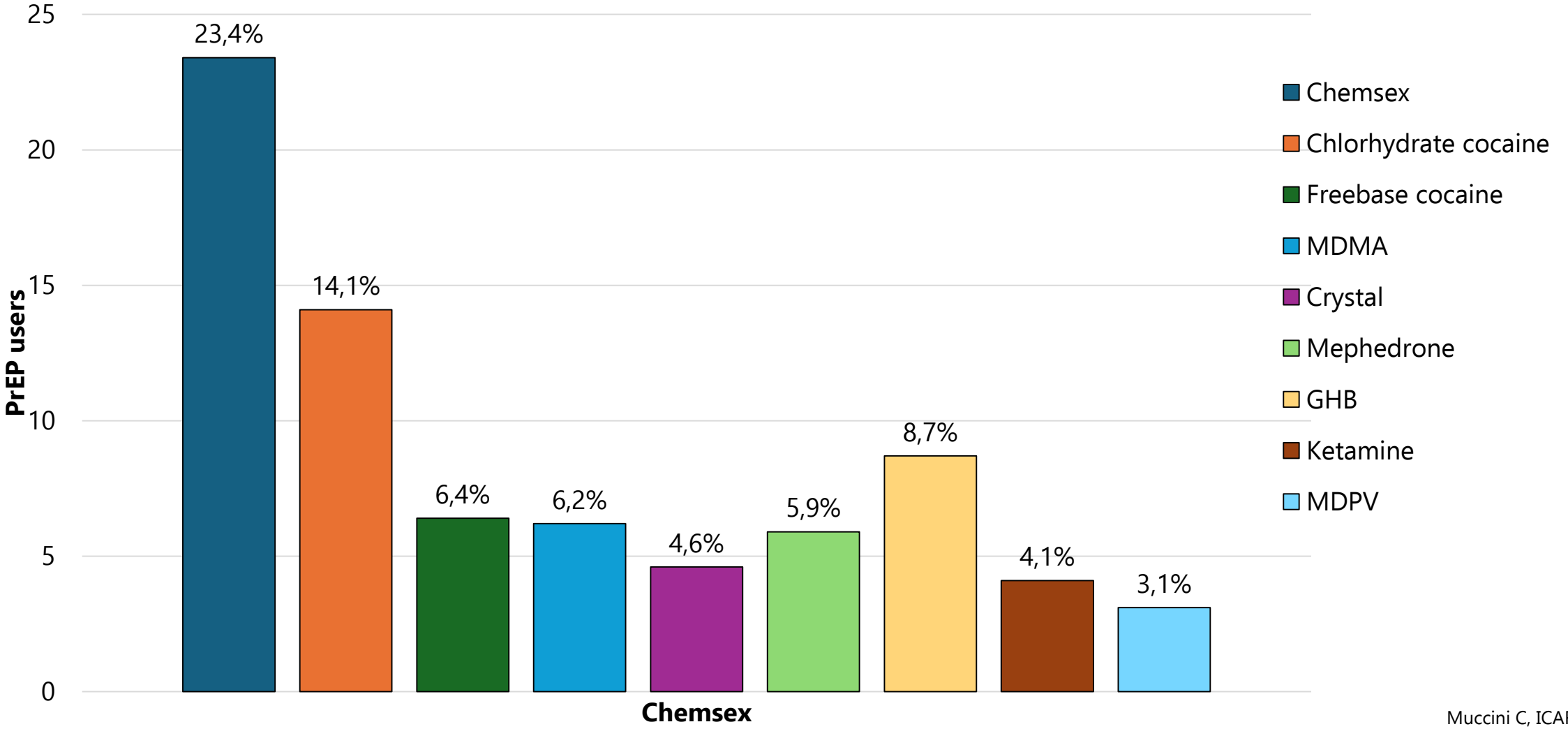
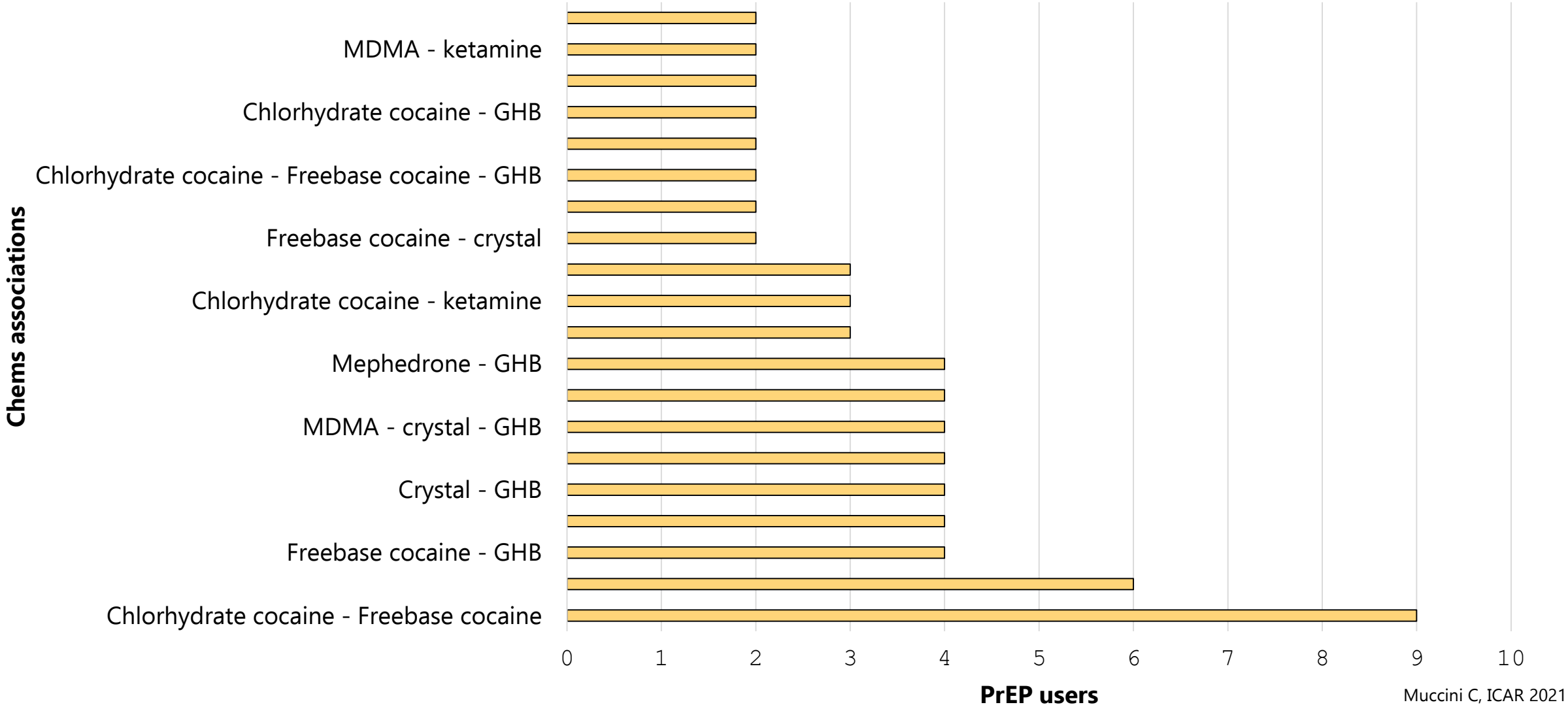


Muccini C, ICAR 2021

Chemsex use in a HIV pre-exposure prophylaxis (PrEP) program based in Milan



Muccini C, ICAR 2021

HIV breakthrough infections at Milano Checkpoint

N	AGE	YEAR START	SEX	MSM	FOREIGNBORN	ETHNICITY	LEVEL EDUCATION	JOB	AGE first sex	LIFETIME SEXUAL PARTNERS	PREVIOUS SYPHILIS	PREVIOUS CT	PREVIOUS NG	DRUG USE	Chems ex	SW	TIME to DROP (days)
1	39	2019	MALE	1	NO	WHITE	UNIVERSITY	LIBEROPROFESS			1	0	1	1	0	0	502
2	24	2021	MALE	1	NO	OTHER	SECONDARY	UNEMPLOYED	13	>30	0	0	1	0	0	0	672
3	28	2021	MALE	1	NO	WHITE	SECONDARY	LIBEROPROFESS	25	>30	0	0	1	0	0	0	784
4	35	2022	MALE	1	NO	WHITE	UNIVERSITY	IMPIEGATO	19	>30	0	0	0	0	0	0	4

HIV breakthrough infections at Niguarda Hospital

N	YEAR	SEX	AGE	COUNTRY of BIRTH	GROUP RISK	CD4	HIVRNA	SUBTYPE	POL RAMs	PI RAMs	INSTI RAMs	REGIMEN	CHEMS	CONC. STI
1	2020	M	49	ITALY	MSM	1.068	76.100	A1	--	10V,36I, 63N,89I,93L	74I	FTC/TAF/DRV/cobi+DTG	YES	YES
2	2020	M	28	ITALY	MSM	467	113.000	CRF02_AG	--	20I,36I, 69K,89M	74I	FTC/TAF/DRV/cobi+DTG	NO	YES
3	2021	M	27	ITALY	MSM	469	28.000	B	**103NRS**	--	--	FTC/TAF/DRV/cobi+DTG	YES	NO
4	2022	M	27	ECUADOR	MSM	441	84.800	CRF02_AG	--	--	--	FTC/TAF/DRV/cobi+DTG	YES	YES
5*	2022	M	25	ITALY	MSM	681	74.600	G	--	--	**163RS,232N**	3TC/DTG	NO	YES
6*	2023	M	30	ITALY	MSM	677	462.000	CRF_AG	--	--	--	FTC/TAF/DRV/cobi+DTG	NO	YES
7	2023	M	27	ITALY	MSM	448	4.390.000	CRF02_AG	--	--	--	FTC/TAF/DRV/cobi+DTG	NO	YES
8	2024	M	37	ITALY	MSM	495	580.000	CRF02_AG	--	--	**148K**	FTC/TAF/BIC	NO°	NO

°Alcohol abuse

Chemsex use & the risk of STIs

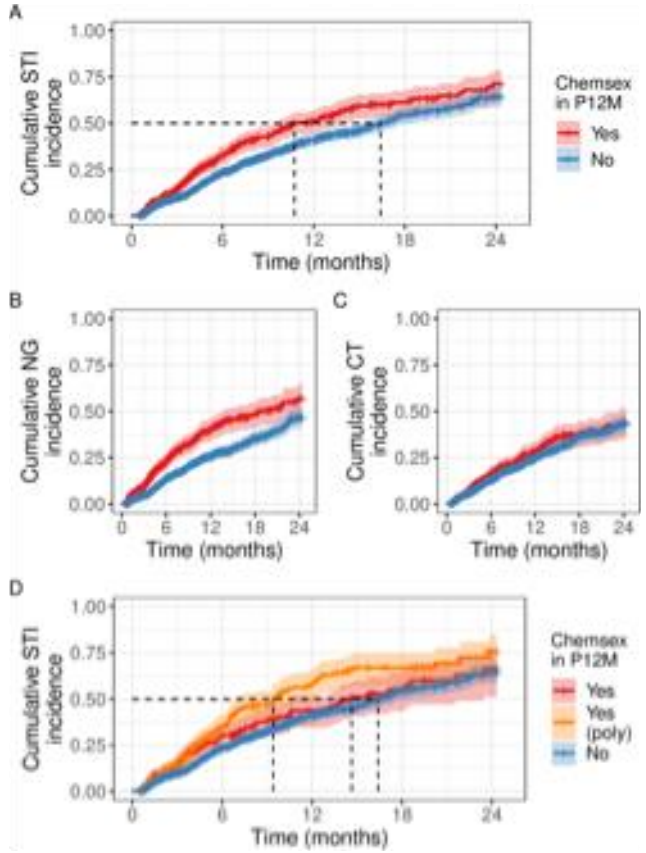


Figure 1 Cumulative STI incidence among pre-exposure prophylaxis users in the l'Actuel PrEP Cohort (2013–2020). (A) Gonorrhoea or chlamydia, any site. (B) Gonorrhoea, any site. (C) Chlamydia, any site. (D) Gonorrhoea or chlamydia, any site, chemsex stratified by polysubstance use (≥2 chemsex substances) or not (1 substance). The 95% CIs are shown as a shaded region, dotted lines show median time to first diagnosis. CT, *Chlamydia trachomatis*; NG, *Neisseria gonorrhoeae*; P12M: past 12 months. Created by the authors.

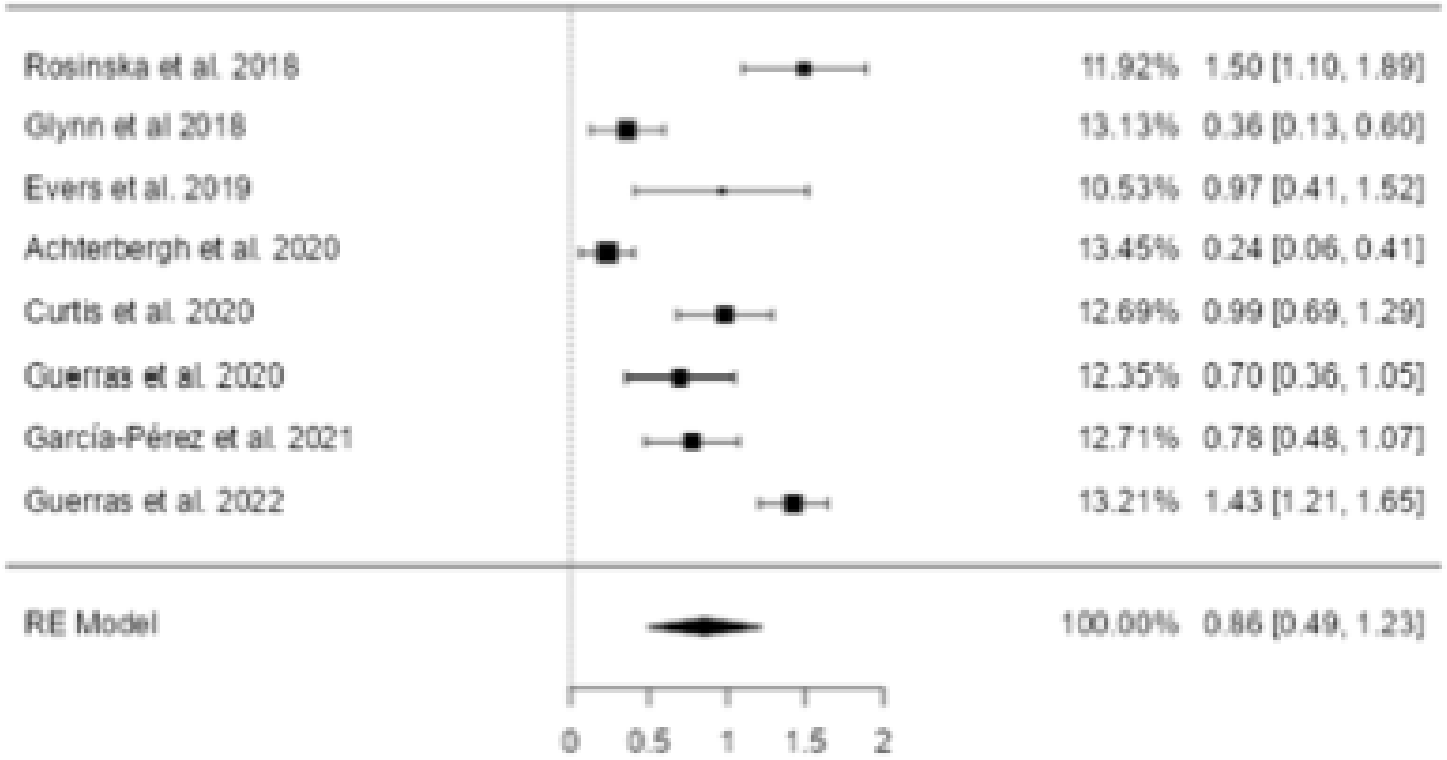


Figure 2. Random-effects model of prevalence of STI in chemsex users [28–35].

Flores Anato JL, Sex Transm Infect 2022;
Coronado-Muñoz, J Clin Med 2024

Chemsex use & the risk of PrEP failure

Table 4
Factors associated with reporting less than 7 of 7 intended doses (< 7/7TD) in a follow-up period, from univariable and multivariable logistic regressions (N = 1479 follow-up visit questionnaires, N = 388 participants)[a].

		Reporting < 7/7TD in a follow-up period						
		Univariable					Multivariable	
		Total[c]	n[d]	(%)[e]	Unadjusted OR (95% CI)	P	Adjusted OR (95% CI)	P
Baseline enrolment questionnaire variables - DEMOGRAPHICS								
Gender	Male	1465	442	(30.17%)				
	Transgender			(0.00%)				
Sexuality	Gay/homosexual	1397	416	(29.79%)	1	0.851		
	Straight/Bisexual/Other	66	21	(31.82%)	1.10 (0.41–2.99)			
Ethnicity	White	1196	336	(28.09%)	1		1	
	Black	51	22	(43.14%)	1.94 (0.78–4.80)	0.151	1.78 (0.71–4.49)	0.222
	Asian	69	30	(43.48%)	1.97 (0.84–4.63)	0.120	3.12 (1.20–8.21)	**0.020**[b]
	Other	151	50	(33.11%)	1.27 (0.76–2.12)	0.368	1.13 (0.64–1.97)	0.678
Born in the UK	No	569	171	(30.05%)	1	0.977		
	Yes	905	271	(29.94%)	0.99 (0.70–1.42)			
Age (years)[f]	18–25	148	62	(41.89%)	2.73 (1.48–5.04)	**0.001**[b]		
	26–35	532	181	(34.02%)	1.98 (1.21–3.16)	**0.006**[b]		
	36–45	435	123	(28.28%)	1.49 (0.90–2.47)	0.118		
	> 45	364	76	(20.88%)	1			
Maximum education level[f]	University degree or higher	965	282	(29.22%)	1			
	A levels / equivalent	201	65	(32.34%)	1.16 (0.70–1.91)	0.565		
	GCSEs / equivalent	149	36	(24.16%)	0.77 (0.46–1.49)	0.441		
	Vocational training/other qualifications	92	32	(34.78%)	1.29 (0.67–2.49)	0.444		
	Still in full-time education	39	20	(51.28%)	2.58 (1.05–6.21)	**0.039**[b]		
	Finished education with no qualifications	29	7	(24.14%)	0.77 (0.24–2.44)	0.658		
Employment status	Employed/self-employed full time	1050	298	(28.38%)	1		1	
	Employed/self-employed part time	134	46	(34.33%)	1.32 (0.77–2.27)	0.318	1.48 (0.81–2.70)	0.203
	Student	107	43	(40.19%)	1.70 (0.88–3.29)	0.118	1.57 (0.75–3.30)	0.233
	Unemployed	77	30	(38.96%)	1.61 (0.72–3.62)	0.248	2.31 (1.06–5.04)	**0.036**[b]
	Retired	70	15	(21.43%)	0.69 (0.24–1.99)	0.491	0.83 (0.12–2.35)	0.403
	Other	30	10	(33.33%)	1.26 (0.45–3.50)	0.655	0.53 (0.23–1.22)	0.138
Relationship status	In relationship, living with partner	429	110	(25.64%)	1			
	In relationship, not living with partner	192	55	(28.65%)	1.16 (0.64–2.13)	0.621		
	Not currently in an ongoing relationship	851	277	(32.55%)	1.40 (0.92–2.12)	0.114		
Baseline enrolment questionnaire variables - Lifestyle								
Recreational drug use in past 3 months	No	371	114	(30.73%)	1	0.718		
	Yes	1071	312	(29.13%)	0.93 (0.61–1.40)			
Alcohol drinking frequency	Never/Once	169	46	(27.22%)				
	2 or 3 times a month	312	103	(33.01%)	1.32 (0.68–2.55)	0.412		
	Once or twice a week	483	133	(27.54%)	1.02 (0.53–1.95)	0.962		
	3 or 4 times a week	286	96	(33.57%)	1.35 (0.67–2.71)	0.396		
	Nearly every day/Daily	140	48	(25.26%)	0.90 (0.43–1.90)	0.790		
Units of alcohol drank on a typical drinking day	0–4	642	202	(31.46%)	1			
	5–9	442	129	(29.19%)	0.90 (0.60–1.34)	0.597		
	≥ 10	212	58	(27.36%)	0.82 (0.50–1.34)	0.431		
Perception of adherence ability throughout the trial	Will find easy to remember to take drug daily	966	249	(25.78%)	1	**0.002**[b]	1	**0.001**[b]
	Might forget to take doses/ will find daily dosing difficult	462	175	(37.88%)	1.76 (1.23–2.51)		1.88 (1.28–2.75)	
Follow-up questionnaire variables - Clinical								
Illness preventing daily activities since last visit	No	1359	398	(29.29%)	1	0.116		
	Yes	120	44	(36.67%)	1.40 (0.92–2.12)			
Side effects to Truvada in last 30 days	No	1433	426	(29.73%)	1	0.599		
	Yes	38	10	(26.32%)	0.84 (0.45–1.59)			
Follow-up questionnaire variables - Lifestyle								
Injected drugs since last visit	No	1348	399	(29.60%)	1	0.684		
	Yes	130	42	(32.31%)	1.14 (0.62–2.09)			
Snorted cocaine since last visit	No	1182	343	(29.02%)	1	0.25		
	Yes	297	99	(33.33%)	1.22 (0.87–1.72)			
Follow-up questionnaire variables - Sexual behaviour								
Number of condomless anal sex partners since last visit	0	77	20	(25.97%)	1			
	1	362	116	(32.04%)	1.34 (0.74–2.43)	0.327		
	2–5	606	176	(29.04%)	1.17 (0.64–2.14)	0.619		
	≥ 6	433	130	(30.02%)	1.22 (0.64–2.32)	0.539		
Chemsex engagement since last visit	No	909	253	(27.83%)	1	0.137	1	0.168
	Yes	570	189	(33.16%)	1.29 (0.92–1.79)		1.29 (0.90–1.87)	
Group sex since last visit	No	783	249	(31.80%)	1	0.194		
	Yes	696	193	(27.73%)	0.82 (0.61–1.10)			
Used sex toys since last visit	No	1124	334	(29.72%)	1	0.843		
	Yes	355	108	(30.42%)	1.03 (0.74–1.44)			
Fisting since last visit	No	1273	386	(30.32%)	1	0.434		
	Yes	205	55	(26.83%)	0.84 (0.55–1.29)			

[a] Missing data from enrolment and visit questionnaires not included in logistic regression analyses.
[b] Association considered significant (P < 0.05).
[c] total number of follow-up visit questionnaires reporting row variable.
[d] total number of follow-up visit questionnaires reporting row variable and < 7/7TD within linked 90-day follow-up period.
[e] Row percentages based on non-missing data.
[f] Not included retained in final multivariable logistic regression analyses as p-value > 0.1 in multivariable model.

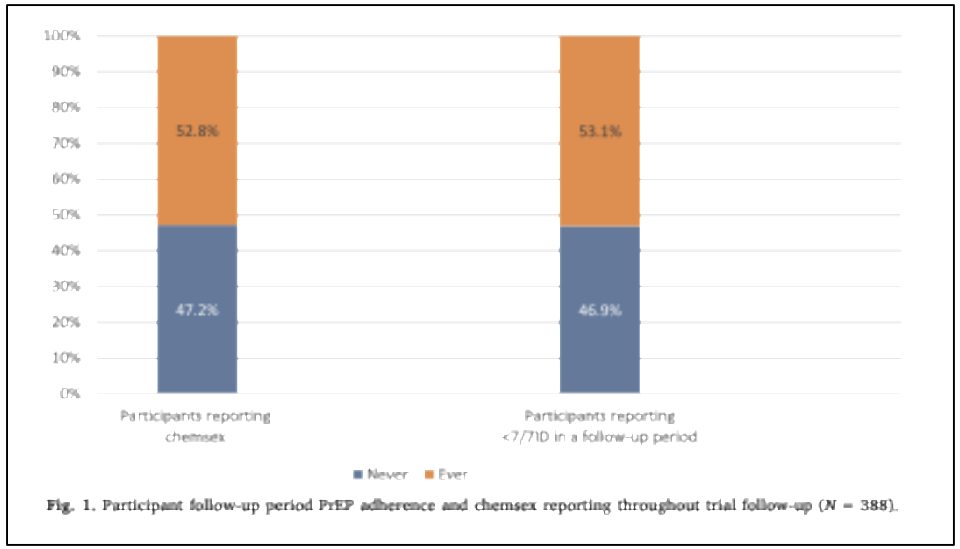


Fig. 1. Participant follow-up period PrEP adherence and chemsex reporting throughout trial follow-up (N = 388).

O'Halloran C, Int J Drug Policy 2019

Chemsex use & the risk of PrEP failure

Table 4
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	36–45	435	123	(28.28%)	1.49 (0			
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Maximum education level[e]	University degree or higher	965	282	(29.22%)	1			
	A levels / equivalent	201	65	(32.34%)	1.16 (0			
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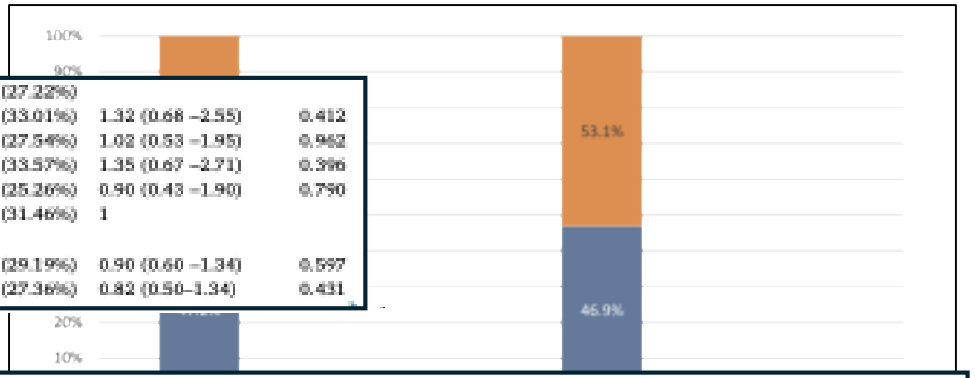
	Vocational training/other qualifications	92	32	(34.78%)	1.29 (0			
	Still in full-time education	39	20	(51.28%)	2.58 (1			
	Finished education with no qualifications	29	7	(24.14%)	0.77 (0			
Employment status	Employed/self-employed full time	1050	298	(28.38%)	1			
	Employed/self-employed part time	134	46	(34.33%)	1.32 (0.77–2.27)	0.318	1.48 (0.81–2.70)	0.203
	Student	107	43	(40.19%)	1.70 (0.88–3.29)	0.118	1.57 (0.75–3.30)	0.233
	Unemployed	77	30	(38.96%)	1.61 (0.72–3.62)	0.248	2.31 (1.06–5.04)	***0.036***[h]
	Retired	70	15	(21.43%)	0.69 (0.24–1.99)	0.491	0.53 (0.12–2.35)	0.403
	Other	30	10	(33.33%)	1.26 (0.45–3.50)	0.655	0.53 (0.23–1.22)	0.138
Relationship status								
Baseline enrolment questionnaire v								
Recreational drug use in past 3 m								
Alcohol drinking frequency								
Units of alcohol drank on a typic drinking day								
Perception of adherence ability throughout the trial	daily							
	Might forget to take doses/ will find daily dosing difficult	462	175	(37.88%)	1.76 (1.23–2.51)		1.88 (1.28–2.75)	
Follow-up questionnaire variables - Clinical								
Illness preventing daily activities since last visit	No	1359	398	(29.29%)	1	0.116		
	Yes	120	44	(36.67%)	1.40 (0			
Side effects to Truvada in last 30 days	No	1433	426	(29.73%)	1			
	Yes	38	10	(26.32%)	0.84 (0			
Follow-up questionnaire variables - Lifestyle								
Injected drugs since last visit	No	1348	399	(29.60%)	1			
	Yes	130	42	(32.31%)	1.14 (0			
Snorted cocaine since last visit	No	1182	343	(29.02%)	1			
	Yes	297	99	(33.33%)	1.22 (0			
Follow-up questionnaire variables - Sexual behaviour								
Number of condomless anal sex partners since last visit	0	77	20	(25.97%)	1			
	1	362	116	(32.04%)	1.34 (0			
	2–5	606	176	(29.04%)	1.17 (0			
	≥6	433	130	(30.02%)	1.22 (0.64–2.32)	0.539		
Chemsex engagement since last visit	No	909	253	(27.83%)	1	0.137	1	0.168
	Yes	570	189	(33.16%)	1.29 (0.92–1.79)		1.29 (0.90–1.87)	
Group sex since last visit	No	783	249	(31.80%)	1	0.194		
	Yes	696	193	(27.73%)	0.82 (0.61–1.10)			
Used sex toys since last visit	No	1124	334	(29.72%)	1	0.843		
	Yes	355	108	(30.42%)	1.03 (0.74–1.44)			
Fisting since last visit	No	1273	386	(30.32%)	1	0.434		
	Yes	205	55	(26.83%)	0.84 (0.55–1.29)			

[a] Missing data from enrolment and visit questionnaires not included in logistic regression analyses.
[b] Association considered significant (P < 0.05).
[c] total number of follow-up visit questionnaires reporting row variable.
[d] total number of follow-up visit questionnaires reporting row variable and < 7/7ID within linked 90-day follow-up period.
[e] Row percentages based on non-missing data.
[h] Not included retained in final multivariable logistic regression analyses as p-value > 0.1 in multivariable model.

Alcohol drinking frequency	Never/Once	169	46	(27.22%)				
	2 or 3 times a month	312	103	(33.01%)	1.32 (0.68–2.55)	0.412		
	Once or twice a week	483	133	(27.54%)	1.02 (0.53–1.95)	0.962		
	3 or 4 times a week	286	96	(33.57%)	1.35 (0.67–2.71)	0.396		
	Nearly every day/Daily	190	48	(25.26%)	0.90 (0.43–1.90)	0.790		
Units of alcohol drank on a typical drinking day	0–4	642	202	(31.46%)	1			
	5–9	442	129	(29.19%)	0.90 (0.60–1.34)	0.597		
	≥ 10	212	58	(27.36%)	0.82 (0.50–1.34)	0.431		



Chemsex engagement since last visit	No	909	253	(27.83%)	1	0.137	1	0.168
	Yes	570	189	(33.16%)	1.29 (0.92–1.79)		1.29 (0.90–1.87)	
Group sex since last visit	No	783	249	(31.80%)	1	0.194		
	Yes	696	193	(27.73%)	0.82 (0.61–1.10)			

Injected drugs since last visit	No	1348	399	(29.60%)	1			0.684
	Yes	130	42	(32.31%)	1.14 (0.62–2.09)			
Snorted cocaine since last visit	No	1182	343	(29.02%)	1			0.25
	Yes	297	99	(33.33%)	1.22 (0.87–1.72)			

O'Halloran C, Int J Drug Policy 2019

Chemsex use & the risk of PrEP loss to FU

Table 1 Characteristics of PrEP users

Characteristics ($N = 568$)	PrEP users 568 patients % (n)
Men	98.1 (557)
Transgender women and men	0.7 (4)
Couple	35.6 (202)
Born abroad	7.7 (44)
Living in Tours city (37,000) ($N = 338$)[a]	51.8 (175)
Living in Tours city agglomeration ("*Tours Métropole*") ($N = 338$)[a]	71.6 (242)
Living in Indre-et-Loire (37) ($N = 338$)[a]	89.1 (301)
Age (mean ± SD)	34.8 ± 11.7
Number of annual sexual partners (mean ± SD)	19.2 ± 36.9
Chemsex practices	12.9 (73)
Slam practices[b]	3.0 (17)
History of sexual abuse	7.0 (40)
History of sex work	3.2 (18)
History of rectitis	2.1 (12)
History of urethritis ($N = 557$)[c]	6.3 (35)
History of syphilis	21.8 (124)
History of VEA	12 (68)
History of LGV	0.2 (1)

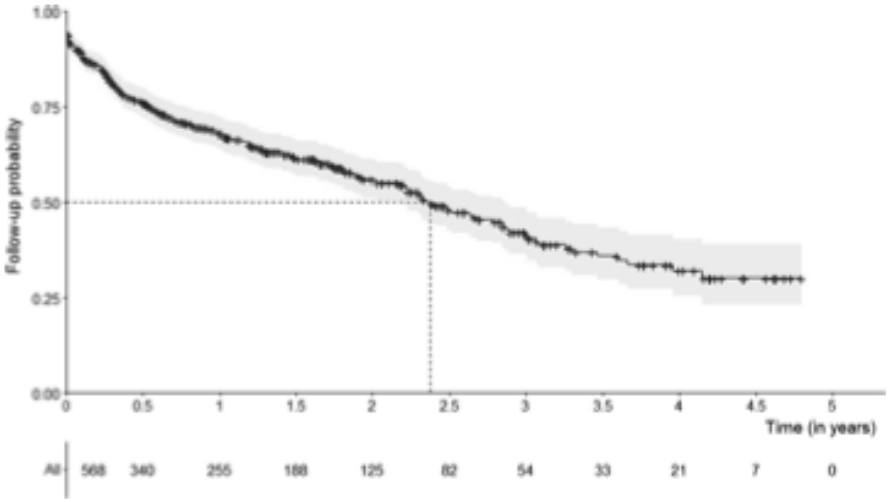
VEA Viral Exposure Accident, *LGV* Lymphogranulomatosis venereum

[a]Proportion calculated on all cis-gender men

[b]Slam practices was defined by chemsex practices with intravenous drug use

[c]Proportion calculated on all cis-gender men

Fig. 1 Kaplan–Meier curve for PrEP follow-up in CeGIDD 37 between June 2016 to June 2021



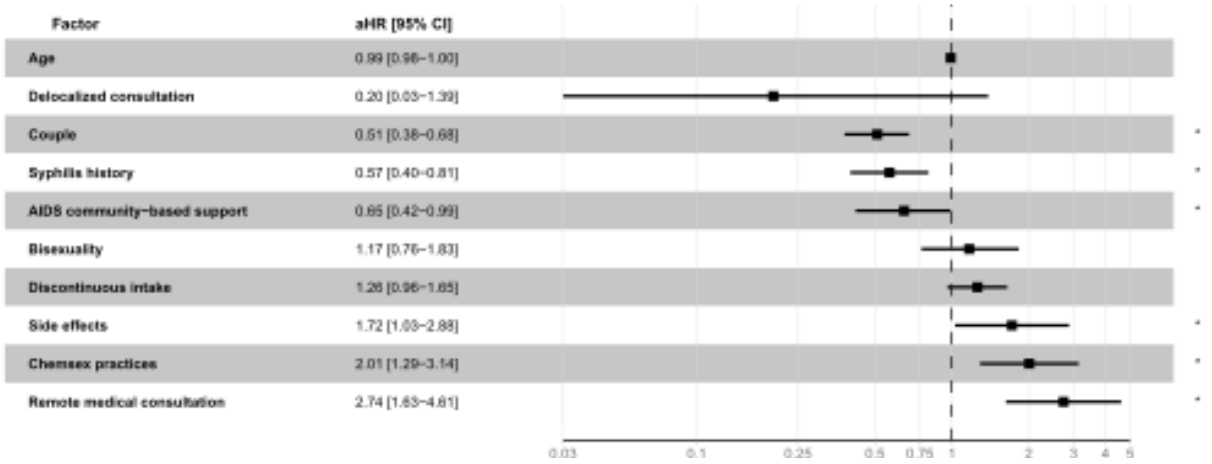


Fig. 2 Factors associated with persistence of PrEP follow-up

Le Roux C, Arch Sex Behav 2024

Chemsex use & the risk of PrEP loss to FU

Table 1 Characteristics of PrEP users

Characteris

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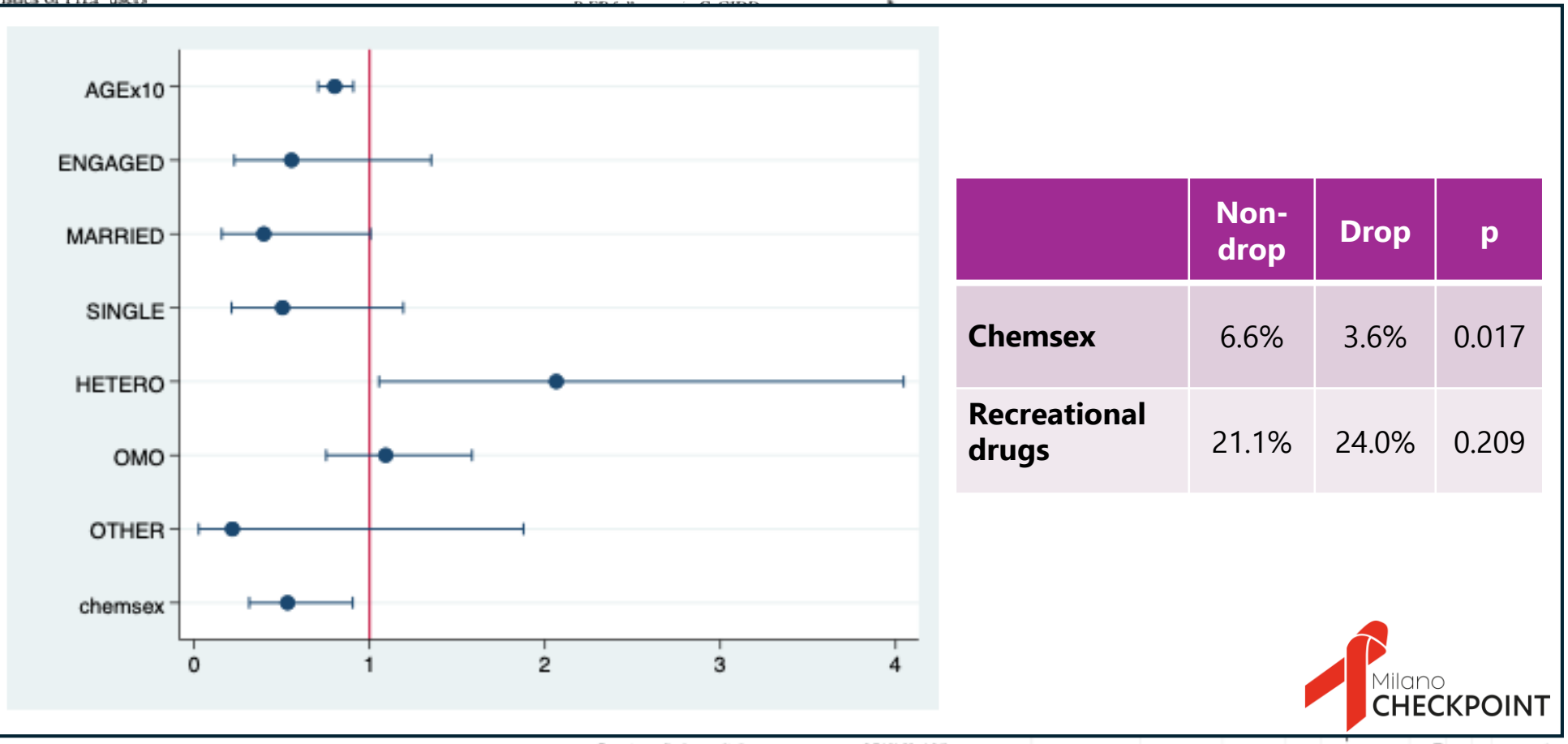
VEA Vira
venereum
[a]Proportion
[b]Slam prac
drug use
[c]Proportion calculated on all cis-gender men

Fig. 1 Kaplan–Meier curve for



	Non-drop	Drop	p
Chemsex	6.6%	3.6%	0.017
Recreational drugs	21.1%	24.0%	0.209

Milano CHECKPOINT

Remote medical consultation 2.74 [1.65–4.61]

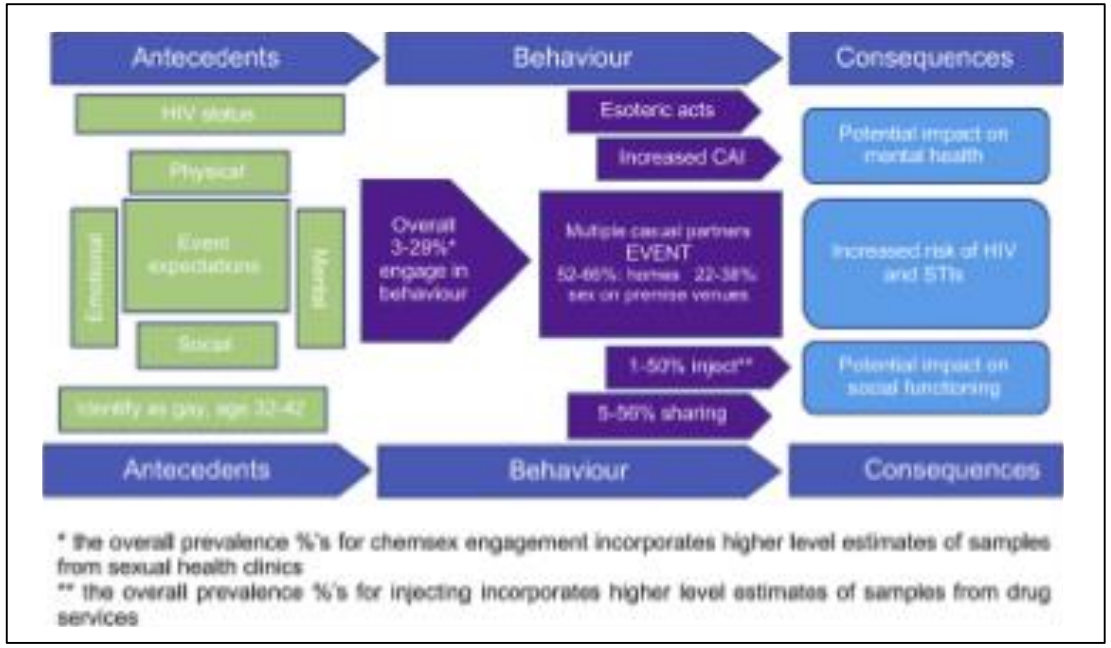
0.03 0.1 0.25 0.5 0.75 1 2 3 4 5

Fig. 2 Factors associated with persistence of PrEP follow-up

Le Roux C, Arch Sex Behav 2024

What is “problematic” chemsex?

- Use that has a harmful and negative impact to a person, their family, friends and others. For example: Use of illegal drugs, impaired driving, binge drinking, combining multiple substances, increasing frequency, increasing quantity.



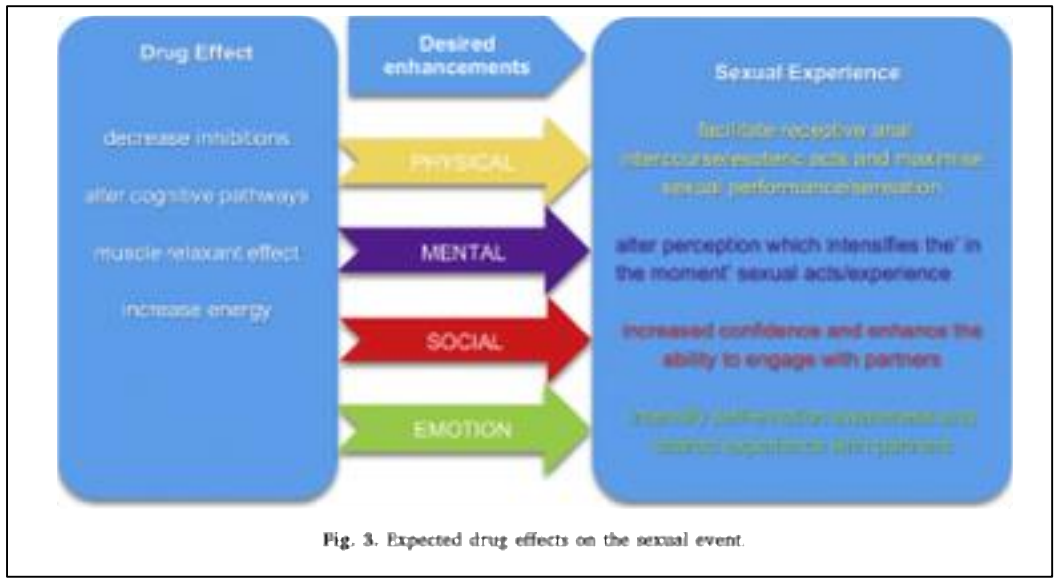


Fig. 3. Expected drug effects on the sexual event.

Canada Health Department 2024; Maxwell S, Int J Drug Policy 2018

The MDPV-MDPHP crisis in Milan

- Among novel psychoactive substances, **synthetic cathinones** (SCs) represent the second-largest category monitored in Europe, with 19 new compounds first reported to the EU Early Warning System between 2020 and 2022 and an increase of illicit laboratories producing them in recent years.
- In the past, some of these compounds were investigated for therapeutic purposes but at present they are mainly consumed as alternative to other stimulants.
- SCs, known as “bath salts”, are analogues of cathinone, the natural compound found in the kath plant whose leaves are consumed for their stimulant effects, and referred as a “**natural amphetamine**” , given the similar chemical structures and the pharmacological properties .

Bassi M, Neurotoxicology 2024

The MDPV-MDPHP crisis in Milan

- Their psychoactive effects are primarily mediated by interactions with **monoamine transporters** (DAT, NET, SERT): some of them are substrate-type releasers at monoamine transporters and others are transporter inhibitors.
- The 3,4-methylenedioxypyrovalerone (**MDPV**) is one of the most popular SCs and an original constituent of psychoactive “bath salts”. It is a methylenedioxy derivative of pyrovalerone, reported for the first time to EWS in 2008 because of fatalities and adverse health effects associated with its consumption.
- The 3,4-methylenedioxy-alpha-pyrrolidinohexanophenone (**MDPHP**) is an analogue of MDPV, it was first reported in 2014 and during 2021 an amount of 149 Kg of it has been seized in EU, representing the 2 % of the total material.

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The MDPV-MDPHP crisis in Milan

- These two compounds were developed during 1960s and differ in the length of carbon chain, which in MDPHP turns out to have an extra carbon than MDPV.
- MDPV has been typically seized in powder form (the free base is a brown or yellow-green amorphous powder), but seizure of tablets, capsules, liquids and, in few cases, paper doses (known as “blotters”) containing MDPV has also been reported. The compound has been detected in 107 non-fatal intoxications and 99 deaths. The subjective effects described are **stimulation** and **euphoria**, **increased libido**, **disinhibition**, and **appetite suppression**. Adverse effects include increase in heart rate, muscle spasms, headaches, confusion, anxiety, and paranoia.
- MDPHP appeared more recently into the illicit drug market and little data exists about its pharmacological properties, metabolism, and toxicity. Users reported that it is usually insufflated, smoked, or orally administered and the effects described are like MDPV’s. According to literature, MDPHP is usually consumed in association to other psychoactive substances, thus, there is few information about its effects when taken alone. Patients manifested euphoria, anxiety, dizziness, **hallucinations**, **psychosis**, and **aggressive behaviors**, in addition to **breathing difficulties**, **pain in the thorax region** and **hypertension**.
- There has also been reported a case that concerned a fetal death and showed that MDPHP can cross the placental barrier into fetal circulation.
- Currently, the first and only case of death due to acute intake of MDPHP alone has been recently reported in Italy.

Bassi M, Neurotoxicology 2024

The **MDPV**-MDPHP crisis in Milan

Table 4
MDPV human poisoning (Pavia Poison Centre - National Toxicology Information Centre data) over a 9-year period (2011–2019). All reported cases were intentional non-fatal intoxications (any lethal event was registered).

Case n./ Sex, Age	EDs admission	Reported/ suspected substance(s), brand name	Reported dose/ route of administration	On-site screening positivity	Signs/Symptoms	Patient Management	Blood/Urine: Analytical confirmation (*) (§, ^, ~, ●, $)	Anamnestic data, Annotations, Hospital stay/ Outcomes	NEWS alert
#1 20, M	*August 2011*	Unknown NPS + Ethanol + THC	oral, smoke	THC	CNS alterations (psychomotor agitation, hallucinations), cardiovascular (tachycardia), dyspnoea	Symptomatic treatment, Benzodiazepines	MDPV, butylone, (§)	Known LSD, GHB and MDMA abuser ? Sexual context (Chem-Sex) 48 hours, discharged home	*EWS 247/ 12 December 05, 2012*
#2 37, M	*May 2012*	Cathinone (Energy3) + GBL + THC	smoke	–	CNS alterations (psychomotor agitation), cardiovascular (tachycardia), hyperthermia	Symptomatic treatment (paracetamol i.v. + ice), Hydration	MDPV, (^)	about 72 hours, discharged home	*EWS alert*
#3 38, M	*October 2012*	Cathinone (Energy, Crystal, Mefre) + MDMA	nasal, smoke	–	CNS alterations (psychomotor agitation, visive and audittive hallucinations, toxic psychosis), cardiovascular (tachycardia)	Symptomatic treatment, Benzodiazepines (delorazepam), Neuroleptics/ Antipsychotic drug (haloperidol), Hydration	MDPV, (^)	Habitual cathinone abuser, HIV positive ? Sexual context (Chem-Sex) >48 hours, transferred to psychiatric ward	*EWS 247/ 12 December 05, 2012*
#4 42, M	*March 2013*	Cathinone (Energy3) + COC + MTD	oral, nasal, smoke	COC, MTD, MDMA	CNS alterations (psychomotor agitation, hallucinations, toxic psychosis - delirium), cardiovascular (tachycardia), mydriasis, sweating, acidosis	Symptomatic treatment, Sedation -Benzodiazepines (propofol + midazolam), Hydration	MDPV, Levamisole, (**)	>24 hours, discharged home	*SNAP alert*
#5 35, M	*June 2013*	Cathinone (Energy)	–	COC	CNS alterations (psychomotor agitation, hallucinations, toxic psychosis - delirium)	Symptomatic treatment, Sedation -Benzodiazepines, Hydration	MDPV, Mephedrone, (**)	Long-lasting Energy abuser under treatment at Ser.D Psychotic delirium; taken to ED by police agency ? Sexual context (Chem-Sex) >24 hours, transferred to psychiatric ward	*SNAP alert*
#6 25, M	*July 2013*	–	–	BZO	CNS depression/Coma (mental confusion), cardiovascular (bradycardia), mydriasis	Antidotal treatment (naloxone, flumazenil), Symptomatic treatment, Sedation (propofol), Hydration	MDPV, (**)	? Sexual context (Chem-Sex) >72 hours, discharged home	*SNAP alert*
#7 26, M	*July 2014*	MDPV + bromazepam	smoke	COC	CNS alterations (psychomotor agitation), cardiovascular (tachycardia), nausea	Symptomatic treatment, Benzodiazepines, Antiemetic agent, Hydration	MDPV, (**)	HIV positive ? Sexual context (Chem-Sex) <24 hours, discharged home	*SNAP alert*
#8 41, M	*August 2015*	Cathinones (mephedrone + MDPV)	nasal, smoke	–	CNS alterations (psychomotor agitation, hallucinations), nausea	Symptomatic treatment, Benzodiazepines, Hydration	MDPV, (●)	Long-lasting mephedrone abuser, HIV positive ? Sexual context (Chem-Sex) <24 hours, discharged home	*SNAP 12/ 18 May 14, 2018*
#9 46, M	*July 2015*	MDPV + MAMP	–	–	CNS alterations (psychomotor agitation, mental confusion, psychosis - dysphoria, logorrhoea)	Symptomatic treatment, Benzodiazepines (delorazepam) + Antipsychotic drug (haloperidol), Hydration	MDPV, (●)	HIV positive ? Sexual context (Chem-Sex) 72 hours, discharged home	*SNAP 12/ 18 May 14, 2018*
#10 36, M	*December 2015*	MDPV	nasal	BZO	CNS alterations (psychomotor agitation, aggressiveness, toxic, violent psychosis - self injuring, i.e. hang himself)	Symptomatic treatment, Benzodiazepines - Sedation	MDPV, (●)	HIV positive ? Sexual context (Chem-Sex) 6 days, discharged home	*SNAP 12/ 18 May 14, 2018*
#11 28, M	*January 2019*	MDPV + Sildenafil	nasal	neg	CNS alterations (psychomotor agitation), cardiovascular (tachycardia, hypertension, thoracic pain)	Symptomatic treatment, Benzodiazepines (diazepam)	MDPV + MDPHP, ($)	HIV positive ? Sexual context (Chem-Sex) 24 hours, discharged home	*SNAP 19/ 19 May 24, 2019*

-: information missing; nasal: "sniffing" or "snorted"; oral: ingestion; neg: negative; AMP: Amphetamines; BZO: Benzodiazepines; COC: Cocaine; MAMP: Methamphetamine; MOP: Opiates; MTD: Methadone; PCP: Phencyclidine; right bundle branch block: RBBB; THC: delta-9-tetrahydrocannabinol (THC); 3-MeO-PCP: 3-Methoxyphencyclidine; 3-MeO-PCE: 3-Methoxyeticyclidine; Ser.D: Pathological Addiction Service (Servizi per le Dipendenze patologiche) - Italian National Health Service Institution; PrEP: Pre-Exposure Prophylaxis; SNAP: Sistema Nazionale Allerta Precoce – Italia; EWS: Early Warning System.
(*) GC-MS and LC-MS methods (based on standard availability).
(§) tested negative for the following substances: 4FA, MDAI, PMA, PMMA, 4MEC, MXE, APB isomers, butylone, ketamine, levamisole, mephedrone, scopolamine, atropine, MDPV (based on standards availability).
(^) tested negative for the following substances: butylone, mephedrone, 4MEC, dimethylcathinone, dimethylmethcathinone, buphedrone, ethcathinone, 4-fluoromethcathinone, pentedrone, methedrone, eylone, pentylone, 1-naphyrone, MDAI, PMA, PMMA, 4FA, ketamine, levamisole, scopolamine, atropine, APB, MXE, DMT, 3C1, 2CT7, 2C8, 2CE, DOB, MDPV.
(●) tested negative for the following substances: butylone, mephedrone, 4MEC, dimethylcathinone, dimethylmethcathinone, buphedrone, ethcathinone, 4-fluoromethcathinone, pentedrone, methedrone, etylone, pentylone, 1-naphyrone, MDAI, PMA, PMMA, 4FA, ketamine, levamisole, scopolamine, atropine, APB, MXE, DMT, 3C1, 2CT7, 2C8, 2CE, DOB, MDPV, 25B-NBOME, 25 C-NBOME, 25I-NBOME.
($) tested negative for the following substances: butylone, mephedrone, 4MEC, dimethylcathinone, dimethylmethcathinone, buphedrone, ethcathinone, 4-fluoromethcathinone, pentedrone, methedrone, mexedrone, etylone, pentylone, 1-naphyrone, alpha-PHP, 3,4-MDPHP, alpha-PVP, MDPV, beaK-2CB, PMA, PMMA, 4-fluoroamphetamine, 4-MTA, ketamine, levamisole, scopolamine, atropine, (amino propyl)benzofurans (APB), methoxetamine, methoxypheridine, diphenidine, dimethyltryptamine. 2C1, 2CT7, 2C8, 2CT2, 2CE, DOB, 25B-NBOME, 25 C-NBOME, 25I-NBOME, 25T7-NBOMT, 25 H-NBOME, 25D-NBOMT, 25E-NBOMT.
Patients tested positive to both MDPV and MDPHP are highlighted in grey.

Bassi M, Neurotoxicology 2024

The MDPV-**MDPHP** crisis in Milan

Table 5
MDPHP human poisoning (Pavia Poison Centre - National Toxicology Information Centre data) over a 6-year period (2018–2023). All reported cases were intentional non-fatal intoxications (any lethal event was registered) and, after hospitalization, patients were discharged home.

Case n., Sex, Age	ED's admission	Reported/ suspected substance(s) (s), brand name	Reported dose/ route of administration	On-site screening positivity	Signs/Symptoms	Patient Management	Blood/Urine Analytical confirmation (*) (§, ¶, ••, ◆)	Anamnestic data, Annotations, Hospital stay / Outcomes	NEWS alert
#1 45, M	January 2018	MDPV	smoke	neg	CNS alterations (psychomotor agitation, psychosis hallucinations, delirium, aggressiveness), cardiovascular (tachycardia, hypertension)	Symptomatic treatment, Benzodiazepines (midazolam), Antibiotics, Hydration	MDPHP, (§)	HIV positive ? Sexual contact (Chem-Sex) 48 hours, discharged home	SNAP 12/18 April 4, 2018
#2 28, M	December 2018	MDPV	nasal, smoke	THC + MDPV	CNS alterations (agitation, mental confusion, migraine), cardiovascular (tachycardia), hyperthermia, pharyngodynia	Symptomatic treatment, Benzodiazepines (delorazepam), paracetamol, Hydration	MDPHP, (§)	? Sexual contact (Chem-Sex) Unknown hospital stay duration, discharged home	SNAP 1/19 May 24, 2019
#3 28, M	January 2019	MDPV + 4-Methaff	nasal	neg	CNS alterations (agitation), cardiovascular (tachycardia, hypertension, thoracic pain)	Symptomatic treatment, Benzodiazepines (diazepam)	MDPV + MDPHP, (§)	HIV positive ? Sexual contact (Chem-Sex) 24 hours, discharged home	SNAP 1/19 May 24, 2019
#4 43, M	May 2019	alpha-PHP + MDMA	smoke	neg	CNS alterations (agitation, psychosis, hallucinations), mydriasis, abdominal pain	Symptomatic treatment, Benzodiazepines	MDPHP + alpha-PHP, (§)	Long-term abuser, HIV positive ? Sexual contact (Chem-Sex) Unknown hospital stay duration, discharged home	SNAP 28/19 August 30, 2019
#5 42, M	September 2019	Cathinones + Ethanol	smoke	BZD	CNS alterations (agitation, tremors, fasciculation, mental confusion, aggressiveness), tachypnoea, hyperthermia, rhabdomyolysis (CPK->), hypertransaminasemia	Symptomatic treatment, Sedation - Benzodiazepines (propofol + midazolam), Neuroleptic/Antipsychotic drugs (promazine, haloperidol, thioridol), Hydration	MDPHP + alpha-PHP, (§)	Long-term abuser, HIV positive, history of BZC therapy. Aggressive, taken to ED by police agency ? Sexual contact (Chem-Sex) 5-days, discharged home	SNAP 3/20 February 11, 2020
#6 15, F	September 2019	Denied consumption	THC		CNS alterations (agitation, blurred vision)	Symptomatic treatment, methylprednisolone i.v.	MDPHP, (§)	Diagnosed for branch retinal arterial occlusion 5-days, discharged home	SNAP 3/20 February 11, 2020
#7 45, M	September 2019	MDPHP + 5-PCC + ? anabolic steroid drugs	oral	–	CNS alterations (agitation, aggressiveness, seizures), cardiovascular (hypotension), acidosis	Symptomatic treatment, Benzodiazepines (diazepam), Hydration	MDPHP + 5 F-MDMB-PICA (*)	HIV positive, history of IDs admission for similar toxidromes ? Sexual contact (Chem-Sex) 48-hours, discharged home	SNAP 3/20 February 11, 2020
#8 19, M	July 2020	Unknown substance – Ethanol	THC	CNS depression, drowsiness	Antidotal treatment (naloxone), Symptomatic treatment	MDPHP, 3-MeO-PCP, 3-MeO-PCE, Methorphan Doxylamine, (§)	24 hours, discharged home	SNAP 36/20 Oct 28, 2020	
#9 39, M	June 2021	MDPHP	smoke	COC, Ethanol	CNS alterations (agitation, hallucinations, tremors/fasciculation, numbness, mental confusion), Cardiovascular (tachycardia, hypertension), rhabdomyolysis (CPK->)	Symptomatic treatment, Benzodiazepines (delorazepam), Hydration	MDPHP (●●)	HIV positive ? Sexual contact (Chem-Sex) <24 hours, discharged home	SNAP 52/21 Dec 30, 2021
#10 26, M	August 2021	COC + MD + GHB	smoke	–	CNS alterations (agitation, insomnia, paranoiac disturb.),	Symptomatic treatment, Hydration	MDPHP, MDMA,	? Sexual contact (Chem-Sex) <24 hours, discharged home	SNAP 52/21 Dec 30, 2021

(continued on next page)

Table 5 (continued)

Case n., Sex, Age	ED's admission	Reported/ suspected substance (s), brand name	Reported dose/ route of administration	On-site screening positivity	Signs/Symptoms	Patient Management	Blood/Urine Analytical confirmation (*) (§, ¶, ••, ◆)	Anamnestic data, Annotations, Hospital stay / Outcomes	NEWS alert
					muscle pain, tongue oedema, rhabdomyolysis (CPK->)				
#11 19, M	August 2021	COC + MD + GHB	smoke		CNS alterations (agitation, insomnia, paranoiac disturb.), muscle pain, tongue oedema, rhabdomyolysis (CPK->)	Symptomatic treatment, Hydration	MDPHP, MDMA, MDA (●●◆)	? Sexual contact (Chem-Sex) <24 hours, discharged home	SNAP 52/21 Dec 30, 2021
#12 28, M	August 2021	α-PHP + MDPHP + COC + MCPPA + ethyl chloride		Ethanol	CNS alterations (agitation, hallucinations)	Symptomatic treatment, Sedation -Benzodiazepines (propofol + midazolam)	MDPHP (◆)	Personality disorder, long-lasting abuser under treatment at Ser.D ? Sexual contact (Chem-Sex) > 5 days, transferred to psychiatric ward	SNAP 52/21 Dec 30, 2021
#13 24, M	November 2021	MCPPA (Magik cook)		BZD	CNS alterations (agitation, paranoid behaviour - scare), cardiovascular (thoracic pain)	Symptomatic treatment, Benzodiazepines	MDPHP (●●)	? Sexual contact (Chem-Sex) Self-discharged after 4 hours	SNAP 12/22 March 24, 2022
#14 36, M	December 2021	COC + GHB – MCPPA – ethyl chloride	nasal, oral	COC, AMP, MAMP	CNS alterations (agitation, anxiety) Impaired motility. General malaise	Symptomatic treatment, Hydration	MDPHP, Mephedrone, AMP/MAMP (●●)	HIV positive ? Sexual contact (Chem-Sex) 48 hours, discharged home	SNAP 13/22 March 24, 2022
#15 28, M	January 2022	MCPPA – poppers	nasal	neg	CNS alterations (agitation, Migraine, paraesthesia), cardiovascular (tachycardia, tachypnoea, cardiac repolarisation disorders, incomplete RBBB (100->QRS<120 ms))	Symptomatic treatment, Benzodiazepines, Hydration	MDPHP (●●)	Sexual contact (Chem-Sex) 24 hours, discharged home	SNAP 12/22 March 24, 2022
#16 30, M	March 2022	MCPPA	smoke		CNS alterations (agitation, hallucinations, aggressiveness, toxic psychosis, delirium), cardiovascular (tachycardia)	Symptomatic treatment, Benzodiazepines (midazolam)	MDPHP (●●)	Psychotic breakdown in a pub: taken to ED by police agency 24 hours, discharged home	SNAP 27/22 June 28, 2022
#17 35, M	March 2022	PHP + Paracetine (2 tablets)	smoke	neg	CNS depression, drowsiness, numbness, slowing, emotional breakdown (crying spells)	Symptomatic treatment Hydration.	MDPHP (●●)	Psychiatric disorder ? Sexual contact (Chem-Sex) 24 hours, discharged home	SNAP 27/22 June 28, 2022
#18 28, M	March 2022	MCPPA + ketamine + mephedrone + COC + GHB + home-made dried fruit extract	0.5-1 g (MDPV) nasal	–	CNS alterations (agitation, paranoid behaviour), abdominal pain, burning sensation at limbs and gastrointestinal tract	Symptomatic treatment, Sedation - Benzodiazepines	MDPHP - Ketamine (●●)	HIV positive ? Sexual contact (Chem-Sex) <24 hours, transferred to psychiatric ward	SNAP 45/22 Oct 5, 2022
#19 33, M	April 2022	Synthetic cathinones (PV) + COC + AMP + Crack	–	COC + BZD	CNS alterations (psychomotor agitation), Mycosis	Antidotal treatment (naloxone, flumazenil), Symptomatic treatment, Sedation - Benzodiazepines, Physical restraint	MDPHP (●●)	Known drug abuser ? Sexual contact (Chem-Sex) <24 hours, transferred to ICU.	SNAP 45/22 Oct 5, 2022
#20 43, M	April 2022	MCPPA + antipsychotic agents - neurodepressants	nasal	neg	CNS depression/Coma		MDPHP (●●)	Known MDPHP abuser Sexual contact (Chem-Sex) <24 hours, discharged home	

Table 5 (continued)

Case n., Sex, Age	ED's admission	Reported/ suspected substance (s), brand name	Reported dose/ route of administration	On-site screening positivity	Signs/Symptoms	Patient Management	Blood/Urine Analytical confirmation (*) (§, ¶, ••, ◆)	Anamnestic data, Annotations, Hospital stay / Outcomes	NEWS alert
#21 29, M	June 2022	Synthetic cathinones (MDPV)	nasal	COC	CNS alterations (psychomotor agitation, toxic psychosis, delirium), cardiovascular (tachycardia), rhabdomyolysis (CPK->)	Symptomatic treatment, Sedation (propofol) – Benzodiazepines, Hydration	MDPHP (●●)	Known drug abuser - 24 hours, discharged home	SNAP 45/22 Oct 5, 2022
#22 33, M	August 2022	MDPV	smoke	COC	CNS alterations (psychomotor agitation)	Symptomatic treatment, Sedation, Hydration	MDPHP (●●)	Self-discharged after 4 hours	SNAP 45/22 Oct 5, 2022
#23 24, M	September 2022	MDPHP	nasal	neg	CNS alterations (psychomotor agitation, toxic psychosis - manic euphoria, aggressiveness, oppositional behaviour)	Symptomatic treatment, Sedation - Benzodiazepines - Neuroleptic/Antipsychotic drugs (promazine)	MDPHP (●●)	Known MDPHP abuser 48 hours, discharged home	SNAP 45/22 Oct 5, 2022
#24 38, M	October 2022	PCP + MCD	smoke, oral	MDP - MCD - BZD	CNS alterations (agitation, tremors/ fasciculation), cardiovascular (tachycardia, respiratory arrest), myosis, hypothermia, rhabdomyolysis (CPK->), severe acidosis	Antidotal treatment (naloxone), Symptomatic treatment, Benzodiazepines (delorazepam)	MDPHP - MCD - EDDP (●●)	Known abuser under Treatment at Ser.D Tx: pregabalin, levomepromazine, olanzapine, methadone 24 hours, discharged home	SNAP 05/23 January 26, 2023
#25 46, M	October 2022	Ethanol + COC + MAMP - "Madonna di Dante"	–	neg	CNS alterations (agitation, mental confusion), cardiovascular (tachycardia), hyperthermia, hypertension/stress, clonic spasms, diffuse pain	Symptomatic treatment, Sedation – Benzodiazepines, Hydration	MDPHP (●)	HIV positive, transgender ? Sexual contact (Chem-Sex) 48 hours, discharged home	SNAP 05/23 January 26, 2023
#26 38, M	December 2022	MDPV + Synthetic cannabinoids	–	BZD	CNS alterations (agitation, hallucinations, persecutory ideation)	Symptomatic treatment, Sedation – Benzodiazepines (midazolam), ketamine, Neuroleptic/Antipsychotic drugs (aripiprazole)	MDPHP - Ketamine (●)	Synthetic cannabinoids/ MDPV occasions, user HIV positive ? Sexual contact (Chem-Sex) 24 hours, discharged home	SNAP 18/23 April 26, 2023
#27 45, M	January 2023	MDPV	3 bags total (time interval 12 h) nasal	AMP + BZD + COC	CNS alterations (agitation, seizures), cardiovascular (tachycardia) dyspnoea, neurotonia, acidosis	Symptomatic treatment, Benzodiazepines (midazolam + diazepam) Decontamination (activated charcoal)	MDPHP (●●)	MDPV habitual recreational use Known abuser referred by private psychiatrist; Tx: quetiapine, haloperidol 24 hours, discharged home	SNAP 18/23 April 26, 2023
#28 42, M	January 2023	GHB	–	AMP + BZD + COC	CNS depression/Coma. Cardiovascular (tachycardia, hypertension), dyspnoea, mydriasis, rhabdomyolysis (CPK->)	Antidotal treatment (naloxone - no efficacy, flumazenil), Symptomatic treatment	MDPHP (●●)	HIV positive Sexual contact (Chem-Sex) <24 hours, discharged home	SNAP 18/23 April 26, 2023
#29 34, M	February 2023	MDPV – COC + GHB + bromazepam + alprazolam + Ethanol	smoke, oral	COC	CNS depression (drowsiness, numbness, mental confusion)	Antidotal treatment (flumazenil), Symptomatic treatment, Hydration	MDPHP (●●)	Psychiatric evaluation 24 hours, discharged home	SNAP 18/23 April 26, 2023
#30 32, M	February 2023	MDPV – MAMP	smoke, oral, nasal	COC	CNS alterations (cephalgia), Cardiovascular (tachycardia, hypertension), Hyperemia/Coma. neutrophilic leucocytosis, rhabdomyolysis (CPK->)	Symptomatic treatment, Benzodiazepines	MDPHP (●●)	AMP habitual use 24 hours, discharged home	SNAP 18/23 April 26, 2023

Table 5 (continued)

Case n., Sex, Age	ED's admission	Reported/ suspected substance (s), brand name	Reported dose/ route of administration	On-site screening positivity	Signs/Symptoms	Patient Management	Blood/Urine Analytical confirmation (*) (§, ¶, ••, ◆)	Anamnestic data, Annotations, Hospital stay / Outcomes	NEWS alert
#32 23, M	February 2023	Cathinones + COC	smoke, oral	–	CNS alterations (psychomotor agitation)	Symptomatic treatment, Benzodiazepines (lorazepam + diazepam)	MDPHP (●●)	Known abuser under treatment at Ser.D Tx: delorazepam 24 hours, discharged home	SNAP 18/23 April 26, 2023
#33 44, M	March 2023	MDPV	nasal	COC + BZD	CNS alterations (psychomotor agitation, hallucinations, psychosis, delirium, aggressiveness), cardiovascular (tachycardia), acidosis, rhabdomyolysis (CPK->)	Symptomatic treatment, Sedation (desmedetomidine) + Benzodiazepines (midazolam + diazepam)	MDPHP (●●)	Known abuser under treatment at Ser.D HIV positive ? Sexual contact (Chem-Sex) Previous TSO admission for CNS alterations: agitation, delusional disorder -persecutory type 9 days, discharged home	SNAP 18/23 April 26, 2023
#34 37, M	May 2023	α-PVP	smoke	BZD	CNS alterations (psychomotor agitation, psychosis, mental confusion)	Symptomatic treatment, Benzodiazepines (midazolam) + Antipsychotic drugs (promazine)	MDPHP + CMC (●●)	Psychotic behaviour, taken to ED by police agency ? Sexual contact (Chem-Sex) 24 hours, discharged home	SNAP 30/23 July 27, 2023
#35 21, M	August 2022	MDPHP	THC		CNS alterations (psychomotor agitation, mental confusion)	Symptomatic treatment, Benzodiazepines (delorazepam + midazolam)	MDPHP (●●)	THC habitual use 24 hours, discharged home	SNAP 30/23 July 27, 2023
#36 26, M	June 2023	MDPHP + Rivotril	smoke (MDPHP) oral (Rivotril 40 drops)	COC	CNS alterations (agitation, tremors/ fasciculation), dysgenesis	Symptomatic treatment	MDPHP - clonazepam (●●)	Known abuser under treatment with methadone HIV and HCV positive <24 hours, discharged home	SNAP 45/23 November 24, 2023
#37 30, M	June 2023	MDPV	oral	–	CNS alterations (agitation, psychosis, aggressiveness)	Symptomatic treatment, Hydration	MDPHP (●●)	- 24 hours, discharged home	SNAP 45/23 November 24, 2023
#38 32, M	July 2023	MDPV + COC	smoke, nasal		CNS alterations (agitation, tremors/ fasciculation)	Symptomatic treatment, Benzodiazepines (delorazepam)	MDPHP (●●)	Psychiatric disorder ? Sexual contact (Chem-Sex) 24 hours, discharged home	SNAP 45/23 November 24, 2023
#39 50, M	July 2023	MDPV	smoke	neg	CNS alterations (psychomotor agitation, hallucinations, psychosis, tremors/fasciculation), cardiovascular (tachycardia), rhabdomyolysis (CPK->)	Symptomatic treatment, Benzodiazepines	MDPHP (●●)	HIV positive ? Sexual contact (Chem-Sex) Previous TSO admission for CNS alterations: agitation, delusional disorder -persecutory type 9 days, discharged home	SNAP 45/23 November 24, 2023
#40 38, M	July 2023	MDPV	–	COC	CNS alterations (psychomotor agitation, hallucinations, psychosis - delirium, aggressiveness, mental confusion), rhabdomyolysis (CPK->)	Symptomatic treatment, Benzodiazepines (lorazepam + diazepam), Antipsychotic drugs (promazine + haloperidol), Hydration	MDPHP - Methorphan (isomers) (●●)	Psychotic, violent behaviour, taken to ED by police agency 10 days, discharged home	SNAP 45/23 November 24, 2023
#41 48, M	July 2023	MDPV + LSNN	oral	neg	CNS alterations (psychomotor agitation, hallucinations)	Symptomatic treatment, Benzodiazepines (lorazepam), Hydration	MDPHP (●●)	MDPV weekly use with partner HIV positive ? Sexual contact (Chem-Sex)	SNAP 45/23 November 24, 2023

(continued on next page)

Table 5 (continued)

Case n., Sex, Age	ED's admission	Reported/ suspected substance (s), brand name	Reported dose/ route of administration	On-site screening positivity	Signs/Symptoms	Patient Management	Blood/Urine Analytical confirmation (*) (§, ¶, ••, ◆)	Anamnestic data, Annotations, Hospital stay / Outcomes	NEWS alert
								24 hours, discharged home	
#42 36, M	August 2023	MDPV	nasal		CNS alterations (psychomotor agitation, hallucinations), cardiovascular (tachycardia, hypotension), hyperthermia, acidosis	Symptomatic treatment, Benzodiazepines, ketamine, Hydration	MDPHP (●●) + ketamine	Psychotic behaviour, taken to ED by police agency Unknown hospital stay duration, discharged home	SNAV 45/23 November 24, 2023
#43 38, M	August 2023	MDPV + COC	ora.	COC	CNS alterations (psychomotor agitation, aggressiveness)	Symptomatic treatment, Benzodiazepines (delorazepam) + Physical restraint	MDPHP (●●)	Outrageous psychotic behaviour, taken to ED by ambulance staff Self-discharged home after 24 hours	SNAV 45/23 November 24, 2023
#44 38, M	August 2023	MDPV	ora.	COC + BZD	CNS alterations (psychomotor agitation, aggressiveness), rhabdomyolysis (CPK->)	Symptomatic treatment, Benzodiazepines (delorazepam) + Physical restraint	MDPHP (●●)	Taken to ED by police agency after assault charge Sexual context (Chem-Sex) Tx: aripiprazole, clonazepam, pregabalin Voluntary missing from the PS after 24 hours	SNAV 45/23 November 24, 2023
#45 38, M	September 2023	MDPV + mephedrone + crack	–	COC	CNS alterations (psychomotor agitation)	Symptomatic treatment, Benzodiazepines (delorazepam)	MDPHP (●●)	HIV positive in therapy, habitual MPS user 4 days lasting new party with continuous MPS use, taken to EDs by colleagues ? Sexual context (Chem-Sex) Voluntary missing from the PS (< 24 hours)	SNAV 45/23 November 24, 2023
#46 48, M	October 2023	MDPV	–	–	CNS alterations (psychomotor agitation, waive and auditive hallucinations)	Symptomatic treatment, Benzodiazepines (diazepam)	MDPHP (●●)	HIV positive in therapy, transferred to the Psychiatric ward in other hospital Sexual context (Chem-Sex) Unknown hospital stay duration, discharged home	SNAV 45/23 November 24, 2023

-: information missing; nasal: "sniffing" or "snorted"; oral: ingestion; neg: negative; AMP: *Amphetamines*, BZD: *Benzodiazepines*; COC: *Cocaine*, MAMP: *Methamphetamine*; MOP: *Opiates*, MTD: *Methadone*, PCP: *Phencyclidine*, right bundle branch block. *RBBB*: THC: *delta-9-tetrahydrocannabinol (THC)*; 3-MeO-PCP: *3-Methoxyphencyclidine*; 3-MeO-PCE: *3-Methoxyeticyclidine*, ICU: *Intensive Care Unit*; Ser.D: *Pathologos of Addiction Service* (Servizi per le Dipendenze patologiche) - *Italian National Health Service Institutions*; PrEP: *Pre Exposure Prophylaxis*; SNAP: *Sistema Nazionale Allerta Precoce - Italia*

(*) GC-MS and LC-MS methods (based on standards availability).

($) tested negative for the following substances: butylone, mephedrone, 4MEC, dimethylcathinone, dimethylmethcathinone, buphedrone, ethcathinone, 4-fluoromethcathinone, pentedrone, methedrone, mexedrone, etylone, pentylone, 1-naphtyrone, α-PHP, 3,4-MDPHP, α-PVP, MDPV, benzylcathinone, 2C-B, PMA, PMMA, 4-fluoroamphetamine, 4-MTA, ketamine, levamisole, scopolamine, atropine, (aminopropyl)benzofurans (APB), methoxetamine, methoxyphenidine, diphenidine, dimethyltryptamine, 2C1, 2CT7, 2CB, 2CT2, 2C5, DOB, 25B-NBOME, 25 C-NBOME, 25I-NBOME, 25T7-NBOME, 25 H-NBOME, 25D-NBOME, 25E-NBOME, 25H-NBOME.

(§) tested negative for the following substances: butylone, mephedrone, methylcathinone, dimethylcathinone, dimethylmethcathinone, buphedrone, ethcathinone, 4-fluoromethcathinone, pentedrone, methedrone, mexedrone, etylone, pentylone, 1-naphyrone, α-PHP, 3,4-MDPHP, α-PVP, MDPV, benzylcathinone, 2C-B, PMA, PMMA, 4-fluoroamphetamine, 4-MTA, ketamine, levamisole, scopolamine, atropine, (aminopropyl)benzofurans (APB), methylphenidate, ethylphenidate, 4 fluoromethylphenidate, phencyclidine (PCP), methoxetamine, methoxyphenidine, diphenidine, dimethyltryptamine, 2C1, 2CT7, 2CB, 2CT2, 2C5, DOB, 25B-NBOME, 25 C-NBOME, 25I-NBOME, 25T7-NBOME, 25D-NBOME, 25E-NBOME.

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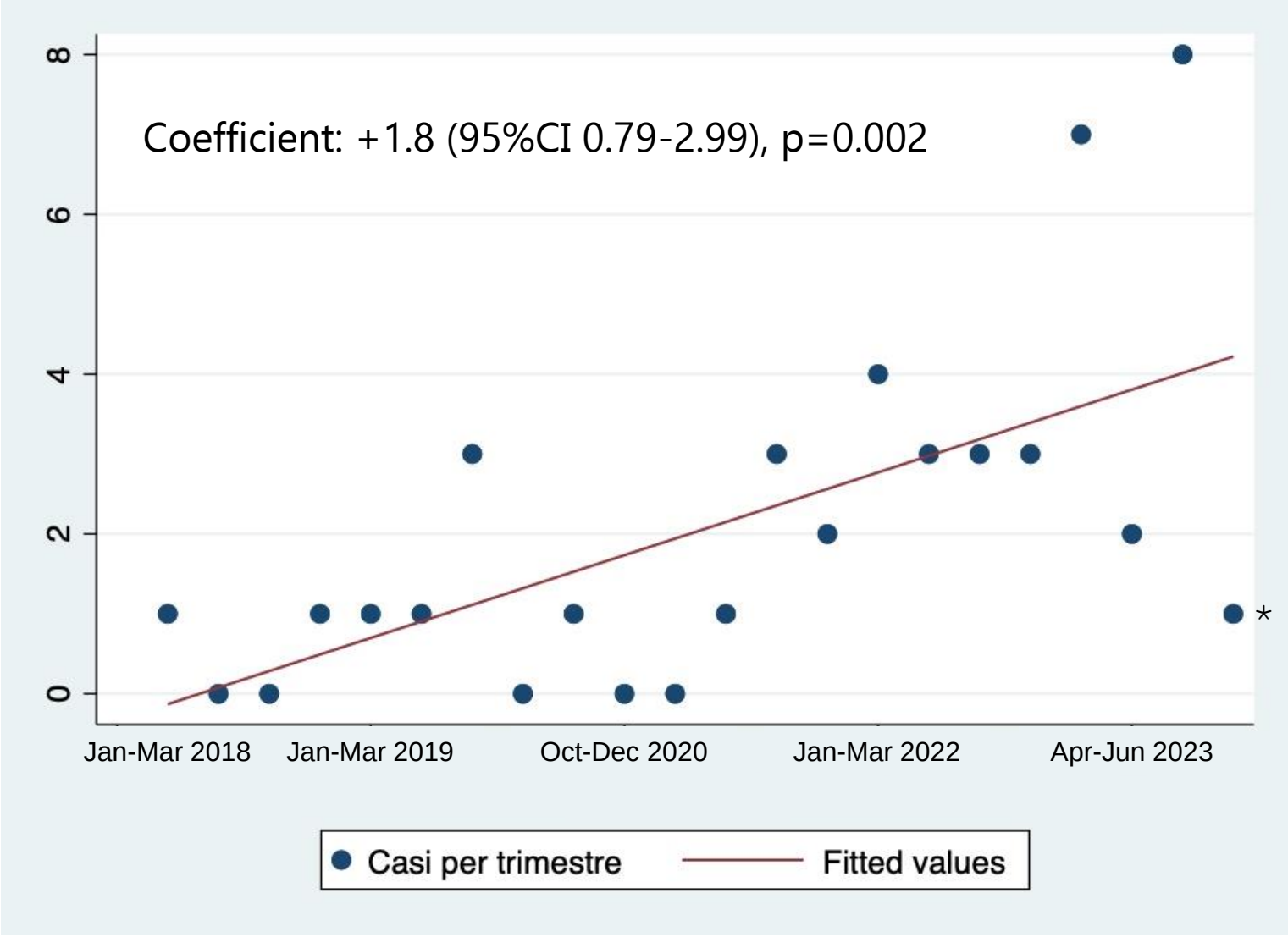
The MDPV-**MDPHP** crisis in Milan



Jan-Mar 2020 and Apr-Jun 2020 trimesters were excluded for COVID-19 pandemic.
* Data limited to Oct month only.

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The MDPV-**MDPHP** crisis in Milan

46 cases, 44 men (97.8%), 1 TGW (2.2%), sexual orientation not reported

13 PLWH (28.2%), 1 HIV/HCV co-infected (2.2%); 14 (30.4%)with known abuse disorders

33 (IQR 28-40) years

CHILL: 35 (76.1%), **POLICE: 9 (19.6%)**, OTHER DISEASE: 2 (4.3%)

NONE: 30 (65.2%), **OTHER CATHINONES: 5 (10.9%)**, KETAMINE: 3 (6.5%), MDMA: 2 (4.3%), METHADONE/OPIOID: 2 (4.3%), BENZO: 1 (2.2%), DISSOCIATIVE ANESTHETICS: 1 (2.2%), MEPHEDRONE: 1 (2.2%), SYNTHETIC CANNABINOID: 1 (2.2%)

DISCHARGED: 35 (76.1%), SELF-DISCHARGED: 7 (15.2%), PSYCHIATRIC ADMISSION: 3 (6.5%), **ICU: 1 (2.2%)**

SMOKE: 11 (25.0%), **NASAL: 9 (20.4%)**, ORAL: 5 (11.4%), SMOKE+ORAL: 4 (9.1%), NASAL+SMOKE: 2 (4.5%), NASAL+ORAL: 1 (2.3%), NASAL+SMOKE+ORAL: 1 (2.3%), **not reported: 11 (25.0%)**

Bassi M, Neurotoxicology 2024

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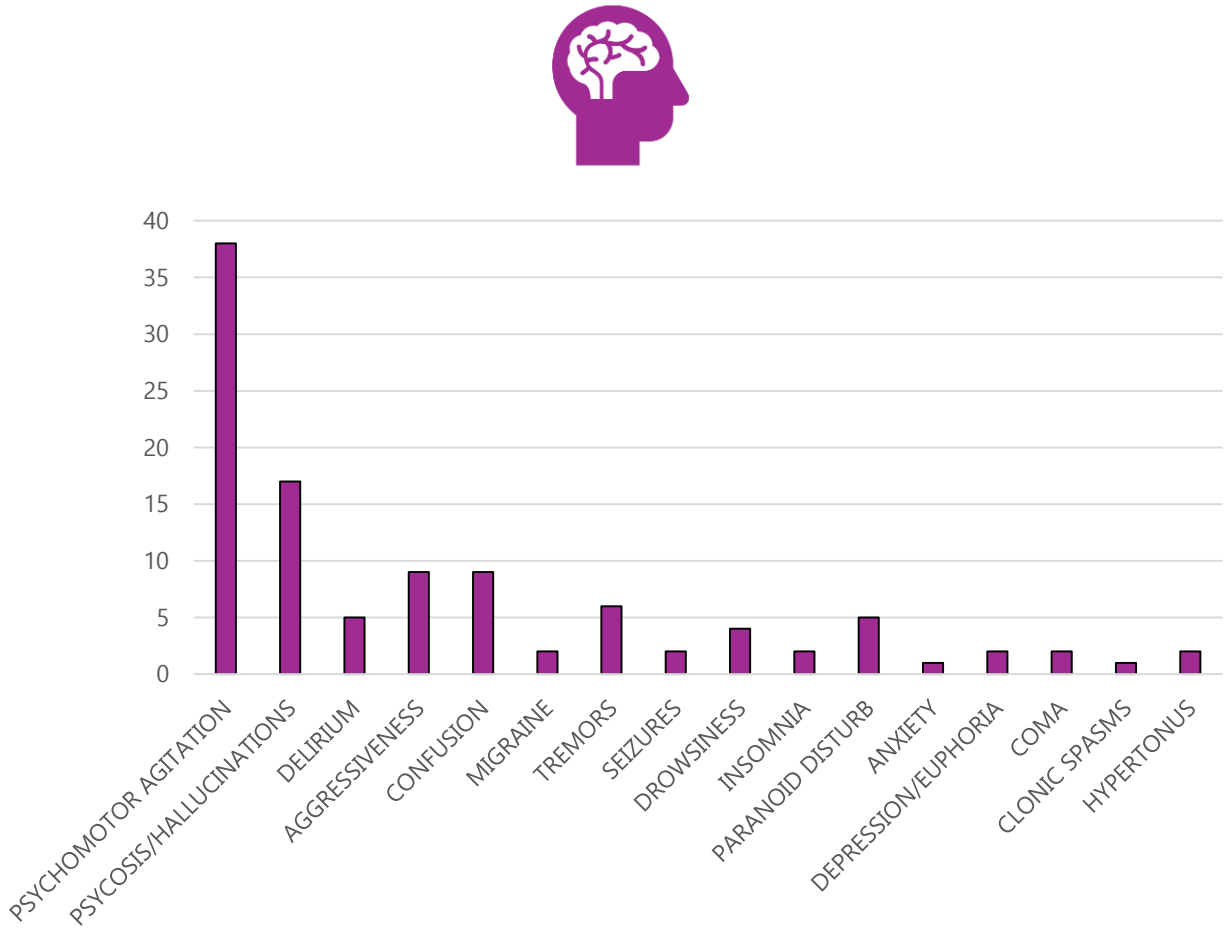

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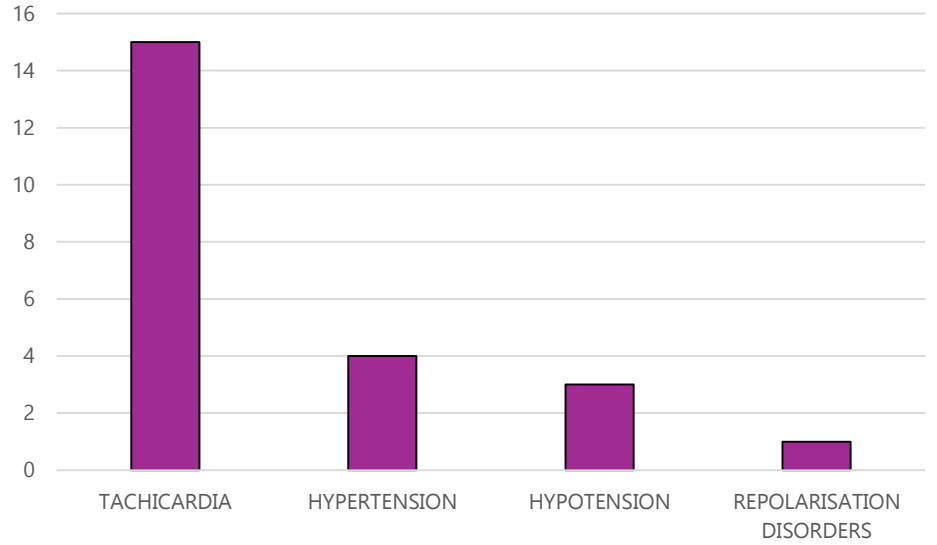

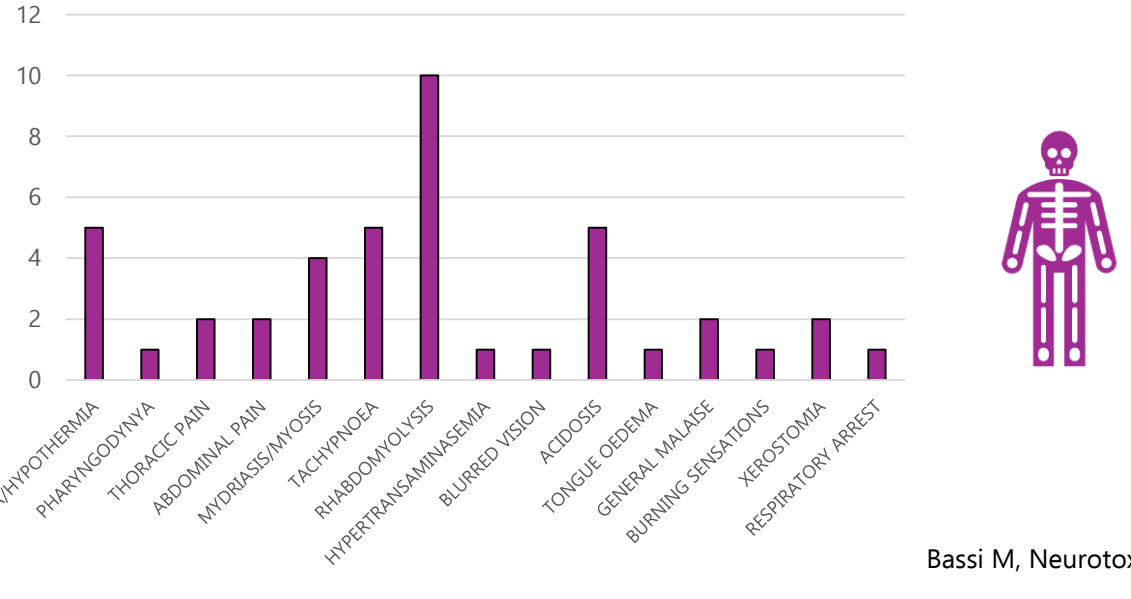

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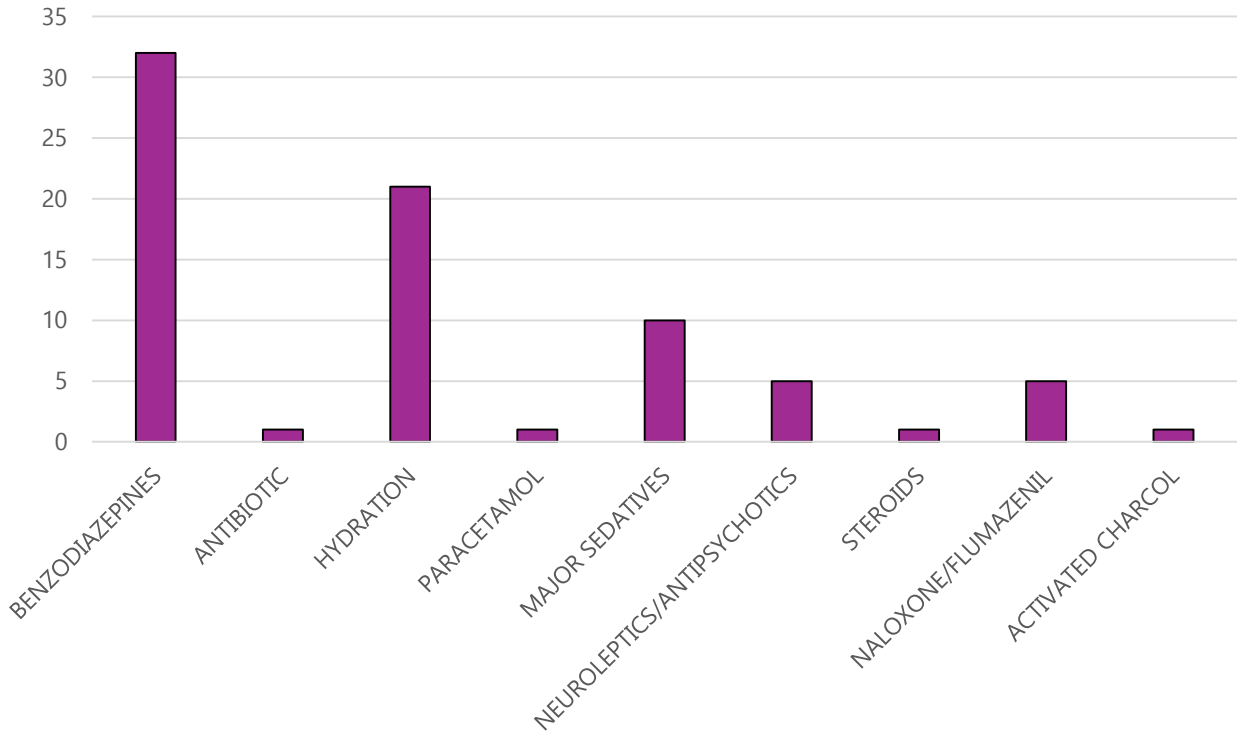

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Take home messages

- A minority of MSM engages in chemsex practices, but there are inter-connected high-risk behaviors associated with this activity.
- The examination of chemsex is limited due to the challenge in defining the activity and there are limitations in comparing prevalence estimates due to the use of different sampling frameworks.
- However, there are potentially multiple consequences associated with chemsex — especially with MDPV/MDPHP — although this remains an under researched area.
- With the increasing availability of PrEP (either oral and injectable), it is important to understand how biomedical interventions can be effectively used to reduce the potential impact of high risk chemsex practices among this population.

GRAZIE!

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