Title: Prevalence of recreational drug use is indiscriminate across antiretroviral regimens of differing drug-drug interactions among MSM.

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We welcome the literature review by Bracchi and colleagues[1] describing potential drug-drug interactions (DDIs) between antiretrovirals (ART) and recreational drugs. Data on potential DDIs are important for HIV clinical management, but remain scarce. We have previously published results from the UK observational Antriretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study (2011/12), in which half of the 2,248 HIV-diagnosed men who have sex with men (MSM) surveyed had used a recreational drug in the previous three months, with 24% using three or more drugs during the same period.[2] Linkage of routine clinical HIV records with the ASTRA questionnaire in a large subset of participants allows for examination of the prevalence of recreational drug use according to ART regimen used. To our knowledge there are no existing data on concurrent use of recreational drugs and ART among HIV-diagnosed MSM outpatients in the UK.

The primary mechanism of ART elimination is mediated through the hepatic cytochrome p450 (CYP) complex of proteins. This pathway is also shared by recreational drugs, which can either induce CYP activity, leading to decrease of ART concentration to sub-therapeutic levels, or inhibit it, resulting in toxic drug accumulation.[3] Bracchi et al suggest the potential for harm arising from DDIs is highest between recreational drugs and ritonavir or cobicistat-boosted protease inhibitors (PI/r), and to a lesser extent between recreational drugs and non-nucleoside reverse transcriptase inhibitors (NNRTI). The potential for interaction is lowest with Nucleoside Reverse Transcriptase Inhibitors, maraviroc (C-C chemokine receptor type 5 antagonist), raltegravir and dolutegravir (integrase inhibitors), and rilpivirine (NNRTI). Specifically, PI/r have highest interaction potential with benzodiazepines, erectile dysfunction drugs (EDDs), and ketamine, moderate with crystal methamphetamine, methylenedioxymethamphetamine (MDMA), and mephedrone, and lowest interaction potential with cocaine. NNRTIs (efavirenz, nevirapine, etravirine) also have the potential to interact with cocaine. Although there is low potential for interaction between cannabis, alcohol, nitrites, and ART, when taken with γ-Hydroxybutyric acid (GHB), ethanol enhances the sedative and respiratory depressant effects of GHB.[4] The interaction between GHB and ritonavir, NRTIs, or NNRTIs, remains unclear.

We therefore examined the prevalence of recreational drug use in the three months prior to ASTRA questionnaire completion according to ART regimen among HIV-diagnosed MSM on ART. A hierarchical variable was created to reflect on degree of DDI from high to low, for MSM on; (i.) ritonavir or cobicistat-boosted PIs (regardless of other drugs included in the regimen), (ii.) efavirenz or nevirapine (but not on ritonavir-boosted PIs), and (iii.) other regimens (excluding ritonavir or efavirenz/nevirapine but including rilpivirine, raltegravir, dolutegravir, or maraviroc based regimens and emtricitabine/tenofovir/etravirine or atazanavir/lamivudine/abacavir combinations). Among 2,248 MSM, 2,117 (94.2%) consented to linkage with clinic data; linked data on ART history is currently available from 4 out of 8 participating clinics for 1,325 (58.9%) MSM, of whom 1,167 (88.1%) reported being on ART at the time of the questionnaire and had a clinical record of being on ART for at least three months prior to ASTRA completion. Thus findings reported are based on 1,167 MSM, of whom 624 (53.5%) were on a regimen including a PI/r, 523 (44.8%) on efavirenz or

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nevirapine but not PI/r and 20 (1.7%) were on other regimens only (Table 1). Among 1,167 MSM, 613 (52.5%) had used recreational drugs in the previous three months, of whom 295 (25.3%) had used 3 or more drugs.

The overall prevalence of recreational drug use was similar across regimens, with over 50% of MSM on each regimen having used recreational drugs in the previous three months. (Table 1) Prevalence of polydrug use was similar for MSM on PI/r regimens and those on efavirenz or nevirapine (26.8 vs 23.3% used ≥3 drugs). The prevalence of specific drugs comparing PI/r and efavirenz or nevirapine regimens (according to range of DDI potential with ritonavir from high to low) was: EDDs ritonavir 24.2% vs. efavirenz or nevirapine 19.7%; ketamine 11.1 vs. 12.6%, chemsex drugs 16.7 vs 15.1%, and MDMA 10.7% for both regimen types. Additionally, among MSM on efavirenz or nevirapine, 22.0% used cocaine, and 9.6% used GHB. Higher alcohol consumption (WHO-AUDIT modified questionnaire score ≥6) was prevalent in 14.7% of those on PI/r and 16.8% of those on efavirenz or nevirapine. Among 180 MSM with higher alcohol consumption, 61.1% (n=110) had used recreational drugs in the previous three months, of whom 32.2% (n=58) used 3 or more drugs; of those, 56.9% (n=33) were on PI/r and 43.1% (n=25) were on efavirenz or nevirapine regimens.

In summary, recreational drug use and polydrug use are common among HIV-positive MSM receiving treatment in the UK, and similarly distributed across both PI/r and NNRTI regimens. This suggests that drug use may not be considered the most important issue by clinicians when deciding on an appropriate ART regimen and that competing concerns, such as choice of regimen most forgiving to periods of non-adherence, may be given higher priority. Alternatively, information on drug use may not routinely be elicited or disclosed in the clinical context. As the potential for DDIs is highest between ritonavir-boosted PI regimens and EDDs, benzodiazepines, ketamine, and chemsex drugs, we highlight the importance of clinician awareness of patients' use of these specific recreational drugs. National HIV treatment guidelines could benefit from inclusion of potential DDIs with specific recreational drugs and guidance on choice of regimen, dosage adjustment, monitoring, and provision of information to patients. There is a need for healthcare providers to maintain a non-judgmental attitude in discussing drug and alcohol use and DDIs, while offering support on ART adherence and safe drug use (including provision of harm reduction materials), or referral to club drug clinics. Community peer-led initiatives play a key role in producing literature about DDIs, however, further studies are needed to describe DDIs between ART and recreational drugs, particularly between PI/r and ketamine, GHB, and when used in conjunction with alcohol.

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Table 1: Recreational drug use in the previous three months according to ART regimen (N=1167 MSM on ART)

	All HIV-diagnosed MSM on ART (N=1,167)		Ritonavir or cobicistat boosted regimen (N=624)		EFV or NVP regimen only (not PI/r) (N=523)		All other regimens (N=20)▪	
	N	col %	n	col %	n	col %	n	col %
Any recreational drug use								
Yes	613	52.5	338	54.2	265	50.7	10	50.0
No	554	47.5	286	45.8	258	49.3	10	50.0
Polydrug use								
1-2 drugs used	318	27.3	171	27.4	143	27.3	4	20.0
3 or more drugs used	295	25.3	167	26.8	122	23.3	6	30.0
Chemsex drug use*								
Yes	184	15.8	104	16.7	79	15.1	1	5.0
No	983	84.2	520	83.3	444	84.9	19	95.0
Crystal methamphetamine								
Yes	111	9.5	62	9.9	48	9.2	1	5.0
No	1056	90.5	562	90.1	475	90.8	19	95.0
GHB								
Yes	118	10.1	67	10.7	50	9.6	1	5.0
No	1049	89.9	557	89.3	473	90.4	19	95.0
Mephedrone								
Yes	75	6.4	42	6.7	32	6.1	1	5.0
No	1092	93.6	582	93.3	491	93.9	19	95.0
Ketamine								
Yes	141	12.1	69	11.1	66	12.6	6	30.0
No	1,026	87.9	555	88.9	457	87.4	14	70.0
Erectile dysfunction drugs ◊								
Yes	259	22.2	151	24.2	103	19.7	5	25.0
No	908	77.8	473	75.8	420	80.3	15	75.0
Cocaine								
Yes	256	21.9	136	21.8	115	22.0	5	25.0
No	911	78.1	488	78.2	408	78.0	15	75.0
MDMA								
Yes	127	10.9	67	10.7	56	10.7	4	20.0
No	1040	89.1	557	89.3	467	89.3	16	80.0
Alcohol consumption ‡								
High	180	15.4	92	14.7	88	16.8	0	-
None/moderate	987	84.6	532	85.3	435	83.2	20	100.0

▪ Includes rilpivirine, raltegravir, dolutegravir, or maraviroc based regimens and emtricitabine/tenofovir/etravirine

* Methamphetamine, GHB/GBL, or mephedrone

◊ Sildenafil, tadalafil

‡ Score ≥6 on modified WHO AUDIT-C questionnaire

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1 Bracchi M, Stuart D, Castles R, Khoo S, Back D, Boffito M. Increasing use of “party drugs” in people living with HIV on antiretrovirals. *AIDS* 2015; **29**:1585–1592.

2 Daskalopoulou M, Rodger A, Phillips AN, Sherr L, Speakman A, Collins S, *et al.* Recreational drug use, polydrug use, and sexual behaviour in HIV-diagnosed men who have sex with men in the UK: results from the cross-sectional ASTRA study. *Lancet HIV* 2014; **1**.

3 Stolbach A, Paziana K, Heverling H, Pham P. A Review of the Toxicity of HIV Medications II: Interactions with Drugs and Complementary and Alternative Medicine Products. *J Med Toxicol* 2015; **11**:326–41.

4 Wynn GH, Cozza KL, Zapor MJ, Wortmann GW, Armstrong SC. Med-psych drug-drug interactions update. Antiretrovirals, part III: antiretrovirals and drugs of abuse. *Psychosomatics* 2005; **46**:79–87.

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