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First reported use of elvitegravir and cobicistat during pregnancy

Data on safety and pharmacokinetics of new antiretroviral agents during pregnancy is usually not available at the time of drug approval [1]. To the best of our knowledge, the use of elvitegravir and cobicistat (both FDA pregnancy category B) in pregnancy has not yet been reported [2]. Here, we present a case of elvitegravir/cobicistat use during pregnancy.

A 30-year-old black woman (1.66 m) was first diagnosed with HIV-1 in 2012. She reported to be abstinent of smoking, recreational drugs and alcohol. To facilitate compliance, elvitegravir/cobicistat/emtricitabine/tenofovir (once-daily, 150/150/200/300 mg; Stribild) fixed-dose therapy was initiated about 8 weeks before conception. At 31 weeks of gestation, viral load was undetectable (<50 copies/ml) and CD4$^+$ cell count was 965 cells/μl.

During week 34 of gestation a pharmacokinetic, (PK) curve was recorded over the 24-h dosing interval (Fig. 1; PK parameters were derived by noncompartmental analysis and reported in the figure legend). The woman (77 kg) had undetectable viral load and CD4$^+$ cell count was 1180 cells/μl.

At 39 weeks of gestation, the woman gave birth via planned cesarean section for obstetrical reasons. Maternal viral load was undetectable and CD4$^+$ cell count was 791 cells/μl. Delivery was without complications and observed congenital abnormalities. The Apgar scores were 9/10/10 at 1, 5 and 10 min, respectively. The newborn (2950 g) received zidovudine (Retrovir syrup) for 4 weeks. HIV RNA was negative at birth and after 1 month. Proviral DNA was also negative at birth, and after 1 and 3 months. At 8 months of age, the girl seemed to have developed normally.

At delivery, elvitegravir concentrations in the maternal and cord plasma were both 0.30 mg/l. Compared with other antiretrovirals this cord-to-maternal concentration ratio of 1 is high [3]. The concentrations of cobicistat in maternal and cord plasma were below the lower limit of quantification of the validated high-performance-liquid-chromatography method (0.03 mg/l).

Six weeks after delivery, a second PK curve was recorded as a postpartum control to assess the effect of pregnancy on elvitegravir and cobicistat pharmacokinetics (Fig. 1). The woman (72 kg) had undetectable viral load and CD4$^+$ cell count was 1183 cells/μl.

Overall, exposure to elvitegravir [area under the curve (AUC) (0–24 h)] during pregnancy was similar to postpartum. Postpartum elvitegravir AUC and C_{max} were relatively low compared with the previously reported values (mean ± SD) of 23 ± 8 mg*h/l and 1.7 ± 0.4 mg/l, respectively [4]. The C_{min} (0.06 mg/l) after observed medication intake in the third trimester was approximately 60% lower than postpartum and was below the suggested target concentration of 0.13 mg/l [5]. However, substantial intra-subject variability was observed during pregnancy for C_{trough} after unobserved intake: predose concentration of 0.48 mg/l ($\sim C_{22 h}$; PK curve) and 0.30 mg/l ($\sim C_{24h}$) at delivery.
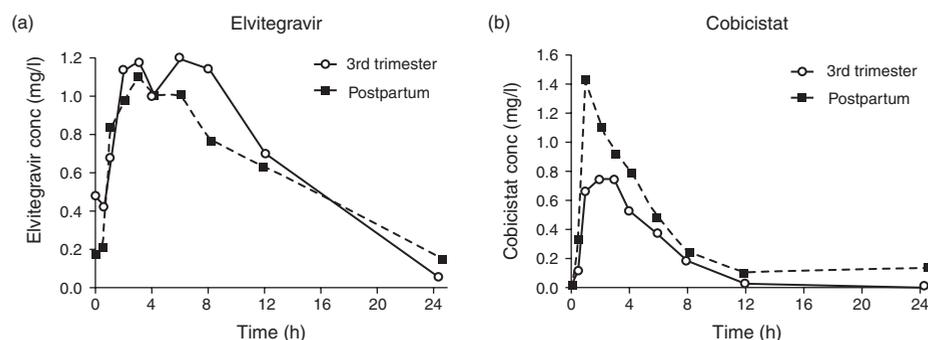

Fig. 1. Elvitegravir and cobicistat plasma concentration–time curves during and after pregnancy. (a) The AUC 0–24 h, C_{max}, C_{min} and half-life for elvitegravir during pregnancy (open circles) were 15.0 h*mg/l, 1.20 mg/l, 0.06 mg/l and 4.1 h, respectively. During postpartum (closed squares) AUC 0–24 h, C_{max}, C_{min} and half-life were 14.0 h*mg/l, 1.10 mg/l, 0.15 mg/l, 6.7 h, respectively. (b) For cobicistat the AUC 0–24 h and C_{max} during pregnancy (open circles) were 4.43 h*mg/l and 0.75 mg/l. The C_{min} of cobicistat was below the lower limit of quantification (0.03 mg/l). The AUC 0–24 h, C_{max} and C_{min} postpartum were 7.88 h*mg/l, 1.43 mg/l and 0.145 mg/l, respectively.

Once-daily elvitegravir requires boosting; for example, by the CYP3A4 inhibitor cobicistat [6]. Exposure (AUC 0−24 h) to cobicistat was 44% lower during pregnancy compared with postpartum. This decrease could hypothetically result in diminished boosting of elvitegravir. This is possibly reflected by the low C_{min} of elvitegravir found in the third trimester. Postpartum AUC and C_{max} for cobicistat were similar to previously reported values (mean $\pm$ SD) of 8.3 ± 3.8 mg*h/l and 1.1 ± 0.4 mg/l, respectively.

In this case, the viral load remained undetectable throughout pregnancy despite a C_{min} below the suggested target concentration. Placental transfer of elvitegravir was relatively high. Until more data about elvitegravir/cobicistat use during pregnancy become available, we recommend employing therapeutic drug monitoring of elvitegravir.

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Whose voices inform online representations of HIV treatment as prevention?

Given the central role of the Internet as a source of information about health [1], it is important to understand how the changing field of HIV prevention is represented online, particularly since the advent of 'game-changing' [2] developments in the science of treatment as prevention. Using Google Search, the engine with the largest market share [3], our team collated search results on HIV prevention over a 2-year period to describe which countries and organizations feature in, and whose 'voices' inform, the most commonly retrieved results.

Keyword searches were conducted on five dates between May 2013 and May 2015 using three English-speaking Google Search domains (Australia, USA, UK) and four phrases: 'HIV prevention', 'HIV treatment as prevention', 'HPTN052', 'PARTNER Study'; the latter two capturing results pertaining to trials which released 'game-changing' findings for the HIV response during this period [4,5]. Although related topics such as 'preexposure prophylaxis' were not included, content related to this and other areas of HIV prevention was consistently retrieved through those main phrases. The

Table 1. Dominant voices and content that directly quote affected communities.

Voice	Number of results	Proportion of results	Including community voice	Proportion total (%)	Explanation of community voice
Informational	68	50	9	6	Content written by and/or for affected communities, with community representatives or individuals quoted directly or implied in author voice
Scientific	39	29	2	1	Direct quotes, included from community representatives as evidence of what the study findings under discussion might mean for affected communities
Instructional	21	16	6	4	No community members directly quoted, but fictionalized consumer voice evoked through Q&A genre, for example, 'I have HIV, do I need to take medication?'
Journalistic	7	5	5	4	Direct quotes provided from members of affected communities, along with quotes from other experts; for example, clinicians, advocates, and government

top ten results of each search were combined, duplicates excluded, and the number of original and unique results calculated (tabulated and original data available on request). Content was firstly coded by source outlet/ agency, host nation, organizational type and purpose, and then analysed qualitatively to identify dominant 'voices' in each result (Table 1).

Of 540 total results, 135 were unique, with content drawn from 70 source outlets/agencies. Although we did not seek to evaluate the reliability of these sources, key organizations involved in leading the global and key national responses to HIV were noted, as were the most influential nongovernment organizations in this sector, and reputable outlets for the communication and governance of science. The vast majority ($n = 121$; 89%) were hosted by high-income, English-speaking nations, and organizational categories balanced across media, government, nongovernment, research and inter-governmental agencies. Although organizations could have a number of purposes, only 15 of the 70 were involved in directly conducting scientific research, and four were peer-reviewed scientific journals. Remaining content was hosted by organizations whose primary purpose was journalism ($n = 11$), consumer informa-tion ($n = 28$), or health promotion and/or advocacy ($n = 12$).

Analysis identified a dominant 'voice' in each result, conveyed through choice of genre and implied audience. An informational voice was most common, featuring in half of all content, and particularly in content reviewing treatment as prevention (and related topics) for a generalist audience through factsheets and short news pieces. This was followed by a scientific voice, featured in 29% of content, directly reporting the results of original research or debates through peer-reviewed journal articles, expert viewpoints or conference reports, assum-ing an expert audience able to understand scientific conventions. An instructional voice was employed in 16% of content, largely targeting health consumers with the implied aim of increasing awareness or changing behaviour through persuasion and instruction. The least common voice was journalistic, conveyed in only 5% of content, mostly long-form journalism, assuming an audience interested and able to engage with longer and deeper explorations of the clinical and social issues relating to treatment as prevention.

Community members were quoted either directly or by implication in 15% of content, but this does not mean the lived experiences of affected communities were evident in all of those results. On the contrary, direct quotes formed only a proportion of the content we coded as representing 'community voices', with some commu-nicated implicitly (written by and for HIV-positive 'peers' by HIV community organizations, for example), or with negligible representative authenticity, in the form of fictionalized voices intended to represent an imagined affected community member, for example, 'I have HIV, do I need to take medication?'

Despite our narrow aims and scope, and without speculating about potential effects on audiences, a number of observations can be made regarding our interest in whose voices inform online representations of HIV prevention, including treatment as prevention, today. Content was dominated by a small number of government, nongovernment, and media outlets from high-income countries. An informational voice domi-nated content, and the direct accounts of affected communities were very limited. Each of these obser-vations point to the influence of a number of 'boundary organizations' [6] in translating developments in the science of HIV prevention for generalist audiences, and suggests that more rigorous community debate and dialogue largely happen elsewhere. Organizations with influence in the field of HIV prevention have both the potential and the obligation to more directly engage with and represent a broad range of community voices, including more in-depth accounts of the lived experi-ences of HIV prevention.

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Prevalence of recreational drug use is indiscriminate across antiretroviral regimens of differing drug–drug interactions among MSM

We welcome the literature review by Bracchi _et al._ [1] describing potential drug–drug interactions (DDIs) between antiretroviral treatments (ARTs) 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 (2011−2012), in which half of the 2248 HIV-diagnosed MSM surveyed had used a recreational drug in the previous 3 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 complex of proteins. This pathway is also shared by recreational drugs, which can either induce cytochrome p450 activity, leading to decrease of ART concentration to subtherapeutic levels, or inhibit it, resulting in toxic drug accumulation [3]. Bracchi _et al._ [1] 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 nonnucleoside reverse transcriptase inhibitors (NNRTIs). 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, nucleoside reverse transcriptase inhibitors, or NNRTIs, remains unclear.

We therefore examined the prevalence of recreational drug use in the 3 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: first, ritonavir or cobicistat–boosted PIs (regardless of other drugs included in the regimen); second, efavirenz or nevirapine (but not on ritonavir–boosted PIs); and third, 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 2248 MSM, 2117

Table 1. Recreational drug use in the previous 3 months according to antiretroviral therapy (ART) regimen (N = 1167 MSM on ART).

All HIV-diagnosed MSM on ART (N = 1167)	N	Col %	Ritonavir or cobi-cistat-boosted regi-men (N = 624)		Efavirenz or nevirapine regimen only (not PI/r) (N = 523)		All other regimens (N = 20)[a]	
	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								
One to two drugs used	318	27.3	171	27.4	143	27.3	4	20.0
Three or more drugs used	295	25.3	167	26.8	122	23.3	6	30.0
Chemsex drug use[b]								
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	1026	87.9	555	88.9	457	87.4	14	70.0
Erectile dysfunction drugs[c]								
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[d]								
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

ART, antiretroviral therapy; GBL, gamma butyrolactone; GHB, γ-hydroxybutyric acid; MDMA, methylenedioxymethamphetamine; MSM, men who have sex with men; PI/r, protease inhibitor.
[a]Includes rilpivirine, raltegravir, dolutegravir, or maraviroc-based regimens and emtricitabine/tenofovir and atazanavir/lamivudine/abacavir combinations.
[b]Methamphetamine, GHB/GBL, or mephedrone.
[c]Sildenafil, tadalafil.
[d]Score ≥6 on modified WHO AUDIT-C questionnaire.

(94.2%) consented to linkage with clinic data; linked data on ART history are currently available from four out of eight participating clinics for 1325 (58.9%) MSM, of whom 1167 (88.1%) reported being on ART at the time of the questionnaire and had a clinical record of being on ART for at least 3 months prior to ASTRA completion. Thus, findings reported are based on 1167 MSM, of whom 624 (53.5%) were on a regimen including a PI/r, 523 (44.8%) on efavirenz or nevirapine but not PI/r, and 20 (1.7%) on other regimens only (Table 1). Among 1167 MSM, 613 (52.5%) had used recreational drugs in the previous 3 months, of whom 295 (25.3%) had used three 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 3 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 three or more 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 24.2% on ritonavir vs. 19.7% on efavirenz or nevirapine; ketamine 11.1% vs. 12.6%; chemsex drugs 16.7% vs. 15.1%; and MDMA 10.7% for both regimen types. In addition, 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 3 months, of whom 32.2% (n = 58) used three 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 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 nonadherence, 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, benzo-diazepines, 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 nonjudgmental attitude in discussing drug and alcohol use and DDIs, while offering support on ART adherence and well tolerated 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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