

# Increasing use of ‘party drugs’ in people living with HIV on antiretrovirals: a concern for patient safety

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Use of ‘party drugs’, a particular set of recreational drugs used in the context of ‘ChemSex’, is frequent among MSM living with HIV. A recently published observational study showed that more than half of HIV-infected MSM interviewed reported use of illicit substances in the previous 3 months, with frequent concomitant use of three or more drugs. These substances are a combination of ‘club drugs’ (methylenedioxy-methamphetamine, gamma-hydroxybutyrate, ketamine, benzodiazepine) and drugs that are more specifically used in a sexualized context (methamphetamine, mephedrone, poppers and erectile dysfunction agents). Although formal data on pharmacokinetic or pharmacodynamic interactions between recreational drugs and antiretroviral agents are lacking, information regarding potentially toxic interactions can be theorized or sometimes conclusions may be drawn from case studies and cohort observational studies. However, the risk of coadministering party drugs and antiretrovirals should not be overestimated. The major risk for a drug–drug interaction is when using ritonavir-boosting or cobicistat-boosting agents, and maybe some nonnucleoside reverse transcriptase inhibitors. Knowledge of the metabolic pathways of ‘party drugs’ may help in advising patients on which illicit substances have a high potential for drug–drug interactions, as this is not the case for all.

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## Introduction

Recreational drug abuse and addiction have been linked with HIV/AIDS since the beginning of the epidemic, with the commonest substances in the early days being ‘street drugs’ such as opiates, crack and cocaine [1]. In the last two decades and even more so in the past few years, different recreational drugs have become more frequently used among MSM and bisexual men, especially within HIV-positive patients [2,3]. These recreational drugs, commonly called ‘party drugs’ or ‘club drugs’, are consumed in club or house parties, and they are often used to have sex,

which can last for entire weekends [4–6]. They consist of a mix of agents such as methylenedioxy-methamphetamine (MDMA), gamma-hydroxybutyrate (GHB), ketamine, benzodiazepine (e.g. diazepam) [7] – and of substances that are more specifically used in a sexualized context. The latter are methamphetamine, mephedrone, poppers and erectile dysfunction agents (EDA). According to the recently published Antiretrovirals, Sexual Transmission Risk and Attitudes (ASTRA) study [3], of 2248 HIV MSM surveyed for HIV-related, sociodemographic and lifestyle factors, half of the individuals (1138, 50.6%) reported use of recreational drugs in the previous 3 months. About a

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quarter of them reported use of at least three types of drugs during that time period. Importantly, numerous studies have shown that MSM living with HIV are more likely to use different substances at the same time, and use the whole variety of recreational drugs, compared with MSM without HIV [3,8–10].

Consumption of party drugs in people living with HIV (PLWH) on combination antiretroviral therapy (cART) creates a series of following risks and concerns: sex under the effect of drugs, also known as ‘ChemSex’ [11], is normally associated with high-risk practices for sexually transmitted infections, and has recently dramatically contributed to the expansion of the HIV epidemic [3,12,13]. This is especially true for specific centres such as London, Berlin, San Francisco, Los Angeles and Sydney, but concerns are rising in many other areas of the world [2,5,14,15]. In particular, since the beginning of 2000, the use of crystal methamphetamine, and since 2009, the use of mephedrone, have boomed, and high-risk practices have become more and more frequent [2,12]; poor adherence and emergence of resistant viruses; risk for drug–drug interactions, with increased morbidity and mortality [16,17]. However, only a few fatal cases of drug–drug interactions between recreational drugs and antiretrovirals have been reported in the literature, and the few published reviews on the topic do not guide clinicians on what interactions really matter, but only illustrate the complex pharmacological characteristics of the drugs [18–23]. Today, it seems possible (especially in light of the new ‘party drugs’ and new antiretrovirals introduced into clinical practice) that some cases of hazardous or fatal interactions could pass unrecognized [24–26]. However, this needs to be better understood. Data on the interaction between substances of abuse and antiretrovirals are scarce, but knowledge of the potential clinical implications of such interactions may be of great importance for HIV care providers.

National and International HIV treatment guidelines recommend initiating therapy with two nucleoside reverse transcriptase inhibitors (NRTI) and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (bPI), or an integrase inhibitor (INSTI), these are drugs that have different effects on metabolic enzymes and transmembrane transporters.

Drug–drug interactions may occur through various mechanisms, including inhibition or induction of CYP450 enzymes, phase II enzymes (e.g. glucuronidation) and cellular transporter/extrusion proteins. The nature and extent of the interaction varies according to the route of administration: intravenous injection (slamming) maximizes the bioavailability of the substance, followed by insertion in the rectum [27], whereas oral ingestion leads to more extensive first pass metabolism; other common ways of intake can be through nasal insufflation (snorting) or smoking.

With induction of a metabolic pathway (e.g. efavirenz-mediated CYP3A4 induction) lower drug concentrations are obtained and potentially a lack of desired effect. This may start a vicious circle, in which the individuals combine more substances or increase their doses, with even greater and more unpredictable risks of toxicity. Lower drug effects consequent to induced metabolism may also theoretically lead to individuals injecting to avoid first pass metabolism rather than continue oral intake. Any subsequent switch in antiretroviral regimen could potentially trigger acute intoxication, as these interactions usually pass unrecognized.

Drug–drug interactions can also be of a pharmacodynamic nature, and severe organ-related toxicity may be exacerbated by some antiretrovirals.

Importantly, not all party drugs or antiretrovirals are characterized by a high potential for drug–drug interactions. Although there is low potential for interaction between antiretrovirals and alcohol, cannabis, opioids and nitrates, drug–drug interactions may occur between party drugs and some NNRTIs or ritonavir-boosted and cobicistat-boosted protease inhibitors, or elvitegravir/cobicistat, as these antiretrovirals can inhibit or induce drug metabolism. On the contrary, NRTIs, rilpivirine, the integrase inhibitors raltegravir and dolutegravir, and maraviroc are characterized by a low potential for drug–drug interactions and may raise lower concerns during coadministration with ‘party drugs’.

Our aim is to limit our discussion to the potential drug–drug interactions occurring only when specific agents are coadministered and highlight the clinical situations that require dedicated monitoring and management.

This was possible following a *Pubmed* literature review over the last 30 years, and brainstorming meetings among experts of the subject.

## Potential specific interactions between party drugs and antiretrovirals

### Crystal methamphetamine

This psychostimulant drug of the phenethylamine and amphetamine class has been reported to be abused by approximately 25 million people in the world, exceeding cocaine and heroin use [28]. Estimates of use among PLWH, mainly MSM, are high [16,28–30]. Crystal methamphetamine is commonly taken in a sexualized context, and it has been linked to high-risk sexual behaviours, as it induces a state of increased energy, elevated mood, confidence and libido. Smoking, snorting or injecting are the most common ways of consumption, and it is frequently used in combination with mephedrone and GHB.

**Table 1. 'Party drugs' pharmacological characteristics.**

Drug name (alternative/street names)	Route of administration	Bioavailability when orally administered	Metabolism	Half-life	Interaction potential
Crystal methamphetamine (Crystal, Tina, Meth)	Oral ingestion, smoke, insufflation, rectal insertion, IV	67–80%	CYP2D6; Other non-CYP pathways (minor)	~12 h	Moderate (COBI/RTV inhibition of CYP2D6)
MDMA (Ecstasy, X, Mandy)	Oral ingestion, insufflation (capsules/ tablets/powder)	40–60%	CYP2D6; CYP1A2, CYP2B6 and CYP3A4 (minor)	~7 h	Moderate (COBI/RTV inhibition of CYP2D6)
Mephedrone (Miaw Miaw, plant food, bath salts)	Oral ingestion, insufflation (most common), rectal insertion (dissolved or as gel forms), IV	10%	CYP2D6; NADPH-dependent enzymes (minor)	30 min–1.5 h	Moderate (COBI/RTV inhibition of CYP2D6)
Cocaine (Charlie, C, Coke)	Oral ingestion, insufflation (most common), smoke, IV	30–60%	Plasma/liver cholinesterases	0.5–2 h	Low to moderate
Ketamine (K, vitamin K, special K)	Oral ingestion, insufflation, IV or IM	20–45%	CYP3A4; CYPB6 and CYP2C9 (minor)	1.8–2.8 h	High (COBI/RTV inhibition of CYP3A4)
GHB/GBL/1,4 GD (G, Gina, liquid E)	Oral ingestion (liquid), (rarely IV)	GHB: 59–65% GBL: 85%	GHB: GHB-DH and SSA-DH GBL: Lactonase 1,4 BD: alcohol DH and aldehyde DH	GHB: 20–60 min (GLB and 1,4 BD are rapidly converted to GHB)	Unknown
Benzodiazepines (alprazolam, diazepam)	Oral ingestion (tablets), rectal (gel forms), IV (crushed tablets)	Diazepam: 100% Alprazolam: 90%	Diazepam: CYP3A4; CYP2C19 (minor) Alprazolam: CYP3A4	Alprazolam: 12–15 h Diazepam: 43–56 h	High (COBI/RTV inhibition of CYP3A4)
EDAs (sildenafil, tadalafil, vardenafil)	Oral ingestion (tablets)	Sildenafil: 41% Tadalafil: 80% Vardenafil: 15%	CYP3A4	Sildenafil: 4 h Tadalafil: 17.5 h Vardenafil: 4.5 h	High (COBI/RTV inhibition of CYP3A4)

1,4 BD, 1,4 butanediol; COBI, cobicistat; DH, dehydrogenase; EDA, erectile dysfunction agents; GBL, gamma-butyrolactone; GHB-DH, gamma-hydroxybutyrate dehydrogenase; IM, intramuscular; IV, intravenous; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form); RTV, ritonavir; SSA-DH, succinic semialdehyde dehydrogenase.

Like many other amphetamines or psychotherapeutic agents, crystal methamphetamine is mainly metabolized by CYP2D6, specifically by *N*-dealkylation (Table 1) [31]. Concomitant administration of CYP2D6 inhibitors, such as high doses of ritonavir given as a treatment agent (e.g. 600 mg twice daily), has been associated with toxicity and mortality, because of increased exposure to crystal methamphetamine and prolonged effects. This pharmacokinetic interaction was considered responsible for a reported fatality in an HIV-infected patient: the patient died after injecting a regular dose of crystal methamphetamine, having recently been started on saquinavir 400 mg and ritonavir 400 mg twice daily and stavudine [25].

Although low-dose ritonavir (e.g. 100 mg once or twice daily) has been shown to have a limited effect on CYP2D6 substrates *in vivo* and cobicistat has been shown to be a weak-to-moderate inhibitor of CYP2D6 *in vivo* [32,33], it remains unclear whether changes in recreational drugs exposure when coadministered with these boosting agents will give rise to life-threatening outcomes. Importantly, clinical drug-drug interactions reported in the literature with CYP2D6 substrates seem to be less relevant than those associated with CYP3A4. However, if the therapeutic index of the illicit drug is very narrow, even small changes may cause life-threatening toxicity that may have not yet been seen with approved psychotherapeutic agents. CYP2D6 activity is also affected by genetic variability, with up to 10% of Caucasians expressing the nonfunctional enzyme (poor metabolizers) [34,35]. In these individuals, 'party drugs' effect would be remarkable and the addition of a CYP2D6 inhibitor would not result in any change in drug plasma concentrations [36,37]. Finally, the lack of linearity of amphetamines pharmacokinetic suggests that limited increases in the 'party drug' dose ingested may cause significant increases in the methamphetamine plasma exposure and development of acute intoxication [31].

### Methylenedioxymethamphetamine

MDMA or ecstasy is similar to methamphetamine and mescaline, and it acts mainly on the serotonin system as an indirect serotonin agonist, with conjunct hallucinogenic properties. The relationship between MDMA use and high-risk sexual behaviour among homosexual and bisexual men attending dance clubs has been reported [38].

Typically consumed as a capsule, a tablet or a powder, it is frequently mixed with other substances, such as aspirin, caffeine, dextromethorphan, pseudoephedrine, ketamine, lysergic acid diethylamide (LSD), and paramethoxyamphetamine, a potent hallucinogen [39].

MDMA is metabolized via *N*-demethylation and oxidation by CYP2D6 to 3,4-dihydromethamphetamine, with a minor contribution from CYP1A2, 2B6 and 3A4

[40,41]. A smaller portion of MDMA is also *N*-demethylated via CYP1A2 and 2D6 to 3,4-methylenedioxymphetamine (Table 1) [42].

An in-vitro study showed that CYP2D6 inhibitors such as fluoxetine, paroxetine, and cocaine all inhibited MDMA metabolism, by blocking its main metabolic pathway [43].

Two cases of fatalities have been reported in the literature in HIV-infected patients taking ritonavir-containing regimens after ingestion of MDMA [24,26].

Increased organ toxicity, as a consequence of pharmacodynamic drug-drug interaction between amphetamines and antiretrovirals, may also be observed (e.g. cardiotoxicity during MDMA and ritonavir-boosted protease inhibitor intake).

### Mephedrone

Mephedrone or 4-methylmethcathinone is a semi-synthetic substance that belongs to the class of cathinone derivatives (a natural amphetamine-like compound found in the African Khat plant, *Catha edulis*) [44]. Similar to methylamphetamine, it elicits stimulant and empathogenic effects [45], provoking euphoria, sociability and intensification of sensory experiences. It is usually taken in nightclubs and parties in combination with crystal methamphetamine and GHB, and because of its short duration of action, and to a tolerance mechanism, users frequently take multiple doses to maintain the desired effects.

Data extrapolated from animal studies and human models show that mephedrone metabolism occurs through a number of different pathways. A proportion of 'orally ingested' mephedrone is excreted unchanged in the urine, whereas the remainder is found as different metabolites [46]. In-vitro analysis has shown how CYP2D6 is mainly responsible for its metabolism, with some minor contribution by other nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH)-dependent enzymes (Table 1) [47]. Therefore, the potential for drug-drug interaction with ritonavir and cobicistat containing cART maybe similar to that described above.

### Cocaine

Cocaine is a natural alkaloid extracted from the leaves of the coca plant, *Erythroxylon coca*. Similar to amphetamines, it acts on presynaptic monoamine reuptake transporters inducing euphoria, increased level of energy and self-confidence [48].

It is available in acidic form, as water-soluble powder that can be snorted or solubilized and injected, and in basic form (crack cocaine), which can be inhaled because of a lower melting point [49].

Cocaine is rapidly metabolized to ecgonine methyl ester and benzoylecgonine by plasma and liver cholinesterases. CYP450 enzymes have low affinity for cocaine, and only a small portion of the substance (about 10%) is metabolized by CYP3A4 (mainly), with the formation of a toxic metabolite, norcocaine [50]. This metabolite has been linked to liver toxicity both in animals and humans [51,52]. Therefore, coadministration with NNRTIs (e.g. efavirenz, nevirapine, etravirine) that induce CYP3A4 activity may lead to an increased production of norcocaine and hepatotoxicity [53,54].

### **Gamma-hydroxybutyrate and gamma-butyrolactone**

GHB and its precursors, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) are central nervous system depressants [55].

Generally taken with the other 'club drugs' to increase relaxation and euphoria, its use, at times for multiple consecutive days, is extremely common among HIV-positive MSM in the context of 'ChemSex' as it enhances libido and facilitates sexual intercourses [56]. GHB is quickly absorbed by the oral route, has a small volume of distribution, and a half-life of about 20–60 min. Its plasma C<sub>max</sub> is approximately 40 minutes after consumption and the majority of the dose is eliminated completely within 4–8 h [57]. Whereas GBL is converted to GHB by endogenous lactonase enzymes [58,59], 1,4-BD is metabolized by alcohol and aldehyde dehydrogenases to form GHB. Of note, ethanol can inhibit this metabolic pathway and acts as a competitive substrate for alcohol dehydrogenase [60], dangerously causing enhancement of 1,4-BD effects. Metabolism of GHB occurs either via GHB dehydrogenase, which transforms it into succinic semialdehyde (SSA), and by a second oxidation step with transformation into succinic acid; it is then ultimately metabolized to water and excreted primarily through breath as carbon dioxide, although only about 2–5% of a dose is eliminated unchanged in the urine [61–63], or by GABA transaminase with transformation into GABA (Table 1) [64].

Animal studies in rats suggest an extensive first pass metabolism for GHB [65]. However, whether this is mediated by the CYP450 system in humans and whether inhibitors of this system (ritonavir or cobicistat) predispose patients to GHB-related toxicity remains unclear, especially with drugs such as GHB, characterized by a narrow therapeutic index (doses up to 3 ml may cause death).

### **Ketamine**

Ketamine is a derivative of phencyclidine hydrochloride, used in medicine as a dissociative anaesthetic since 1960s. Since the early 1990s it started to become popular at 'raves' [7], and as with the other 'club drugs', trends in use seem to have increased worldwide in the past decade

because of its strong hallucinogenic effect [3,19,66]. Ketamine is not considered a 'ChemSex' drug, as it lost its popularity among MSM, although drug services across the United Kingdom have reported an increased use among heterosexuals. It is commonly snorted, ingested (liquid form) or injected. Following nonintravenous administration, it has a low bioavailability (20–45%) because of large first-pass metabolism [67].

CYP3A4 is the principal enzyme responsible for ketamine *N*-demethylation, whereas CYP2B6 and CYP2C9 participate with a minor role in its metabolism (Table 1) [67,68]. Although the interaction between antiretrovirals and ketamine has not been studied, data can be extrapolated from the known interaction with other drugs with similar effects on CYP3A4 and CYP2B6. Clarithromycin, a CYP3A4 inhibitor, causes a three-fold to four-fold increase in ketamine C<sub>max</sub>, with a 50% reduction of its active metabolite norketamine C<sub>max</sub>. [69] Concomitant use of CYP3A4 and CYP2B6 inhibitors such as ritonavir and cobicistat (for CYP3A4) could increase ketamine toxicity due to drug accumulation.

Interestingly, the gene encoding for *CYP2B6* is highly polymorphic, with a 20-fold to 250-fold interindividual variation in protein expression.[70,71] Although CYP2B6 plays a minor role in ketamine metabolism, slow metabolizers may experience increases in ketamine exposure and greater risk of toxicity. Whether ritonavir has any significant or differential inhibitory impact on ketamine exposure through CYP2B6 and its genetic polymorphisms remains unclear.

Zhou *et al.* [72] have recently reported two cases of HIV-infected patients on treatment with protease inhibitors (one with lopinavir/ritonavir and one with darunavir/ritonavir, both in combination with NRTIs) who developed epigastric pain and hepatobiliary disorder triggered by short-term ketamine use.

Rifampicin and barbiturates, which induce CYP3A4 and CYP2B6 by several folds, cause a small but significant decrease in ketamine C<sub>max</sub>, and reduce norketamine concentrations.[73,74] Therefore, a possible reduction in ketamine exposure could be observed during coadministration with efavirenz and nevirapine, well known inducers of CYP3A4 and CYP2B6.

### **Benzodiazepines**

High rates of nonmedical use of benzodiazepines have been reported in cohorts of HIV patients [75], with consumption in parties or during 'ChemSex' along with multiple other drugs, to obtain enhanced effect of other psychotropic substances, or to moderate the effects of stimulants. Moreover, because diazepam is used in the detox regimen for GBL/GHB, many heavy users keep recreational supplies of diazepam on hand to manage withdrawal symptoms.

Most benzodiazepines are metabolized by CYP3A4 or by glucuronyltransferases. Their exposure may be increased by coadministration of CYP3A4 inhibitors giving rise to potential respiratory depression and oversedation [76,77].

Diazepam and alprazolam seem to be the benzodiazepines mostly used in these scenarios. Both are CYP3A4 substrates, and diazepam is also a substrate of CYP2C19 (Table 1) [78–80]. Poor *CYP2C19* metabolizers have been found to have significantly lower plasma clearance of both diazepam and desmethyldiazepam (one of its metabolites) [81,82].

### Erectile dysfunction agents

PLWH use EDA more frequently than HIV-uninfected men [83,84], and several epidemiologic studies have reported that EDA are used recreationally, in the context of ‘ChemSex’, to sustain long-lasting sexual activity and reverse the impotence-inducing effects of other substances [8,85]. Data from the ASTRA study show that up to 21% of the PLWH recruited reported use of EDA in the previous 3 months [3].

EDA are sildenafil, tadalafil and vardenafil. Sildenafil is mainly metabolized by CYP3A4 and partially by CYP2C9 (minor route), and is excreted via the biliary system (80%) and the kidneys [86]. The effect of ritonavir (500 mg twice daily) on a single dose of sildenafil (100 mg) was investigated in 28 healthy volunteers and caused an approximate 11-fold increase in sildenafil exposure [87]. Similarly, tadalafil and vardenafil are metabolized by CYP3A4 (Table 1). Coadministration of tadalafil (20 mg single dose) and ritonavir (200 mg twice daily) resulted in a 124% increase in tadalafil exposure. Finally, coadministration of vardenafil (5 mg single dose) and ritonavir (600 mg twice daily) increased vardenafil area under the curve by 49-fold and  $C_{min}$  by 13-fold [88]. Therefore, coadministration with CYP3A4 inhibitors (ritonavir and cobicistat) is associated with significant increases of the EDA and with cardiotoxicity, at times lethal [87,89,90]. In clinical practice, low doses of EDA are prescribed and patients are monitored for toxicity. However, when used as party drugs, EDA doses are not controlled and important side-effects may be developed by PLWH on ritonavir or cobicistat. Decreased concentrations of EDA may be achieved during coadministration with efavirenz, nevirapine and etravirine, via CYP3A4 induction [91].

### Conclusion

Use of ‘party drugs’ by MSM living with HIV is common [3]. Theoretical knowledge regarding which coadministered agents may be a cause for concern is important for clinicians caring for PLWH who practice ‘ChemSex’ and take ‘party drugs’, although cohort observational data are accumulated to provide information on the real risks associated with party drugs intake by people on long-term cART.

It is important to recognize that not all party drugs or antiretrovirals are characterized by a high potential for drug–drug interactions. NRTIs, rilpivirine, raltegravir, dolutegravir and maraviroc are all antiretroviral agents with a low potential for interaction with ‘party drugs’. They may be preferred in patients who use illicit drugs to avoid additional toxicity; however, they may not be ideal or they must be coadministered with ritonavir/cobicistat-boosted agents in certain clinical scenarios (e.g. presence of viral resistance, poor adherence, etc.).

The potential for harm arising from drug interactions with recreational drugs is greatest in patients receiving ritonavir-containing or cobicistat-containing regimens, and to a lesser extent NNRTIs such as efavirenz, nevirapine and etravirine. The actual risk of harm is not only related to the metabolic pathways involved, but also to the specific characteristics of the recreational drugs used including the amount of active drug taken, the route of administration and drug bioavailability, the pharmacokinetic linearity of the active compound, the therapeutic index, the half-life of the substance, and polydrug use. The persistent and significant underrecognition by healthcare workers of recreational drug use in patients receiving cART represents, in our view, the greatest barrier to limiting avoidable harm. Clinicians should actively solicit any history of drug use, and provide counselling on toxicity, common adverse effects of substance of abuse, and potential serious drug–drug interactions with antiretrovirals in order to avoid unintentional overdosing or fatal toxicity. However, many patients will persist in use of these agents despite best advice, and a switch to cART with lower propensity for drug interactions should be considered.

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### Conflicts of interest

There are no conflicts of interest.

### References

1. Des Jarlais DC, Friedman SR, Hopkins W. **Risk reduction for the acquired immunodeficiency syndrome among intravenous drug users.** *Ann Intern Med* 1985; **103**:755–759.
2. Kirby T, Thornber-Dunwell M. **High-risk drug practices tighten grip on London gay scene.** *Lancet* 2013; **381**:101–102.
3. Daskalopoulou MRA, Philips A. **Recreational drug use, poly-drug 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**:e22–e31.
4. Theodore PS, Duran RE, Antoni MH. **Drug use and sexual risk among gay and bisexual men who frequent party venues.** *AIDS Behav* 2014; **18**:2178–2186.

5. Colfax G, Guzman R. **Club drugs and HIV infection: a review.** *Clin Infect Dis* 2006; **42**:1463–1469.
6. Stuart D. **Sexualised drug use by MSM: background, current status and response.** *HIV Nursing* 2013; **14**:1415.
7. Smith KM, Larive LL, Romanelli F. **Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and gamma-hydroxybutyrate.** *Am J Health Syst Pharm* 2002; **59**:1067–1076.
8. De Ryck I, Van Laeken D, Noestlinger C, Platteau T, Colebunders R. **The use of erection enhancing medication and party drugs among men living with HIV in Europe.** *AIDS Care* 2013; **25**:1062–1066.
9. Li J, McDaid LM. **Alcohol and drug use during unprotected anal intercourse among gay and bisexual men in Scotland: what are the implications for HIV prevention?** *Sex Transm Infect* 2014; **90**:125–132.
10. Grov C, Kelly BC, Parsons JT. **Polydrug use among club-going young adults recruited through time-space sampling.** *Subst Use Misuse* 2009; **44**:848–864.
11. Stuart D, Colin S. **ChemSex vs recreational drug use: a proposed definition for health workers.** *HIV Treatment Bulletin.* May/June 2015 ed; 2015.
12. Halkitis PN, Parsons JT, Storratt MJ. **A double epidemic: crystal methamphetamine drug use in relation to HIV transmission among gay men.** *J Homosex* 2001; **41**:17–35.
13. Ostrow DG, Plankey MW, Cox C, Li X, Shoptaw S, Jacobson LP, et al. **Specific sex drug combinations contribute to the majority of recent HIV seroconversions among MSM in the MACS.** *J Acquir Immune Defic Syndr* 2009; **51**:349–355.
14. Colfax GN, Mansergh G, Guzman R, Vittinghoff E, Marks G, Rader M, et al. **Drug use and sexual risk behavior among gay and bisexual men who attend circuit parties: a venue-based comparison.** *J Acquir Immune Defic Syndr* 2001; **28**:373–379.
15. Rawstorne P, Digusto E, Worth H, Zablotska I. **Associations between crystal methamphetamine use and potentially unsafe sexual activity among gay men in Australia.** *Arch Sex Behav* 2007; **36**:646–654.
16. Rajasingham R, Mimiaga MJ, White JM, Pinkston MM, Baden RP, Mitty JA. **A systematic review of behavioral and treatment outcome studies among HIV-infected men who have sex with men who abuse crystal methamphetamine.** *AIDS Patient Care STDS* 2012; **26**:36–52.
17. Degenhardt L, Mathers B, Guarinieri M, Panda S, Phillips B, Strathdee SA, et al. **Meth/amphetamine use and associated HIV: Implications for global policy and public health.** *Int J Drug Policy* 2010; **21**:347–358.
18. Kumar S, Rao P, Earla R, Kumar A. **Drug-drug interactions between antiretroviral therapies and drugs of abuse in HIV systems.** *Expert Opin Drug Metab Toxicol* 2014; **11**:1–13.
19. Romanelli F, Smith KM, Pomeroy C. **Use of club drugs by HIV-seropositive and HIV-seronegative gay and bisexual men.** *Top HIV Med* 2003; **11**:25–32.
20. Antoniou T, Tseng AL. **Interactions between recreational drugs and antiretroviral agents.** *Ann Pharmacother* 2002; **36**:1598–1613.
21. Wynn GH, Cozza KL, Zapor MJ, Wortmann GW, Armstrong SC. **Mind-psych drug-drug interactions update. Antiretrovirals, part III: antiretrovirals and drugs of abuse.** *Psychosomatics* 2005; **46**:79–87.
22. Pal D, Kwatra D, Minocha M, Paturi DK, Budda B, Mitra AK. **Efflux transporters- and cytochrome P-450-mediated interactions between drugs of abuse and antiretrovirals.** *Life Sci* 2011; **88**:959–971.
23. Staltari O, Leporini C, Caroleo B, Russo E, Siniscalchi A, De Sarro G, et al. **Drug-drug interactions: antiretroviral drugs and recreational drugs.** *Recent Pat CNS Drug Discov* 2014; **9**:153–163.
24. Henry JA, Hill IR. **Fatal interaction between ritonavir and MDMA.** *Lancet* 1998; **352**:1751–1752.
25. Hales G, Roth N, Smith D. **Possible fatal interaction between protease inhibitors and methamphetamine.** *Antivir Ther* 2000; **5**:19.
26. Baker R, Bowers M. **Ritonavir and ecstasy.** *BETA* 1997:5.
27. Dargan PI, Sedefov R, Gallegos A, Wood DM. **The pharmacology and toxicology of the synthetic cathinone mephedrone (4-methylmethcathinone).** *Drug Test Anal* 2011; **3**:454–463.
28. Report UNOoDaCWD. **United Nations Publication Sales No. E08X11.** 2008.
29. Shoptaw S, Reback CJ, Freese TE. **Patient characteristics, HIV serostatus, and risk behaviors among gay and bisexual males seeking treatment for methamphetamine abuse and dependence in Los Angeles.** *J Addict Dis* 2002; **21**:91–105.
30. Buchacz K, McFarland W, Kellogg TA, Loeb L, Holmberg SD, Dilley J, et al. **Amphetamine use is associated with increased HIV incidence among men who have sex with men in San Francisco.** *AIDS* 2005; **19**:1423–1424.
31. Cook CE, Jeffcoat AR, Sadler BM, Hill JM, Voyksner RD, Pugh DE, et al. **Pharmacokinetics of oral methamphetamine and effects of repeated daily dosing in humans.** *Drug Metab Dispos* 1992; **20**:856–862.
32. Aarnoutse RE, Kleinnijenhuis J, Koopmans PP, Touw DJ, Wieling J, Hekster YA, et al. **Effect of low-dose ritonavir (100 mg twice daily) on the activity of cytochrome P450 2D6 in healthy volunteers.** *Clin Pharmacol Ther* 2005; **78**:664–674.
33. German P MA, Wei L, Murray B, Warren D, Kearney BP. **The effect of cobicistat on cytochrome P450 2D6, 2B6 and P-glycoprotein using phenotypic probes.** In: *12th International Workshop on Clinical Pharmacology of HIV Therapy.* Miami; 2011.
34. Alvan G, Bechtel P, Iselius L, Gundert-Remy U. **Hydroxylation polymorphisms of debrisoquin and mephenytoin in European populations.** *Eur J Clin Pharmacol* 1990; **39**:533–537.
35. Bertilsson L, Lou YQ, Du YL, Liu Y, Kuang TY, Liao XM, et al. **Pronounced differences between native Chinese and Swedish populations in the polymorphic hydroxylations of debrisoquin and S-mephenytoin.** *Clin Pharmacol Ther* 1992; **51**:388–397.
36. Steiner E, Spina E. **Differences in the inhibitory effect of cimetidine on desipramine metabolism between rapid and slow debrisoquin hydroxylators.** *Clin Pharmacol Ther* 1987; **42**:278–282.
37. Hamelin BA, Bouayad A, Methot J, Jobin J, Desgagnes P, Poirier P, et al. **Significant interaction between the nonprescription antihistamine diphenhydramine and the CYP2D6 substrate metoprolol in healthy men with high or low CYP2D6 activity.** *Clin Pharmacol Ther* 2000; **67**:466–477.
38. Klitzman RL, Pope HG Jr, Hudson JL. **MDMA ('Ecstasy') abuse and high-risk sexual behaviors among 169 gay and bisexual men.** *Am J Psychiatry* 2000; **157**:1162–1164.
39. Sherlock K, Wolff K, Hay AW, Conner M. **Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department.** *J Accid Emerg Med* 1999; **16**:194–197.
40. Steele TD, McCann UD, Ricaurte GA. **3,4-Methylenedioxy-methamphetamine (MDMA, 'Ecstasy'): pharmacology and toxicology in animals and humans.** *Addiction* 1994; **89**:539–551.
41. Kreth K, Kovar K, Schwab M, Zanger UM. **Identification of the human cytochromes P450 involved in the oxidative metabolism of 'Ecstasy'-related designer drugs.** *Biochem Pharmacol* 2000; **59**:1563–1571.
42. Maurer HH, Bickeboeller-Friedrich J, Kraemer T, Peters FT. **Toxicokinetics and analytical toxicology of amphetamine-derived designer drugs ('Ecstasy').** *Toxicol Lett* 2000; **112–113**:133–142.
43. Ramamoorthy Y, Yu AM, Suh N, Haining RL, Tyndale RF, Sellers EM. **Reduced (+/-)-3,4-methylenedioxy-methamphetamine ('Ecstasy') metabolism with cytochrome P450 2D6 inhibitors and pharmacogenetic variants in vitro.** *Biochem Pharmacol* 2002; **63**:2111–2119.
44. Schifano F, Albanese A, Fergus S, Stair JL, Deluca P, Corazza O, et al. **Mephedrone (4-methylmethcathinone; 'meow meow'): chemical, pharmacological and clinical issues.** *Psychopharmacology (Berl)* 2011; **214**:593–602.
45. Gregg RA, Rawls SM. **Behavioral pharmacology of designer cathinones: a review of the preclinical literature.** *Life Sci* 2014; **97**:27–30.
46. Meyer MR, Wilhelm J, Peters FT, Maurer HH. **Beta-keto amphetamines: studies on the metabolism of the designer drug mephedrone and toxicological detection of mephedrone, butylone, and methylone in urine using gas chromatography-mass spectrometry.** *Anal Bioanal Chem* 2010; **397**:1225–1233.
47. Pedersen AJ, Reitzel LA, Johansen SS, Linnert K. **In vitro metabolism studies on mephedrone and analysis of forensic cases.** *Drug Test Anal* 2013; **5**:430–438.
48. Ciccarone D. **Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy.** *Prim Care* 2011; **38**:41–58v-vi.

49. Hatsukami DK, Fischman MW. **Crack cocaine and cocaine hydrochloride. Are the differences myth or reality?** *JAMA* 1996; **276**:1580–1588.
50. LeDuc BW, Sinclair PR, Shuster L, Sinclair JF, Evans JE, Greenblatt DJ. **Norcocaine and N-hydroxynorcocaine formation in human liver microsomes: role of cytochrome P-450 3A4.** *Pharmacology* 1993; **46**:294–300.
51. Perino LE, Warren GH, Levine JS. **Cocaine-induced hepatotoxicity in humans.** *Gastroenterology* 1987; **93**:176–180.
52. Wanless IR, Dore S, Gopinath N, Tan J, Cameron R, Heathcote EJ, et al. **Histopathology of cocaine hepatotoxicity. Report of four patients.** *Gastroenterology* 1990; **98**:497–501.
53. Bornheim LM. **Effect of cytochrome P450 inducers on cocaine-mediated hepatotoxicity.** *Toxicol Appl Pharmacol* 1998; **150**:158–165.
54. Pellinen P, Honkakoski P, Stenback F, Niemitz M, Alhava E, Pelkonen O, et al. **Cocaine N-demethylation and the metabolism-related hepatotoxicity can be prevented by cytochrome P450 3A inhibitors.** *Eur J Pharmacol* 1994; **270**:35–43.
55. Andresen H, Aydin BE, Mueller A, Iwersen-Bergmann S. **An overview of gamma-hydroxybutyric acid: pharmacodynamics, pharmacokinetics, toxic effects, addiction, analytical methods, and interpretation of results.** *Drug Test Anal* 2011; **3**:560–568.
56. Camacho A, Matthews SC, Dimsdale JE. **Use of GHB compounds by HIV-positive individuals.** *Am J Addict* 2004; **13**:120–127.
57. Brenneisen R, Elsohly MA, Murphy TP, Passarelli J, Russmann S, Salamone SJ, et al. **Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects.** *J Anal Toxicol* 2004; **28**:625–630.
58. Kohrs FP, Porter WH. **gamma-Hydroxybutyrate intoxication and overdose.** *Ann Emerg Med* 1999; **33**:475–476.
59. Schwartz RH, Miller NS. **MDMA (ecstasy) and the rave: a review.** *Pediatrics* 1997; **100**:705–708.
60. Schep LJ, Knudsen K, Slaughter RJ, Vale JA, Megarbane B. **The clinical toxicology of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol.** *Clin Toxicol (Phila)* 2012; **50**:458–470.
61. Kaufman EE, Nelson T. **Evidence for the participation of a cytosolic NADP+-dependent oxidoreductase in the catabolism of gamma-hydroxybutyrate in vivo.** *J Neurochem* 1987; **48**:1935–1941.
62. Snead OC 3rd, Gibson KM. **Gamma-hydroxybutyric acid.** *N Engl J Med* 2005; **352**:2721–2732.
63. Palatini P, Tedeschi L, Frison G, Padriani R, Zordan R, Orlando R, et al. **Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers.** *Eur J Clin Pharmacol* 1993; **45**:353–356.
64. Vayer P, Mandel P, Maitre M. **Conversion of gamma-hydroxybutyrate to gamma-aminobutyrate in vitro.** *J Neurochem* 1985; **45**:810–814.
65. Lettieri J, Fung HL. **Absorption and first-pass metabolism of 14C-gamma-hydroxybutyric acid.** *Res Commun Chem Pathol Pharmacol* 1976; **13**:425–437.
66. McCambridge J, Winstock A, Hunt N, Mitcheson L. **5-Year trends in use of hallucinogens and other adjunct drugs among UK dance drug users.** *Eur Addict Res* 2007; **13**:57–64.
67. Yanagihara Y, Kariya S, Ohtani M, Uchino K, Aoyama T, Yamamura Y, et al. **Involvement of CYP2B6 in n-demethylation of ketamine in human liver microsomes.** *Drug Metab Dispos* 2001; **29**:887–890.
68. Hijazi Y, Bouliou R. **Contribution of CYP3A4, CYP2B6, and CYP2C9 isoforms to N-demethylation of ketamine in human liver microsomes.** *Drug Metab Dispos* 2002; **30**:853–858.
69. Hagelberg NM, Peltoniemi MA, Saari TI, Kurkinen KJ, Laine K, Neuvonen PJ, et al. **Clarithromycin, a potent inhibitor of CYP3A, greatly increases exposure to oral S-ketamine.** *Eur J Pain* 2010; **14**:625–629.
70. Zanger UM, Klein K. **Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance.** *Front Genet* 2013; **4**:24.
71. Wang H, Tompkins LM. **CYP2B6: new insights into a historically overlooked cytochrome P450 isozyme.** *Curr Drug Metab* 2008; **9**:598–610.
72. Zhou J, Shaw SG, Gilleece Y. **Dilated common bile duct and deranged liver function tests associated with ketamine use in two HIV-positive MSM.** *Int J STD AIDS* 2013; **24**:667–669.
73. Noppers I, Olofsen E, Niesters M, Aarts L, Mooren R, Dahan A, et al. **Effect of rifampicin on S-ketamine and S-norketamine plasma concentrations in healthy volunteers after intravenous S-ketamine administration.** *Anesthesiology* 2011; **114**:1435–1445.
74. Koppel C, Arndt I, Ibe K. **Effects of enzyme induction, renal and cardiac function on ketamine plasma kinetics in patients with ketamine long-term analgesation.** *Eur J Drug Metab Pharmacokinet* 1990; **15**:259–263.
75. Vijayaraghavan M, Freitas D, Bangsberg DR, Miaskowski C, Kushel MB. **Nonmedical use of nonopioid psychotherapeutic medications in a community-based cohort of HIV-infected indigent adults.** *Drug Alcohol Depend* 2014; **143**:263–267.
76. Greenblatt DJ, von Moltke LL, Harmatz JS, Durol AL, Daily JP, Graf JA, et al. **Differential impairment of triazolam and zolpidem clearance by ritonavir.** *J Acquir Immune Defic Syndr* 2000; **24**:129–136.
77. Greenblatt DJ, von Moltke LL, Daily JP, Harmatz JS, Shader RI. **Extensive impairment of triazolam and alprazolam clearance by short-term low-dose ritonavir: the clinical dilemma of concurrent inhibition and induction.** *J Clin Psychopharmacol* 1999; **19**:293–296.
78. Jung F, Richardson TH, Raucy JL, Johnson EF. **Diazepam metabolism by cDNA-expressed human 2C P450s: identification of P4502C18 and P4502C19 as low K(M) diazepam N-demethylases.** *Drug Metab Dispos* 1997; **25**:133–139.
79. Ono S, Hatanaka T, Miyazawa S, Tsutsui M, Aoyama T, Gonzalez FJ, et al. **Human liver microsomal diazepam metabolism using cDNA-expressed cytochrome P450s: role of CYP2B6, 2C19 and the 3A subfamily.** *Xenobiotica* 1996; **26**:1155–1166.
80. Venkatakrisnan K, Greenblatt DJ, von Moltke LL, Shader RI. **Alprazolam is another substrate for human cytochrome P450-3A isoforms.** *J Clin Psychopharmacol* 1998; **18**:256.
81. Bertilsson L, Henthorn TK, Sanz E, Tybring G, Sawe J, Villen T. **Importance of genetic factors in the regulation of diazepam metabolism: relationship to S-mephenytoin, but not debrisoquin, hydroxylation phenotype.** *Clin Pharmacol Ther* 1989; **45**:348–355.
82. Sohn DR, Kusaka M, Ishizaki T, Shin SG, Jang JJ, Shin JG, et al. **Incidence of S-mephenytoin hydroxylation deficiency in a Korean population and the interphenotypic differences in diazepam pharmacokinetics.** *Clin Pharmacol Ther* 1992; **52**:160–169.
83. Chu PL, McFarland W, Gibson S, Weide D, Henne J, Miller P, et al. **Viagra use in a community-recruited sample of men who have sex with men, San Francisco.** *J Acquir Immune Defic Syndr* 2003; **33**:191–193.
84. Zona S, Guaraldi G, Luzi K, Beggi M, Santi D, Stentarelli C, et al. **Erectile dysfunction is more common in young to middle-aged HIV-infected men than in HIV-uninfected men.** *J Sex Med* 2012; **9**:1923–1930.
85. Romanelli F, Smith KM. **Recreational use of sildenafil by HIV-positive and -negative homosexual/bisexual males.** *Ann Pharmacother* 2004; **38**:1024–1030.
86. Cheitlin MD, Hutter AM Jr, Brindis RG, Ganz P, Kaul S, Russell RO Jr, et al. **Use of sildenafil (Viagra) in patients with cardiovascular disease. Technology and Practice Executive Committee.** *Circulation* 1999; **99**:168–177.
87. Geelen P, Drolet B, Rail J, Berube J, Daleau P, Rousseau G, et al. **Sildenafil (Viagra) prolongs cardiac repolarization by blocking the rapid component of the delayed rectifier potassium current.** *Circulation* 2000; **102**:275–277.
88. Norvir Summary of Product Characteristics. AbbVie Limited. November 2014.
89. Kobayashi M, Takata Y, Goseki Y, Mizukami H, Hara S, Kuriwa F, et al. **A sudden cardiac death induced by sildenafil and sexual activity in an HIV patient with drug interaction, cardiac early repolarization, and arrhythmogenic right ventricular cardiomyopathy.** *Int J Cardiol* 2015; **179**:421–423.
90. Loulergue P, Gaillard R, Mir O. **Interaction involving tadalafil and CYP3A4 inhibition by ritonavir.** *Scand J Infect Dis* 2011; **43**:239–240.
91. Intencele Summary of Product Characteristics. Janssen-Cilag Ltd. June 2014.