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' (methylenedioxymethamphetamine, 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 methylenedioxymethamphetamine (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 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 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].

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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 ritonavir-boosted protease inhibitor, or an integrase inhibitor; 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.

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,

AQ9 **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)
AQ10 Mephedrone (Miaw Miaw, plant food, bath salts)	Oral ingestion, insufflation (most common), rectal insertion (dissolved or as gel forms), IV	10%	CYP2D6; NAPDH-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; RTV, ritonavir; SSA-DH, succinic semialdehyde dehydrogenase.

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 PK 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, 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-methylenedioxyamphetamine (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 semisynthetic 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 NAPDH-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 pot [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 norcaine 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 Cmax is approximately 40 min 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 Cmax, with a 50% reduction of its active metabolite norketamine Cmax.[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 Cmax, 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 AUC by 49-fold and Cmin 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 PK 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.

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