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ORIGINAL RESEARCH

Do ART and Chemsex Drugs Get Along? Potential Drug–Drug Interactions in a Cohort of People Living with HIV Who Engaged in Chemsex: A Retrospective Observational Study

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ABSTRACT

Introduction: People living with HIV (PLWH) who engaged in chemsex are at risk of potential drug–drug interactions (pDDIs) with recreational drugs. This study aimed to characterize pDDIs between antiretroviral treatment (ART) and chemsex drugs and evaluate their association with unscheduled relevant hospital consultations.

Methods: We conducted a single-center, retrospective, observational study in a series of gay, bisexual, and other men who have sex with men (gbMSM) living with HIV who engaged in chemsex and who attended a tertiary hospital in Barcelona, Spain, from February 2018 through August 2019. Associations between all recorded pDDIs and relevant unscheduled consultations were estimated using the incidence rate (IR) per 100 person-years of those events compared between patients with no pDDI (green flag) or moderate severity pDDI (orange flag) with patients with high severity pDDI (red flag) using the incidence rate ratio (IRR).

Lorena De La Mora and Maria Martinez-Rebollar contributed equally to the study as first and co-corresponding authors.

Josep Mallolas and José L. Blanco contributed equally to the study as co-senior authors.

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Results: Among 172 PLWH engaged in chemsex, 249 ART regimens were prescribed: 44% based on integrase inhibitors, 30% on boosted ART, and 26% based on non-nucleoside reverse transcriptase inhibitors. The substances and recreational drugs most frequently used were erectile dysfunction agents (83%), methamphetamine (79%), GHB (77%), and alkyl nitrites (71%). Polydrug use was reported in 52%. We observed 2048 pDDIs. Of these, 23% were orange flag pDDIs; 88% related to boosted ARTs. The IR of the 285 unscheduled relevant episodes in patients with orange flag pDDIs was 64.67 (95% CI 40.07–89.28). The IRR of green flag pDDIs was 1.05 (95% CI 0.60–1.8; $p = 0.876$).
Conclusion: One in four pDDIs were of moderate severity but no significant increase in the incidence of unscheduled relevant consultations was observed. A high number of unscheduled consultations, predominantly for psychiatric events and intoxication, were observed. Beyond using non-boosted ART to minimize pDDIs, other factors related to the practice of chemsex must be addressed, in order to offer a better approach.

Keywords: Chemsex; Drug–drug interactions; HIV; Antiretroviral therapy

Key Summary Points

People living with HIV (PLWH) prescribed with ART are at risk of potential drug–drug interactions (pDDIs) with recreational drugs.

This article describes the pDDIs between ART and chemsex drugs in a cohort of PLWH engaged in chemsex from a tertiary Hospital in Barcelona, Spain, and evaluate their association with unscheduled relevant hospital consultations.

Among 172 participants, we observed 2048 pDDIs. Of these, 23% were orange flag pDDIs and mainly related to boosted ARTs. The IR of the 285 unscheduled relevant episodes in patients with orange flag pDDIs was 64.67 (95% CI 40.07–89.28). The IRR of green flag pDDIs was 1.05 (95% CI 0.60–1.8; $p = 0.876$).

Despite one in four pDDIs being of moderate severity, no significant increase in the incidence of unscheduled relevant consultations was found. Beyond using non-boosted ART to minimize pDDIs, other factors related to the practice of chemsex must be addressed, to offer a better approach.

INTRODUCTION

HIV infection has evolved from a deadly disease to a chronic condition as a result of many improvements in antiretroviral treatment (ART) alongside the provision of specialized follow-up of people living with HIV (PLWH) [1]. Life-long treatment with ART for PLWH confers a risk of potential drug–drug interactions (pDDIs) due to co-administration of other drugs, potentially leading to toxicity or decreased efficacy of ART or non-ART treatment [2–5].

Previous studies of pDDIs between ART and other medications have been conducted in specific populations including elderly PLWH [2], people who require opioid therapy [6], and patients with a high burden of comorbidities [7]. Severe manifestations of pDDIs have been reported with evidence for the involvement of several metabolic pathways [8, 9]. Other studies have described polypharmacy in PLWH and its implications on adherence to ART, risk of pDDIs, and related adverse effects [10].

Interactions between ART and illicit recreational drugs represent a substantial clinical concern. Drugs use patterns and trends have changed in recent years; chemsex is an example of a new phenomenon related to drug use and sex. Chemsex is defined as the intentional use of recreational drugs, before or during sex, among gay, bisexual, and other men who have sex with men (gbMSM) to facilitate, enhance, and prolong sexual intercourse [11]. Chemsex has an impact on sexual health and increases the risk of transmission of HIV, hepatitis C virus (HCV), and other sexually transmitted diseases (STDs) [12]. Data from our hospital corroborate the aforementioned concerns and describe a heterogeneous cohort of chemsex users with health, social, and psychological implications [13].

The most commonly used drugs for chemsex are γ-hydroxybutyric acid (GHB) and analogues, mephedrone, and methamphetamine [14]. Other frequently used substances include cocaine, ecstasy, ketamine, erectile dysfunction agents, and alkyl nitrites (poppers) [15].

The complexity of drug use during chemsex increases the potential risk of pDDIs between drugs and prescribed medications—specifically ART [16]. To date, only one clinical trial of pDDIs between ART and chemsex drugs has been reported in non drug users [17]. The existence of pDDIs between ART and drugs has been hypothesized on the basis of the results of in vitro assays and pharmacokinetic and pharmacodynamic studies [18–20]. Further, clinical cases of pDDIs between ART and recreational drugs have been reported [21–25].

Cytochrome P450-CYP3A4 and CYP2D6 inhibitors, such as ritonavir or cobicistat, and CYP450 inductors, such as non-nucleoside reverse transcriptase inhibitors (NNRTI), confer an increased risk of interactions with other cytochrome-metabolized drugs [11]. Specific chemsex drugs are also metabolized through CYP3A4 or CYP2D6 which can lead to increased or decreased plasma levels of the drugs involved. Nucleoside reverse transcriptase inhibitors (NRTI), unboosted integrase inhibitors (INSTI), and maraviroc appear to be associated with less potent pDDIs [19].

Despite reported pDDIs between chemsex drugs and ART, the increased risk of clinical events associated to pDDIs between ART and chemsex drugs has yet to be determined. Accordingly, the main objective of the present study was to evaluate pDDIs between ARTs and chemsex drugs in a series of gbMSM living with HIV who engaged in chemsex and who attended our hospital. We further aimed to evaluate the association between pDDIs and unscheduled clinical visits.

METHODS

Study Design

We conducted a retrospective, observational, single-center study on pDDIs between ART and recreational drugs in a series of PLWH gbMSM who engaged in chemsex and who attended the Hospital Clinic de Barcelona (HCB). Methods are summarized in Fig. 1.

Study Period, Setting, and Population

HCB is a referral hospital for the treatment of HIV infection located in an area with a large gay population in Barcelona. The subjects included retrospectively in this study belong to an ongoing prospective study, named the Care_ChemS_CliniC Study (CSC Study), funded by an international grant from ViiV Healthcare through its Positive Pathways program. The CSC study aims to provide facilities for the diagnosis, treatment, and follow-up of HIV, HCV, and other STDs to chemsex users. We performed a comprehensive analysis of relevant pDDIs between ARTs and chemsex drugs among participants included in the CSC Study between February 2018 and August 2019. Participants met the following eligibility criteria: age greater than 18 years; gbMSM on ART; history of intentional drug use in a sexualized context (at least once a month in the previous 6 months or more than 10 times during the previous year); and provision of signed informed consent.

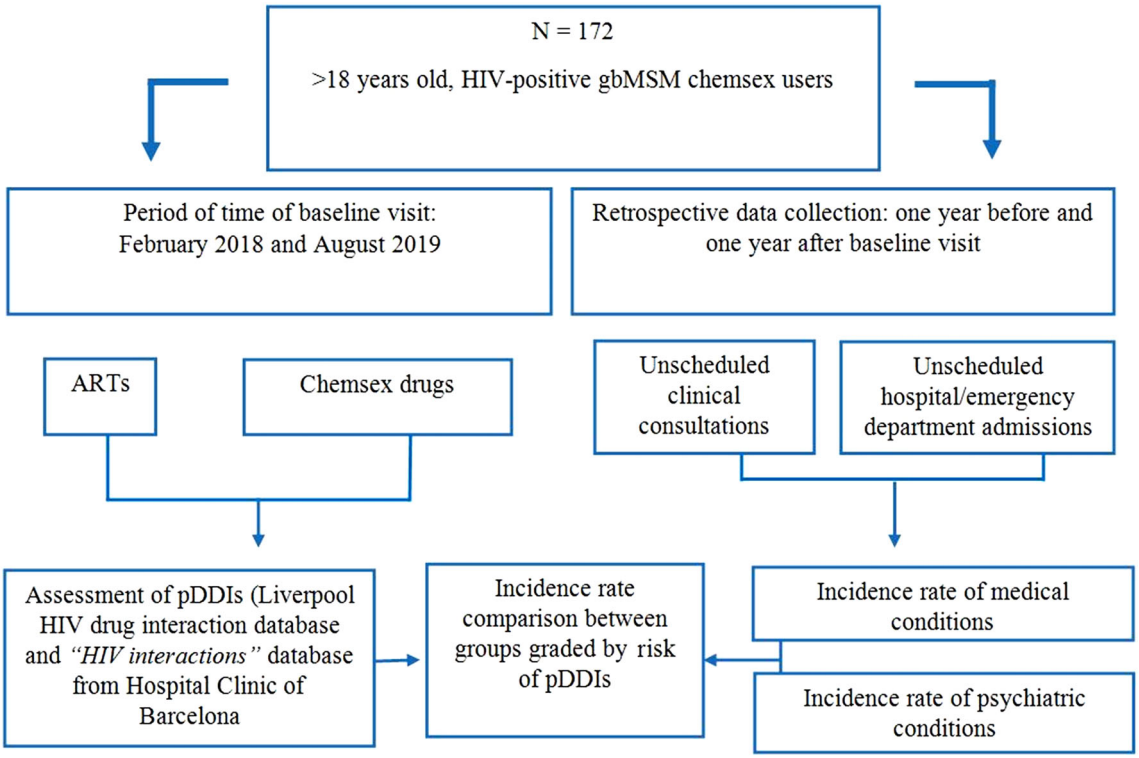

Fig. 1 Flow diagram

Study Variables and Data Collection

Data on the following variables were collected: age; place of birth; type of drug; polydrug use (defined as use of at least three drugs); route and frequency of drug use; ART regimen 1 year after and 1 year before baseline visit; viral load (VL); and $CD4^+$ lymphocyte count at the time of inclusion. pDDIs were interpreted according to ART and chemsex drugs used by each patient.

To evaluate the potential association between pDDIs and clinical events, we recorded unscheduled medical visits of study participants, defined as non-appointed medical consultations and/or hospital/emergency department admissions due to medical or psychiatric conditions in an interval of 1 year before and 1 year after their baseline visit. Diagnoses made during unscheduled visits were codified according to the ICD-10-CM [26]. We defined relevant unscheduled visits as those that may have been associated with drug effects (adverse and side effects or intoxication).

Sources of Information

Data were collected in the electronic medical record system of the HIV Unit and in specific electronic case report form (eCRF) implemented in REDCap hosted at HCB.

Potential DDIs were checked using two freely available online software tools: the Liverpool HIV drug interaction database website [26] and "HIV Interactions" from HCB [27]. The Liverpool HIV drug interactions database categorized pDDI into four groups, illustrated by colored flags, as follows: green for "no expected interactions"; yellow for "potential weak interaction"; orange for "potential interaction"; and red for "interaction contraindicating its co-administration." The allocation of each flag is based on available evidence, whose level of quality ranged according to GRADE criteria [28]. The HCB database, "HIV interactions," analyses pDDIs between ART and other drugs (including recreational drugs and herbal medicine). The HCB database color-codes potential interactions into three categories: green when there is no

clinically significant interaction; orange when there is a pDDI that may justify a dose adjustment; and red when co-administration is contraindicated. To simplify results, we coded interactions using colors described in the Liverpool database and have provided descriptions of differences between the Liverpool and HCB databases.

Statistical Analysis

Descriptive statistics of qualitative variables were based on frequencies and percentages. Quantitative variables are described as the mean and standard deviation (SD) or median and interquartile range (IQR). The incidence rate (IR) of unscheduled consultations was estimated as the number of new events per 100 person-years using the negative binomial regression model and was compared between groups using the incidence rate ratio (IRR). IR and IRR were reported along with their 95% confidence intervals (CI). Statistical analyses were performed using Stata (Release 17. StataCorp, College Station, TX).

Ethical Considerations

The present study adhered to the ethical principles as set forth in the Declaration of Helsinki and followed all principles of good clinical practice. Ethics approval was previously obtained from the local research ethics committee for the CSC Study (HCB/2017/0909).

RESULTS

Study Population

A total of 172 PLWH gbMSM who engaged in chemsex were included. Demographic, clinical, and HIV-related characteristics are summarized in Table 1. The median $CD4^+$ T cell count was 677 (IQR 523–854) cells/mm^3. Detectable VL (at least 50 copies/ml) was observed in 24 (14%) patients, two of whom were treatment-naive. Among the 249 ART regimens registered during the study period, INSTI-based regimens were the

Table 1 Baseline demographics and HIV-related characteristics

Demographic characteristics	
	Mean (SD)
Age (years)	39 (9)
	n (%)
Region of origin (*n* = 172)	
Spain	56 (33%)
Europe (w/o Spain)	29 (17%)
Latin America	82 (48%)
Australia/Oceania	1 (1%)
Asia	1 (1%)
Africa	2 (1%)
USA	1 (1%)
Clinical characteristics	
	Median (IQR)
CD4 (cells/mm^3) (*n* = 171)	677 (523; 854)
CD8 (cells/mm^3) (*n* = 170)	811 (617; 1010)
CD4/CD8 ratio (*n* = 170)	0.8 (0.6; 1.1)
	n (%)
Plasma HIV RNA-VL (copies/ml)	
Detectable	24 (14%)
Undetectable[a]	147 (86%)
	Median (IQR)
Plasma HIV RNA-VL (copies/ml) (*n* = 24)	4950 (109; 88,750)
ART characteristics	
ART (*n* = 249)[b]	*n* (%)
InSTI/b or PI/b	75 (30%)
InSTI	109 (44%)

Table 1 continued

NNRTI	65 (26%)

SD standard deviation, *IQR* interquartile range, *VL* viral load, *InSTI/b* integrase strand transfer inhibitors boosted with cobicistat/ritonavir, *PI/b* protease inhibitors boosted with cobicistat/ritonavir, *InSTI* integrase strand transfer inhibitors, *NNRTI* non-nucleoside reverse transcriptase inhibitors.

[a]Undetectable VL: < 50 copies/ml

[b]249 treatment regimens (in 172 patients), 1 year before and 1 year after the baseline visit

Table 2 Drug-use characterization

	n **(%)**
Chemsex drugs	
Cocaine (*n* = 172)	96 (56%)
Ketamine (*n* = 172)	74 (43%)
GHB/GBL (*n* = 172)	132 (77%)
Methamphetamine (*n* = 172)	136 (79%)
Mephedrone (*n* = 172)	85 (49%)
Speed (*n* = 172)	60 (35%)
Ecstasy (*n* = 172)	76 (44%)
MDMA (*n* = 172)	62 (36%)
Alkyl nitrites (poppers) (*n* = 172)	122 (71%)
Erectile dysfunction agents (*n* = 172)	143 (83%)
Cannabis (*n* = 172)	51 (30%)
Number of drugs used (before or during chemsex)	
1 drug (*n* = 167)	16 (9%)
2 drugs (*n* = 167)	65 (38%)
Polydrug use[a] (*n* = 167)	88 (52%)
Route of drug administration	
Oral (*n* = 170)	128 (75%)
Inhaled (*n* = 171)	135 (79%)
Sniffed (*n* = 172)	113 (66%)
Sublingual (*n* = 171)	18 (11%)
Rectal (*n* = 172)	29 (17%)
Intravenous (slamming) (*n* = 170)	26 (15%)
Frequency of use	
Every day (*n* = 167)	11 (7%)
Every week (*n* = 169)	76 (45%)
Every month (*n* = 168)	65 (39%)
< 1 time per month (*n* = 165)	29 (18%)

Ecstasy includes "designer drugs", *MDMA* 3,4-methylenedioxymethamphetamine, *GHB* γ-hydroxybutyric acid, *GBL* γ-butyrolactone

Erectile dysfunction agents include sildenafil, tadalafil, vardenafil

[a]Active use of three or more drugs before or during chemsex

most frequently prescribed (44%). Boosted ART (INSTI boosted with cobicistat or protease inhibitors boosted with cobicistat or ritonavir) was prescribed in 30% of participants, and NNRTI in 26%.

The most frequently used drugs were erectile dysfunction (ED) agents (143/172; 83%), methamphetamine (136/172; 79%), GHB (132/172; 77%), poppers (122/172; 71%), and cocaine (96/172; 56%). Polydrug use was reported in 88/169 individuals (52%) and alcohol consumption during chemsex in 33/143 (23%). Drug use characterization is displayed in Table 2.

pDDIs Among PLWH Chemsex Users

By identifying all combinations of chemsex drugs and ARTs taken by each patient we obtained 2048 pDDIs. According to the Liverpool interaction checker, the proportions of each pDDI category were 76% green flags (*n* = 1565); 1% yellow flags (*n* = 21); 23% orange flags (*n* = 462); and no red flag interactions, as illustrated in Fig. 2.

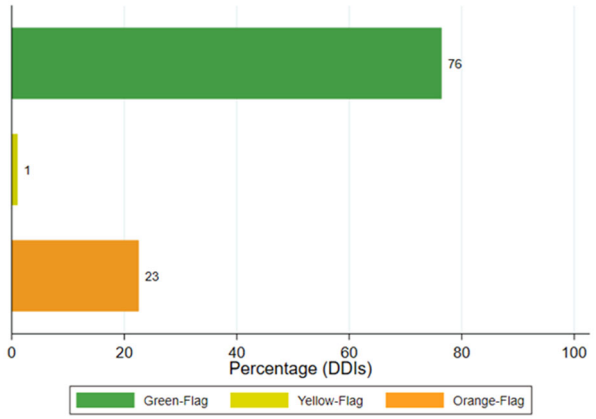

Fig. 2 Proportions of potential DDIs (ART–chemsex drug interactions) according to severity. Potential DDIs between ART and recreational drugs are represented as different colors according to the severity of potential DDIs: orange flag (potential interaction), yellow flag (potential weak interaction), and green flag (no expected interactions). No red flags were reported

According to the Liverpool interaction checker, 88% of orange flags involved boosted ARTs whereas the remaining 8% were due to NNRTI (Fig. 3).

The HCB "HIV Interactions" webpage had some differences compared to the Liverpool database: red flags were described for atazanavir–methamphetamine (less than 1%), elvitegravir/cobicistat–3,4-methylenedioxy-*N*-methamphetamine (MDMA) (1%), and darunavir/cobicistat–MDMA (1%) interactions; and orange flags (potential DDI) were found for efavirenz–MDMA (less than 1%), efavirenz–methamphetamine (less than 1%), and efavirenz–mephedrone (less than 1%) interactions.

We calculated the proportions of ART–chemsex drug interactions for each severity category. Figure 4 illustrates the proportions of green, yellow, and orange flags for each

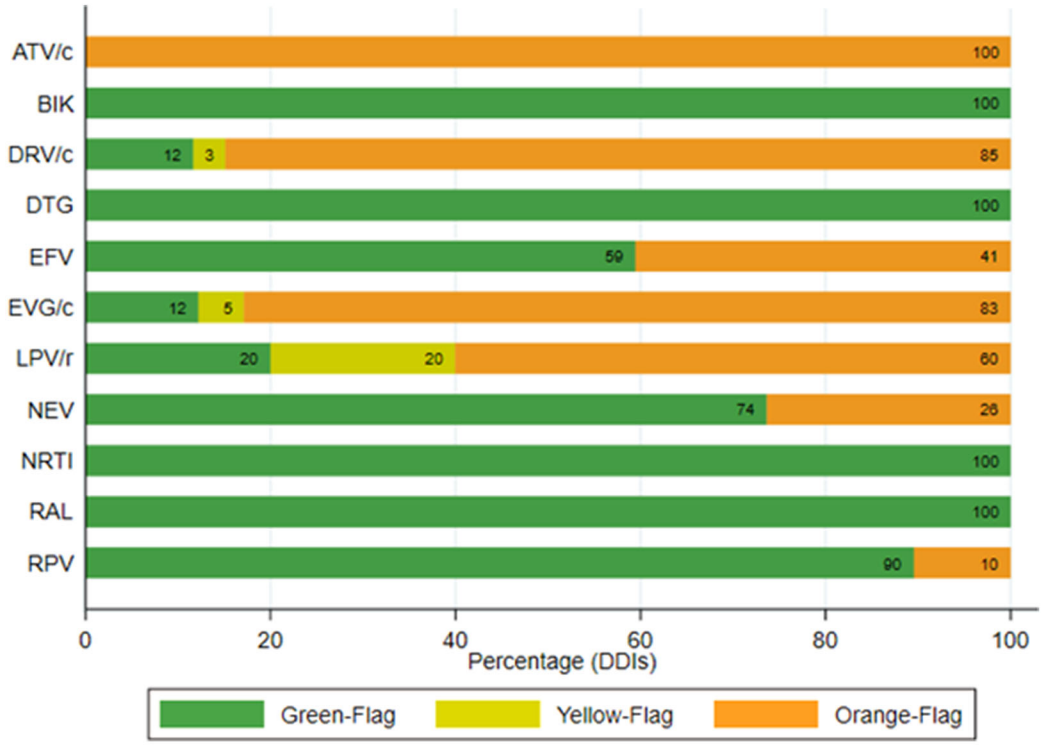

Fig. 3 pDDI severity according to ART. Potential DDIs between ART and chems are represented as different colors according to the severity of potential DDIs: orange flag (potential clinical relevance), yellow flag (weak clinical relevance), and green flag (absence of potential DDIs). *ATV/c* atazanavir/cobicistat, *BIK* tenofovir-alafenamide/emtricitabine/bictegravir, *DRV/c* darunavir/cobicistat, *DTG* dolutegravir, *EFV* efavirenz, *EVG/c* elvitegravir/cobicistat, *LPV/r* lopinavir/ritonavir, *NEV* nevirapine, *NRTI* nucleosides reverse transcriptase inhibitors, *RAL* raltegravir, *RPV* rilpivirine

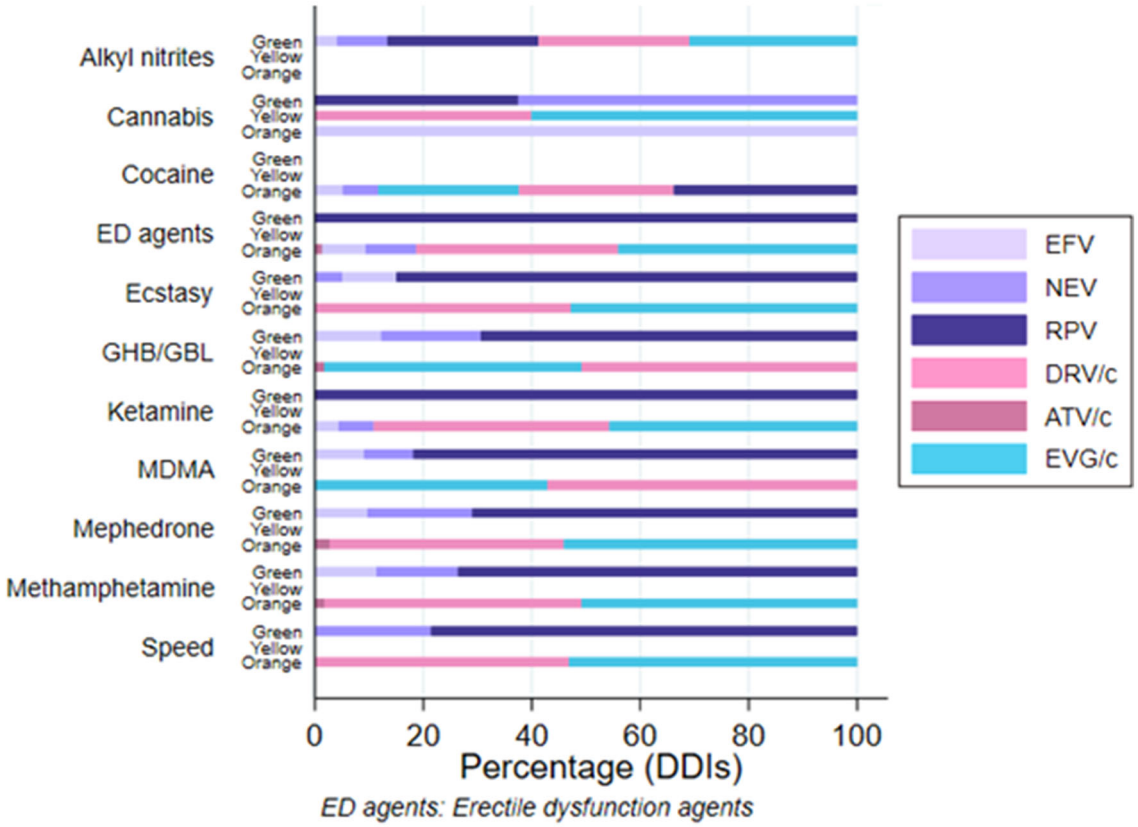

Fig. 4 Distribution of ARTs, chems, and DDIs. Chemsex drugs are displayed on the ordinate axis and are subdivided according to green, yellow, and orange flags. Bars are illustrated with colors representing the proportion of ART corresponding to each flag. On every bar appearing from left to right, the proportion of flags is presented from lowest to highest. Lilac represents NNRTI, rose represents boosted PI, and turquoise represents boosted InSTI. *EFV* efavirenz, *NEV* nevirapine, *RPV* rilpivirine, *DRV/c* darunavir/cobicistat, *ATV/c* atazanavir/cobicistat, *EVG/c* elvitegravir/cobicistat

chemsex drug in our cohort according to the Liverpool interaction checker. Only the seven ARTs associated with yellow and/or orange flags are shown. Cocaine was associated with the most orange flags ($n = 77$), with 55% due to interactions with boosted ARTs. ED agents were associated with 75 orange flags, with 82% due to interactions with boosted ARTs and 18% due to interactions with NNTRI. Methamphetamine was associated with 59 orange flags, all due to interactions with boosted ART. GHB was associated with 59 orange flags, all due to interactions with boosted ART. Other drugs are described in Appendix 1 in the supplementary material.

Unscheduled Clinical Visits

A total of 85% (146/172) of patients attended for unscheduled clinical visits. We identified 603 clinical attendances, according to the ICD-10-CM, of 437 (72%) corresponded to medical reasons and 166 (28%) to psychiatric reasons. The IR (95%CI) of unscheduled visits was 175.29 (151.6–202.69) per 100 person-years.

Of these 603 unscheduled clinical visits, 218 were selected as relevant episodes (36%) and these involved 73 patients. The IR (95% CI) of relevant unscheduled visits was 63.37 (47.95–83.76) per 100 person-years. Of these episodes, 24% ($n = 52$) were due to medical reasons and 76% ($n = 166$) to psychiatric

Table 3 Unscheduled clinical visits and hospital admissions

Diagnosis	ICD-10 code	Prevalence of consultations and admissions by flag color		Prevalence of consultations and admissions
		Green	Orange	
Adjustment disorders	F43.2	1 (1%)	2 (2%)	3 (1%)
Anxiety disorder, unspecified	F41.9	32 (32%)	30 (25%)	62 (28%)
Chest pain, unspecified	R07.9	2 (2%)	4 (3%)	6 (3%)
Dehydration	E86.0	0 (0%)	1 (1%)	1 (0%)
Insomnia and other sleep disorders	G47.0	5 (5%)	3 (3%)	8 (4%)
Ischemic heart disease	I20.9	1 (1%)	0 (0%)	1 (0%)
Other stimulant abuse with stimulant-induced mood disorder	F15.14	7 (7%)	10 (8%)	17 (8%)
Other stimulant abuse with stimulant-induced psychotic disorder	F15.15	9 (9%)	20 (17%)	29 (13%)
Other stimulant dependence or abuse	F15.2	11 (11%)	15 (13%)	26 (12%)
Stimulant abuse with intoxication	F15.12	23 (23%)	26 (22%)	49 (22%)
Suicide attempt and suicidal ideations	T14.91	7 (7%)	5 (4%)	12 (6%)
Syncope and collapse	R55	1 (1%)	2 (2%)	3 (1%)
Toxic liver disease with acute hepatitis	K71.2	0 (0%)	1 (1%)	1 (0%)
Total		99 (100%)	119 (100%)	218 (100%)

ICD-10 10th revision of the International Statistical Classification of Diseases and Related Health Problems

reasons. The IR (95% CI) for relevant unscheduled visits due to medical reasons was 15.12 (9–21.23) per 100 person-years and the IRR for unscheduled visits due to psychiatric reasons was 3.19 (1.89–5.4; $p < 0.0001$).

The most frequent relevant diagnoses were related to anxiety disorders 62/218 (28%), intoxication 49/218 (22%), and psychotic disorders 29/218 (13%) (Table 3).

To analyze clinical and psychiatric unscheduled visits, a single flag was assigned to each patient. In patients taking multiple drugs at risk of causing DDIs (i.e., polydrug users), the flag with the highest severity was assigned. Of these, 47% of patients ($n = 80$) were assigned a green flag and reported 99 unscheduled visits, with an IR (95% CI) of 61.97 (36.5–87.25) per 100 person-years. Orange flags were assigned to 53% of participants ($n = 92$) accounting for 119 unscheduled visits with an IR (95% CI) of 64.67 (40.07–89.28) per 100 person-years. The IRR for green flag DDIs was 1.05 (95% CI 0.60–1.8; $p = 0.876$).

There were 75 unscheduled visits identified as being due to intoxication and stimulant abuse, corresponding to 38 patients. Of these, 18 patients (47%) were labelled with green flags and 20 (53%) with orange flags. The IR of patients with orange flag DDIs was 22.28 (95% CI 10.78–33.79), and the IRR for green flag DDIs was 1.05 (95% CI 0.49–2.24; $p = 0.902$).

DISCUSSION

To our knowledge, this is the first study to assess pDDIs between chemsex drugs and ART in a sample comprised exclusively of PLWH who engaged in chemsex. A recent study described intoxication caused by potential chemsex-related drugs; however, the results were not evaluated on the basis of pDDIs as in the present study [27].

Unboosted INSTI-based regimens were the most widely prescribed in our series, yet 30% of individuals were receiving boosted ART, predominantly with cobicistat; this was a lower percentage than reported by previous studies that evaluated ART interactions in chemsex users [28].

We found that most combinations of ART and chemsex drugs did not result in significant drug interactions, as demonstrated by 76% of pDDIs being green-flagged in the present study. Only 1% of pDDIs were yellow-flagged and 23% orange-flagged. Although no red-flagged pDDIs were observed according to the Liverpool interaction checker, we observed red-flagged pDDIs described on the HCB "HIV Interactions" webpage [29]. The differences were minimal between the two databases and most theoretical pDDIs were based on low to very low levels of evidence due to a lack of reported data regarding pDDIs between chemsex drugs and ART [19]. We recommend confirming pDDIs using a range of databases when there is scare evidence.

As expected, boosted ARTs were associated with the highest proportions of yellow- and orange-flagged pDDIs, followed by NNRTI (efavirenz and nevirapine). Boosted ARTs inhibit CYP3A4 and present a higher risk of pDDI when co-administered with other drugs as they may increase plasma levels of drugs that are metabolized by the same pathway [19]. As almost all NNRTIs are inducers of CYP3A4, co-administration of NNRTIs may decrease the efficacy of the other substances leading to increased drug dosages and intoxication [8].

Among the substances used in this series of chemsex users, cocaine was associated the highest number of orange-flagged DDIs, followed by ED agents, methamphetamine, and GHB, respectively. Despite this, cocaine pDDIs were weaker compared to other drugs [19]. Only a small proportion of cocaine is metabolized by CYP3A4 which leads to the formation of norcocaine, a toxic metabolite associated with liver toxicity [19].

ED agents are predominantly metabolized via CYP3A. Co-administration with cobicistat or ritonavir may result in increased plasma concentrations of ED agents and lead to adverse reactions [24, 25].

GHB and GBL are central nervous system depressants (CNS) used recreationally to increase relaxation and euphoria. The metabolism of GHB and its precursors is mediated by dehydrogenases; the role of CYP450 to GHB metabolism remains unclear [19]. A recent study reported that neither pharmacokinetic nor pharmacodynamic pDDIs were found between GHB and cobicistat; however, this study had a small sample size of 10 participants [17]. Increases in deaths associated with GHB overdose have been reported in recent years, including in PLWH [23, 28, 30–32]; however, other pharmacokinetic or pharmacodynamic factors may contribute. For example, the narrow therapeutic index of GHB (doses greater than 3 ml can be lethal) and co-administration with ethanol or ketamine may increase the risk of CNS depression [19]. Methamphetamine, the second most frequent drug used in our cohort, is predominantly metabolized by CYP2D6 [19]. A case of severe toxicity has been reported as a result of co-administration of methamphetamine and ritonavir [33].

During the study period, 85% of participants attended for unscheduled clinical visits. These patients are likely to require extra care and higher health budgets. Other studies evaluating unscheduled care in PLWH have concluded that a large number of emergency room visits and hospital admissions could be prevented by early, low-cost interventions and primary care [34]. The implementation of such measures should be further evaluated in the chemsex population.

Seventy-three patients attended as a result of adverse drug effects, 23% for medical reasons, and the rest as a result of psychiatric reasons. A high prevalence of psychiatric comorbidity has

been reported among chemsex users [35]. In a study of methamphetamine users, 72% were found to have psychiatric comorbidity [36]. In our study, the IRR of relevant unscheduled medical consultations for psychiatric versus medical reasons was statistically significant.

However, a causal association between moderate pDDIs and a higher incidence of unscheduled clinical consultations could not be demonstrated. We also evaluated pDDIs in the subgroup of patients who attended for intoxication, with no differences observed in IRR between patients classified with green-flagged pDDIs and orange-flagged pDDIs.

Despite these results we consider it is necessary to individualize ART regimens in every patient who uses drugs and provide education regarding pDDIs, particularly when initiating or changing treatments. Clinicians should be aware of other factors that may increase the risk of intoxication and events related to drug consumption and abuse, such as polydrug use [37], frequency and routes of drug use that may increase bioavailability, such as rectal and intravenous routes [8, 38].

In our study population, 14% of participants had detectable VL, a rate comparable to a recent study on chemsex use and its impacts across European countries [39]. Detectable VL in PLWH who engaged in chemsex may be related to suboptimal ART adherence, for which clinical assessment is of particular importance. Methamphetamine, GHB, cocaine, and mephedrone were the most frequently used drugs in our study, corroborating previous reports [11, 40]. Half of participants self-reported polydrug use, which is known to be associated with harmful physical and psychiatric effects such as dependence, overdose, psychiatric disorders, and death [37].

Our study has limitations related to its observational and retrospective nature. We analyzed participants included in the CSC Study, which probably are not all the people who practice chemsex that we are following in our HIV Unit. We were unable to assess pDDIs between recreational or chemsex drugs and non-ART medications. Further, the number of unscheduled visits may have been underestimated as a result of a number of factors: potentially incomplete information on admissions to other hospitals; pDDIs may have led to toxicity not serious enough to prompt participants to seek medical advice; and our classification of relevant diagnoses may not have included other drug-related events. Finally, we have not differentiated between patients with or without pre-existing medical and psychiatric comorbidities, and their potential impact on the unscheduled visits.

CONCLUSION

One in four pDDIs between drugs and ART were of moderate severity predominantly with boosted ARTs. A very high rate of unscheduled clinical consultations was observed in PLWH who practice chemsex, predominantly related to psychiatric events and intoxication.

We observed no evidence of an increased incidence of unscheduled relevant medical and psychiatric consultations related to orange-flagged pDDI. Other factors such as polydrug use, high-risk routes of administration, toxic doses, and duration of exposure to substance use should be considered. However, we think that the recommended ART for these users should be based on unboosted regimens, as one more strategy, but not the only one, in the holistic and multidisciplinary management of PLWH engaged in chemsex.

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contributed equally to the study. L.D.M., M.J.N and M.M.R designed the study. D.S. collaborated in the study design as a ViiV representative. L.D.M, M.L, M.J.N, A.U, B. T., A.G.C., A.I., J.A, I.C., E.M., J.L.B., J.B., L.M., J.M. and M.M.R recruited patients for the study. M.T. and E.S. contributed to pharmacological and toxicological analyses. L.D.M., E.D.L., J.M. and M.M.R analyzed and interpreted data. L.D.M., M.J.N, M.T., M.L., J.L.B., J.M and M.M.R were involved in drafting the manuscript. All authors were involved in reviewing the manuscript and approved the final version.

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Compliance with Ethics Guidelines. The present study adhered to the ethical principles as set forth in the Declaration of Helsinki and followed all principles of good clinical practice. Ethics approval was previously obtained from the local research ethics committee for the CSC Study (HCB/2017/0909).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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