POSTULATED AND ACTUAL INTERACTIONS BETWEEN RECREATIONAL DRUGS AND ANTIRETROVIRALS

Drug	Metabolism	Actual/Potential Interaction	Potential Significance	Recommendation
Alcohol	Principally metabolized by alcohol dehydrogenase and aldehyde dehydrogenase. Acute ingestion may lead to enzyme inhibition. Chronic alcohol use may induce activity of CYP2E1 and 3A.	Due to the induction of CYP 3A, it is possible that chronic alcohol use may induce the metabolism of drugs which are substrates of the 3A system (i.e. protease inhibitors, NNRTIs, elvitegravir/cobicistat).	Induction of the metabolism of ARVs may result in subtherapeutic levels of these agents, predisposing to resistance and decreasing efficacy.	The possible deleterious effects of alcohol on PIs, NNRTIs or elvitegravir/cobicistat would be expected only with chronic use. Such effects need to be confirmed by appropriately conducted pharmacokinetic studies before dosage adjustments can be recommended.
		Theoretical possibility of an interaction between ***abacavir*** and ethanol, since both are metabolized by alcohol dehydrogenase.	In a cross-over study of HIV-infected subjects, no change in ethanol parameters or disulfiram reaction was noted with concomitant administration of 600 mg abacavir and 0.7 g/kg ethanol, while 41% ↑ abacavir AUC was observed[1]	Interaction not likely to be clinically significant.
Amphetamines	CYP 2D6[2-4]	Possible ↑ levels with ritonavir and cobicistat.	Hypertension, hyperthermia, seizures, arrhythmias, tachycardia, tachypnea.	Avoid combination with ritonavir or cobicistat if possible; alternatively, start with ¼ - ½ of initial amount of amphetamine used.
Cocaine	3 pathways: • serum and hepatic cholinesterases to 1ecgonine methyl ester (32-49%) • spontaneous	A potential interaction could exist between cocaine and inhibitors of CYP 3A3/4. (incl. protease inhibitors, elvitegravir/cobicistat, delavirdine, macrolides, azoles), by increasing levels of parent compound.	Clinical significance unclear, since other metabolic pathways involved in cocaine metabolism; risk may be higher if patient is cholinesterase deficient.	Monitor for signs and symptoms of cocaine toxicity, such as: • CNS: tremor, muscle twitches, or seizures, severe agitation, anxiety, paranoid ideation • cardiovascular: increased

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	hydrolysis and hepatic carboxyesterase to benzoylecgonine (35-45%) • CYP 3A4 to norcocaine (< 10%) Cocaine may also induce CYP 2B1 with chronic use, while acute use may inhibit CYP 1A2, 2A4/5 and 2CX.	<u>CYP3A inducers</u> (e.g., rifamycins, nevirapine, efavirenz) may lead to increasing amounts of the norcocaine metabolite being produced.	Increased levels of norcocaine may predispose patients to increased cocaine toxicity; patients who are cholinesterase deficient may be at risk of life threatening cocaine toxicity, as a greater proportion of cocaine will be available for metabolism by the CYP 3A4 pathway. In animal models, high levels of norcocaine have led to hepatotoxicity (the significance of this finding in humans is unclear).	blood pressure, headache, pallor, rapid weak pulse, increase in body temperature • GI: nausea, vomiting • respiratory: rapid, irregular, shallow respiration
Codeine	3 pathways:[5] • Glucuronidation to codeine-6-glucuronide (~ 70%) • N-demethyla-tion to nor-codeine (3A4) (< 10%) • O-demethyl-ation to morphine (2D6) (10-15%)[6-11]	<u>↓ morphine levels:</u> 2D6 inhibition (inhibit O-demethylation) 3A4/glucuronide induction (less substrate available for 2D6) <u>↑ morphine levels:</u> 3A4 inhibition (shunting of substrate to 2D6 pathway)	Opiate withdrawal, loss of analgesia Opiate toxicity	Monitor for signs/symptoms of opiate withdrawal (see under "Meperidine"). Reassess level of analgesia. Monitor for signs/symptoms of opiate toxicity (e.g. miosis, drowsiness, ↓ rate and depth of respiration, N/V, constipation, hypotension, bradycardia).
Gamma hydroxy-butyrate (GHB)	Expired breath as CO_2 First pass metabolism[12-14]	Possible ↑ levels/prolonged effect with antiretrovirals, especially ritonavir or cobicistat.	1 case GHB toxicity with ritonavir/saquinavir.[15] Myoclonic or seizure activity, bradycardia, respiratory depression, loss of consciousness.	Use cautiously with inhibitors of the cytochrome P-450 system (i.e. PIs, elvitegravir/cobicistat, and delavirdine). Ensure patient aware of signs/symptoms of GHB toxicity.
Heroin	Rapidly metabolized to 6-monoacetyl-morphine	As heroin is rapidly converted to morphine, potential interactions of	Possible opiate withdrawal, loss of analgesia, although may be attenuated by ↑	Monitor for signs/symptoms of opiate withdrawal (e.g. lacrimation, rhinorrhea,

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	& morphine by plasma and liver esterases, respectively. Blood levels of heroin and 6-monoacetyl-morphine attain maximal levels within minutes and are cleared rapidly, while morphine levels rise and decrease more slowly.	concern would be similar to those noted with morphine: ***Nelfinavir*** and ***ritonavir*** may ↑ glucuronidation: accelerate morphine metabolism, ↓ levels of morphine, ↑ levels of pharmacologically active M6G.	formation of M6G.	diaphoresis, restlessness, insomnia, dilated pupils, piloerection).
Ketamine	CYP 2B6 (main) 3A, 2C9 (both to lesser extent)[16-19]	Possible ↑ levels with antiretrovirals, especially with ritonavir and cobicistat-boosted agents.	Respiratory depression, loss of consciousness, hallucinations.	Use cautiously with inhibitors of the cytochrome P-450 system, especially ritonavir and cobicistat-boosted ARVs. Ensure patient aware of signs/symptoms of ketamine toxicity.
Lysergic acid diethylmide (LSD)	Unknown[20, 21]	Possible ↑ LSD concentrations.	Hallucinations, agitation, psychosis, "flashbacks"	Use cautiously with inhibitors of the cytochrome P-450 system (i.e. PIs, elvitegravir/cobicistat, and delavirdine). Ensure patient aware of signs/symptoms of LSD toxicity.
Meperidine	2 pathways: Hydrolysis to meperidinic acid by liver carboxylesterases and demethylation by cytochrome P-450 system to normerperidine (exact isoenzyme unknown)[22, 23]	AUC of meperidine ↓ 67% and AUC of normeperidine ↑ 47% in open label study of eight volunteers receiving treatment with 50 mg meperidine prior to and following 10 days of treatment with ritonavir.[24]	Possible opiate withdrawal, loss of analgesia. Possible ↑ risk of seizures with normeperidine accumulation.	Monitor for signs/symptoms of opiate withdrawal (e.g. lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection). Reassess level of analgesia. Avoid combination of ritonavir and meperidine in patients with renal failure and patients who use meperidine regularly for

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				analgesia or recreationally due to risk of neurotoxicity.
Methylenedioxy - methamphetamine (MDMA), "Ecstasy"	CYP 2D6 (main)[25-27], 1A2, 2B6, 3A4 (to lesser extent)[27]	Possible ↑ levels with PIs and elvitegravir/cobicistat.	1 death reported (see text)[28] Monitor for dose-related toxicities, including hyponatremia, hyperthermia, arrhythmias, tremor, hyperreflexia, sweating, seizures, tachycardia, rhabdomyolysis.	Avoid combining with ritonavir or cobicistat if possible. Alternatively, advise patient to use ~ ¼ - ½ of usual amount used, and watch for signs of MDMA toxicity. Other precautions include staying well hydrated at party, avoiding alcohol and taking breaks from dancing.
Morphine	Glucuronidated to morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G)[29-31]	***Nelfinavir*** and ***ritonavir*** may ↑ glucuronidation: accelerate morphine metabolism, ↓ levels of morphine, ↑ levels of pharmacologically active M6G.	Possible opiate withdrawal, loss of analgesia, although may be attenuated by ↑ formation of M6G.	Monitor for signs/symptoms of opiate withdrawal (e.g. lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection). Reassess level of analgesia.
Oxycodone	3 pathways: CYP2D6 to oxymorphone CYP3A4 to noroxycodone ketoreductase[32]	↓ levels oxymorphone Inhibition of 2D6 3A4 induction (less substrate for 2D6 pathway) ↑ oxymorphone levels 3A4 inhibition (shunting to 2D6 pathway)	Possible opiate withdrawal and loss of analgesia, although ↓ oxymorphone levels does not appear to alter pharmacodynamics of oxycodone. Possible opiate toxicity.	Monitor for signs/symptoms of opiate withdrawal (see under "Meperidine"). Reassess level of analgesia. Monitor for signs/symptoms of opiate toxicity (see under "Codeine").
Phencyclidine (PCP)	CYP 3A[33], CYP2C11[34], inhibits CYP2B1[35]	Possible ↑ levels with antiretrovirals	Seizures, hypertension, rhabdomyolysis, hyperthermia	Use cautiously with inhibitors of the cytochrome P-450 system (i.e. PIs, elvitegravir/cobicistat, and delavirdine). Ensure patient aware of signs/symptoms of PCP toxicity.
Tetrahydro-cannabinol (THC; active moiety of marijuana, hashish	Hydroxylated to several active metabolites. CYP3A3/4, 2C9 and 2C6 likely involved in	↑ THC concentrations: Drugs which inhibit CYP3A or 2C9 (e.g., protease inhibitors or cobicistat)	Dose-related effects of THC (e.g. hallucinations, delusions, paranoid thinking, altered time sense, anxiety, panic,	Considering the widespread use of THC derivatives for appetite stimulation and control of nausea and vomiting, and the lack of

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and hash oil) [34-36]	metabolism. Levels of active metabolites vary with the route of administration. In general, oral administration produces more active metabolite than either IV or inhaled routes, probably due to a significant first pass effect.	↓ THC concentrations: Drugs which induce CYP3A (e.g., efavirenz, nevirapine) Indinavir, nelfinavir: • Patients on stable indinavir or nelfinavir therapy were randomized to receive either 4% THC cigarettes, THC 2.5 mg capsules or placebo TID • Nelfinavir and indinavir levels were obtained at baseline and on day 14. • Smoked THC ↓ nelfinavir AUC by 17%, and ↓ indinavir Cmax 21% (both statistically sig.). Oral THC did not produce significant changes in indinavir or nelfinavir kinetics.[36] Atazanavir: In a series of 67 HIV-positive subjects with or without substance-related disorders who were taking **atazanavir**, significant ↓ ATV Ctrough among tobacco and marijuana users were noted, with 36% tobacco and 50% marijuana users having an ATV Ctrough below the therapeutic range as	depersonalization, loss of insight, orthostatic hypotension, ↑ heart rate). Potential for ↓ duration of THC effect. The long-term clinical consequence of these changes is unknown, but with increasing use of boosted protease inhibitor regimens, such changes are unlikely to significantly impact antiviral efficacy. The cause of this association remains to be determined.	reports documenting deleterious effects secondary to the combination of THC and protease inhibitors, a clinically significant drug interaction may not exist when THC is used in moderate amounts. Patients who use THC and are beginning antiretrovirals should be warned about a possible accentuating of the effects of THC, and that they may need to use less THC for the same effect following treatment initiation. If using non-boosted protease inhibitor regimen, may consider therapeutic drug monitoring.

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		compared to non-users ($p<0.05$).[37]		

Key: AUC = area under the concentration-time curve, Cmax = maximum plasma concentration, CYP = cytochrome P450, HAART = highly active antiretroviral therapy, IV = intravenous, PIs = protease inhibitors, sgc = soft gel capsule

Please note: This chart summarizes some of the major drug interactions identified to date, based on current available data; other drug interactions may exist. Please use caution whenever adding/modifying therapy. The information in this table is intended for use by experienced physicians and pharmacists. It is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Due to the rapidly changing nature of information about HIV treatment and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

References

1. McDowell JA, Chittick GE, Pilati-Stevens C, Edwards KD, Stein DS. Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus-infected adults. Antimicrobial Agents and Chemotherapy 2000;44:1686-90.

2. Lin LY, Kumagai Y, Hiratsuka A, Narimatsu S, Suzuki T, Funae Y, et al. Cytochrome P4502D isozymes catalyze the 4-hydroxylation of methamphetamine enantiomers. Drug Metabolism & Disposition 1995;23:610-14.

3. Geertsen S, Foster BC, Wilson DL, Cyr TD, Casley W. Metabolism of methoxyphenamine and 2-methoxyamphetamine in P4502D6-transfected cells and cell preparations. Xenobiotica 1995;25:895-906.

4. Lin LY, Di Stefano EW, Schmitz DA, Hsu L, Ellis SW, Lennard MS, et al. Oxidation of methamphetamine and methylenedioxymethamphetamine by CYP2D6. Drug Metabolism & Disposition 1997;25:1059-64.

5. Inaba T, Stewart DJ, Kalow W. Metabolism of cocaine in man. Clinical Pharmacology and Therapeutics 1978;23:547-52.

6. Dayer P, Desmeules J, Striberni R. In vitro forecasting of drugs that may interfere with codeine bioactivation. Eur J Drug Metab Pharmacokinet 1992;17:115-20.

7. Poulsen L, Brosen K, Arendt-Neilsen L, Gram LF, Elbaek K, Sindrup SH. Codeine and morphine in extensive and poor metabolizers of sparteine: pharmacokinetics, analgesic effect and side effects. European Journal of Clinical Pharmacology 1996;51:289-95.

8. Caraco Y, Tateishi T, Guengerich FP, Wood AJ. Microsomal codeine N-demethylation: cosegregation with cytochrome P4503A4 activity. Drug Metabolism & Disposition 1996;24:761-4.

9. Yue QY, Sawe J. Different effects of inhibitors on the O- and N-demethylation of codeine in human liver microsomes. European Journal of Clinical Pharmacology 1997;1997:41-7.

10. Caraco Y, Sheller J, Wood AJ. Pharmacogenetic determinants of codeine induction by rifampin: the impact on codeine's respiratory, psychomotor and miotic effects. J Pharmacol Exp Ther 1997;281:330-6.

11. Caraco Y, Sheller J, Wood AJ. Pharmacogenetic determination of the effects of codeine and prediction of drug interactions. J Pharmacol Exp Ther 1996;278:1165-74.

12. Lettieri JT, Fung HL. Absorption and first pass metabolism of 14C-gamma-hydroxybutyric acid. Res Commun Chem Pathol Pharmacol 1976;13:425-37.

13. Lettieri JT, Fung HL. Dose-dependent pharmacokinetics and hypnotic effects of sodium gamma-hydroxybutyrate in the rat. J Pharmacol Exp Ther 1979;208:7-11.

14. Teter CJ, Guthrie SK. A comprehensive review of MDMA and GHB: two common club drugs. Pharmacotherapy 2001;21:1486-1513.

15. Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. Archives of Internal Medicine 1999;159:2221-4.

16. White PF, Way WL, Trevor AJ. Ketamine-its pharmacology and therapeutic uses. Anesthesiology 1982;56:119-36.

17. 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 Metabolism & Disposition 2001;29:887-890.

18. Loch JM, Potter J, Bachman KA. The influence of anesthetic agents on rat hepatic cytochromes P450 in vivo. Pharmacology 1995;50:146-53.

19. Menuguz A, Fortuna S, Lorenzini P, Volpe MT. Influence of urethane and ketamine on rat hepatic cytochrome P450 in vivo. Exp Toxicol Pathol 1999;51:392-96.

20. Inoue T, Niwaguchi T, Murata T. Effects of inducers and/or inhibitors on metabolism of lysergic acid diethylamide in rat liver microsomes. Xenobiotica 1980;10:913-20.

21. Cai J, Henion J. Elucidation of LSD in vitro metabolism by liquid chromatography and capillary electrophoresis coupled with tandem mass spectrometry. J Anal Toxicol 1996;20:27-37.

22. Edwards DJ, Svensson CK, Visco JP, Lalka D. Clinical pharmacokinetics of pethidine. Clinical Pharmacokinetics 1982;7:421-33.

23. Zhang J, Burnell JC, Dumaual N, Bosron WF. Binding and hydrolysis of meperidine by human liver carboxylesterase hCE-1. J Pharmacol Exp Ther 1999;290:314-8.

24. Piscitelli S, Rock-Kress D, Bertz R, Pau A, Davey R. The effect of ritonavir on the pharmacokinetics of meperidine and normeperidine. Pharmacotherapy 2000;20:549-53.

25. Tucker GT, Lennard MS, Ellis SW, Woods HF, Cho AK, Lin LY, et al. The demethylenation of methylenedioxymethamphetamine ("ecstasy") by debrisoquine hydroxylase (CYP2D6). Biochem Pharmacol 1994;47:1151-6.

26. Colado MI, Williams JL, Green AR. The hyperthermic and neurotoxic effects of 'Ecstasy' (MDMA) and 3,4 methylenedioxyamphetamine (MDA) in the Dark Agouti (DA) rat, a model of the CYP2D6 poor metabolizer phenotype. British Journal of Pharmacology 1995;115:1281-9.

27. Kreth K, Kovar K, Schwab M, Zangar UM. Identification of the human cytochromes P450 involved in the oxidative metabolism of "Ecstasy" - related drugs. Biochem Pharmacol 2000;15:1563-71.

28. Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. Lancet 1998;352:1751-2.

29. Coffman BL, Rios GR, King CD, Tephly TR. Human UGT2B7 catalyzes morphine glucuronidation. Drug Metabolism & Disposition 1997;25:1-4.

30. Fromm MF, Eckhardt K, Li S, Schanzle G, Hofmann U, Mikus G, et al. Loss of analgesic effect of morphine due to coadministration of rifampin. Pain 1997;72:261-7.

31. Osborne R, Joel S, Trew D, Slevin M. Analgesic activity of morphine-6-glucuronide [letter]. Lancet 1988;1:828.

32. Heiskanen T, Olkkola KT, Kalso E. Effects of blocking CYP2D6 on the pharmacokinetics and pharmacodynamics of oxycodone. Clinical Pharmacology and Therapeutics 1998;64:603-11.

33. Laurenzana EM, Owens SM. Metabolism of phencyclidine by human liver microsomes. Drug Metabolism & Disposition 1997;25:557-63.

34. Shelnutt SR, Badger TM, Owens SM. Phencyclidine metabolite irreversible binding in the rat: gonadal steroid regulation and CYP2C11. Journal of Pharmacology & Experimental Therapeutics 1996;277:292-8.

35. Crowley JR, Hollenberg PF. Mechanism-based inactivation of rat liver cytochrome P4502B1 by phencyclidine and its oxidative product, the iminium ion. Drug Metabolism & Disposition 1995;23:786-93.

36. Kosel BW, Aweeka FT, Benowitz NL, Shade SB, Hilton JF, Lizak PS, et al. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. AIDS 2002;16:543-50.

37. Ma Q, Fehintola F, Zingman B, Reichman R, Fischl M, Gripshover B, et al. Tobacco and marijuana uses significantly decrease atazanavir trough concentrations in HIV-infected individuals [H-231]. 49th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco. September 12-15, 2009.