

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. <u>Acute</u> ingestion may lead to enzyme inhibition. <u>Chronic</u> 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). Theoretical possibility of an interaction between abacavir and ethanol, since both are metabolized by alcohol dehydrogenase.	Induction of the metabolism of protease inhibitors may result in subtherapeutic levels of these agents, predisposing to resistance and decreasing efficacy. 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	The possible deleterious effects of alcohol on protease inhibitors would be expected only with chronic use. Such effects need to be confirmed by appropriately conducted pharmacokinetic studies before dosage adjustments can be recommended. Interaction not likely to be clinically significant.
Amphetamines	CYP 2D6 ²⁻⁴	Possible ↑ levels with ritonavir.	Hypertension, hyperthermia, seizures, arrhythmias, tachycardia, tachypnea.	Avoid combination with ritonavir if possible; alternatively, start with ¼ - ½ of initial amount of amphetamine used.
Cocaine	3 pathways: <ul style="list-style-type: none"> serum and hepatic cholinesterases to 1ecgonine methyl ester (32-49%) spontaneous hydrolysis and 	A potential interaction could exist between cocaine and <u>inhibitors of CYP 3A3/4</u> . (incl. protease inhibitors, delavirdine, macrolides, azoles), by increasing levels of parent compound. <u>CYP3A inducers</u> (e.g.,	Clinical significance unclear, since other metabolic pathways involved in cocaine metabolism; risk may be higher if patient is cholinesterase deficient. Increased levels of	Monitor for signs and symptoms of cocaine toxicity, such as: <ul style="list-style-type: none"> CNS: tremor, muscle twitches, or seizures, severe agitation, anxiety, paranoid ideation cardiovascular: increased blood pressure, headache,

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	<p>hepatic carboxyesterase to benzoylecgonine (35-45%)</p> <ul style="list-style-type: none"> CYP 3A4 to norcocaine (< 10%) <p>Cocaine may also induce CYP 2B1 with chronic use, while acute use may inhibit CYP 1A2, 2A4/5 and 2CX.</p>	<p>rifamycins, nevirapine, efavirenz) may lead to increasing amounts of the norcocaine metabolite being produced.</p>	<p>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).</p>	<p>pallor, rapid weak pulse, increase in body temperature</p> <ul style="list-style-type: none"> GI: nausea, vomiting respiratory: rapid, irregular, shallow respiration
Codeine	<p>3 pathways:⁵</p> <ul style="list-style-type: none"> Glucuronidation to codeine-6-glucuronide (~ 70%) N-demethylation to nor-codeine (3A4) (< 10%) O-demethylation to morphine (2D6) (10-15%)⁶⁻¹¹ 	<p><u>↓ morphine levels:</u> 2D6 inhibition (inhibit O-demethylation) 3A4/glucuronide induction (less substrate available for 2D6)</p> <p><u>↑ morphine levels:</u> 3A4 inhibition (shunting of substrate to 2D6 pathway)</p>	<p>Opiate withdrawal, loss of analgesia</p> <p>Opiate toxicity</p>	<p>Monitor for signs/symptoms of opiate withdrawal (see under "Meperidine"). Reassess level of analgesia.</p> <p>Monitor for signs/symptoms of opiate toxicity (e.g. miosis, drowsiness, ↓ rate and depth of respiration, N/V, constipation, hypotension, bradycardia).</p>
Gamma hydroxybutyrate (GHB)	<p>Expired breath as CO₂ First pass metabolism¹²⁻¹⁴</p>	<p>Possible ↑ levels/prolonged effect with antiretrovirals, especially ritonavir.</p>	<p>1 case GHB toxicity with ritonavir/saquinavir.¹⁵ Myoclonic or seizure activity, bradycardia, respiratory depression, loss of consciousness.</p>	<p>Use cautiously with inhibitors of the cytochrome P-450 system (i.e. PI's, delavirdine, efavirenz). Ensure patient aware of signs/symptoms of GHB toxicity.</p>
Heroin	<p>Rapidly metabolized to 6-monoacetyl-morphine & morphine by</p>	<p>As heroin is rapidly converted to morphine, potential interactions of concern would be similar to</p>	<p>Possible opiate withdrawal, loss of analgesia, although may be attenuated by ↑ formation of M6G.</p>	<p>Monitor for signs/symptoms of opiate withdrawal (e.g. lacrimation, rhinorrhea, diaphoresis, restlessness,</p>

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	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.	those noted with morphine: Nelfinavir and ritonavir may ↑ glucuronidation: accelerate morphine metabolism, ↓ levels of morphine, ↑ levels of pharmacologically active M6G.		insomnia, dilated pupils, piloerection).
Ketamine	CYP 2B6 (main) 3A, 2C9 (both to lesser extent) ¹⁶⁻¹⁹	Possible ↑ levels with antiretrovirals, especially with ritonavir, nelfinavir and efavirenz.	Respiratory depression, loss of consciousness, hallucinations.	Use cautiously with inhibitors of the cytochrome P-450 system, especially ritonavir, nelfinavir and efavirenz. Ensure patient aware of signs/symptoms of ketamine toxicity.
Lysergic acid diethylamide (LSD)	Unknown ^{20, 21}	Possible ↑ LSD concentrations.	Hallucinations, agitation, psychosis, "flashbacks"	Use cautiously with inhibitors of the cytochrome P-450 system (i.e. PI's, delavirdine, efavirenz). 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 normeperidine (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 analgesia or recreationally due to risk of neurotoxicity.

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Methylenedioxy - methamphetamine (MDMA), "Ecstasy"	CYP 2D6 (main) ²⁵⁻²⁷ , 1A2, 2B6, 3A4 (to lesser extent) ²⁷	Possible ↑ levels with ritonavir, other PIs, efavirenz	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 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. PI's, delavirdine, efavirenz). Ensure patient aware of signs/symptoms of PCP toxicity.
Tetrahydrocannabinol (THC; active moiety of marijuana, hashish and hash oil) ³⁴⁻³⁶	Hydroxylated to several active metabolites. CYP3A3/4, 2C9 and 2C6 likely involved in metabolism. Levels of active metabolites vary with the route of administration.	↑ THC concentrations: Drugs which inhibit CYP3A or 2C9 (e.g., protease inhibitors) ↓ THC concentrations:	Dose-related effects of THC (e.g. hallucinations, delusions, paranoid thinking, altered time sense, anxiety, panic, depersonalization, loss of insight, orthostatic hypotension, ↑ heart rate). Potential for ↓ duration of	Considering the widespread use of THC derivatives for appetite stimulation and control of nausea and vomiting, and the lack of reports documenting deleterious effects secondary to the combination of THC and protease inhibitors, a

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	<p>In general, oral administration produces more active metabolite than either IV or inhaled routes, probably due to a significant first pass effect.</p>	<p>Drugs which induce CYP3A (e.g., efavirenz, nevirapine)</p> <p><u>Indinavir, nelfinavir:</u></p> <ul style="list-style-type: none"> • 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 C_{max} 21% (both statistically sig.). Oral THC did not produce significant changes in indinavir or nelfinavir kinetics.³⁶ <p><u>Atazanavir:</u> In a series of 67 HIV-positive subjects with or without substance-related disorders who were taking atazanavir, significant ↓ ATV C_{trough} among tobacco and marijuana users were noted, with 36% tobacco and 50% marijuana users having an ATV C_{trough} below the therapeutic range as compared to non-users (p<0.05).³⁷</p>	<p>THC effect.</p> <p>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.</p> <p>The cause of this association remains to be determined.</p>	<p>clinically significant drug interaction may not exist when THC is used in moderate amounts.</p> <p>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.</p>

Key: AUC = area under the concentration-time curve, C_{max} = 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.

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