**ONLINE APPENDIX:**

**Supplementary Table 1: Antiretroviral drugs: cytochrome P450 substrate and inhibiting/inducing properties**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Class** | **Drug** | **Substrate for** | | | **Inhibits** | **Induces** |
|  |  | CYPs | Transporters | Other |  |  |
| INSTIs | RAL |  |  | UGT |  |  |
|  | EVG/c | 3A4, 2D6 |  | UGT | 3A4, 2D6, P-gp, OATP | 2C9 |
|  | DTG | 3A4 | P-gp | UGT | OCT2, MATE |  |
| PIs | ATV | 3A4 | P-gp, MRP |  | 3A4, 2C8, P-gp, UGT, OATP | P-gp |
|  | DRV | 3A4 | P-gp, MRP |  | 3A4, OATP | 2C9 |
|  | FPV | 3A4 | P-gp |  | 3A4, P-gp | 3A4 |
|  | IDV | 3A4 | P-gp, MRP |  | 3A4, P-gp |  |
|  | LPV/r | 3A4 | P-gp |  | 3A4, P-gp, OATP | 2B6 |
|  | NFV | 3A4, 2C19 | P-gp |  | 3A4, P-gp | 2B6 |
|  | RTV | 3A4, 2D6 | P-gp |  | 3A4, 2D6, P-gp | 1A2, 2B6, 2C8, 2C9, 2C19, UGT |
|  | SQV | 3A4 | P-gp |  | P-gp, OATP |  |
|  | TPV | 3A4 | P-gp |  | 2D6, OATP | 1A2, 3A4, 2C19, P-gp |
| NNRTIs | DLV | 3A4, 2D6 |  |  | 3A4, 2C9, 2D6, 2C19 |  |
|  | EFV | 2B6, 2A6, 3A4 |  |  | 2C9, 2C19, 3A4 | 3A4, 2B6 |
|  | ETV | 3A4, 2C9, 2C19 |  | UGT | 2C9, 2C19 | 3A4, P-gp |
|  | NVP | 3A4, 2B6 | P-gp |  |  | 3A4, 2B6 |
|  | RPV | 3A4 |  |  |  |  |
| NRTIs | 3TC |  |  | Renal |  |  |
|  | ABC |  |  | ADH, UGT |  |  |
|  | D4T |  |  | Renal |  |  |
|  | ddI |  |  | Renal |  |  |
|  | FTC |  |  | Renal |  |  |
|  | TAF |  | P-gp, OATP | CA, renal |  |  |
|  | TDF |  | P-gp | Renal |  |  |
|  | ZDV |  |  | Renal, glucor-onidation |  |  |
| Entry inhibitors | MVC | 3A4 | P-gp | Renal |  |  |
|  | T20 |  |  | Hydrolysis |  |  |

3TC = lamivudine, ABC = abacavir, ADH = alcohol dehydrogenase, ATV = atazanavir, CA = cathepsin A, CYP = cytochrome P450, D4T = stavudine, ddI = didanosine, DLV = delavirdine, DRV = darunavir, EFV = efavirenz, ETV = etravirine, EVG/c = elvitegravir and cobicistat, FTC = emtricitabine, IDV = indinavir, INSTIs = integrase strand transfer inhibitors, LPV/r = lopinavir/ritonavir, MATE = multidrug and toxin extrusion transporter, MRP = multi-drug resistance protein, MVC = maraviroc, NFV = nelfinavir, NNRTIs = non-nucleoside reverse transcriptase inhibitors, NRTIs = nucleoside reverse transcriptase inhibitors, NVP = nevirapine, OATP = organic anion-transporting polypeptide, OCT2 = organic cation transporter 2, RAL = raltegravir, RTV = ritonavir, SQV = saquinavir, T20 = enfuvirtide, TAF = tenofovir alafenamide, TDF = tenofovir disoproxil fumarate, TPV = tipranavir, UGT = UDP-glucuronosyltransferase, ZDV = zidovudine

**Supplementary Table 2: Notable human studies on pharmacokinetic interactions between antiretrovirals and antidepressants**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug-drug combination** | **Study** | **Study design** | **n** | **ARV regimen** | **Change in PK parameters or drug levels** | **Need for dose adjustment** | **Clinical toxicity** | **Other comments** |
| NFV, RTV, or EFV + bupropion | Park-Wyllie et al. (2003) | Case series | 10 | NFV 1250 mg BID + RTV 100 mg BID + EFV 600 mg qHS | NR | N/A | None | No episodes of seizure documented |
| ARVs + bupropion | Currier et al. (2003) | Prospective, open-label, flexible-dose study | 20 | 70% PI + 2 NRTIs | NR | Mean dose 265 mg/day in responders | 25% discontinuation due to adverse events (headaches,  panic attacks, irritability) | 60% response rate |
| ARVs + fluvoxamine | Grassi et al. (1995) | Case series | 16 | NR | NR | N/A | 62.5% discontinuation due to severe adverse effects (CNS, GI) |  |
| RTV + nefazodone | Elliott et al. (1999) | Open-label trial | 11 | NR | NR | ↓ nefazodone to ≤ 50–100 mg daily recommended | Headache, confusion, dizziness,  anxiety | Reaction rate 1/11 |
| RTV + trazodone | Greenblatt et al. (2003) | Blinded, four-way crossover study | 10 | RTV 200 mg BID X 2 days | Trazodone AUC↑240%, Cmax↑130% | NR | Sedation, fatigue, and performance impairment |  |
| NVP + fluvoxamine or fluoxetine | De Maat et al. (2003) | Case-control study | 14 (case group) | Most NVP + 2 NRTIs | NVP 34%↓CL with fluvoxamine, fluoxetine ↓conc. | NR | N/A |  |
| Fluoxetine + RTV or EFV | DeSilva et al. (2001) | Case series | 4 | RTV 400-1200 mg daily + EFV 600 mg daily | NR | Fluoxetine ↓20 mg (2 patients), RTV ↓100mg BID (1 patient) | Serotonin syndrome |  |

ARV = antiretrovirals, ATV = atazanavir, CL = clearance, DRV = darunavir, EFV = efavirenz, FTC = emtricitabine, N/A = not applicable, NFV = nefinavir, NR = not reported, NRTI = nucleoside reverse transcriptase inhibitor, NVP = nevirapine, PI = protease inhibitor, PK = pharmacokinetic, RTV or r = ritonavir, TDF = tenofovir disoproxil fumarate

**Supplementary Table 3: Notable human studies on pharmacokinetic interactions between antiretrovirals and antipsychotics**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug-drug combination** | **Study** | **Study design** | **n** | **ARV regimen** | **Change in PK parameters or drug levels** | **Need for dose adjustment** | **Clinical toxicity** | **Other comments** |
| DRV/r + aripiprazole | Aung et al. (2010) | Case report | 1 | DRV/r 800/100 mg daily + TDF 300 mg daily + FTC 200 mg daily | Random aripiprazole level = 1100 ng/ml | N/A | Asymptomatic at time random level drawn, however previous admissions with headache, neck stiffness, nausea, back pain, and blurred vision | Aripiprazole D/C’d |
| LPV/r + SQV + aripiprazole depot injection | Hahn et al. (2016) | Case report | 1 | LPV/r 400/100 mg BID + SQV 1000 mg BID | Aripirazole level = 143 on 200 mg IM dose; Level = 95 on 300 mg IM dose; Level = 95 on 400 mg IM dose | Yes, ↑ aripiprazole from 200 mg to 400 mg | N/A | Patient stabilized with good effect on 400 mg IM monthly aripiprazole injection |
| LPV/r + quetiapine | Geraci et al. (2010) | Case report | 1 | LPV/r 400/100mg BID + ABC/3TC/ZDV 300/150/300 mg BID | N/A | N/A | Priapism |  |
| ATV/r + quetiapine | Pollack et al. (2009) | Case series | 2 | ATV/r 300/100 mg daily + [ABC 600 mg daily + TDF 300 mg daily + 3TC 300 mg daily] or [FTC 200 mg daily + TDF 300 mg daily] | N/A | N/A | Patient #1: 50 lb weight gain, hyperglycemia, worsened obstructive sleep apnea.  Patient #2: ↑ sedation, AMS | Return to baseline status following D/C quetiapine +/- change in ART |
| ATV/r + quetiapine | Hantson et al. (2010) | Case report | 1 | ATV/r 300/100 mg daily + 3TC 300 mg daily + TDF 300 mg daily | After 8000 mg quetiapine overdose – quetiapine half-life calculated as 62.4 hours | N/A | Comatose, tachycardia, hypotension | Required intubation and initiation of norepinephrine |
| RTV + risperidone | Gonzalez et al. (2016) | Case series | 3 | DRV/r + FTC + TDF | N/A | N/A | Angioedema | Risperidone D/C’d, swelling resolved |
| RTV + risperidone | Jover et al. (2002) | Case report | 1 | ZDV 250 mg BID + ddI 300 mg daily + IDV/r 400/200 mg BID | N/A | N/A | Ataxia, progressive drowsiness and disorientation, lethargy, coma | Risperidone D/C’d, symptoms resolved within 24 hours |
| IDV/r + risperidone | Kelly et al. (2002) | Case report | 1 | IDV/r 800/200 mg BID | N/A | N/A | Shortness of breath, fatigue, difficulty swallowing and talking, jerky movements, resting tremor | Risperidone D/C’d and switched to lorazepam |
| IDV/r + risperidone | Lee et al. (2000) | Case report | 1 | IDV/r 800/400 mg daily + ddI 300 mg daily + ABC 600 mg daily | N/A | Yes, risperidone ↓ from 1.5 to 1 mg daily | Neuroleptic malignant syndrome (NMS) | RTV D/C’d while patient experiencing NMS; risperidone ultimately D/C’d and ritonavir ultimately restarted |
| ATV + lurasidone | Naccarato et al. (2016) | Case report | 1 | ATV 400 mg daily + DTG 50 mg daily + RPV 25 mg daily + ABC/3TC/ZDV 300/150/300 mg BID | Lurasidone 2 hr peak = 100 ng/ml while on original ART;  Lurasidone 2 hr peak = 24 ng/ml one month after ATV D/C’d | N/A | Muscle rigidity, worsening tremor, Parkinsonian shuffling gait, cogwheeling rigidity | ATV D/C’d, EPS caused a fall that resulted in hospitalization |

3TC = lamivudine, ABC = abacavir, APV = amprenavir, ART = antiretroviral therapy, ARV = antiretroviral, ATV = atazanavir, D/C’d = discontinued, d4T = stavudine, ddI = didanosine, DRV = darunavir, DTG = dolutegravir, FTC = emtricitabine, IDV = indinavir, LPV = lopinavir, N/A = not applicable, NFV = nefinavir, NR = not reported, PK = pharmacokinetic, RAL = raltegravir, RPV = rilpivirine, RTV or r = ritonavir, SQV = saquinavir, TDF = tenofovir disoproxil fumarate, ZDV = zidovudine

**Supplementary Table 4: Notable human studies on pharmacokinetic interactions between antiretrovirals and anxiolytics**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug-drug combination** | **Study** | **Study design** | **n** | **ARV regimen** | **Change in PK parameters or drug levels** | **Need for dose adjustment** | **Clinical toxicity** | **Other comments** |
| IDV/r + buspirone | Clay et al. (2002) | Case report | 1 | ddI 400 mg daily + d4T 40 mg BID + IDV/r 400/400 mg BID | NR | Buspirone ↓ from 75 to 45 mg daily | Ataxia, shuffling gait, rigidity, resting tremor, sad affect with masked features | IDV/r switched to APV |

APV = amprenavir, ARV = antiretroviral, d4T = stavudine, ddI = didanosine, IDV = indinavir, LPV = lopinavir, NR = not reported, PK = pharmacokinetic, r = ritonavir

**Supplementary Table 5: Notable human studies on pharmacokinetic interactions between antiretrovirals and mood stabilizers**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug-drug combination** | **Study** | **Study design** | **n** | **ARV regimen** | **Change in PK parameters or drug levels** | **Need for dose adjustment** | **Clinical toxicity** | **Other comments** |
| ***Carbamazepine (CBZ)*** | | | | | | | | |
| + IDV | Hugen et al. (2000) | Case report | 1 | IDV 800mg TID + 3TC 150mg BID + ZDV 200mg TID | ↓ IDV plasma levels | N/A | N/A | IDV plasma concentrations rose upon CBZ D/C |
| + RTV | Kato et al (2000) | Case report | 1 | RTV 200mg TID | ↑ CBZ plasma levels | N/A | Vomiting and vertigo requiring isotonic saline, ALT elevations |  |
| + RTV | Garcia et al. (2000) | Case report | 1 | RTV 600 mg BID + 3TC 150 mg BID + ddI 400 mg daily + SQV 400 mg BID | ↑ CBZ plasma levels | N/A | Unspecified dizziness and progressive gait disorder |  |
| + RTV | Burman et al. (2000) | Case report | 1 | RTV 400 mg BID + SQV 400 mg BID + EFV 600 mg daily | ↑ CBZ plasma levels | Yes, 83% CBZ dose reduction | Limb and truncal ataxia resulting in falls |  |
| + RTV | Mateu-de Antonio et al. (2001) | Case report | 1 | RTV 300 mg BID + SQV 400 mg BID + NVP 200 mg daily | ↑ CBZ plasma levels | N/A | Vertigo, drowsiness, disorientation, diplopia,  and severe ataxia |  |
| + LPV/r | Bates et al. (2006) | Case report | 1 | LPV/r 133/33 mg TID + TDF 300 mg daily + 3TC 150 mg BID | ↑ CBZ plasma levels | Yes, 33% CBZ dose reduction | CBZ toxicity resulting in hospitalization for adverse skin reaction | LPV/r switched to NVF, however CBZ toxicity recurred (below) |
| + NFV | NFV 1250 mg BID + TDF 300 mg daily + 3TC 150 mg BID | ↑ CBZ plasma levels | Yes, 33% CBZ dose reduction | CBZ toxicity resulting fatigue and “unsteady on feet” | N/A |
| + EFV | Ji et al. (2008) | Randomized, open-label, crossover, study | 36 | EFV 600 mg daily | ↓ EFV + ↓ CBZ exposures; no effect on CBZ metabolite | EFV likely subtherapeutic when used with CBZ; CBZ titration may be required | No deaths or serious adverse events observed, no clinically relevant effects on vital signs, ECG, or physical exam | 8 patients D/C’d the study due to mild hematuria, ALT elevation, ALT and AST elevation, moderate macropapular rash, neutropenia (n = 1 each), and mild thrombocytopenia (n=3) |
| + DTG | Song et al. (2013) | Single center, open-label, crossover study | 14 | Period I: DTG 50mg daily X 5 days, Period II: CBZ 100 mg BID X 3 days, then 200 mg BID X 3 days, then 300 BID X 10 days; Period III: DTG 50mg daily + CBZ 300 BID X 5 days | ↓ DTG levels, ↑ DTG clearance | Yes ↑ DTG from 50 mg daily to 50 mg BID | N/A | N/A |
| ***Divalproex sodium (DVP)/Valproic acid (VPA)*** | | | | | | | | |
| + ZDV | Akula et al. (1997) | Case report | 1 | ZDV 100 mg 5x daily | ↑ ZDV CSF levels | N/A | N/A | Results correlated to VPA mediated inhibition of ZDV glucuronidation |
| Lertora et al. (1994) | Prospective, PK study | 6 | ZDV 100 mg TID | ↑ ZDV plasma levels, ↓ ZDV metabolite plasma levels | May require ↓ ZDV dose | N/A |
| + RTV, NVP | Cozza et al. (2000) | Case report | 1 | SQV/r 400/400 mg BID + d4T 50 mg BID + NVP 200 mg BID | No significant changes observed | N/A | Hepatic dysfunction despite normal PK |  |
| + ZDV | Antoniou et al. (2004) | Case report | 1 | ZDV 300 mg BID + 3TC 150 mg BID + ABC 300 mg BID | N/A | N/A | Severe anemia |  |
| + EFV | DiCenzo et al 2004) | Prospective PK study | 11 | EFV 600mg daily | No significant changes observed | N/A | N/A | N/A |
| + LPV/r | 11 | LPV/r 400/100 mg BID | ↑ LPV plasma levels | N/A | N/A | Findings were deemed unlikely clinically significant |
|  | Sheehan et al. (2006) | Case report | 1 | LPV/r 400/100 mg BID + 3TC/ZDV 150/300 mg BID | ↓ VPA levels | N/A | Hypomania and mania |  |
| + ATV/r | DiCenzo et al. (2008) | Prospective PK study | 12 | ATV/r 300/100 mg daily | No significant changes observed | No | N/A | Patients also received minocycline 100 mg BID which independently ↓ ATV plasma concentrations prior to VPA administration; no further decrease upon VPA administration |
| + EFV | Saraga et al. (2006) | Case report | 1 | EFV 600 mg daily + ddI 400 mg daily + 3TC 300 mg daily | ↓ VPA concentrations | N/A | Mania | Of note, the patient was also consuming cocaine |
| ***Lamotrigine (LAM)*** | | | | | | | | |
| + LPV/r | van der Lee et al. (2006) | Open-label, sequential, 3-period,  phase IV trial | 24 | LPV/r 400/100 mg BID | Significant ↓ in LAM t1/2 and overall exposure, ↑ in LAM clearance | Yes | N/A | ↑ LAM dose by 200% in presence of LPV/r resulted in same PK parameters as LAM without LPV/r |
| + ATV | Burger et al. (2008) | Open-label, sequential, 3-period,  phase IV trial | 18 | ATV 400mg daily | No significant changes observed | N/A | N/A | Results correlated to RTV component given lack of significant changes when ATV administered without RTV |
| + ATV/r | ATV/r 300mg/100mg daily | Significant ↓ in LAM t1/2 and overall exposure, ↑ in LAM clearance |
| + RAL | van Luin, et al. (2009) | Open-label crossover, PK study | 24 | RAL 400 mg BID | No significant changes observed | N/A | N/A |  |
| ***Lithium (Li+)*** | | | | | | | | |
| + TDF | Decloedt et al. (2017) | RCT | 53 | N/A | No significant changes observed | N/A | N/A |  |

a Limited to those agents that are FDA-approved; b Removed from market in 2006; 3TC = lamivudine, ABC = abacavir, ARV = antiretroviral, AST = aspartate transaminase, ATV = atazanavir, CSF = cerebrospinal fluid, D/C’d = discontinued, d4T = stavudine, ddI = didanosine, DTG = dolutegravir, ECG = electrocardiogram, EFV = efavirenz, IDV = indinavir, LPV = lopinavir, N/A = not applicable, NFV = nefinavir, NVP = nevirapine, PK = pharmacokinetic, RAL = raltegravir, RTV or r = ritonavir, SQV = saquinavir, ZDV = zidovudine

**Supplementary Table 6: Notable human studies on pharmacokinetic interactions between antiretrovirals and treatments for opioid dependence**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug-drug combination** | **Study** | **Study design** | **n** | **ARV regimen** | **Change in PK parameters or drug levels** | **Need for dose adjustment** | **Clinical toxicity** | **Other comments** |
| ***Buprenorphine (BUP)*** | | | | | | | | |
| + RAL | Bruce et al. (2013 Mar) | Non-randomized, open-label study | 12 | RAL 400 mg BID | No | No | Toothache, cold symptoms, tiredness for > 1 day | Dizziness, Nausea, right lower quadrant abdominal pain, back pain, headache, joint pain, hot/cold flashes also experienced but self-limited to 1 day |
| + EVG/c | Bruce et al. (2013 Dec) | Non-randomized, open label study | 17 | EVG/c 150/150 mg daily with food | ↑ BUP and norBUP plasma levels | No | No significant signs of withdrawal or excess noted |  |
| + ATV | Vergara-Rodriguez et al. (2011) | Prospective cohort study | 303 | ATV 400 mg daily | No significant changes observed | No | No hepatotoxicity observed |  |
| + ATV, ATV/r | Bruce et al (2006) | Case report | 1 | ATV/r 300/100 mg daily + ddI 250 mg daily + TDF 300 mg daily | NR | N/A | Drowsiness, “mental cloudiness” | Researchers noted that ATV or RTV may inhibit CYP3A4 causing ↓ buprenorphine metabolism |
| Case report | 1 | ATV/r 300/100 mg daily + ddI 250 mg daily + TDF 300 mg daily | Drowsiness |
| Case report | 1 | ATV 400 mg daily + 3TC 300 mg daily + TDF 300 mg daily | Sensation of ‘high’ and ‘overmedicated’ |
| + ATV, ATV/r | McCance-Katz et al. (2007) | Non-randomized, open label study | 10 | ATV 400 mg daily or ATV/r 300/100 mg daily | ↑BUP, norBUP, BUP-3G plasma levels | May require ↓ BUP dose | Mild to moderate sedation | Researchers concluded that ATV/r ↑ bioavailability of buprenorphine |
| + DRV/r | Sekar et al. (2011) | Prospective, open label study | 11 | DRV/r 600/100 mg BID | NS ↓ in BUP plasma levels(11% ↓ AUC) | No | Reports of nausea (n=7) and headache (n=3) | Mean plasma concentrations of norBUP (46% inc in AUC) were ↑ when BUP/NLX were coadministered with DRV/r |
| + DRV/r | Gruber et al. (2012) | Non-randomized, open label study | 11 | DRV/r 800/100 mg daily | No significant changes observed | No | No serious adverse effects observed |  |
| + LPV/r | Bruce et al (2010) | Non-randomized,open label study | 12 | LPV/r 800/200 mg daily | No significant changes observed | No | No serious adverse events observed |  |
| + RTV | McCance-Katz et al. (2006) | Non-randomized open label study | 76 | NFV 1250 mg BID + LPV/r 400/100 mg daily + RTV 100 mg daily | RTV ↑ BUP plasma levels; NFV and LPV/r had NS effect on BUP levels | Likely unnecessary | No signs of opiate excess observed |  |
| + TPV/r | Bruce et al. (2011) | Non-randomized open label study | 10 | TPV/r 500/200 mg BID | Plasma levels of metabolite BUP-3G ↑ significantly, norBUP plasma levels ↓ significantly | N/A | N/A | Researchers hypothesized that TPV/r inhibits enzyme CYP3A4 but spares UGT2B7 causing ↑ in BUP-3G metabolite and ↓ in norBUP. |
| + TPV/r | Bruce et al. (2009) | Non-randomized, open label study | 10 | TPV/r 500/200 mg BID | Plasma levels of norBUP were ↓ significantly | No | Occasional yawning, restlessness, hot flashes were reported | A ↓ of norBUP should not compromise the treatment of opioid dependence due to low analgesic activity by norBUP |
| + EFV, NFV, DLV, RTV, LPV/r | Baker et al. (2006) | Non-randomized, open label study | 50 | EFV 600mg daily, NFV 1250 mg BID, DLV 600 mg BID, RTV 100 mg BID, LPV/r 400/100mg BID | All ARVs had a slight ↑ in QTc prolongation (greatest = DLV, + 13.12 ms) | N/A | No adverse events reported | Results showed a statistically (p=0.005) increase, but not clinically significant increase in QTc prolongation. UA revealed cocaine use in 30 subjects of study |
| + EFV | McCance-Katz et al. (2006) | Non-randomized, open label study | 35 | EFV 600 mg daily + DLV 600 mg BID | ↓ BUP plasma levels | No | No serious adverse events observed | No signs of opiate withdrawal noted in any participants |
| + NVP | McCance-Katz et al. (2010) | Non-randomized, open label study | 7 | NVP 200 mg daily | NS ↓ BUP levels | No | No serious adverse effects observed | N/A |
| + 3TC, ddI, TDF | Baker et al. (2010) | Non-randomized, open label study | 27 | 3TC 300mg daily + ddI 400 mg daily + TDF 300 mg daily | No significant changes observed | N/A | N/A | N/A |
| + ZDV | McCance-Katz et al. (2001) | Non-randomized, open label study | 52 | ZDV 200 mg TID | Delayed ZDV absorption | N/A | No serious adverse effects observed |  |
| ***Methadone*** | | | | | | | | |
| + RTV | Geletko et al. (2000) | Case report | 1 | RTV 400 mg BID + SQV 400 mg BID + d4T 40 mg BID | Methadone plasma level = 210 ng/ml | Yes, 90 mg to 130 mg daily | Symptoms of withdrawal | Stabilized after IVF and ↑ methadone |
| - LPV/r | Luthi et al. (2007) | Case report | 1 | D/C of LPV/r 400/100 mg BID + FPV 700 mg BID + ddI 250 mg daily + TDF 245 mg daily | NR | N/A | Palapations, QTc 654 ms, TdP | QTc normalization after morphine substituted for methadone |
| + NFV | McCance-Katz. (2000) | Case report | 1 | NFV 750 mg TID + d4T 40 mg BID + IDV 800 mg TID + DDC 0.75 mg TID | NR | Yes, 100 mg to 285 mg | Symptoms of withdrawal | ARVs D/C’d, methadone dose titrated down to 125 mg daily |
| + ATV/r | Gallagher et al. (2008) | Case series | 2 | ATV/r 300/100 mg + [TDF 300 mg + FTC 200 mg daily] or [ABC 600 mg + 3TC 300 mg daily] | NR | N/A | Symptomatic VT associated with prolonged  QT interval | QT interval reduction and cessation of arrhythmia upon ATV D/C |
| + ART | Prosser et al. (2008) | Case report | 1 | ABC 600 mg + NVP 200 mg + TDF 300 mg daily | NR | N/A | Seizure, AMS, QTc 690 ms, TdP | ART held during admission, methadone tapered with planned D/C |
| + EFV | Marzolini et al. (2000) | Case report | 1 | EFV 600 mg daily | ↓ methadone plasma levels | Methadone dose was increased to 180mg daily | Symptoms of withdrawal |  |
| + EFV | Perez-Molina. (2002) | Prospective cohort study | 1,033 | EFV 600 mg daily | NR | N/A | Patients taking methadone had ↑39.7% incidence of ADEs, e.g. dizziness, insomnia, drowsiness, treatment interruption | Only 6.6% of the subject population concurrently taking methadone |
| + EFV | Boffito et al. (2002) | Case report | 3 | EVP | 70% ↓ in methadone plasma levels | Yes, ↑133% methadone dose | Symptoms of withdrawal |  |
| + EFV | Clarke et al. (2001 Mar) | Prospective cohort Study | 11 | EFV 600 mg daily + [d4T + ddI] or [ZDV + 3TC] or [d4T + 3TC] or [d4T + ABC] | ↓ methadone plasma levels | Yes, ↑22% methadone dose | 9 patients described symptoms of withdrawal |  |
| + NVP | Staszewski et al. (1998) | Prospective pilot study | 45 | NVP 400 mg TID + ddI 400 mg daily + 3TC 300 mg daily | ↓ methadone plasma leve | ↑ methadone dose req. in 30% of patients | N/A |  |
| + NVP | Otero et al. (1999) | Case series | 5 | NVP 200 mg daily x 14 days then NVP 200 mg BID | NR | Yes, ↑33-100% methadone dose | 4 experienced mild-severe withdrawal symptoms |  |
| + NVP | Altice et al. (1999) | Retrospective chart review | 7 | NVP 200 mg daily x 14 days then NVP 200 mg BID + other ARVs | NR | 7 required ↑ methadone dose | 7 experienced withdrawal symptoms | 1 did not receive titration of NVP to 200 mg BID |
| + NVP | Heelon et al. (1999) | Case report | 1 | NVP 200 mg BID +  d4T 40 mg BID +  NFV 750 mg TID +  SQV 800 mg TID | NR | Yes, ↑ methodone dose from 80 to 130 mg | Withdrawal symptoms | Pt was on methadone 3 years prior to NVP without relapse, withdrawal, or change in dose |
| + NVP | Clarke et al. (2001 Nov) | Prospective PK study | 8 | NVP 200 mg daily, increased to NVP 400 mg TID thereafter | ↓ mean methadone AUC, ↓36% reduction in mean Cmax | Yes, mean methodone dose ↑16% | N=6 complained of withdrawal symptoms | Symptoms emerged 8-10 days after NVP |
| + NVP | Stocker et al. (2004) | Prospective, open-label, crossover, PK study | 20 | NVP 200 mg daily x 14 days then NVP 200 mg BID | ↓29% mean methadone AUC | Yes, mean methodone dose ↑14% | 14 displayed mild-moderate withdrawal symptoms |  |
| + NVP | Arroyo et al. (2007) | Prospective, open-label PK study | 10 | NVP 200 mg daily x 14 days then NVP 200 mg BID | ↓62% mean methadone AUC, ↓55% reduction in mean Cmax | Yes, mean methodone dose ↑19% | 9 displayed withdrawal symptoms | Symptoms emerged 4-14 days after NVP |
| + EFV, NVP | Pelet et al. (2011) | Case series | 9 | EFV 600 mg daily or NVP 200 mg BID | NR | EFV: Median ↑57% in methadone dose  NVP: Median ↑157% in methadone dose | Symptoms of withdrawal |  |
| + EFV, NVP | Esteban et al. (2008) | Case control study | 66 | EFV + NVP | ↑ R/S enantiomeric ratio in both NVP (179%) and EFV (39%) | 11 patients required median dose ↑31% | 11 patients reported symptoms of withdrawal | Measured R/S enantiomer ratio, not plasma concentration |
| + EFV, NVP | Manfredi et al. (2005) | Prospective cohort study | 623 | EFV + NVP | ↑2-fold AST/ALT levels for both EFV & NVP patient groups | N/A | No adjunctive toxicity was shown in the subjects taking methadone | 12% of patient population concurrently taking methadone at baseline |
| + EFV, NVP | Pinzani et al. (2000) | Case report/ Letter to editor | 1 | EFV 600 mg daily | NR | Yes, ↑ methodone dose from 30 to 80mg | Symptoms of withdrawal |  |

3TC = lamivudine, ABC = abacavir, ADE = adverse drug event, AMS = altered mental status, ARV = antiretroviral, ART = antiretroviral therapy, ATV = atazanavir, d4T = stavudine, D/C’d = discontinued, DDC = zalcitabine, ddI = didanosine, DLV = delavirdine, DRV = darunavir, EFV = efavirenz, EVG/c = elvitegravir/cobicistat, IDV = indinavir, LPV = lopinavir, NFV = nefinavir, NR = not reported, NS = nonsignificant, NVP = nevirapine, RAL = raltegravir, SQV = saquinavir, TDF = tenofovir disoproxil fumarate, TdP = torsades de pointes, TPV = tipranavir, UA = urinalysis, VT = ventricular tachycardia

**Supplementary Table 7: Notable human studies on pharmacokinetic interactions between antiretrovirals and treatments for alcohol use disorder**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Drug-drug combination** | **Study** | **Study design** | **n** | **ARV regimen** | **Change in PK parameters or drug levels** | **Need for dose adjustment** | **Clinical toxicity** | **Other comments** |
| ***Disulfiram (DIS)*** | | | | | | | | |
| + ATV | McCance-Katz et al. (2014) | Open-label, four component, PK study | 10 | ATV 400 mg daily | Lack of ALDH inhibition | No | N/A | DIS unlikely to be effective if co-administered with ATV |
| + ETV | 10 | RTV 200 mg daily | No statistically significant changes observed | N/A | N/A |
| + EFV | 10 | EFV 600 mg daily | Significant decrease in DIS carbamatea | N/A | Results not clinically significant |
| ***Naltrexone (NLT)*** | | | | | | | | |
| + ZDV | McCance-Katz et al (2001) | Open-label, between-subject study | 15 | ZDV 200 mg TID | No statistically significant changes observed | No | N/A | Naltrexone was administered orally |

a Metabolite of disulfiram; ARV = antiretroviral, ATV = atazanavir, ALDH = aldehyde dehydrogenase, RTV = ritonavir, EFV = efavirenz; PK = pharmacokinetic, ZDV = zidovudine