ANTIRETROVIRAL-METHADONE INTERACTIONS

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
Integrase Inhibitors				
Dolutegravir[1]	Open-label, 2-period study, pharmacokinetic study.	Adult opiate-dependent, HIV$^-$ subjects who received their current individual doses of methadone once daily for 3 days followed by dolutegravir 50 mg BID for 5 days with stable methadone therapy.	Kinetics of R- and S-methadone were not altered by concomitant dolutegravir and there were no clinically relevant differences in pharmacodynamic measures.	No dose adjustment in methadone is required when given in combination with dolutegravir.
Elvitegravir/ cobicistat[2]	Pharmacokinetic study	11 subjects on stable methadone (80-120 mg/day) who received elvitegravir 150 mg/cobicistat 150 mg daily for 10 days.	The kinetics of R-methadone were unaffected in the presence of elvitegravir/ cobicistat (AUC ↑ 7%, Cmin ↑ 10%); elvitegravir and cobicistat exposures were similar to historical controls.	No dose adjustments are needed.
Raltegravir[3]	Pharmacokinetic (randomized, placebo-controlled, 2-period crossover study)	Twelve HIV negative male and female patients on methadone maintenance therapy who received either 400-mg raltegravir or matching placebo every 12 hours from days 1 through 10 for each treatment period with a washout of 7 days between periods.	The geometric mean ratio (GMR) (90% CI) for (methadone + raltegravir/ methadone) was 1.00 (0.93, 1.09) for $AUC_{0\text{-}24hr}$ and 1.00 (0.94, 1.07) for C_{max}. There were no serious clinical or laboratory adverse experiences.	No dose adjustment is required for methadone when co-administered with raltegravir.[4]
NNRTIs				
Delavirdine[5]	Pharmacokinetic	16 HIV negative volunteers maintained on methadone and 15 controls, each treated with delavirdine 600	Methadone did not alter pharmacokinetics of delavirdine or N-delavirdine. Effect of delavirdine on methadone not studied.	Since delavirdine an inhibitor of 3A4, monitor for symptoms of opiate toxicity (e.g. miosis,

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		mg bid for 5 days.		drowsiness, ↓ rate and depth of respiration, N/V, constipation, bradycardia, hypotension) until further data available.
Efavirenz[6]	Pharmacokinetic	11 patients on stable methadone maintenance, due to begin antiretroviral therapy with two reverse transcriptase inhibitors and efavirenz	EFV ↓ methadone Cmax (p=0.007) and ↓ methadone AUC by mean of 60%. 9/11 patients complained of symptoms of methadone withdrawal from day 8-10 onwards of starting efavirenz, and received ↑ in methadone dose in increments of 10 mg until symptoms resolved (mean ↑ in methadone dose required: 22%)	Monitor for symptoms of opiate withdrawal (e.g. lacrimation, rhinorrhea, diaphoresis, restlessness, insomnia, dilated pupils, piloerection) and adjust methadone dose if necessary.[7]
Efavirenz[8]	Case report	1 patient on methadone 100 mg a day for over one year; switched from nelfinavir/lamivudine/stavu-dine to an efavirenz containing regimen.	Four weeks after the introduction of efavirenz, patient reported tiredness, headache, cold sweats and shivering. Concentrations of (R)-methadone (active enantiomer of methadone) before and after the introduction of efavirenz were 168 and 90 ng/ml, respectively. Dose of methodone ↑ to 180 mg/day before symptoms disappeared.	
Efavirenz[9]	Case report	3 HIV infected IV drug users on methadone treatment.	Opiate withdrawal symptoms emerged 4 to 7 days following the introduction of efavirenz. Methadone levels were obtained in one patient and were 65% lower with efavirenz than at baseline. Patients required a 66-133% ↑ in methadone dose to compensate.	
Nevirapine, then Efavirenz[10]	Case report	Patient stabilized on methadone 40 mg daily. Antiretroviral therapy changed from zidovudine/lamivudine to d4T/ddI/nevirapine, and	2 days following change, patient experienced symptoms compatible with opiate withdrawal (i.e. cramps, tremor, rhinorrhea etc). Symptoms stopped with the discontinuation of nevirapine, and recurred with nevirapine rechallenge.	

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		later d4T/ddI/efavirenz.	Symptoms recurred again following change to efavirenz, in spite of dose ↑ to 80 mg/day. Methadone levels stable despite dose increase.	
Etravirine[11]	Open-label interaction trial	16 male volunteers on stable methadone maintenance therapy received etravirine 100 mg BID for 14 days.	No clinically relevant effect of combination; methadone dose adjustment not required and no withdrawal symptoms were observed.	Methadone dosage adjustment likely not necessary when coadministered with etravirine.
Lersivirine[12]	Open-label, single-sequence study	13 HIV-negative volunteers on stable methadone maintenance therapy (50-150 mg QD) for ≥3 months received lersivirine 1000 mg daily plus their same methadone dose to steady-state (Days 2-11).	No clinically relevant change in R/S-methadone exposure resulted from co-administration. Opioid withdrawal symptoms were not observed when lersivirine was co-administered with methadone.	No methadone dose adjustment is required when lersivirine is administered.
Nevirapine[13]	Case report	1 patient on methadone 80 mg/day for 3 years; switched from ddI/d4T/SQV-hgc/NFV after 1 month (because of ddI intolerance) to d4T/NFV/SQV-sgc/nevirapine.	One week following the change to a nevirapine containing regimen, the patient experience symptoms of methadone withdrawal (total body pain, nausea, vomiting, insomnia, sweats, sense of impending doom). Over the course of 4 weeks, the dose ↑ to 130 mg/day and her symptoms resolved.	Monitor for symptoms of opiate withdrawal (see under "Efavirenz") and adjust methadone dose if necessary.
Nevirapine[14]	Retrospective chart review.	7 patients on chronic methadone maintenance following initiation of treatment with nevirapine containing regimens.	Methadone withdrawal precipitated in all patients within 4-8 days of initiating treatment with nevirapine. Methadone levels were determined for 3 patients, and were subtherapeutic in each case. Dose ↑ necessary, and 4 patients chose to discontinue therapy.	

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
Nevirapine[15]	Case series	5 patients on methadone maintenance program starting nevirapine based HAART.	4 of the 5 patients exhibited symptoms consistent with opiate withdrawal 6-15 days after beginning nevirapine therapy. Two patients discontinued therapy; two patients remained on therapy but required ↑ in methadone dose of 33% and 100%.	
Nevirapine[16]	Prospective study	45 intravenous drug users, stabilized on methadone and treated with nevirapine, didanosine and lamivudine, all once a day.	30% of the 45 patients required ↑ in their methadone dose due to withdrawal symptoms.	
Nevirapine[17]	Pharmacokinetic study	8 patients on stable daily methadone, beginning treatment with nevirapine based HAART.	Nevirapine ↓ methadone AUC by a mean of 50%. 6 of the 8 patients reported symptoms of methadone withdrawal from days 8-10 onwards of starting nevirapine, and received an ↑ in methadone dose in increments of 10 mg (mean ↑ in methadone dose required: 16%).	
Nevirapine[18]	Pharmacokinetic study	24 patients on stable methadone, beginning treatment with nevirapine based HAART. 12-hour PK measurements done at baseline and after 28 days.	Nevirapine ↓ methadone AUC by mean of 40%; mean methadone dose ↑ by 24% (range 0-80%) during study.	
Rilpivirine[19]	Pharmacokinetic study	13 HIV-negative volunteers on stable methadone received rilpivirine 25 mg daily for 11 days.	In the presence of rilpivirine, active R-isomer exposures decreased (mean Cmin ↓ 22%, Cmax ↓ 14%, AUC ↓ 16%); exposures of inactive S-methadone also decreased to a similar extent. The AUC ratio for S-/R-methadone did not change. No methadone withdrawal symptoms were observed.	No a-priori adjustment of methadone dosage is recommended. Patients should be monitored for symptoms of clinical withdrawal in case methadone dosage needs to be adjusted.[20]
Protease Inhibitors				

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
Amprenavir[21]	Pharmacokinetic study	Methadone blood concentrations were measured in five patients receiving methadone maintenance therapy before and after introduction of abacavir plus amprenavir for 14 days.	Methadone concentrations ↓ by 35% (range 28-87%, p = 0.043). Two patients reported on several occasions nausea in the morning before the intake of the daily methadone dose, which is suggestive of a withdrawal reaction.	
Amprenavir[22, 23]	Pharmacokinetic study	16 opiate dependent, HIV-patients on at least 30 days stable methadone treatment; methadone levels reassessed after 10 days of amprenavir 1200 mg bid.	Prospective, open-label study in HIV-negative subjects (n=19) maintained on methadone for at least 30 days, addition of amprenavir 1200 mg BID for 10 days resulted in delayed APV absorption, 13% ↓ AUC, 21% ↓ Cmin of active methadone enantiomer. The inactive S-enantiomer AUC and Cmin were decreased by 40% and 52%, respectively. No clinical evidence of methadone withdrawal was observed, and no methadone dosage was adjusted in any patient. Compared to a non-matched historical control group, a 30%, 27%, and 25% ↓ in AUC, Cmax, and Cmin of amprenavir was observed. Clinical significance unclear.	Methadone dosage adjustment likely not necessary when coadministered with amprenavir. Monitor for amprenavir efficacy.
Atazanavir[24]	Pharmacokinetic study	16 HIV-negative subjects on chronic methadone received concomitant atazanavir 400 mg daily for 14 days.	Prospective, open-label study; in the presence of atazanavir, no significant changes were observed in the pharmacokinetic parameters of the active (R)-isomer of methadone; exposure to the inactive (S)-isomer was modestly reduced but changes were not deemed significant. No clinical symptoms of opiate withdrawal were observed. Pharmacokinetic parameters of atazanavir were comparable to previously reported data.	Atazanavir and methadone may be co-adnimistered without dosage adjustment.

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
Darunavir/ ritonavir[25]	Pharmacokinetic study	16 HIV-negative subjects on stable methadone (range 55-200 mg/day, mean dose 86 mg, median dose 75 mg) received **darunavir 600/100 mg BID** for 7 days	Prospective, open-label study; in the presence of darunavir/ritonavir, mean *R*-METH Cmin, Cmax, and AUC24h were decreased by 15%, 24%, and 16%, respectively, while mean *S*-METH Cmin, Cmax, and AUC24h values were decreased by 40%, 44%, and 36%, respectively. Coadministration of DRV/r with METH results in a greater decrease in *S*-isomer exposure than *R*-isomer exposure.	Methadone dose adjustment is not likely to be required during DRV/r coadministration because the *R*-isomer is the biologically active enantiomer; however, monitoring for withdrawal symptoms during initial combination treatment should still be considered.
Fosamprenavir /ritonavir[26]	Pharmacokinetic	19 methadone-maintained, healthy subjects received fosamprenavir 700 mg/ ritonavir 100 mg BID for 14 days.	AUC and Cmax of active (R-) methadone ↓ 18% and 21%, respectively, while AUC and Cmax of inactive (S-) methadone ↓ 42% and 43%, respectively. Pharmacokinetics of amprenavir were similar to historical controls. No subject experienced symptoms of opiate withdrawal and methadone dosage adjustment was not required during the study.	Methadone dosage adjustment likely not necessary when coadministered with fosamprenavir/ritonavir.
Indinavir[27]	Pharmacokinetic	12 HIV + patients on methadone 20 – 60 mg per day; indinavir 800 mg po q8h added.	No significant effect of indinavir on methadone AUC when compared to historical controls. No significant effect of methadone on indinavir AUC, but ↑ indinavir Cmin 50-100% and ↓ indinavir Cmax 16-36%, all vs. historical controls.	Combination appears safe.
Indinavir, Nelfinavir, Ritonavir, Saquinavir[28]	Case series	Methadone levels measured prior to and at least one week following addition of a PI to stable dual RTI therapy in ten patients on methadone maintenance program.	Methadone concentrations unchanged in six patients switched to indinavir and one patient switched to saquinavir; methadone steady state concentrations ↓ 40-50% in one patient switched to ritonavir and two patients switched to nelfinavir.	Monitor for symptoms of opiate withdrawal (see under “Efavirenz”) with neflvinavir and ritonavir; adjust methadone dose if necessary.
Lopinavir/	Pharmacokinetic	Eleven healthy volunteers	Lopinavir/ritonavir ↓ methadone AUC and	Observed decreases in

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
ritonavir (Kaletra)[29]		received a single 5 mg dose of methadone. Methadone levels measured prior to and following ten days of lopinavir/ritonavir (400mg/100mg twice a day).	Cmax 47%.	methadone levels not always associated with opioid withdrawal symptoms; possible that lopinavir/ritonavir may produce stereoselective induction of methadone metabolism that would differentially decrease concentrations of the inactive S-isomer more than the active R-isomer. Likely no need for routine methadone dose adjustment when initiating lopinavir/ritonavir; however, as a precaution it is still recommended to monitor for opioid withdrawal (see under "Efavirenz") when initiating therapy.
Lopinavir/ ritonavir vs. ritonavir[30]	Pharmacokinetic	In two parallel, PK studies, healthy subjects on stable methadone received 7 days of either lopinavir/ritonavir 400/100 mg BID or ritonavir 100 mg BID.	Methadone AUC ↓ 26%, Cmax and Cmin ↓ 28% in presence of lopinavir/r, and was associated with a significant ↑ in number of opiate withdrawal symptoms. In contrast, methadone PK were not affected by ritonavir alone.	
Lopinavir/ ritonavir[31]	Pharmacokinetic study	Eight HIV-infected patients on methadone maintenance (median dose, 80 mg; range, 40–100 mg) initiated lopinavir/ritonavir plus 2 NRTIs.	A 36% ↓ in methadone AUC0–24h occurred after 14 days of lopinavir/ritonavir. However, none of the patients experienced opioid withdrawal symptoms or needed supplemental methadone added to their maintenance dose.	
Lopinavir/ ritonavir[32]	Observational study	Twenty HIV-positive subjects maintained on methadone for >1 month initiated lopinavir/rtv HAART regimens. Changes in methadone dose and opioid withdrawal symptoms were assessed daily for 28 days. Median (range) methadone dose at study entry was 95 (40–130) mg/d. Two subjects did not complete the observational period.	None of the 18 evaluable patients experienced symptoms of opioid withdrawal and no patients requested a change in methadone dosing during the evaluation period.	
Nelfinavir[33]	Prospective pharmacokinetic	14 patients stabilized on a fixed methadone dose for at least 1 month before	Levels of (+)-methadone and (-)-methadone ↓ by 47% and 39%, respectively. No patient exhibited	Observed decreases in methadone levels not always associated with

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
	study.	nelfinavir 1250 mg po bid for 8 days was added	withdrawal symptoms, and no dosage adjustments were necessary.	opioid withdrawal symptoms. Monitor for symptoms of opiate withdrawal (see under "Efavirenz") and adjust methadone dose if necessary.
Nelfinavir[34]	Retrospective case series	75 patients on stable methadone dose started on nelfinavir.	2 of 75 patients needed slight ↑ in methadone dose (10 mg/day). Otherwise, no impact of nelfinavir on methadone.	
Nelfinavir[35]	Case report	Patient on stable methadone dose of 100 mg daily, indinavir and ddC; d4T and nelfinavir added to regimen.	Within 6 weeks of medication change, patient began to complain of opiate withdrawal symptoms, which ↑ in severity over 3 months. Methadone dose ↑ at 1-2 week intervals, and subtherapeutic methadone levels documented until dose of 285 mg/d attained.	
Nelfinavir[36]	Pharmacokinetic	16 non-HIV infected volunteers on stable methadone dose for 4 weeks and 13 controls; received NFV 1250 mg po bid for 5 days.	Nonsignificant ↑ in median NFV 12 hour trough with methadone. 12 hour AUC of M8 53% lower vs. control.	
Nelfinavir[37]	Multi-site, retrospective	32 patients on stable methadone dose, receiving NFV based HAART; 84% of patients co-infected with hepatitis C.	17% of patients required methadone dose adjustments (mean 26 mg); otherwise, well tolerated combination.	
Ritonavir/ Saquinavir[38]	Case report	1 patient on methadone 90 mg/day for 2 years. Antiretrovirals changed from indinavir, lamivudine, and zidovudine to ritonavir 400 mg/saquinavir 400 mg BID and stavudine because of virologic progression.	One week following initiation of ritonavir containing regimen, patient was admitted to hospital with shakiness, diaphoresis, blurred vision, anxiety and hypotension. Methadone plasma level on admission was 210 ng/ml (within therapeutic range, however no levels prior to initiation of ritonavir). Methadone dose was gradually ↑ to 130 mg/day.	Potential for ↓ methadone with higher doses of ritonavir. Monitor for symptoms of opiate withdrawal (see under "Efavirenz") and adjust methadone dose if necessary.
Ritonavir/	Pharmacokinetic	12 HIV negative volunteers	Clinically insignificant change in unbound	Methadone dosage adjustment may not be

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
Saquinavir[39]		on stable methadone dose evaluated before and after 14 days of once daily saquinavir/ritonavir 1600mg/100mg.	methadone levels. 83% of subjects had Cmin of saquinavir > EC_{50}.	necessary when using doses of ritonavir.
Ritonavir/ Saquinavir[40]	Pharmacokinetic	12 HIV negative volunteers on stable methadone maintenance therapy (60-120 mg daily); evaluated effect of saquinavir/ritonavir 1000/100 mg BID for 14 days on the pharmacokinetics of methadone	A 19% ↓ AUC of R-methadone was observed in the presence of saquinavir/ritonavir, with no significant plasma protein-binding displacement of methadone. No clinically significant adverse effects were observed. There appears to be no need for methadone dose adjustment when methadone (60-120 mg qd) and SQV/RTV (1000/100 mg bid) are coadministered.	
Ritonavir/ Saquinavir[41]	24 hour pharmacokinetic study before and after 15 days of antiretroviral therapy to examine effect of ritonavir/saquinavir on methadone kinetics.	12 patients receiving stable methadone dose for at least 2 weeks.	↓ S-methadone AUC 40%, and ↓ R-methadone AUC 32%. However, when change in methadone AUC expressed in terms of unbound methadone, change in AUC was no longer significant; no evidence of opiate withdrawal.	
Ritonavir/ Saquinavir[42]	Retrospective	18 HIV + patients beginning once daily therapy with ritonavir 100 mg and saquinavir – soft gel capsule 1600 mg and 5 HIV + patients beginning once daily therapy with ritonavir 200 mg and indinavir 1200 mg. All patients on methadone, 19 patients co-infected with hepatitis C.	No patient required methadone dose adjustment.	
Tipranavir[43]	Pharmacokinetic study	15 adult healthy volunteers on steady-state tipranavir	53% ↓ methadone levels; large ↓ in both R-	Dosage of methadone may need to be increased

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		500/ritonavir 100 mg BID plus single-dose methadone 5 mg	and S-enantiomers.	when co-administered with tipranavir and 200 mg of ritonavir.
Reverse Transcriptase Inhibitors				
Abacavir[44]	Pharmacokinetic study.	19 patients titrated to constant methadone dose (≥ 40 mg/day) over 14 days. Days 15-28, received concomitant methadone and abacavir.	Slight ↑ in clearance of methadone by abacavir; no statistically significant change in Cmax, half-life or renal clearance of methadone. Methadone causes slight delay in rate but not extent of abacavir absorption.	Combination appears safe.
Didanosine buffered tablets (ddI), stavudine (d4T)[45]	Pharmacokinetic study	17 patients on methadone maintenance and 10 control patients. Two pharmacokinetic studies were completed for each study subject and control (one each for ddI and d4T).	d4T AUC ↓ 23% ddI tablets AUC ↓ 57% Effect primarily related to reduced bioavailability.	Greater reduction in ddI exposures when given as buffered tablet vs. EC capsule with methadone. If coadministration of methadone and didanosine is necessary, use ddI EC formulation and monitor for HIV clinical response.[46] Since formulation characteristics for the pediatric powder and the buffered tablet are similar, **do not coadminister methadone with ddI pediatric powde**r due to significant ↓ in ddI concentrations.
Didanosine enteric-coated	Pharmacokinetic	HIV-negative patients (n = 17) on stable methadone	ddI buffered tablet: trend to decreased ddI	If coadministration of methadone and

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
(EC) capsule[47]		dose; randomized to EC or tablet formulation, and crossed-over to alternative regimen after PK monitoring over 24 hours; comparisons made to historical data in non-methadone patients.	AUC in presence of methadone. EC formulation provided ddI plasma AUC levels comparable to historical controls in non-methadone patients.	didanosine is necessary, use ddI EC formulation and monitor for HIV clinical response.[46]
Tenofovir[48]	Pharmacokinetic study	13 HIV-negative subjects on stable methadone received 14 days of tenofovir 300 mg daily; kinetics of methadone and its R- and S-isomers done at baseline and on day 14. Short Opiate Withdrawal Scale (SOWS) questionnaire and pupillary diameter measurements also done at baseline and on day 14.	No change in kinetics of total methadone, R- and S-isomers when coadministered with tenofovir versus alone. No clinical or laboratory signs of opiate-related toxicity or withdrawal (including changes in SOWS scores or pupillary diameters) were noted.	Methadone pharmacokinetics and dynamics not affected by tenofovir. Combination appears safe.
Zidovudine[49]	Pharmacokinetic study	14 HIV positive patients on methadone maintenance for at least 6 months and five control patients. Patients were receiving zidovudine 200 mg po every 4 hours.	Zidovudine AUC ↑ 43% vs. control. No effect on methadone maintenance.	Monitor for zidovudine related toxicities, such as nausea, vomiting, and bone marrow suppression. Other opioid pharmacotherapies such as l-a-acetylmethadol LAAM, buprenorphine, or naltrexone not found to significantly affect zidovudine pharmacokinetics.[50]
Zidovudine[51]	Phamacokinetic within subject study.	8 patients started on acute methadone therapy as inpatients. Both oral and intravenous zidovudine pharmacokinetics determined before starting methadone, following acute methadone treatment and	Zidovudine AUC ↑ 41% during acute methadone treatment, and 29% during chronic treatment.	

Antiretroviral	Study Type	Patient(s)	Nature of interaction	Recommendation
		following two months of daily methadone.		

Key: AUC = area under the concentration-time curve, bid = twice daily, Cmax = maximum plasma concentration, ddC = zalcitabine, ddI = didanosine, d4T = stavudine, EFV = efavirenz, HAART = highly active antiretroviral therapy, PI = protease inhibitor, NFV = nelfinavir, RTI = reverse transcriptase inhibitor, SQV-hgc = hard gel saquinavir

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. Song I, Mark S, Borland J, et al. Dolutegravir has no effect on pharmacokinetics of methadone or oral contraceptives with norgestimate and ethinyl estradiol [abstract 535]. 20th Conference on Retroviruses and Opportunistic Infections, March 3-6, 2013, Atlanta, GA.

2. Bruce RD, Winkle P, Custodio JM, et al. Investigation of the interactions between methadone and elvitegravir-cobicistat in subjects receiving chronic methadone maintenance. Antimicrob Agents Chemother 2013 Dec;57(12):6154-7.

3. Anderson MS, Mabalot Luk JA, Hanley WD, et al. Effect of raltegravir on the pharmacokinetics of methadone. J Clin Pharmacol 2010;12(1461-6).

4. Merck Frosst Canada Ltd. Isentress (raltegravir) Prescribing Information. Kirkland, QC January 28, 2014.

5. McCance-Katz EF, Rainey PM, Smith P, et al. Drug interactions between opioids and antiretroviral medications: interaction between methadone, LAAM, and delavirdine. Am J Addict 2006;15:23-34.

6. Clarke SM, Mulcahy FM, Tjia J, et al. The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase inhibitor efavirenz. British Journal of Clinical Pharmacology 2001;51(3):213-7.

7. Bristol-Myers Squibb Canada. Sustiva (efavirenz) Prescribing Information. Montreal, QC June 11, 2012.

8. Marzolini C, Troillet N, Telenti A, et al. Efavirenz decreases methadone blood concentrations. AIDS 2000;14:1291-2.

9. Boffito M, Rossati A, Dal Conte I, et al. Opiate withdrawal syndrome in new efavirenz recipients under methadone maintenance regimen (abstr). 1st IAS Conference on HIV Pathogenesis and Treatment, July 8-11, 2001, Buenos Aires.

10. Pinzani V, Faucherre V, Peyriere H. Methadone withdrawal symptoms with nevirapine and efavirenz. Annals of Pharmacotherapy 2000;34:405-7.

11. Scholler-Gyure M, Van den Brink W, Kakuda TN, et al. Pharmacokinetic and pharmacodynamic study of the concomitant administration of methadone and TMC125 in HIV-negative volunteers. J Clin Pharmacol 2008;48:322-9.

12. Vourvahis M, Wang R, Gruener DM, et al. Effect of lersivirine co-administration on pharmacokinetics of methadone in healthy volunteers. Drug Alcohol Depend 2012;Jun 8 [Epub ahead of print].

13. Heelon MW, Meade LB. Methadone withdrawal when starting an antiretroviral regimen including nevirapine. Pharmacotherapy 1999;19:471-2.

14. Altice FL, Friedland GH, Cooney E. Nevirapine induced opiate withdrawal among injection drug users with HIV infection receiving methadone. AIDS 1999;13:957-62.

15. Otero MJ, Fuertes A, Sanchez R, et al. Nevirapine-induced withdrawal symptoms in HIV patients on methadone maintenance programme: an alert. AIDS 1999;13(8):1004-5.

16. Staszewski S, Haberl A, Gute P, et al. Nevirapine/didanosine/lamivudine once daily in HIV-1 infected intravenous drug users. Antiviral Ther 1998;3(Suppl 4):55-6.

17. Clarke SM, Mulcahy FM, Tjia J, et al. Pharmacokinetic interactions of nevirapine and methadone and guidelines for use of nevirapine to treat injection drug users. Clin Infec Dis 2001;33:1595-7.

18. Stocker H, Kruse G, Kreckel P, et al. Nevirapine significantly reduces the levels of racemic methadone and (R)-methadone in human immunodeficiency virus-infected patients. Antimicrobial Agents and Chemotherapy 2004;48:4148-53.

19. Crauwels HM, van Heeswijk RPG, Vandevoorde A, et al. Pharmacokinetic interaction study between TMC278, a next-generation non-nucleoside reverse transcriptase inhibitor and methadone [abstract 33]. 11th International Workshop on Clinical Pharmacology of HIV Therapy, April 5-7, 2010, Sorrento, Italy.

20. Janssen Inc. Edurant (rilpivirine) Product Monograph. Toronto, ON July 20, 2011.

21. Bart PA, Rizzardi PG, Gallant S, et al. Methadone blood concentrations are decreased by the administration of abacavir plus amprenavir. Therapeutic Drug Monitoring 2001;23(5):553-5.

22. Hendrix CW, Wakeford J, Wire MB, et al. Pharmacokinetics and pharmacodynamics of methadone enantiomers after coadministration with amprenavir in opioid-dependent subjects. Pharmacotherapy 2004;24:1110-21.

23. ViiV Healthcare ULC. Telzir (fosamprenavir) Prescribing Information. Montreal, QC February 11, 2014.

24. Friedland G, Andrews L, Schreibman T, et al. Lack of an effect of atazanavir on steady-state pharmacokinetics of methadone in patients chronically treated for opiate addiction AIDS 2005;19:1635-41.

25. Sekar V, Tomaka F, Lefebevre E, et al. Pharmacokinetic interactions between darunavir/ritonavir and opioid maintenace therapy using methadone or buprenorphine/naloxone. J Clin Pharmacol 2011;51(2):271-8.

26. Cao Y, Wire MB, Lou Y, et al. Pharmacokinetics and pharmacodynamics of methadone enantiomers following co-administration with fosamprenavir and ritonavir in opioid-dependent subjects (col102577) [abstract 72]. 8th International Workshop on Clinical Pharmacology of HIV Therapy, April 16-18, 2007, Budapest, Hungary.

27. Cantilena L, McCrea J, Blazes D, et al. Lack of a pharmacokinetic interaction between indinavir and methadone [abstract PI-74]. Clin Pharmacol Ther 1999;65:135.

28. Beauverie P, Taburet AM, Dessalles MC, et al. Therapeutic drug monitoring of methadone in HIV-infected patients receiving protease inhibitors. AIDS 1998;12(18):2510-1.

29. Bertz R, Hsu A, Lam W, et al. Pharmacokinetic interaction between lopinavir/ritonavir (ABT-378/r) and other non-HIV drugs [abstract P291]. 5th International Congress on Drug Therapy in HIV Infection, October 22-26, 2000, Glasgow, Scotland.

30. McCance-Katz EF, Rainey PM, Friedland G, et al. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. Clinical Infectious Diseases 2003;37(4):476-82.

31. Clarke S, Mulcahy F, Bergin C, et al. Absence of opioid withdrawal symptoms in patients receiving methadone and the protease inhibitor lopinavir-ritonavir. Clinical Infectious Diseases 2002;34(8):1143-5.

32. Stevens RC, Rapaport S, Maroldo-Connelly L, et al. Lack of methadone dose alterations or withdrawal symptoms during therapy with lopinavir/ritonavir. JAIDS 2003;33(5):650-1.

33. Hsyu PH, Lillibridge JH, Maroldo L, et al. Pharmacokinetic and pharmacodynamic interactions between nelfinavir and methadone [abstract 87]. 7th Conference on Retroviruses and Opportunistic Infections, January 30-February 2, 2000, San Francisco.

34. Maroldo L, Manocchio S, Artenstein A, et al. Lack of effect of nelfinavir mesylate on maintenance methadone dose requirement (abstract WePeB4120). XIII International AIDS Conference, July 9-14, 2000, Durban, South Africa.

35. McCance-Katz EF, Farber S, Selwyn PA, et al. Decrease in methadone levels with nelfinavir mesylate [letter]. Am J Psychiatry 2000;157:481.

36. Smith PF, Booker BM, Difrancesco R, et al. Effect of methadone or LAAM on the pharmacokinetics of nelfinavir & M8 [abstract A-491]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, December 16-19, 2001, Chicago, IL.

37. Brown LS, Chu M, Aug C, et al. The use of nelfinavir and two nucleosides concomitantly with methadone is effective and well-tolerated in HepC co-infected patients [abstract I-206]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy, December 16-19, 2001, Chicago, IL.

38. Geletko SM, Erickson AD. Decreased methadone effect after ritonavir initiation. Pharmacotherapy 2000;20(1):93-94.

39. Shelton MJ, Cloen D, DiFrancesco R, et al. The effects of once-daily saquinavir/minidose ritonavir on the pharmacokinetics of methadone. Journal of Clinical Pharmacology 2004 April 2-4;44(3):293-304.

40. Jamois C, Smith P, Morrison R, et al. Effect of saquinavir/ritonavir (1000/100 mg bid) on the pharmacokinetics of methadone in opiate-dependent HIV-negative patients on stable methadone maintenance therapy. Addict Biol 2009;14(3):321-7.

41. Gerber JG, Rosenkranz S, Segal Y, et al. The effect of ritonavir/saquinavir on the stereoselective pharmacokinetics of methadone: results of AIDS clinical trials group (ACTG) 401. J Acq Immune Def Synd 2001 July 9-14;27:153-60.

42. Munsiff AV, Patel J. Regimens with once daily ritonavir + Fortovase are highly effective in PI-experienced HIV-HCV co-infected patients on methadone [abstract 684]. 39th Annual meeting of the Infectious Diseases Society of America, October 25-28, 2001, San Francisco, CA.

43. Sabo J, Macha S, Oksala C, et al. Stereoselective pharmacokinetics of methadone after co-administration with steady-state tipranavir/ritonavir 500/200 mg BID in healthy volunteers [abstract 42]. 7th International Workshop on Clinical Pharmacology of HIV Therapy, April 20-22, 2006, Lisbon.

44. Sellers E, Lam R, McDowell J, et al. The pharmacokinetics of abacavir and methadone following coadministration: CNAA1012 [abstract 663]. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 26-28, 1999, San Francisco, CA.

45. Rainey PM, Friedland G, McCance-Katz EF, et al. Interaction of methadone with didanosine and stavudine. Journal of the Acquired Immune Deficiency Syndrome 2000;24(3):241-8.

46. Bristol-Myers Squibb Canada. Videx EC (didanosine enteric coated) Product Monograph. Montreal, QC May 12, 2010.

47. Friedland G, Rainey P, Jatlow P, et al. Pharmacokinetics (pK) of didanosine (ddI) from encapsulated enteric coated bead formulation (EC) vs chewable tablet formulation in patients (pts) on chronic methadone therapy (abstract TuPeB4548). XIV International AIDS Conference, July 7-12, 2002, Barcelona.

48. Smith P, Kearney BP, Liaw S, et al. Effect of tenofovir disoproxil fumarate on the pharmacokinetics and pharmacodynamics of total, R-, and S-methadone. Pharmacotherapy 2004;24(8):970-7.

49. Schwartz EL, Brechbuhl AB, Kahl P, et al. Pharmacokinetic interactions of zidovudine and methadone in intravenous drug-using patients with HIV infection. J Acq Immune Def Synd 1992;5:619-26.

50. McCance-Katz EF, Rainey PM, Friedland G, et al. Effect of opioid dependence pharmacotherapies on zidovudine disposition. American Journal of Addictions 2001;10(4):296-307.

51. McCance-Katz EF, Rainey PM, P PJ, et al. Methadone effects on zidovudine disposition (AIDS clinical trials group 262). Journal of the Acquired Immune Deficiency Syndrome 1998;18:435-43.