Analgesia and HIV

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Disclaimer
Although the author is up to date with the latest information, she wishes to point out that developments in the management of HIV and pain are constantly changing.

This document has been designed for reference only, and the author encourages readers to consult as many health professionals as required. People using the information in this document do so at their own risk.

As for the author, she neither recommends nor supports any of the treatments described in this work. Consequently, she assumes no liability for damages, costs and consequences that may result from the use of this information, nor for any error that it may contain. Any decision on specific treatments should be made in consultation with a health care professional with the relevant experience.

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Preface

Antiretroviral drugs are known to be very often responsible for drug interactions due to their pharmacokinetic properties and their ability to alter the absorption, metabolism and excretion of other drugs.

This booklet concerns drug interactions between antiretrovirals and various drugs used to control pain. It has been written to sum up the literature, to initiate reflection and to make recommendations based on the in the information available at the time of writing.

The aim of the document is to serve as a basic tool in discussions among professionals, to ensure the safest possible management of drug interactions. We thus hope to avoid serious adverse reactions, ensure optimal and effective treatment, and prevent non-compliance with treatment, namely ceasing to take the drugs required to control HIV and analgesia.

Antiretroviral therapy usually involves at least two classes of antiretrovirals. In this document, you will find drug interactions with NNRTIs (Non-Nucleoside Reverse Transcriptase Inhibitors), PIs (Viral Protease Inhibitors), the CCR5 inhibitor (Maraviroc), and integrase inhibitors. The class of NRTIs (Nucleoside Reverse Transcriptase Inhibitors) is not included in this document as they have no, or minimal, involvement in drug interactions with analgesics. Throughout the document, the trade names of the most well-known drugs are included for information purposes only, to facilitate the reader's understanding.

Legend

The arrows indicate the potential or observed change in the area under the curve (AUC) of the associated drug (light blue arrows) or of the antiretroviral (dark blue arrows). The solid arrow refers to pharmacokinetic studies or case reports in the literature. The outlined arrow refers to an analysis of the pharmacokinetics of the two drugs and an extrapolation of the drug interaction:

No interaction is anticipated.
No interaction was observed.

Potential increase in the plasma concentration of the associated drug, in its active form (parent drug or active metabolite), or of the antiretroviral. A decreased dose may be required. Monitor the occurrence of adverse reactions.|

Increase observed in the plasma concentration of the associated drug in its active form (parent drug or active metabolite), or of the antiretroviral. A decreased dose may be required. Monitor the occurrence of adverse reactions.

Potential decrease in the plasma concentration of the associated drug in its active form (parent drug or active metabolite), or of the antiretroviral. An increased dose may be required. Monitor clinical efficacy.

Decrease observed in the plasma concentration of the associated drug in its active form (parent drug or active metabolite), or of the antiretroviral. An increased dose may be required. Monitor clinical efficacy.

The color of the box indicates the level of interaction.

Green : No interaction or interaction deemed to be clinically not significant.
Yellow : Combination that requires close monitoring. Dose adjustments may be recommended.
Orange : Combination to be avoided. If it cannot be avoided, monitor it closely.
Red : Combination is contraindicated. Choose an alternative to the associated drug or the antiretroviral.

No interaction | Adjustment and/or monitoring | To be avoided | Contraindicated

Lexicon

Elimination Half-life (T ½)
Time required to eliminate 50% of the plasma-drug concentration

Area Under Curve (AUC)
Total drug exposure during the dosing interval; calculated by taking repeated measurements of concentrations over after a drug has been administered

Maximum Concentration (Cmax)
The highest concentration value in the dosing interval; usually reached during the absorption phase

Minimum Concentration (Cmin)
The lowest concentration value in the dosing interval; usually before the drug is taken again.

CYP
Cytochrome

NNRTI
Non-Nucleoside Reverse-Transcriptase Inhibitor

PI
Viral Protease Inhibitor

UGT
Uridine Diphosphate Glucuronosyl Transferase

INI
Integrase Inhibitor

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Metabolism of NNRTIs

	Substrates	Inhibitors/Inducers	Elimination
Efavirenz *Sustiva, Atripla*	3A4 and 2B6 (major) Inactive hydroxylated metabolites P-gp (weak)	**Inhibitor** 2C9, 2C19 and 3A4 (moderate) BCRP, MRP1, MRP2 and MRP3 (weak) **Inducer** 3A4 (powerfil) CYP 2B6 and UGT (weak)	**Urine:** 14% - 34% as metabolites **Feces:** 16% - 61%, mainly unchanged **T ½ life:** Single dose: 52 - 76 hrs Multiple doses: 40 - 55 hrs (induces its own metabolism)
Etravirine *Intelence*	3A4, 2C9 and 2C19 (major) Principal metabolites ~ 10% of the activity of Etravirine against HIV P-gp	**Inhibitor** 2C9 and 2C19 (moderate) P-gp (weak) **Inducer** 3A4 (powerful)	**Urine:** 1% **Feces:** 94%, up to 86% unchanged **T ½ life:** 41 hrs (± 20 hrs)
Nevirapine *Viramune*	3A4 (major) 3A4 and 2B6 (minor) Inactive hydrolyzed 2B6 and 3A4 metabolites	**Inducer** 3A4 (powerful) and 2B6 (potentially) **Inhibitor** 1A2, 2D6 and 3A4 (weak) BCRP, MRP1, MRP2 and MRP3 (weak)	**Urine:** 81%, mainly as metabolites, and less than 3% unchanged **Feces:** 10% **T ½ life:** Single dose: 45 hrs Multiple doses: 25 - 30 hrs (induces its own metabolism)
Rilpivirine *Edurant, Complera*	3A4 (major) 2C19 (negligible) P-gp (negligible)	**Inducer** 3A4 (weak)	**Urine:** 6.1%, less than 1% unchanged **Feces:** 85%, with 25% unchanged **T ½ life:** 45 - 50 hrs

Metabolism of PIs

	Substrates	Inhibitors/Inducers	Elimination
Atazanavir *Reyataz*	3A4 (major) Inactive metabolites BCRP, MRP1, MRP2 and P-gp	**Inhibitor** 3A4 (powerful) 2C8 (moderate) * UGT1A1 (moderate) BCRP, MRP1, MRP2, OATP1B1, OATP1B3, OATP2B1 and P-gp *Caution if Atazanavir without Ritonavir is associated with other drugs whose metabolism is strongly dependent on CYP2C8 and whose therapeutic index is narrow (for example: paclitaxel, repaglinide etc.). However, no significant interaction is clinically anticipated during concomitant administration of the Atazanavir/Ritonavir combination and of substrates of CYP2C8. **Inducer** Increased P-gp and MRP1 expression	**Urine:** 13%, with 7% of the total dose unchanged **Feces:** 79%, with 20% of the total dose unchanged **T ½ life:** 7 - 8 hrs without Ritonavir, 9 - 18 hrs with Ritonavir
Darunavir *Prezista*	3A4 (major) OATP1A2, OATP1B1 and P-gp	**Inhibitor** 3A4 (powerful), 2D6 (Ritonavir effect) MRP2, OATP1B1, OATP1B3 and P-gp **Inducer** 2C9, 2C19 and 2C8 (Ritonavir effect)	**Urine:** 14%, with 8% unchanged **Feces:** 80%, with 41% unchanged **T ½ life:** 15 hrs combined with Ritonavir
Fosamprenavir *Telzir*	Rapidly and almost completely converted to Amprenavir by cellular phosphatases in the intestinal epithelium 3A4 (major) P-gp	**Inhibitor** 3A4 (powerful) BCRP, MRP1, OATP 1B1, OATP 1B3 and P-gp **Inducer** 3A4 (possible, net effect with Ritonavir would be an inhibition)	**Urine:** 14% as metabolites, with approximately 1% unchanged **Feces:** 75% as metabolites, less than 1% unchanged **T ½ life:** 15 - 23 hrs with Ritonavir

Metabolism of PIs

	Substrates	Inhibitors/Inducers	Elimination
Lopinavir/r *Kaletra*	3A4 (major) 13 metabolites identified, including 5 metabolites associated with the metabolism of Ritonavir MRP1, MRP2, P-gp, OATP1A2 and OATP1B1	**Inhibitor** 3A4 and 2D6 (powerful) BCRP, MPR2, OATP1A2 , OATP1B1, OATP1B3, OATP2B1 and P-gp* **Inducer** 2C19 (powerful) 1A2, 2C9 and UGT (moderate) P-gp* (moderate) * *In vitro* data suggest that Lopinavir and Ritonavir are P-gp inducers, while *in vivo* data show that the net effect of Ritonavir is inhibited P-gp, and that the net effect of Lopinavir is induced P-gp when treatment is prolonged.	**Urine:** 10%, with less than 3% unchanged **Feces:** 83%, with 20% unchanged **T ½ life:** 5 to 6 hrs
Nelfinavir *Viracept*	3A4 (major) 2C19 (major): M8 active metabolite (similar activity to Nelfinavir) 2C9 and 2D6 (minor) P-gp, MRP1, MRP2	**Inhibitor** 3A4 (powerful) BCRP, MRP1, OATP1A2, OATP1B1, OATP2B1, OCT1, OCT2 and P-gp **Inducer** CYP 2C8, 2C9, 2B6, 2C19 and 1A2UGT (potential) Increased P-gp expression	**Urine:** 1% to 2% **Feces:** 98% to 99%, with 78% as metabolites and 22% unchanged **T ½ life:** 3.5 to 5 hrs
Ritonavir *Norvir*	3A4 and 2D6 (major) 1A2 and 2B6 (minor) 5 metabolites including a low concentration of an active metabolite (M-2) P-gp, MRP1, MRP2	**Inhibitor** 3A4 and 2D6 (powerful) BCRP, OATP1A2, OATP1B1, OATP1B3, MRP1, MRP2, OCT1, OCT2 and P-gp **Inducer** 2B6, 2C8, 2C9, 1A2 and 2C19 (moderate) UGT (moderate)	**Urine:** 11%, with 4% unchanged **Feces:** 86%, with 34% unchanged **T ½ life:** 3 - 5 hrs

Metabolism of PIs

	Substrates	Inhibitors/Inducers	Elimination
Saquinavir *Invirase*	3A4 (major), significant hepatic first-pass Quickly metabolized into a range of inactive mono- and bi-hydrolyzed compounds MRP1, MRP2, OTP1A2, OATP1B1, OATP1B3 and P-gp	**Inhibitor** 3A4 (moderate) BCRP, MRP1, MRP2, OATP1A2, OATP1B1, OATP1B3, OATP2B1, OCT1, OCT2 and P-gp	**Urine:** 1% - 3% **Feces:** 81% - 88% **T ½ life:** 7 - 12 hrs with ritonavir
Tipranavir *Aptivus*	3A4 (major) P-gp	**Inhibitor** 3A4 and 2D6 (powerful) P-gp **Inducer** 3A4 (powerful) 2C19 and 1A2 (weak) P-gp (powerful) A Tipranavir and Ritonavir combination can have an inhibition and induction effect. The net effect is often inhibition but it depends on the substrate.	**Urine:** 4%, mainly unchanged **Feces:** 82% **T ½ life:** 6 hrs with Ritonavir

Metabolism of INIs

	Substrates	Inhibitors/Inducers	Elimination
Dolutegravir *Tivicay*	UGT1A1 (51%) CYP3A4 (21%) UGT1A9 (6%) UGT1A3 (3%) Transporters: P-gp and BCRP	**Inhibitor** OCT2, MATE1 and MATE-2K (weak)	**Urine:** < 1% unchanged, 18.9% as an ether glucuronide metabolite of dolutegravir, 3.6% as N-dealkylated metabolite and 3% as a metabolite formed by benzylic carbon oxidation **Feces:** 53% **T ½ life:** 14 hrs
Elvitegravir/Cobicistat *Stribild*	Elvitegravir 3A4 and then UGT1A1/3 Cobicistat 3A4 (adult) and 2D6 (child)	**Inhibitor** 3A4 (powerful), 2D6 (moderate) P-gp, BCRP, OATP1B1 and OATP1B3 **Inducer** 2C9 (moderate)	Elvitegravir **Urine:** 6.7% **Feces:** 94.8% (hepatobiliary secretion) **T ½ life:** 12.9 hrs Cobicistat **Urine:** 8.2% **Feces:** 86% (hepatobiliary secretion) **T ½ life:** 3.5 hrs
Raltegravir *Isentress*	UGT1A1		**Urine:** 32%, with 9% unchanged **Feces:** 51% unchanged, **T ½ life:** biphasic Phase 1: 1 hr Phase 2: 9 hrs

Metabolism of the CCR5 inhibitor

	Substrates	Inhibitors/Inducers	Elimination
Maraviroc *Celsentri*	3A4 (major) P-gp	P-gp According to the monograph, Maraviroc could influence the bioavailability of certain drugs transported by P-gp in the intestine. No known clinical effect to date	**Urine:** 20%, with 8% unchanged In the presence of a CYP 3A4 inhibitor, the renal clearance of Maraviroc apparently increases to 70% **Feces:** 76%, with 25% unchanged **T ½ life:** 14 - 18 hrs

Metabolism of Opioids

	Substrates Phase I: CYP Phase II: UGT Transporters	Inhibitors/Inducers Phase I: CYP Phase II: UGT Transporters	Elimination
Codeine Prodrug	Codeine has several metabolites, some with analgesic effects and others with adverse reactions. Morphine (10%) Hydrocodone (minor) Morphine-6-glucuronide (to be considered especially in rapid metabolizers) Norcodeine Normorphine (potential analgesic activity) Morphine-3-Glucuronide Codeine-6-Glucuronide 2D6 (major): transformed into Morphine (10%) (active metabolite). Morphine is then conjugated by UGT2B7 and UGT1A3, into Morphine-6-Glucuronide (M6G) and Morphine-3-Glucuronide (M3G). As M6G is an active metabolite that contributes to the analgesic effect. 3A4 (minor): Norcodeine (10-15%) (relatively inactive metabolite) UGT2B7: metabolizes into Codeine-6-Glucuronide (50-70%) (active metabolite)	**Inhibitor** 2D6 (weak)	**Urine:** 3 - 16% unchanged, free and conjugated Norcodeine and Morphine **Urine:** 90% **Feces:** 10%
Fentanyl *Duragesic*	3A4 (major): inactive metabolites (99% Norfentanyl and several metabolites that are considered inactive)	**Inhibitor** 3A4 (weak)	**Urine:** up to 75% mainly as metabolites, and 7 - 10% unchanged **Feces:** approximately 9% as metabolites
Hydrocodone *Hycodan*	2D6 (major): Hydromorphone metabolite (1-7%). Is apparently 30 times more powerful than Hydrocodone. 3A4 (minor): Norhydrocodone metabolite (5%): probably inactive. Approximately 1/20th of the potency of Morphine and 50% of the potency of Hydrocodone UGT2B7 and UGT1A3: into Hydromorphone, which is then conjugated (see Hydromorphone) Other metabolites (ketoreduction): Norcodine (in low quantity – active) Dihydrocodeine (active) Dihydromorphine (active)		**Urine:** 26% mainly Hydrocodone and Hydromorphone 6-Hydrocodol (Dihydrocodeine) 5% as Hydromorphone and conjugates of Hydromorphone Conjugated metabolites 65%

Metabolism of Opioids

	Substrates Phase I: CYP Phase II: UGT Transporters	Inhibitors/Inducers Phase I: CYP Phase II: UGT Transporters	Elimination
Hydromorphone *Dilaudid*	UGT2B7 and UGT1A3: into active and/or toxic metabolites, namely Hydromorphone-3-Glucuronide, Hydromorphone-6-Glucuronide And other metabolites: Dihydromorphine (DHM) Norhydromorphone: minor metabolites with nearly the same potency as Morphine		**Urine:** 1.3 - 13.2% unchanged 22 - 51% conjugated
Meperidine *Demerol*	**Active metabolite:** Normeperidine with 30-50% of Meperidine's analgesic activity and 2-3 times the effects of Meperidine on the CNS (♂♌●□◆ the seizure threshold). This metabolite can accumulate with strong doses of 600 or more mg/day or with decreased renal or hepatic function. CYP 2B6 57% CYP 3A4 28% CYP 2C19 15% **Inactive metabolites:** Meperidinic acid and Normeperidinic acid		**Urine:** 0.5 - 5.2% unchanged 0.6 - 21% as active metabolites
Morphine *Statex*	Morphine would appear to be 50-60% converted by UGT 2B7 and UGT 1A3 into Morphine-3-Glucuronide (inactive and apparently with neuroexcitatory effects which would seem to be responsible for some adverse reactions (myocloni, hallucinations, convulsions, etc.)) and approximately 10-15% into Morphine-6-Glucuronide (analgesic effect). 2D6, 3A4 and 2C8 (minor) Morphine also seems to be transported by intestinal P-gp and P-gp in the blood–brain barrier area.		**Urine:** 90% mainly as Morphine-6-Glucuronide and 2-12% unchanged **Feces:** 7-10%

	Substrates Phase I: CYP Phase II: UGT Transporters	Inhibitors/Inducers Phase I: CYP Phase II: UGT Transporters	Elimination
Oxycodone *Supeudol, OxyNEO*	**Mainly oxydative metabolism (CYP 450). As CYP 3A4 and 2D6 are the main CYPs.** **Two active metabolites:** Oxymorphone and Noroxycodone 3A4 (major): Noroxycodone: (~ 1% of the Oxycodone activity). But considered to be an inactive metabolite. 2D6 (minor): Oxymorphone contributes to the analgesic effect. Oxymorphone is then metabolized into Noroxymorphone by CYP 3A4 and UGT 2B7 into Oxymorphone-6-Glucuronide. N. B.: probably transported by p-gp via the blood-brain barrier.		**Urine:** 19% as parent drug and more than 64% as metabolites
Tapentadol *Nucynta IR and CR*	UGT1A9 and UGT2B7: Tapentadol-O-Glucuronide (inactive) 2C19, 2C9, 2D6 (minor): inactive metabolites	***Inhibitor*** 2D6: but probably not significant in clinical concentrations.	**Urine:** 99%, with 70% as conjugated metabolites and 3% unchanged
Tramadol Tramacet *Ralivia, Tridural, Ultram, Zytram XL*	2D6 (major): Mono-O-Desmethyltramadol (M1), six times more powerful than the parent drug 3A4 (minor): Nortramadol Nortramadol (M2: 1/5 the potency of M1 (deemed to be inactive), and M2 is then transformed into mildly active M5 (less than M1) 2B6 (minor) And numerous other inactive metabolites		**Urine:** 90% urinary excretion (60% metabolites and 30% unchanged) **Feces:** 10%

Opioids and NNRTIs

Table 1/2

	Codeine	Fentanyl *Duragesic*	Hydrocodone *Hycodan*	Hydromorphone *Dilaudid*
Efavirenz *Sustiva, Atripla*	⇔ ⇩ 1	⇔ ⇩ 3	⇔ ⇩ 4	⇔ ⇔ 5
Etravirine *Intelence*	⇔ ⇩ 1	⇔ ⇩ 3	⇔ ⇩ 4	⇔ ⇔ 5
Nevirapine *Viramune*	⇔ ⇩ 1	⇔ ⇩ 3	⇔ ⇩ 4	⇔ ⇔ 5
Rilpivirine *Edurant, Complera*	⇔ ⇔ 2	⇔ ⇔ 2	⇔ ⇔ 2	⇔ ⇔ 5

Table 2/2

	Meperidine	Morphine	Oxycodone *Supeudol, OxyNEO*	Tapentadol *Nucynta IR or CR*	Tramadol Tramacet *Ralivia, Tridural, Ultram, Zytram XL*
Efavirenz *Sustiva, Atripla*	⇔ ⇧ 6	⇔ ⇔ 5	⇔ ⇩ 7	⇔ ⇔ 5	⇔ ⇩ 8
Etravirine *Intelence*	⇔ ⇧ 5	⇔ ⇔ 5	⇔ ⇩ 7	⇔ ⇔ 5	⇔ ⇩ 8
Nevirapine *Viramune*	⇔ ⇧ 6	⇔ ⇔ 5	⇔ ⇩ 7	⇔ ⇔ 5	⇔ ⇩ 8
Rilpivirine *Edurant, Complera*	⇔ ⇔ 5	⇔ ⇔ 5	⇔ ⇔ 2	⇔ ⇔ 5	⇔ ⇔ 2

No interaction | Adjustment and/or monitoring | To be avoided | Contraindicated

Opioids and NNRTIs

There is very little information in the literature regarding interactions between analgesics and antiretrovirals. Most of the information presented here is based on the extrapolation of each agent's metabolism.

1. ↓ possible decrease of the analgesic effect of Codeine due to the induction of CYP 3A4, the cytochrome forming a mildly active minor metabolite (Norcodeine). Consequently, it is possible that less Codeine is available for CYP 2D6 to convert Codeine into its active metabolite, Morphine.

   Recommendation: no dose adjustment is required immediately. Monitor for opioid withdrawal signs* and adjust the Codeine dose if necessary.

2. Rilpivirine appear to have little inductive effect on CYP 3A4. No clinically significant interaction is anticipated.

   Recommendation: no dose adjustment is recommended.

3. ↓ possible decreasein the plasma-Fentanyl concentration due to the induction of CYP 3A4.

   Recommendation: monitor for opioid withdrawal signs* and adjust the Fentanyl dose if necessary, or choose an alternative, such as Morphine or Hydromorphone at a suitable dosage, if there are no contraindications.

4. ↓ possible from the analgesic effect of the Hydrocodone due to the induction of CYP 3A4, the cytochrome forming an inactive minor metabolite (Norhydrocodone). Consequently, it is possible that less Hydrocodone is available for CYP 2D6 to convert Hydrocodone into its active metabolite, Hydromorphone.

   Recommendation: monitor the efficacy of Hydrocodone and adjust the Hydrocodone dose if necessary or choose an alternative, such as simple syrup and Dextromethorphan if Hydrocodone was prescribed for a cough, or Morphine or Hydromorphone at a suitable dosage, if Hydrocodone was prescribed for analgesic purposes and there are no contraindications.

5. No clinically significant interaction is anticipated.

   Recommendation: no dose adjustment is recommended.

6. ↑ possible decrease in the active metabolite of Meperidine due to induction of CYP 3A4 by Efavirenz, Etravirine and Nevirapine. Actual clinical effect is unknown.

   Recommendation: monitor the adverse reactions associated with Meperine when it is given for more than one dose.

7. ↓ possible decrease in the analgesic effect of Oxycodone due to the induction of CYP 3A4, the cytochrome forming metabolites having a weak analgesic effect. There are no studies concerning antiretrovirals and Oxycodone. In the case of Rifampicin and St. John's Wort, however, both CYP 3A4 inducers have been observed to reduce the AUC of Oxycodone by 86% and 50% in respectively. . A decrease in T½ life from 3.7 to 2.4 hours with Rifampicin and from 3.8 to 3 hours with St. John's Wort has also been observed.

   Recommendation: monitor clinical efficacy and opioid withdrawal signs and symptoms*. increase the Oxycodone dose if necessary, or choose an alternative, such as Morphine or Hydromorphone at a suitable dosage, if there are no contraindications.

8. ↓ possible decrease in the analgesic effect of Tramadol due to induction of CYP 3A4, the cytochrome forming an inactive minor metabolite (Nortramadol). It is suspected that there will be less Tramadol available to be transformed by CYP 2D6 into its active metabolite.

   Recommendation: monitor for opioid withdrawal signs and symptoms* and increase the Tramadol dose if necessary, or choose an alternative, such as Morphine or Hydromorphone at a suitable dosage, if there are no contraindications.

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* Opioid withdrawal signs and symptoms: craving for an opioid, irritability, muscle pain, muscle spasms, rash, abdominal pain, nausea, vomiting, diarrhea, diaphoresis, lacrimation, rhinorrhea, mydriasis, yawning, piloerection, tachycardia, and tremors.

Opioids and PIs

Table 1/2

	Codeine	Fentanyl *Duragesic*	Hydrocodone *Hycodan*	Hydromorphone *Dilaudid*	Meperidine *Demerol*
Atazanavir *Reyataz*	⇔ ⇔ 1	⇔ ↑ 3	⇔ ↑ 4	⇔ ⇔ 6	⇔ ⇔ 8
Atazanavir/r *Reyataz/Norvir*	⇔ ↓ 2	⇔ ↑ 3	⇔ ↑↓ 5	⇔ ↓ 7	⇔ ↑↓ 9
Darunavir/r *Prezista/Norvir*	⇔ ↓ 2	⇔ ↑ 3	⇔ ↑↓ 5	⇔ ↓ 7	⇔ ↑↓ 9
Fosamprenavir/r *Telzir/Norvir*	⇔ ↓ 2	⇔ ↑ 3	⇔ ↑↓ 5	⇔ ↓ 7	⇔ ↑↓ 9
Lopinavir/r *Kaletra*	⇔ ↓ 2	⇔ ↑ 3	⇔ ↑↓ 5	⇔ ↓ 7	⇔ ↑↓ 9
Nelfinavir *Viracept*	⇔ ⇔ 1	⇔ ↑ 3	⇔ ↑ 4	⇔ ↓ 7	⇔ ⇔ 8
Saquinavir/r *Invirase/Norvir*	⇔ ↓ 2	⇔ ↑ 3	⇔ ↑↓ 5	⇔ ↓ 7	⇔ ↑↓ 9
Tipranavir/r *Aptivus*	⇔ ↓ 2	⇔ ↑ 3	⇔ ↑↓ 5	⇔ ↓ 7	⇔ ↑↓ 9

No interaction | Adjustment and/or monitoring | To be avoided | Contraindicated

Table 2/2

	Morphine	Oxycodone [c] *Supeudol, OxyNEO*	Tapentadol *Nucynta CR*	Tramadol [d]Tramacet *Ralivia, Tridural, Ultram, Zytram XL*
Atazanavir *Reyataz*	⇔ ⇔ 6	⇔ ⇑ 11	⇔ ⇔ 13	⇔ ⇑ 14
Atazanavir/r *Reyataz/Norvir*	⇔ ⇓ 10	⇔ ⇑ 12	⇔ ⇔ 13	⇔ ⇓ 15
Darunavir/r *Prezista/Norvir*	⇔ ⇓ 10	⇔ ⇑ 12	⇔ ⇔ 13	⇔ ⇓ 15
Fosamprenavir/r *Telzir/Norvir*	⇔ ⇓ 10	⇔ ⇑ 12	⇔ ⇔ 13	⇔ ⇓ 15
Lopinavir/r *Kaletra*	⇔ ⇓ 10	⇔ ⇑ 12	⇔ ⇔ 13	⇔ ⇓ 15
Nelfinavir *Viracept*	⇔ ⇓ 10	⇔ ⇑ 11	⇔ ⇔ 13	⇔ ⇑ 14
Saquinavir/r *Invirase/Norvir*	⇔ ⇓ 10	⇔ ⇑ 12	⇔ ⇔ 13	⇔ ⇓ 15
Tipranavir/r *Aptivus*	⇔ ⇓ 10	⇔ ⇑ 12	⇔ ⇔ 13	⇔ ⇓ 15

No interaction | Adjustment and/or monitoring | To be avoided | Contraindicated

Opioids and PIs

There is very little information in the literature regarding interactions between analgesics and antiretrovirals. Most of the information presented is based on an extrapolation of each agent's metabolism.

1. No clinically significant interaction is anticipated.
   Inhibition of CYP 3A4 seems to have little effect on the pharmacokinetics of Codeine. Furthermore, no pharmacokinetic case or study suggesting a significant interaction between Codeine and a CYP 3A4 inhibitor has been reported.

   Recommendation: no dose adjustment is recommended.

2. ↓ possible from the analgesic effect due to the decreased formation of the active Codeine metabolite (Morphine) due to the inhibition of CYP 2D6 by Ritonavir.

   Recommendation:monitor clinical efficacy and adjust the Codeine dose if necessary, or choose an alternative.

3. ↑ in Fentanyl observed due to inhibition of CYP3A4. A pharmacokinetic study has shown that Ritonavir significantly decreases the metabolism of Fentanyl and increases its T½ life.

   Furthermore, one death has been reported with the combination of Lopinavir/Ritonavir and Fentanyl. One case of delirium has been reported with Diltiazem (a powerful CYP 3A4 inhibitor) and Fentanyl. Fentanyl overdose cases have also been reported with the use of an antifungal, such as Itraconazole (a powerful CYP 3A4 inhibitor).

   Recommendation: requires special attention.

   If the patient is already using Fentanyl and then antiretroviral therapy is started: remove the patch and start a decreased dose of Fentanyl eight hours later (recommended: 50% of the dose), and then adjust based on efficacy and tolerance, or choose an alternative (Morphine or Hydromorphone). As a precaution, use 60-75% of the converted dose. If possible, remove the Fentanyl patch 48 hours before introducing the antiretrovirals, and start alternative analgesia 8 hours after discontinuing Fentanyl. Monitor closely for signs and symptoms of opioid toxicity*.

   If Fentanyl is added to an existing antiretroviral therapy: start with a small dose and gradually increase, based on tolerance and efficacy, or choose an alternative (Morphine or Hydromorphone). Monitor closely for signs and symptoms of opioid toxicity*.

4. No clinically significant effect is anticipated since Hydrocodone is primarily metabolized by CYP 2D6. One could also think that because Atazanavir and Nelfinavir inhibit CYP 3A4, they could increase the Hydrocodone concentration and thereby increase the amount metabolized by CYP 2D6 into Hydromorphone (active metabolite with a greater analgesic effect than Hydrocodone).

   Recommendation: no dose adjustment is recommended. Monitor for the occurrence of adverse reactions associated with opioids* and adjust the dose if necessary.

5. ↓ possible reduction of the formation of an active metabolite (Hydromorphone) due to the inhibition of CYP 2D6. Hydrocodone is generally used for its antitussive effect. The parent drug and the active metabolite contribute to this effect, and the clinical impact of CYP 2D6 inhibition is hard to predict.

   Recommendation: start with a smaller dose and monitor clinical efficacy and opioid toxicity signs and symptoms*. Adjust the dose of Hydrocodone if necessary, or choose another antitussive (simple syrup or Dextromethorphan), or change to another analgesic if this is the required effect (Morphine or Hydromorphone at a suitable dosage if there are no contraindications).

6. No clinically significant interaction is anticipated.

7. ↓ possible decrease of Hydromorphone but also an increase in glucuroconjugated ↑ metabolites (metabolites with analgesic effects or inactive neuro-exciters) due to the induction of UGT. Unknown clinical effect. The accumulation of conjugated metabolites would be higher if there is renal failure.

   Recommendation: no dose adjustment is recommended. Hydromorphone is considered an alternative with less risk of drug interactions. Monitor clinical efficacy and the occurrence of adverse reactions. An adjustment of the Hydromorphone dose may be required.

8. The effect of Atazanavir and Nelfinavir on Meperidine is unknown.

   Recommendation: use with caution.

9. The effect of a low dose of Ritonavir on Meperidine is unknown. However, a study with high doses of Ritonavir has shown a decrease ↓ of 67% in the AUC for Meperidine and an increase ↑ of 47% in the AUC for Normeperidine. Normeperidine is apparently responsible for neurotoxic effects, such as seizures.

   Recommendation: use this combination with caution. Long term use is not recommended. Monitor clinical efficacy and the occurrence of adverse reactions associated with Meperidine**.

10. ↓ possible decrease of Morphine, but also an increaseof glucuroconjugated ↑ metabolites (metabolites with analgesic effects or inactive neuro-exciters) due to the induction of UGT. Unknown clinical effect. The accumulation of conjugated metabolites would be higher if there is renal failure.

    Recommendation: no dose adjustment is recommended. Morphine is considered an alternative with less risk of drug interactions. Monitor clinical efficacy and the occurrence of adverse reactions. An adjusted dose of Morphine may be required.

11. ↑ possible increase of Oxycodone and Oxymorphone metabolite due to CYP 3A4 inhibition.

    Recommendation: use the lowest effective dose and titrate the dose based on clinical response and the occurrence of opioid side effects*. (see c).

12. ↑ increase observed of 2.6 to 3 times the AUC of Oxycodone, in a study with Lopinavir/Ritonavir and Ritonavir. Voriconazole, a powerful CYP 3A4 inhibitor, increases the AUC of Oxycodone by 3.6 times and the T½ life from 3.5 to 7 hours.

    Recommendation: use the lowest effective dose and titrate the dose based on clinical response and the occurrence of opioid side effects*. (see c).

13. According to the pharmacokinetic data available for Tapentadol, no clinically significant interaction is anticipated.

14. ↑ possible increase in the analgesic effect of Tramadol due to CYP3A4 inhibition, which would favor the transformation of Tramadol into its active CYP 2D6 metabolite.

    Recommendation: use the lowest effective dose and titrate the dose based on clinical response and the occurrence of opioid side effects*.

15. ↓ possible decrease in the analgesic effect of Tramadol due to CYP 2D6 inhibition. It is suspected that increased Tramadol and a decrease in the active metabolite, M1, would have a greater effect on μ-opioid receptors (see d). A study with Paroxetine, a CYP 2D6 inhibitor, showed a decrease of approximately 50% in the active Tramadol metabolite (M1) and a partial decrease in the analgesic effect.

    Recommendation: monitor clinical efficacy and opioid withdrawal signs and symptoms* and adjust the Tramadol dose if necessary, or choose an alternative.

Additional information

a. In rapid metabolizers of CYP2D6, an increase is observed in the conversion of Codeine to Morphine and in the efficacy or toxicity associated with to opioids. In slow metabolizers of CYP 2D6, a decrease is observed in the conversion of Codeine to Morphine and in the analgesic effect. An increase in adverse reactions associated with Codeine accumulation is also observed.

b. In poor metabolizers of CYP 2D6, a decrease can be observed in the conversion of Hydrocodone into Hydromorphone and also an accumulation of the parent drug, Hydrocodone. Actual clinical effect is unknown.

c. An increase of the toxicity of Oxycodone was observed in slow 2D6 metabolizers, including suspected deaths.

d. In rapid CYP 2D6 metabolizers, an active metabolite (M1)/Tramadol ratio was observed to be 14 times higher compared to slow CYP 2D6 metabolizers. The efficacy/toxicity will therefore be increased.

* Signs and symptoms of opioid toxicity: miosis, euphoria, dysphoria, drowsiness, confusion, excessive sedation, decreased alertness, hallucinations, dizziness, bradycardia, myocloni, hypotension, prolonged or recurrent respiratory depression.

** The main risks associated with Meperidine are respiratory depression and, to a lesser degree, circulatory depression; there have been cases of respiratory arrest, shock and cardiac arrest. The most frequently observed adverse reactions include: lightheadedness, dizziness, sedation, nausea, vomiting and sweating.

Opioids and Maraviroc/INI

Table 1/2

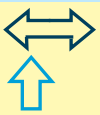
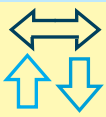
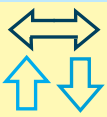
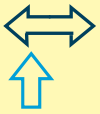
	Codeine	Fentanyl *Duragesic*	Hydrocodone *Hycodan*	Hydromorphone *Dilaudid*	Meperidine *Demerol*
Elvitegravir/ Cobicistat *Stribild*	 2	 2	 2	 1	 2
Dolutegravir *Tivicay*	 1	 1	 1	 1	 1
Maraviroc *Celsentri*	 1	 1	 1	 1	 1
Raltegravir *Isentress*	 1	 1	 1	 1	 1

Table 2/2

	Morphine	Oxycodone (c) *Supeudol, OxyNEO*	Tapentadol *Nucynta CR*	Tramadol (d)Tramacet *Ralivia, Tridural, Ultram, Zytram XL*
Elvitegravir/ Cobicistat *Stribild*	 1	 2	 1	 2
Dolutegravir *Tivicay*	 1	 1	 1	 1
Maraviroc *Celsentri*	 1	 1	 1	 1
Raltegravir *Isentress*	 1	 1	 1	 1

No interaction | Adjustment and/or monitoring | To be avoided | Contraindicated

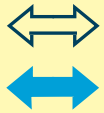
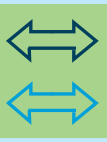
1. No clinically significant interaction is anticipated.

2. Cobicistat inhibits the same cytochromes as Ritonavir, but, unlike Ritonavir, it does not seem to affect glucuronidation, and the effect on CYP 2D6 appears to be rather minimal. The anticipated interactions with opioids are thus the same as with Ritonavir, except for Morphine and Hydromorphone, both metabolized by UGTs. See Ritonavir and Opioids.

Buprenorphine and Methadone Metabolism

	Substrates Phase I: CYP Phase II: UGT Transporters	Inhibitors/Inducers Phase I: CYP Phase II: UGT Transporters	Elimination
Buprenorphine *Suboxone* *BuTrans* *Sublinox*	3A4 (major-65%) and 2C8 (minor-30%): Norbuprenorphine (weak analgesic activity) Buprenorphine and Norbuprenorphine: Probable P-gp UGT1A1: Buprenorphine glucuronide (10%) and Norbuprenorphine glucuronide (30%), UGT1A3: Norbuprenorphine glucuronide, UGT2B7 (major): Buprenorphine glucuronide (40%) Glucuronide metabolites: (probable analgesic activity)	**Inhibitor** 1A2, 2A6, 2C19 and 2D6 (weak) **P-gp:** probable	**Urine:** 30% as Norbuprenorphine and low quantity of Buprenorphine-3-Glucuronide **Feces:** 70% unchanged
Methadone *Metadol*	Racemic mixture of R and S enantiomers. The R enantiomer is mainly responsible for the opioid activity. 2B6 and 3A4* (major) 2D6, 2C18, 2C8, 2C9, 1A2 and 2C19 (minor) P-gp Stereoselectivity 2B6 (S isomer) 2C19 (R isomer)	**Inhibitor** 2D6 (moderate) 3A4 (weak)	**Urine:** 4-21% unchanged (pH dependent) Feces: 10-45% If the case of renal failure, excretion occurs primarily by the biliary route (derivation of excretion route).

Buprenorphine/ Methadone and NNRTIs

	Buprenorphine *Suboxone*	Methadone *Metadol*
Efavirenz *Sustiva, Atripla*	 1	 5
Etravirine *Intelence*	 2	 6
Nevirapine *Viramune*	 3	 5
Rilpivirine *Edurant, Complera*	 4	 7

No interaction | Adjustment and/or monitoring | To be avoided | Contraindicated

1. ↓ decrease of 50% observed in the AUC for Buprenorphine and ↓ decrease of 71% observed in the AUC for Norbuprenorphine (active). No clinical opioid withdrawal signs were observed.

   No effect on Efavirenz was observed.

   Buprenorphine may be preferable to Methadone in patients requiring Efavirenz. No clinically significant effect is anticipated.

   Recommendation: No clinically significant effect is anticipated. As a precaution, monitor opioid withdrawal signs and symptoms* and adjust the Buprenorphine dose if necessary.

2. ↓ 25% decrease in Buprenorphine. However, no clinically significant effect is anticipated.

   Recommendation: monitor opioid withdrawal signs and symptoms* and adjust the Buprenorphine dose if necessary.

3. No significant interaction has been observed.

   Recommendation: no dose adjustment is recommended.

4. No significant interaction is suspected.

   Recommendation: no dose adjustment is recommended.

5. ↓ decrease observed of approximately 50% in the AUC of Methadone after 7 days of treatment. Withdrawal signs and symptoms were observed 4 to 15 days after starting Efavirenz or Nevirapine, and the Methadone dose had to be adjusted for many patients. An average increase of 20% to 50% of Methadone was required when combined with Nevirapine or Efavirenz.

   Recommendation: monitor opioid withdrawal signs and symptoms* in the days (particularly the first 2 weeks) following the introduction of the antiretroviral, and increase the dose if necessary.

6. ↑ increase of 8% in the AUC for R-methadone after 14 days, probably secondary to the CYP2 C19 inhibition by Etravirine. No clinically significant opioid withdrawal or toxicity symptoms were observed for the 14 day observation period.

   It is possible to see an enzymatic induction and decreased plasma concentration of Methadone following this observation period. However, we have no study with an observation period longer than 14 days.

   Recommendation: as a precaution, clinical monitoring of opioid withdrawal symptoms is recommended, and also an adjustment to the Methadone dose if necessary

7. ↓ decrease of 15-20% in R-methadone and S-methadone observed; however, no clinically significant effect is anticipated.

   Recommendation: no adjustment to the Methadone dose is recommended. However, monitor withdrawal signs and symptoms* and adjust the dose if necessary. Caution is recommended as Methadone and Rilpivirone may increase the QTc interval.

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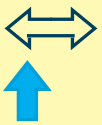
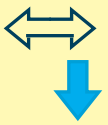
* Opioid withdrawal signs and symptoms: craving for an opioid, irritability, muscle pain, muscle spasms, rash, abdominal pain, nausea, vomiting, diarrhea, diaphoresis, lacrimation, rhinorrhea, mydriasis, yawning, piloerection, tachycardia, and tremors.

Buprenorphine/ Methadone and PIs

	Buprenorphine *Suboxone*	Methadone *Metadol*
Atazanavir *Reyataz*	 1	 6
Atazanavir/r *Reyataz/Norvir*	 1	 7
Darunavir/r *Prezista/Norvir*	 2	 8
Fosamprenavir/r *Telzir/Norvir*	 3	 9
Lopinavir/r *Kaletra*	 4	 10
Nelfinavir *Viracept*	 4	 11
Saquinavir/r *Invirase/Norvir*	 3	 12
Tipranavir/r *Aptivus*	 5	 13

No interaction | Adjustment and/or monitoring | To be avoided | Contraindicated

Buprenorphine/ Methadone and PIs

1. ↑ increase observed of 67% in the AUC for Buprenorphine and ↑ of 100% in the AUC for Norbuprenorphine when associated with Atazanavir, whether or not in combination with Ritonavir. Case reports describe patients who presented with adverse reactions and for whom a reduction in the dose of Buprenorphine was necessary.

   Recommendation: monitor opioid overdose signs and symptoms* and adjust the Buprenorphine dose if necessary, or for a new combination, start with a low dose.

   It should be noted that Buprenorphine is a partial agonist of opioid receptors. The clinical significance of increased plasma concentrations of the drug may (though we can't be certain) be less dramatic than for another powerful opioid, such as Morphine.

   N. B.: : With Atazanavir alone, without Ritonavir, there is a tendency to see a decrease in the Atazanavir concentration. The clinical significance of this observation is unknown.

   Recommendation: some authors recommend caution and to avoid using Atazanavir without Ritonavir when associated with Buprenorphine.

2. No significant change in Buprenorphine. ↑ increase observed of 46% in the AUC for Norbuprenorphine.

   The increase in Norbuprenorphine doesn't seem to be associated with an increased risk of an overdose.

   Recommendation: monitor opioid overdose signs and symptoms* and adjust the Buprenorphine dose if necessary, or for a new combination, start with a low dose.

3. As with most of the other PIs combined with Ritonavir, no significant clinical effect is anticipated.

   Recommendation: monitor opioid overdose signs and symptoms* and adjust the Buprenorphine dose if necessary, or for a new combination, start with a low dose.

4. No clinically significant interaction has been observed.

   Recommendation: no dose adjustment is recommended.

5. No effect on Buprenorphine. ↓ decrease of 80% observed in the Norbuprenorphine concentration. No opioid withdrawal signs or symptoms have been observed. ↓ decrease of 40% observed in the Cmin of Tipranavir. The effect on Tipranavir is deemed clinically insignificant.

   Recommendation: monitor Buprenorphine withdrawal signs and symptoms* and adjust the dose if necessary.

6. No significant effect on R-methadone. ↓ decrease of 15% observed in the AUC or S-methadone. Some patients required an increase in their daily dose of Methadone.

   Recommendation: as a precaution, monitor opioid withdrawal signs and symptoms** and adjust the Methadone*** dose if necessary.

7. No significant interaction has been observed. However, some patients required an increase in their daily dose of Methadone.

   Recommendation: as a precaution, monitor opioid withdrawal signs and symptoms** and adjust the Methadone*** dose if necessary.

8. ↓ decrease of 15% observed in the AUC for R-methadone, and ↓ of 36% in the AUC for S-methadone. No clinically significant effect has been observed.

   Recommendation: as a precaution, monitor opioid withdrawal signs and symptoms** and adjust the Methadone*** dose if necessary.

9. ↓ decrease observed of 18% in the AUC for R-methadone and ↓ of 42% in the AUC for S-methadone. No clinically significant effect observed.

   Recommendation: as a precaution, monitor opioid withdrawal signs and symptoms** and adjust the methadone*** dose if necessary.

10. ↓ decrease observed of more than 40% in the AUC for total Methadone. Few patients appear to have had withdrawal symptoms.

    Recommendation: as a precaution, monitor opioid withdrawal signs and symptoms** and adjust the Methadone*** dose if necessary.

    N.B. : A case report describes potential Methadone toxicity (torsade de pointes) eight days after discontinuation of Lopinavir/Ritonavir. The proposed mechanism is that when discontinuing Lopinavir/Ritonavir, the induction effect was lost and the Methadone concentration increased.

11. ↓ decrease of 43% observed in the AUC for R-methadone and ↓ of 51% in the AUC for S-methadone. ↓ decrease observed in a study of M8 (active metabolite of Nelfinavir), and no effect on Nelfinavir was observed. Few patients appear to have had opioid withdrawal symptoms**.

    Recommendation: as a precaution, monitor opioid withdrawal signs and symptoms** and adjust the Methadone*** dose if necessary. Also monitor the efficacy of Nelfinavir.

12. ↓ decrease of 37% observed in the AUC for R-methadone. No clinical effect has been observed.

    Recommendation: as a precaution, monitor opioid withdrawal signs and symptoms** and adjust the Methadone*** dose if necessary.

13. ↓ decrease observed of 48% in the AUC for R-methadone (active) and ↓ of 63% in the AUC for S-methadone (inactive form).

    Recommendation: as a precaution, monitor opioid withdrawal signs and symptoms** and adjust the Methadone*** dose if necessary.

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* Signs and symptoms of opioid toxicity: miosis, euphoria, dysphoria, drowsiness, confusion, excessive sedation, decreased alertness, hallucinations, dizziness, bradycardia, myocloni, hypotension, prolonged or recurrent respiratory depression.

** Opioid withdrawal signs and symptoms: craving for an opioid, irritability, muscle pain, muscle spasms, rash, abdominal, muscular or bone pain, nausea, vomiting, diarrhea, diaphoresis, lacrimation, rhinorrhea, mydriasis, yawning, piloerection, tachycardia, and tremors.

*** If there are withdrawal symptoms, increase the Methadone dose if necessary. If this combination is discontinued, the Methadone dose must be decreased over a 1-2 week period.

Buprenorphine/Methadone and Maraviroc/INIs

	Buprenorphine *Suboxone*	Methadone *Metadol*
Elvitegravir/Cobicistat *Stribild*	 1	 2
Dolutegravir *Tivicay*	 3	 2
Maraviroc *Celsentri*	 3	 3
Raltegravir *Isentress*	 3	 2

No interaction | Adjustment and/or monitoring | To be avoided | Contraindicated

1. ↑ increase of 35% in the AUC (↑ 66% Cmin) for Buprenorphine and of ↑ 42% in the AUC (↑ 57% Cmin) for Norbuprenorphine. This increase has been deemed to be not significant. No clinically significant interaction is anticipated.

   Recommendation: no dose adjustment is recommended.

2. No clinically significant interaction has been observed.

   Recommendation: no dose adjustment is recommended.

3. No interaction is anticipated.

   Recommendation: no dose adjustment is recommended.

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