

## Appendix 3

***Drug Interactions of Antiretrovirals*****Authors**

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**At a Glance**Table A3.1:  
Drug Interactions  
of Antiretrovirals**Overview**

This table covers the antiretroviral drugs (ARVs) considered the most common first-line and second-line ARVs in antiretroviral therapy (ART) regimens being used in sub-Saharan Africa in 2005. Interactions with these drugs are listed for medications that are suggested for use in palliative care in Appendix 2. In addition, some common drugs such as oral contraceptives are included.

The table here is an abbreviated version of Table 14.6 in *A Guide to the Clinical Care of Women with HIV, 2005 Edition*. The original drug interaction table has been modified to include primarily medications that are listed on the WHO Essential Medicines List or in Appendix 2.

Health care workers are encouraged to consult their national ART programmes as well as the resources in Appendix 1 for the most up-to-date information on drug interactions.

**Note:** Additional drug interactions are possible. Please consult additional resources for updated information and when co-administering ARVs with drugs not found in this table. Resources include:

- Manufacturer labeling
- Johns Hopkins HIV Guide at <http://www.hopkins-hivguide.org>
- Drug Interaction Charts maintained by the University of Liverpool (<http://www.hiv-druginteractions.org>)

Adapted from Table 14.6 in Chapter 14: Pharmacologic Considerations in HIV-Infected Pregnant Patients, by Paul Pham, Pharm D, in: Anderson J, ed. *A Guide to the Clinical Care of Women with HIV, 2005 Edition*. Rockville, MD: Health Resources and Services Administration HIV/AIDS Bureau. Available at <http://www.hab.hrsa.gov>.

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**Key to Table A3.1**

- AUC = Area Under the Concentration Time Curve
- C<sub>max</sub> = Peak serum concentration
- C<sub>min</sub> = Trough serum concentration
- CrCl = Creatinine clearance
- TDM = Therapeutic drug monitoring

**Time course:**

- Delayed = maximal interaction occurring at 14 days
- Immediate = interaction occurring immediately

**Severity:**

- Major = Significant pharmacokinetic interaction. Avoid co-administration or use with specific dose adjustments.
- Moderate = Can be co-administered with caution and possible dose adjustment.
- Minor = Can be co-administered.

**Table A3.1 Drug Interactions of Antiretrovirals**

Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
<b>Drug Interactions with Nucleoside Reverse Transcriptase Inhibitors</b>						
AZT (Zidovudine) (Retrovir®)	Paracetamol (Acetaminophen)	Competitive inhibition of glucuronidation	May rarely result in granulocytopenia and hepatotoxicity	Delayed	Minor	Intermittent use of paracetamol is considered safe. Adverse effects not consistently reported.
AZT	Stavudine	In vitro and in vivo antagonism	Decreased antiviral efficacy	Immediate	Major	Concomitant administration not recommended.
AZT	Rifampin	Enzymatic induction resulting in increased glucuronidation of AZT	Increased clearance of AZT	Delayed	Moderate	Clinical significance unknown.
AZT	Zalcitabine	Low potency combination	Non-responsive regimen	Delayed	Moderate	Avoid combination.
ddl (Didanosine) (Videx®)	Tenofovir	Unknown	ddl AUC increased by 40–60%. Suboptimal response in 91% of patients with ddl/TDF/3TC only	Delayed	Major	May increase rate of peripheral neuropathy and pancreatitis. Lower dose of ddl EC to 250 mg qd with TDF co-administration for pts >60kg. Dose for pts <60kg 200 mg qd. Avoid combination in NNRTI-containing regimen due to high failure rates.
ddl	Indinavir Ritonavir Delavirdine	Increase in gastric pH due to the buffer in ddl formulation	Decreased absorption of indinavir, ritonavir, and delavirdine	Immediate	Moderate	Separate administration time by at least 2 hours or use ddl EC formulation.
ddl	Dapsone	Increase in gastric pH due to the buffer in ddl formulation	No significant interaction	Immediate	Mild	Use standard dose.
ddl	Itraconazole Ketoconazole	Increase in gastric pH due to the buffer in ddl formulation	Decreased absorption of antifungal agent	Immediate	Major	Separate administration time by at least 2 hours or use ddl EC formulation. Fluconazole may be preferred as an alternative azole antifungal.
ddl	Pentamidine IV Ethambutol	Pharmacodynamic interaction /additive toxicity	May increase the risk of pancreatitis	Delayed	Moderate	Should avoid in patients with current alcohol use. Use caution when administering to patients with a history of alcoholism.
ddl	Atazanavir	Decreased absorption of ATV due to buffer in ddl formulation	ATV AUC decreased 87% with buffered ddl given simultaneously; no significant interaction expected with ddl EC	Immediate	Severe	buffered ddl: Take ATV with food 2 hr before or 1 hr after ddl (if this timing of dosing not followed, 90% reduction in ATV level); ddl EC: take at different times (ATV with food and ddl on empty stomach).
ddl	ddC, hydroxyurea, INH, cisplatin, disulfiram, thalidomide, vincristine, gold, hydralazine, and long-term metronidazole	Pharmacodynamic interaction/Additive toxicity	May increase the risk of peripheral neuropathy	Delayed	Moderate	Avoid co-administration or give with careful monitoring for symptoms of peripheral neuropathy. Incidence of peripheral neuropathy increases with low CD4 count.

Appendix 3: Drug Interactions of Antiretrovirals

Table A3.1: Drug Interactions of Antiretrovirals continued						
Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
ddl	d4T	Pharmacodynamic interaction/Additive toxicity	Increased risk lactic acidosis in pregnant women. Peripheral neuropathy and pancreatitis also reported with this combination.	Delayed	Major	Avoid co-administration especially during pregnancy, unless no other antiretroviral options are available and potential benefits outweigh risks.
ddl	Methadone	Unknown	buffered ddl AUC decreased by 63%. methadone levels remain unchanged. No interaction with ddl EC	Delayed	Moderate	Consider using ddl EC (no interaction).
ddC (Zalcitabine) (Hivid®)	ddl, d4T, INH, cisplatin, disulfiram, thalidomide, vincristine, gold, hydralazine, pyridoxine, and long-term metronidazole.	Pharmacodynamic interaction/Additive toxicity	May increase the risk of peripheral neuropathy	Delayed	Moderate	Avoid or give with careful monitoring of symptoms of peripheral neuropathy. Risk of peripheral neuropathy increases with total exposure and low CD4 count.
ddC	Lamivudine	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Moderate	To be avoided.
ddC	Al or Mg-containing antacid	Interference with absorption	ddC absorption decreased by 25%	Immediate	Moderate	Do not take simultaneously.
d4T (Stavudine) (Zerit®)	ddC, INH, cisplatin, disulfiram, thalidomide, vincristine, gold, hydralazine, pyridoxine, and long-term metronidazole.	Pharmacodynamic interaction/Additive toxicity	May increase the risk of peripheral neuropathy	Delayed	Moderate	Avoid or give with careful monitoring of symptoms of peripheral neuropathy. Peripheral neuropathy increases with total exposure and low CD4 count.
d4T	ddl	Pharmacodynamic interaction/Additive toxicity	Increased risk lactic acidosis in pregnant women. Peripheral neuropathy and pancreatitis also reported with this combination.	Delayed	Major	Avoid co-administration during pregnancy, unless no other antiretroviral options are available and potential benefits outweigh risks.
d4T	Methadone	Unknown	d4T drug levels decreased by 23%. Methadone levels unchanged	Delayed	Mild	Clinical significance unknown, no dose adjustment needed (unlikely to be significant).
d4T	Zidovudine	In vitro and in vivo antagonism	Decreased efficacy of the combination therapy	Immediate	Major	Concomitant administration not recommended due to antagonism.

Table A3.1: Drug Interactions of Antiretrovirals continued						
Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
3TC (Lamivudine) (EpiVir®)	Bactrim	Trimethoprim competitively inhibits renal tubular secretion.	AUC of lamivudine increased by 44%	Immediate	Minor	No dosage adjustment required due to the safety profile of 3TC (not clinically significant).
3TC	Abacavir + tenofovir	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Major	Avoid use of this combination without an NNRTI or a PI.
3TC	Emtricitabine	Overlapping resistance profile	Non-suppressive regimen	Delayed	Major	Avoid use together.
FTC (Emtricitabine) (Etriva®)	-					In vitro data suggest potential for CYP450-mediated interactions involving emtricitabine with other agents is low; in human studies, no significant PK changes in either drug with tenofovir, indinavir, famciclovir, or stavudine.
FTC	Lamivudine	Overlapping resistance profile	Non-suppressive regimen	Delayed	Major	Avoid.
Abacavir (Ziagen®)	Alcohol	Unknown	Alcohol increases ABC levels by 41%. No effect on alcohol levels	Immediate	Minor	Clinical significance unknown. No dose adjustment recommended.
Drug Interactions with Nucleotide Reverse Transcriptase Inhibitors						
Tenofovir (Viread®)	Atazanavir	Possible interference with absorption	Atazanavir AUC decreased by 25%; decreased C <sub>min</sub> by 23%	Immediate	Moderate	ATV 300 mg + RTV 100 mg should be used with co-administration.
Tenofovir	ddl	Unknown Low-potency combination	ddl AUC increased by 40–60%.	Delayed	Major	May increase rate of peripheral neuropathy and pancreatitis. Lower dose of ddl to 250 mg qd with TDF co-administration for pts >60kg. Dose adjustments for pts <60kg 200 mg qd.
Drug Interactions with Non-Nucleoside Reverse Transcriptase Inhibitors						
Nevirapine (Viramune®) (NVP)	Ethinyl estradiol (Oral contraceptives)	Induction of hepatic metabolism	Ethinyl estradiol AUC decreased by 23%	Delayed	Major	Patients should be aware of the potential interaction. Alternative or additional birth control method should be recommended.
NVP	Methadone	Induction of hepatic metabolism	Substantially decreased methadone AUC by 46%	Delayed	Moderate	Opiate withdrawal may occur. May need to increase dose of methadone by 15–25% (some patients may require doses of greater than 150 mg per day).
NVP	Rifampin/Rifabutin	Induction of hepatic metabolism	Nevirapine levels decreased by 37% with rifampin and 16% with rifabutin	Delayed	Major	Co-administration not generally recommended with rifampin, but good clinical outcome has been described. Rifabutin is the preferred alternative agent.
NVP	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism by both NVP and anticonvulsants.	May decrease serum levels of NVP and anticonvulsants	Delayed	Moderate	Consider alternative anticonvulsants (i.e valproic acid, levetiracetam, or topiramate).

Appendix 3: Drug Interactions of Antiretrovirals

Table A3.1: Drug Interactions of Antiretrovirals continued						
Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
NVP	St. John's wort	Induction of hepatic metabolism by St. John's wort	NVP clearance increased by 35%	Delayed	Major	Co-administration is contraindicated.
NVP	Saquinavir	Induction of hepatic metabolism	Saquinavir AUC decreased by 38%. NVP level not affected.	Delayed	Moderate	Avoid concurrent use unless saquinavir is 'boosted' with ritonavir (SQV 1000 mg/RTV 100 mg bid).
NVP	Ritonavir	Induction of hepatic metabolism	Ritonavir AUC decreased by 11%. NVP level not affected	Delayed	Minor	Use standard doses.
NVP	Indinavir	Induction of hepatic metabolism	Indinavir AUC decreased by 28%. NVP level not affected	Delayed	Minor	Clinical trials demonstrated good efficacy with standard dose. Consider increasing IDV to 1000 mg q8h (or IDV 800 mg/RTV 200 mg bid) with NVP coadministration.
NVP	Nelfinavir	Induction of hepatic metabolism	Nelfinavir levels increase by 10%. NVP level not affected	Delayed	Minor	Use standard doses.
NVP	Lopinavir/r	Induction of hepatic metabolism	LPV/r AUC decreased by 22%. C <sub>min</sub> decreased by 55%. NVP level not affected	Delayed	Major	Dose: LPV/r 533 mg/133 mg (4 caps) bid with food (NVP standard dose).
NVP	Efavirenz	Induction of hepatic metabolism	EFV AUC decreased by 22%. NVP AUC not affected	Delayed	Moderate	Though pharmacokinetic data exist, co-administration is not recommended due to overlapping resistance.
NVP	Atazanavir	Induction of hepatic metabolism	May decrease atazanavir	Delayed	Moderate	Consider using ATV 300 mg/RTV 100 mg qd. Avoid ATV 400 mg qd.
NVP	Fluconazole	Inhibition of NVP metabolism	May increase NVP serum level	Immediate	Moderate	Monitor NVP-associated side effects.
Delavirdine (Rescriptor®) (DLV)	Indinavir	Induction of hepatic metabolism	Indinavir AUC increased by 40%. DLV no change	Immediate	Moderate	May reduce indinavir dose to 600 mg q8h. DLV standard dose.
DLV	Nelfinavir	Inhibition of hepatic metabolism by delavirdine; Induction of hepatic metabolism by nelfinavir	NFV AUC increased by 72%. DLV AUC decreased by 42% C <sub>min</sub> decreased by 52%.	Immediate; delayed	Moderate	Do not co-administer.
DLV	Ritonavir	Inhibition of hepatic metabolism	Ritonavir AUC increased by 61%. DLV no change	Immediate	Minor	Standard doses likely (no data).
DLV	Saquinavir	Inhibition of hepatic metabolism	Invirase® C <sub>min</sub> increased by 500%; DLV AUC decreased by 15%.	Delayed	Minor	A beneficial interaction. No dose adjustment necessary. Monitor transaminase levels.

**Table A3.1: Drug Interactions of Antiretrovirals continued**

Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
DLV	Lopinavir/r	Inhibition of hepatic metabolism	LPV AUC increased by 8–134%. DLV no change	Immediate	Minor	Limited data. No dose adjustment.
DLV	ddl and antacid	Decreased delavirdine absorption due to antacid content in ddl	Delavirdine AUC decreased by 41%	Immediate	Moderate	Separate administration by at least 1 hour or use ddl EC.
DLV	Midazolam, Triazolam	Inhibition of hepatic metabolism	Midazolam and triazolam AUCs increased	Immediate	Major	Concurrent administration contraindicated due to potential for prolonged sedation. Lorazepam and temazepam may be safe alternatives.
DLV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease serum level of delavirdine	Delayed	Major	Co-administration is contraindicated.
DLV	Ethinyl estradiol	Unknown	Ethinyl estradiol levels decreased by 20%	Delayed	Major	Patients should be aware of the potential interaction. Alternative or additional birth control method should be recommended.
DLV	Quinidine	Inhibition of hepatic metabolism	May increase quinidine serum concentration	Immediate	Major	No data. Use with caution with close EKG monitoring and serum levels of quinidine.
DLV	Ketoconazole	Inhibition of hepatic metabolism by delavirdine	Ketoconazole AUC increased by 50%	Immediate	Minor	Consider dose reduction of ketoconazole. DLV 200–400 mg tid.
DLV	Rifampin	Inhibition of hepatic metabolism	Delavirdine C <sub>min</sub> decreased below the level of detection AUC decreased by 96%	Delayed	Major	Concurrent administration contraindicated due to sub-therapeutic level of delavirdine.
Efavirenz (Sustiva®) (EFV)	Saquinavir	Induction of hepatic metabolism	Invirase® AUC decreased by 60%. Efavirenz AUC decreased by 12%	Delayed	Moderate	Avoid using SQV as sole protease inhibitor with efavirenz. If RTV/SQV/efavirenz regimen used: dose SQV 1000 mg/RTV 100–200 mg bid plus EFV 600 mg qhs or RTV/SQV 400 mg/400 mg bid plus EFV 600 mg qhs.
EFV	Nelfinavir	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 21%	Immediate	Minor	A beneficial pharmacokinetic interaction. No dose adjustment needed.
EFV	Indinavir	Induction of hepatic metabolism	Indinavir AUC decreased by 31%	Delayed	Moderate	May need to increase indinavir dose to 1000 mg q8h or consider IDV 'boosted' with 200 mg RTV.
EFV	Ritonavir	Dual inhibition of hepatic metabolism	Efavirenz AUC increased by 21%. Ritonavir AUC increased by 17%	Immediate	Minor	No adjustment needed.
EFV	Lopinavir/r	Induction of hepatic metabolism	LPV AUC decreased by 19%. C <sub>min</sub> decreased by 39%	Delayed	Major	Dose: LPV/r 533 mg/133 mg (4 caps) bid + EFV 600 mg qhs.
EFV	Midazolam, Triazolam	Induction of hepatic metabolism	AUCs of midazolam and triazolam increased	Immediate	Major	Concurrent administration contraindicated due to potential for prolonged sedation. Lorazepam and temazepam may be safe alternatives.

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Table A3.1: Drug Interactions of Antiretrovirals continued						
Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
EFV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease efavirenz serum level	Delayed	Major	Co-administration is contraindicated.
EFV	Ethinyl estradiol	Inhibition of hepatic metabolism	Ethinyl estradiol AUC increased by 37%	Immediate	Minor	No dose changes recommended. Clinical significance of interaction unknown. Alternative or additional form of birth control recommended.
EFV	DMPA	No interaction	EFV levels not significantly affected. DMPA levels not reported.	N/A	Minor	Use standard dose. DMPA activity not affected by EFV.
EFV	Rifampin	Inhibition of hepatic metabolism	Efavirenz AUC decreased by 26%. No change in rifampin levels	Delayed	Moderate	Consider increasing EFV to 800 mg qhs with rifampin co-administration. An alternative is to use rifabutin dose adjusted to 450-600 mg qd (or 600 mg 3x/week) with standard dose EFV.
EFV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism by both EFV and anticonvulsants.	May decrease serum levels of EFV and anticonvulsants	Delayed	Moderate	Consider alternative anticonvulsants (i.e. valproic acid, levetiracetam, or topiramate). Consider increasing EFV to 800 mg po qd with co-administration. Monitor anticonvulsant level.
EFV	Nevirapine	Induction of hepatic metabolism	EFV AUC decreased by 22%. NVP AUC not affected	Delayed	Moderate	Though pharmacokinetic data exist, co-administration is not recommended due to overlapping resistance.
EFV	Methadone	Induction of hepatic metabolism	Decrease methadone AUC by 57%	Delayed	Moderate	Opiate withdrawal may occur. May need to increase dose of methadone.
EFV	Atazanavir	Induction of hepatic metabolism	ATV decreases AUC by 74%	Delayed	Major	Use ATV 300 mg + RTV 100 mg qd with food. Standard EFV dose.
EFV	Indinavir	Induction of hepatic metabolism	IDV decreases 31%	Delayed	Major	Increase IDV dose to 1000 mg q8h or consider IDV 800 mg + RTV 200 mg q12h.
Drug Interactions with Protease Inhibitors						
Indinavir (Crixivan®) (IDV)	ddl	Impairment of indinavir absorption by ddl buffer	Decreases absorption of indinavir	Immediate	Moderate	Separate indinavir and ddl dosing by at least 2h or use ddl EC formulation.
IDV	Rifampin	Induction of hepatic metabolism	Indinavir AUC decreased by 90%	Immediate	Major	Concurrent administration contraindicated.
IDV	Ketoconazole, Itraconazole	Inhibition of hepatic metabolism	Indinavir AUC increased by 70%	Immediate	Moderate	Dose Indinavir at 600 mg q8h. No dose adjustment when 'boosted' with RTV.
IDV	Midazolam, Triazolam	Inhibition of hepatic metabolism	AUCs of midazolam and triazolam are increased	Immediate	Major	Concurrent administration contraindicated due to potential for prolonged sedation.
IDV	St. John's wort	Induction of hepatic metabolism by St. John's wort	Indinavir AUC decreased by 57%	Delayed	Major	Co-administration is contraindicated.

**Table A3.1: Drug Interactions of Antiretrovirals continued**

Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
IDV	Oral contraceptives	Inhibition of hepatic metabolism	Ethinyl estradiol AUC increased by 24% and norethindrone AUC increased by 26%.	Immediate	Minor	No dose adjustment but patient should be counselled on potential for increased OC ADR (adverse drug reaction).
IDV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease serum levels of IDV. IDV may increase anticonvulsant serum level.	Delayed	Moderate	Consider alternative anticonvulsants (i.e. valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level.
IDV	Nelfinavir	Inhibition of hepatic metabolism.	Indinavir AUC increased by 50% Nelfinavir AUC increased by 80%	Immediate	Minor	Limited dosing data using IDV 1200 mg bid + NFV 1250 mg bid.
IDV	Ritonavir	Inhibition of hepatic metabolism	Indinavir AUC increased by 2 to 5-fold.	Immediate	Minor	Interaction allows indinavir to be dosed twice a day. Dose: IDV 400 mg/RTV 400 mg or IDV 800 mg bid/RTV100 bid.
IDV	Lopinavir/r	Inhibition of hepatic metabolism	Indinavir AUC increased by 3-fold	Immediate	Moderate	Dose: IDV 600 mg or 666 mg bid plus LPV/r 400 mg/100 mg bid.
IDV	Saquinavir	Inhibition of hepatic metabolism	Saquinavir AUC increased 4 to 7-fold. No effect on indinavir level	Immediate	Moderate	In vitro antagonism. Avoid co-administration.
IDV	Nevirapine	Induction of hepatic metabolism	Indinavir AUC decreased by 28%. NVP level not affected.	Delayed	Minor	Clinical trials demonstrated good efficacy with standard doses. Some experts recommend increasing the dose of IDV to 1000 mg q8h. When using 'boosted' IDV consider RTV dose 200 mg bid.
IDV	Efavirenz	Induction of hepatic metabolism	Indinavir AUC decreased by 31%	Delayed	Moderate	May need to increase indinavir dose to 1000 mg q8h or IDV 800/RTV 100-200 q12h.
IDV	Delavirdine	Inhibition of hepatic metabolism	Indinavir AUC increased by 40%. DLV no change.	Immediate	Moderate	May reduce indinavir dose to 600 mg q8h. DLV standard dose.
IDV	Methadone		No change in serum level		Minor	Minor interaction. Use standard dose
Saquinavir (Invirase®) (Fortovase®) (SQV)	Ritonavir	Inhibition of hepatic metabolism	Saquinavir AUC increased by 20-fold.	Immediate	Minor	Recommended doses: RTV 400 mg bid plus SQV 400 mg bid. RTV 100 mg bid plus SQV 1000 mg bid. RTV 100 mg plus SQV 1600 mg qd.
SQV	Indinavir	Inhibition of hepatic metabolism	Saquinavir AUC increased 4 to 7-fold No effect on Indinavir	Immediate	Moderate	In vitro antagonism. Avoid co-administration.
SQV	Nelfinavir	Inhibition of hepatic metabolism	Fortovase®AUC increased by 3 to 5-fold. Nelfinavir AUC increased by 20%	Immediate	Minor	Recommended doses are nelfinavir 750 mg tid and Fortovase® 800 mg tid or 1200 mg bid (limited data).
SQV	Lopinavir/r	Inhibition of hepatic metabolism	Saquinavir C <sub>min</sub> increased by 3 to 6-fold	Immediate	Minor	Dose: SQV 800–1000 mg bid plus LPV/r 400/100 mg bid.

Appendix 3: Drug Interactions of Antiretrovirals

Table A3.1: Drug Interactions of Antiretrovirals continued						
Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
SQV	Ketoconazole	Inhibition of hepatic metabolism	Saquinavir level increased by 3-fold.	Immediate	Minor	Beneficial pharmacokinetic interaction. Use standard doses. If ketoconazole dose is >200 mg/day, monitor for GI side effects and adjust doses accordingly.
SQV	Midazolam, Triazolam	Inhibition of hepatic metabolism	Midazolam and triazolam AUCs increased	Immediate	Major	Concurrent administration contraindicated due to potential for prolonged sedation. Consider lorazepam, temazepam.
SQV	Dexamethasone	Induction of hepatic metabolism	May decrease SQV serum level	Delayed	Moderate	Clinical significance unknown.
SQV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease SQV serum level	Delayed	Moderate	Consider alternative anticonvulsants (i.e. valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level.
SQV	Rifabutin/Ritampin	Induction of hepatic metabolism	Rifabutin and ritampin decrease AUC of saquinavir by 40% and 80% respectively.	Delayed	Major	Concurrent administration contraindicated with rifampin due to high incidence of hepatotoxicity. Consider rifabutin 150 mg 3x/week with SQV 1000 mg + RTV 100 mg bid.
SQV	Oral contraceptives					No data.
SQV	Methadone	Induction of hepatic metabolism	8–10% reduction in methadone level.	Delayed	Minor	Insignificant interaction. No dose adjustment needed.
SQV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease SQV serum level	Delayed	Major	Co-administration is contraindicated.
SQV	Garlic supplement (3.5 mg bid)	Unknown	SQV C <sub>min</sub> decreased by 49%	Delayed	Moderate	Avoid concurrent administration.
SQV	Delavirdine	Inhibition of hepatic metabolism	SQV increases 5-fold	Immediate	Minor	Decrease SQV-sgc dose to 800 mg tid, and monitor transaminase levels.
SQV	Efavirenz	Induction of hepatic metabolism	SQV decreases 62%, EFV decreases 12%	Delayed	Moderate	Use SQV-sgc 400 mg + RTV 400 mg bid with EFV. Consider SQV 1000 mg + RTV 100 mg bid.
SQV	Nevirapine	Inhibition of hepatic metabolism	SQV decreases 25%	Delayed	Moderate	SQV-sgc 400 + RTV 400 mg or SQV-sgc 1000 mg + RTV 100 mg bid or SQV-hgc 1000 mg + RTV 100 mg bid with NVP.
SQV	Amitriptyline Imipramine	Inhibition of hepatic metabolism	May increase tricyclics	Immediate	Minor	Monitor tricyclic antidepressant concentration.
Ritonavir (Norvir®) (RTV)	Metronidazole	Alcohol in ritonavir liquid may precipitate a disulfiram-like reaction.	Unexpected nausea	Immediate	Moderate	Warn patient of the alcohol content in ritonavir liquid.
RTV	Oral contraceptives	Induction and increase in glucuronosyl transferase activity.	Ethinyl estradiol level decreased by 40%	Delayed	Major	Warn patient of interaction. Use alternative or additional method of contraception.

**Table A3.1: Drug Interactions of Antiretrovirals continued**

Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
RTV	Ketoconazole	Inhibition of hepatic metabolism	Ketoconazole AUC increased by greater than 3-fold.	Immediate	Moderate	Use with caution; may need to decrease ketoconazole dose; do not exceed 200 mg ketoconazole per day.
RTV	Rifampin	Induction of hepatic metabolism	Ritonavir AUC decreased by 35%	Delayed	Moderate	Not recommended. Increased risk of liver toxicity.
RTV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease RTV serum level	Delayed	Major	Co-administration is contraindicated.
RTV	Benzodiazepines	Inhibition of hepatic metabolism	Prolonged sedation due to accumulation of benzodiazepine	Delayed	Major	Concurrent administration of midazolam and triazolam are contraindicated. Alternative benzodiazepines that can be used: Temazepam, oxazepam, and lorazepam.
RTV	Antiarrhythmics	Inhibition of hepatic metabolism	AUC of antiarrhythmics increased	Immediate	Major	Concurrent administration of propafenone, quinidine, flecainide, encainide, amiodarone, and bepridil are contraindicated.
RTV	Methadone	Induction of hepatic metabolism	Methadone levels decreased by 37% with RTV/SQV.	Delayed	Moderate	Clinical significance unknown. Monitor for withdrawal symptoms.
RTV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease serum levels of RTV. RTV may increase serum level of anticonvulsants	Delayed	Moderate	Consider alternative anticonvulsants (i.e. valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level. Carbamazepine toxicity has been reported.
RTV	Antidepressant (TCAs: desipramine, amitriptyline) SSRIs, Bupropion	Inhibition of hepatic metabolism	Desipramine AUC increased by 145%. Increased serum levels of SSRIs, bupropion	Immediate	Major	Monitor desipramine levels. Consider citalopram, sertraline, or fluoxetine. Monitor for increased effects from SSRIs, bupropion. Doses of RTV used in boosted PI regimens may have minimal effects.
RTV	Didanosine (buffered)	Interference with absorption	Decreased ritonavir absorption.	Immediate	Major	Consider using ddl EC or separate administration by > 2 hours.
RTV	Saquinavir	Inhibition of hepatic metabolism.	Saquinavir AUC increased by 20-fold.	Immediate	Minor	Recommended doses: ritonavir 400 mg bid and SQV (Fortovase® or Invirase®) 400 mg bid or SQV 1000 mg + RTV 100 mg bid or SQV 1600 mg + RTV 100 mg qd.
RTV	Indinavir	Inhibition of hepatic metabolism.	Indinavir AUC increased by 2 to 5-fold.	Immediate	Minor	Interaction allows indinavir to be dosed twice a day, which may reduce renal stones associated with higher dose indinavir. Dose: IDV 400 mg bid and RTV 400 mg bid or IDV 800 mg bid + RTV 100 bid.
RTV	Nelfinavir	Inhibition of hepatic metabolism.	Nelfinavir AUC increased by 2.5-fold.	Immediate	Minor	Only marginal PK benefit. Clinical trials have used ritonavir 400 mg bid and nelfinavir 500 mg or 750 mg bid (limited data).
RTV	Atazanavir	Inhibition of hepatic metabolism	ATV AUC increased by 238%	Immediate	Minor	A beneficial PK interaction, use ATV 300 mg + RTV 100 mg qd.

Appendix 3: Drug Interactions of Antiretrovirals

Table A3.1: Drug Interactions of Antiretrovirals continued						
Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
Nelfinavir (Viracept®) (NFV)	Fluconazole	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 30%	Immediate	Minor	May be beneficial. No dose adjustment needed.
NFV	Methadone	Induction of hepatic metabolism	Decreased serum level of inactive methadone (S)-isomer. No change in active methadone (R)-isomer.	Delayed	Minor	Use standard dose. No withdrawal symptoms observed.
NFV	Rifampin	Induction of hepatic metabolism	Nelfinavir AUC decreased by 82%	Delayed	Major	Concurrent administration contraindicated.
NFV	Benzodiazepines	Inhibition of hepatic metabolism	Prolonged sedation due to accumulation of benzodiazepine	Immediate	Major	Midazolam and triazolam are contraindicated. Alternative benzodiazepines include temazepam and lorazepam.
NFV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease NFV serum level	Delayed	Major	Co-administration is contraindicated.
NFV	Oral contraceptives	Induction of hepatic metabolism	Ethinyl estradiol AUC decreased by 47%	Delayed	Major	Advise patient to use alternative or additional method of contraception.
NFV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease serum levels of NFV. NFV may increase serum levels of anticonvulsants	Delayed	Moderate	Consider alternative anticonvulsants (i.e. valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level.
NFV	Indinavir	Inhibition of hepatic metabolism.	Indinavir AUC increased by 50%. Nelfinavir AUC increased by 80%	Immediate	Minor	Limited data for dosing IDV 1200 mg bid + NFV 1250 mg bid.
NFV	Saquinavir	Inhibition of hepatic metabolism	Fortovase® AUC increased by 3–5 fold. Nelfinavir AUC increased by 20%	Immediate	Moderate	Dose nelfinavir 750 mg tid and Fortovase 800 mg tid or 1200 mg bid (limited data).
NFV	Amprenavir	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 15%. Amprenavir AUC increased by 50%.	Immediate	Minor	Limited data: NFV 1250 mg bid plus APV 1200 mg bid.
NFV	Ritonavir	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 1.5-fold. Increase in Nelfinavir metabolite.	Immediate	Moderate	Limited data: ritonavir 400 mg bid and nelfinavir 500 mg or 750 mg bid. Boosting with ritonavir will yield only minimal pharmacokinetic enhancement of nelfinavir serum concentration.
NFV	Lopinavir/r	Induction of hepatic metabolism by NFV. Inhibition of hepatic metabolism by LPV/r.	LPV decreased by 33%. NFV increased 25%	Delayed	Moderate	Consider increasing LPV/r dose to 4 caps bid with NFV co-administration.
NFV	Nevirapine					No significant drug interaction. Use standard dose.

**Table A3.1: Drug Interactions of Antiretrovirals continued**

Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
NFV	Delavirdine	Induction of hepatic metabolism	Delavirdine AUC decreased by 50%. NFV AUC increased by 2-fold.	Immediate	Moderate	Avoid. Consider alternative PI.
NFV	Efavirenz	Inhibition of hepatic metabolism	NFV AUC increased by 20%. EFV levels unchanged.	Immediate	Minor	No significant drug interaction. Use standard dose.
NFV	Voriconazole	Potential for bi-directional interaction	NFV and voriconazole may be increased	Immediate	Moderate	Monitor for toxicities.
Ampronavir (Agenerase®) (APV)	Rifampin	Induction of hepatic metabolism	Ampronavir AUC decreased by 80%	Delayed	Major	Concurrent administration contraindicated.
APV	Ketoconazole	Inhibition of hepatic metabolism	Ampronavir AUC increased by 32%. Ketoconazole AUC increased by 44%.	Immediate	Minor	May be beneficial. No dose adjustment needed.
APV	Oral contraceptives	Induction of hepatic metabolism	Ethinyl estradiol decreased by 32%. Norethindrone decreased by 18%.	Delayed	Major	Contraindicated. Advise patient of potential risk and the use of an alternative or additional method of contraception.
APV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease APV serum level	Delayed	Major	Co-administration is contraindicated.
APV	Saquinavir	Induction of hepatic metabolism	Saquinavir level decreased by 18%. Ampronavir level decreased by 36%.	Delayed	Minor	No dose adjustment. Insufficient data for dose recommendation.
APV	Indinavir	Inhibition of hepatic metabolism	Ampronavir AUC increased by 33%. Indinavir AUC decreased by 38%.	Immediate	Minor	No dose adjustment. IDV 800 mg tid plus APV 800 mg tid (limited data).
APV	Nelfinavir	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 15%. Ampronavir AUC increased by 50%.	Immediate	Minor	No dose adjustment. NFV 750 mg tid plus APV 800 mg tid (limited data).
APV	Ritonavir	Inhibition of hepatic metabolism	Ampronavir AUC increased by 2.5-fold.	Immediate	Minor	Dose: APV 600 bid/RTV 100 bid or APV 1200 mg qd /RTV 200 mg qd.

Appendix 3: Drug Interactions of Antiretrovirals

Table A3.1: Drug Interactions of Antiretrovirals continued						
Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
APV	Lopinavir/r	Induction of hepatic metabolism by APV. Inhibition of hepatic metabolism by LPV/r	APV C <sub>min</sub> increased 5-fold. LPV AUC decreased 30–50%.	Delayed	Moderate	Dose: LPV/r 533 mg/133 mg (4 caps) + APV 750 mg bid (+/- EFV).
APV	Efavirenz	Induction of hepatic metabolism	Amprrenavir AUC decreased by 36%. Efavirenz AUC increased by 15%	Delayed	Moderate	Dose: APV 600 mg/RTV 100 mg bid + EFV 600 mg qHS.
APV	Nevirapine	Induction of hepatic metabolism	APV level may be significantly decreased			No data.
APV	Delavirdine	Induction of hepatic metabolism by APV. Inhibition of hepatic metabolism by DLV	DLV AUC decreased by 60% and C <sub>min</sub> decreased by 90%. APV AUC increased by 25%.	Delayed	Major	Co-administration not recommended.
APV	Methadone	Induction of hepatic metabolism	Decreased serum level of inactive methadone (S)-isomer. No change in active methadone (R)-isomer	Delayed	Minor	Use standard dose. No withdrawal symptoms observed.
APV	Midazolam, Triazolam	Inhibition of hepatic metabolism	AUC of midazolam and triazolam are increased.	Immediate	Major	Concurrent administration contraindicated due to potential for prolonged sedation. Lorazepam and temazepam may be safe alternatives.
APV	Amiodarone, lidocaine (systemic), quinidine, and bepridil	Inhibition of hepatic metabolism	May increase serum level of antiarrhythmics.	Immediate	Moderate	Use with caution. Monitor antiarrhythmic serum level.
APV	Dexamethasone	Inhibition and induction of hepatic metabolism	May decrease APV serum level.	Delayed	Moderate	Use with caution.
APV	Amitriptyline, imipramine, and desipramine	Inhibition of hepatic metabolism	May increase TCA serum level.	Immediate	Moderate	Consider therapeutic drug monitoring or use SSRI (i.e. citalopram, sertraline, or fluoxetine).
APV	Phenytoin, carbamazepine, and phenobarbital	Induction of hepatic metabolism	May significantly decrease APV serum level.	Delayed	Moderate	Consider alternative anticonvulsant (i.e. valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level.
APV	Didanosine	May interfere with absorption	APV serum level may be decreased	Immediate	Moderate	Dosing should be separated by 1 hour.
Fosamprenavir drug-drug interactions						
Since fosamprenavir is converted to amprenavir, all drug interaction data for 'unboosted' amprenavir should also apply to 'unboosted' fosamprenavir. However, there are some interactions that are more pronounced with fosamprenavir.						

**Table A3.1: Drug Interactions of Antiretrovirals continued**

Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
Lopinavir/r	Methadone	Induction of hepatic metabolism	Methadone AUC decreased by 53%	Delayed	Minor	No withdrawal symptoms observed in 2 out of 3 studies. Standard dose recommended. Monitor and increase dose of methadone if needed.
LPV/r	Rifampin	Induction of hepatic metabolism	LPV AUC decreased 75%	Delayed	Major	Concurrent administration contraindicated. Consider using rifabutin 150 mg qod with LPV/r.
LPV/r	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease LPV serum level	Delayed	Major	Co-administration is contraindicated.
LPV/r	Benzodiazepines	Inhibition of hepatic metabolism	Prolonged sedation due to accumulation of benzodiazepine	Delayed	Major	Concurrent administration of midazolam and triazolam are contraindicated. Alternative benzodiazepine that can be used: Temazepam, oxazepam, and lorazepam.
LPV/r	Antidepressants (TCA)	Inhibition of hepatic metabolism	Increase in TCA serum level	Immediate	Moderate	May increase toxicities.
LPV/r	Antiarrhythmics	Inhibition of hepatic metabolism	AUC of antiarrhythmics increased	Immediate	Major	Concurrent administration of propafenone, flecainide, and encainide are contraindicated. Use amiodarone and quinidine with close monitoring.
LPV/r	Antipsychotic (Pimozide)	Inhibition of hepatic metabolism	May significantly increase pimozide serum level resulting in QTc prolongation	Immediate	Major	Concurrent administration of pimozide is contraindicated.
LPV/r	Phenytoin (also carbamazepine and phenobarbital)	Induction of hepatic metabolism	LPV decreased by 33%. Phenytoin decreased by 31%.	Delayed	Major	Consider alternative anticonvulsants. Consider TDM. Monitor anticonvulsant levels with co-administration.
LPV/r	Indinavir	Inhibition of hepatic metabolism	Indinavir AUC increased by 3-fold	Immediate	Moderate	Dose: IDV 600 mg or 666 mg bid plus LPV/r 400 mg/100 mg bid.
LPV/r	Efavirenz	Induction of hepatic metabolism	LPV AUC decreased by 40%.	Delayed	Major	Dose: LPV/r 533 mg/133 mg (4 caps) bid + EFV 600 mg qhs.
LPV/r	Delavirdine	Inhibition of hepatic metabolism	LPV AUC increased by 8-134%. DLV no change	Immediate	Minor	Limited data. No dose adjustment.
LPV/r	Nevirapine	Induction of hepatic metabolism	LPV C <sub>min</sub> decreased by 55%. NVP level not affected.	Delayed	Major	Dose: LPV/r 533 mg/133 mg (4 caps) bid (NVP standard dose).
LPV/r	Saquinavir	Inhibition of hepatic metabolism	Saquinavir C <sub>min</sub> increased by 3-6-fold	Immediate	Minor	Dose: SQV 1000 mg bid plus LPV/r 400/100 mg bid.
LPV/r	Nelfinavir	Induction of hepatic metabolism by NVP. Inhibition of hepatic metabolism by LPV/r	LPV decreased by 33%. NVP increased 25%.	Delayed	Moderate	Consider increasing LPV/r dose to 4 caps bid with NVP co-administration.

Appendix 3: Drug Interactions of Antiretrovirals

Table A3.1: Drug Interactions of Antiretrovirals continued						
Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation
LPV/r	Itraconazole	Inhibition of hepatic metabolism	May increase itraconazole serum level	Immediate	Moderate	Use with caution; do not exceed 200 mg itraconazole.
LPV/r	Ethinyl estradiol	Induction of hepatic metabolism	EE AUC decreases 42%		Major	Use alternative or additional method.
Atazanavir (ATV)	ddl (buffered)	Interference with absorption	No effect on ddl serum level. ATV AUC decreased by 87%.	Immediate	Major	Administer ATV 400 mg one hour after ddl (buffered) administration. Consider ddl EC.
ATV	EFV	Induction of hepatic metabolism (inhibition of hepatic metabolism with RTV boosting)	ATV AUC decreased by 74%. EFV not measured (ATV AUC increased by 39% with RTV boosting)	Delayed (Immediate)	Major (Minor)	Co-administration of ATV as a sole PI with EFV is not recommended. Boosting ATV 300 mg with 100 mg RTV recommended with EFV co-administration (doubles total ATV exposure and increases ATV trough by 300%).
ATV	Oral contraceptives	Inhibition of glucuronidation.	Ethinyl estradiol AUC increased by 48%. Norethindrone AUC increased by 110%. ATV not measured.	Delayed	Minor	Clinical significance unknown. Monitor for adverse reactions with oral contraceptive; consider alternative method of contraception.
ATV	SQV	Inhibition of hepatic metabolism	SQV AUC increased by 5.5-fold. ATV not affected	Immediate	Minor	Beneficial PK interactions which allows once-a-day. Consider SQV 1500 mg/ATV 300 mg/RTV 100 mg qd.
ATV	AZT/3TC	No effect	AZT and 3TC not affected. ATV not measured			Standard dose AZT/3TC with ATV.
ATV	Ketoconazole	No effect	ATV not affected. Ketoconazole not measured			Standard dose ATV with ketoconazole co-administration.
ATV	Tenofovir	Interference with absorption	ATV AUC decreased by 25%. TDF not measured	Immediate	Moderate	Dose: ATV 300 mg/RTV 100 mg qd with TDF co-administration.
ATV	Rifampin	Induction of hepatic metabolism	ATV may be decreased	Delayed	Moderate	Contraindicated. Rifabutin may be a safer alternative. Dose: ATV 400 mg qd plus rifabutin 150 mg 3x/week.
ATV	St. John's wort	Induction of hepatic metabolism by St. John's wort	May decrease ATV serum level	Delayed	Major	Concurrent administration contraindicated until more data become available.
ATV	Benzodiazepines	Inhibition of hepatic metabolism	May prolong sedation due to accumulation of benzodiazepine	Delayed	Major	Concurrent administration of midazolam and triazolam are contraindicated until more data become available. Alternative benzodiazepines that can be used: Temazepam, oxazepam, and lorazepam.
ATV	Antiarrhythmics	Inhibition of hepatic metabolism	AUC of antiarrhythmics increased	Immediate	Major	Concurrent administration of propafenone, flecainide, encainide, and bepridil are contraindicated. Use with caution with amiodarone and quinidine.

Table A3.1: Drug Interactions of Antiretrovirals continued							
Primary Drug	Interacting Drug	Mechanism of Interaction	Effect	Time Course	Severity	Comments/Management Recommendation	
ATV	Proton-pump inhibitors	Decreased ATV absorption	Significantly decreases ATV levels	Immediate	Major	Avoid concomitant use.	
ATV	H-2 blocker	Decreased ATV absorption	Significantly decreases ATV levels	Immediate	Major	Dose: ATV300 mg / 100 mg qd 2 hours before or 10 hours after H-2 blocker.	
ATV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease serum levels of ATV. ATV may increase serum levels of anticonvulsants	Delayed	Moderate	Consider alternative anticonvulsant (i.e. valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level. Carbamazepine toxicity has been reported.	
ATV	Methadone	No data				No data. Interaction unlikely.	
ATV	Nevirapine	Induction of hepatic metabolism	May decrease ATV levels	Delayed	Moderate	Consider using ATV 300 mg + RTV 100 mg qd.	
ATV	Ritonavir	Inhibition of hepatic metabolism	ATV AUC increased by 238%	Immediate	Minor	Use ATV 300 mg + RTV 100 mg.	
Drug Interactions with Fusion Inhibitors							
Enfuvirtide (Fuzeon)	No significant drug interactions						

