XIV: PHARMACOLOGIC CONSIDERATIONS IN HIV-INFECTED PREGNANT PATIENTS

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II. INTRODUCTION

The decision to administer drugs to a pregnant woman is largely based on the therapeutic benefit to the mother and/or fetus vs. the potential risk to the mother and the developing fetus. Clinicians are often advised to avoid prescribing drugs for pregnant patients because human safety data in pregnancy are lacking for many, if not most medications. However, in some clinical situations the benefits of treatment far outweigh the risks. These are important considerations when selecting agents to treat patients with human immunodeficiency virus (HIV), to prevent mother-to-child HIV transmission, and to prevent or treat opportunistic infections.

There is limited information concerning the safety of many antiretrovirals in pregnancy. Mutagenicity, carcinogenicity, and teratogenicity studies in animals are the basis for most data on safety in pregnancy. However, generally animals are administered doses 5 to 20 times higher than those given to humans; clinical applicability to human treatment is not always clear.

It is now standard care to treat HIV-infected patients with an "antiretroviral cocktail" or a combination of antiretroviral agents, making it difficult to assess the safety of a single antiretroviral agent. More prospective

clinical data are needed. Clinicians are encouraged to report all in utero exposures to the Antiretroviral Pregnancy Registry (telephone 1-800-258-4263; Fax 1-800-800-1052; Internet access www.APRegistry.com), a collaborative effort of pharmaceutical manufacturers with an advisory committee of obstetric and pediatric practitioners. Observational data on antiretroviral exposure during pregnancy are collected and are used to assess potential teratogenicity of these drugs.

The tables contained in this chapter include detailed information about pharmacologic agents commonly used in the treatment of HIV-infected women and drugs often used in pregnancy or as complementary therapies, with particular emphasis on issues related to their use in pregnancy.

III. PHARMACOKINETICS OF DRUGS IN PREGNANCY

Although many physiologic changes occur during pregnancy, few trials have been conducted to evaluate their clinical significance on the pharmacokinetics of commonly used drugs. Physiologic changes that may affect drug pharmacokinetics include delayed gastric emptying, decreased intestinal motility, increased volume of distribution (an average increase of 8L), increased renal blood flow (by 25–50%), and increased glomerular filtration rate (by 50%) (Davidson, 1974; Dunnihoo, 1992; Parry, 1970). Pharmacokinetics parameters of nevirapine given as a single dose of 200 mg at the onset of labor were similar but more variable than in nonpregnant adults, possibly due to incomplete absorption associated with altered gastrointestinal function during labor (Mirochnick, 1998). Recent data suggests that NVP levels may be detectable as long as 3 weeks after a single dose given at onset of labor (Jourdain, 2004). Pregnancy does not change the pharmacokinetics of ZDV, 3TC, d4T, and ddI (Moodley, 1998; Schuman, 1990; Wang, 1999). Serum concentrations of the PIs that have been studied in pregnancy (indinavir [IDV], ritonavir [RTV], and saquinavir [SQV]) appear to be lower in pregnancy when given as single PIs (without boosting) (Perinatal Guidelines Working Group, 2004). SQV achieves adequate drug levels when boosted with RTV (Acosta, 2001) and nelfinavir (NFV) achieves adequate levels when given as 1250 mg twice daily (Bryson, 2002). A recent pharmacokinetic study including 4 women on an IDV-containing regimen with or without ritonavir (RTV) found a decrease in plasma concentrations of IDV during pregnancy with spontaneous increase postpartum in two women on IDV alone, consistent with metabolic induction of cytochrome P450 activity in pregnancy; this induction was offset by the concomitant use of RTV (Kosel, 2003). The clinical significance of these differences in pregnancy is unclear.

Table 14-1: Abbreviations	
Drug Abbreviations	
ABC: Abacavir (Ziagen)	INV: Invirase (saquinavir, HGC)
APV: Amprenavir (Agenerase)	IVIG: Intravenous immune globulin
ATV: Atazanavir (Reyataz)	LPV/r: Lopinavir/Ritonavir (Kaletra)
AZT: Zidovudine (Retrovir)	NFV: Nelfinavir (Viracept)
CBV: Combivir (AZT+3TC)	NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor
ddI: Didanosine (Videx)	NRTI: Nucleoside Reverse Transcriptase Inhibitor
d4T: Stavudine (Zerit)	NVP: Nevirapine (Viramune)
ddC: Zalcitabine (Hivid)	PI: Protease Inhibitor
DLV: Delavirdine (Rescriptor)	RBT: Rifabutin (Mycobutin)
EFV: Efavirenz (Sustiva)	RTV: Ritonavir (Norvir)
FTC: Emtricitabine (Emtriva)	SQV: Saquinavir (Invirase, Fortovase)
ENF: Enfuvirtide (Fuzeon, T-20)	3TC: Lamivudine (Epivir)
FTV: Fortovase (saquinavir, SGC)	TDF: Tenofovir (Viread)
fAPV: Fosamprenavir (Lexiva)	TMP-SMX: Trimethoprim sulfamethoxazole (Bactrim, etc.)
HU: Hydroxyurea	TZV: Trizivir (ABC+AZT+3TC)
IDV: Indinavir (Crixivan)	VZIG: Varicella zoster immune globulin
INH: Isoniazid	ZDV: Zidovudine (Retrovir)
Miscellaneous Abbreviations	
ART: Antiretroviral Therapy	pk: pharmacokinetcs
ARV: antiretroviral	po: by mouth
AUC: area under the concentration time curve (i.e. total drug exposure)	qd: daily
Cmax: peak serum concentration	qid: four times per day
Cmin: trough serum concentration	qm: monthly
EC: Enteric Coated	qod: every other day
HAART: Highly Active Antiretroviral Therapy	qw: every week
IV: Intravenous	soln: solution
IM: Intramuscular	tid: three times per day
VL: Viral Load	tiw: three times per week
bid: twice per day	TAM: thymidine analogue mutation
biw: twice per week	TDM: Therapeutic drug monitoring
hs: bedtime (hour of sleep)	ULN: upper limit of normal
mo: month	

Table 14-2: FDA Pregnancy Categories	
A	Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters).
B	Animal reproduction studies fail to demonstrate a risk to the fetus and adequate and well-controlled studies of pregnant women have not been conducted.
C	Safety in human pregnancy has not been determined, animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.
D	Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks.
X	Studies in animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

Table 14-3: Antiretrovirals

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
Abacavir (Ziagen®, ABC)	300 mg bid or 600 mg qd Available as 300 mg tablets; 10 mg/ml oral solution; Trizivir: ZDV 300 mg/ 3TC 150 mg/ ABC 300 mg Epzicom: 3TC 300 mg ABC 600 mg	Hypersensitivity reaction—fever, rash, fatigue, malaise, GI symptoms, and arthralgias (noted in 2–3% of patients). Mandatory and permanent discontinuation with hypersensitivity reaction. Deaths reported upon rechallenge; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	C	Rodent studies demonstrated placental passage, anasarca, skeletal malformation at 1000 mg/kg dose (35 times human therapeutic levels) during organogenesis. However rabbits receiving 8.5 times human therapeutic levels did not have fetal malformation.	Based on ex vivo data, placental transfer was 32–66% (Bawdon, 1998).	No data on use for prevention of perinatal transmission.
Zidovudine (Retrovir®, AZT, ZDV)	300 mg po bid, PACTG protocol dosing: Prenatal: 100 mg 5x per day (alternatively 300 mg bid) beginning at weeks 14–34; Intrapartum 2 mg/kg IV for first hour then 1 mg/kg IV until birth. Infant received 2 mg/kg po q 6 h for the first 6 wk of life beginning 8–12 hr after birth Available as 100 mg capsules; 300 mg tablets; 10 mg/ml IV solutions; 10 mg/mL oral solution; 300 mg Combivir (ZDV 300 mg/3TC 150 mg), Trizivir (ZDV 300 mg/3TC 150 mg/ABC 200 mg)	GI intolerance, malaise; headache (in 5–10%); bone marrow suppression (anemia and neutropenia seen more commonly with late stage AIDS); myalgia; myopathy; transaminase elevation; fingernail discoloration; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	C	Prolonged high dose ZDV exposure associated with nonmetastasizing vaginal squamous tumors in 13% of adult rodents, possibly due to concentration of unmetabolized ZDV in rodent urine (but not in humans). Transplacental carcinogenicity studies in mice with differing results: (1) doses 25-50 times human dose given in late gestation resulted in increase in lung, liver, female reproductive tract tumors in offspring exposed to highest dose level; (2) doses approximately 3 times human therapeutic exposure in pregnancy associated with no increase in tumor incidence in offspring. No evidence of fetal malformations or developmental toxicity with doses up to 500-600 mg/kg/day in pregnant rats, mice, rabbits	Human studies demonstrated 85% placental passage. No excess maternal toxicities or fetal defects noted with AZT during pregnancy. Long-term toxicity data (up to 6 yrs.) for infants exposed to AZT in utero and postpartum did not show an increased risk of tumors or abnormal developmental parameters.	The nucleoside analogue with the most extensive clinical data on safety and efficacy during pregnancy. When feasible all antiretroviral regimens for the prevention of perinatal transmission should include AZT.

Table 14-3: Antiretrovirals *(continued)*

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Stavudine (Zerit®, d4T)	Wt >60 kg dose: 40 mg po bid. Wt <60 kg dose: 30 mg po bid XR: wt >60kg 100 mg po qd. Wt <60 kg 75 mg po qd. Available as 15, 20, 30, 40 mg capsules; 1mg/mL for oral solution. New 100 mg extended release capsule (Zerit XR) Released early 2003.	Peripheral neuropathy (in 5–15% of patients); transaminase elevation (in 8% of patients); rare cases of lactic acidosis and severe hepatomegaly with steatosis, lipodystrophy; pancreatitis; rare cases of rapidly progressive ascending neuromuscular weakness	C	Studies in rhesus monkeys demonstrated 76% placental passage. Not teratogenic in rodents, but decreased sternal bone calcium. Carcinogenic studies not completed.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving combination of d4T and ddI as component of ARV therapy. No increase in birth defects noted in Antiretroviral Pregnancy Registry	Combination of d4T and ddI should be prescribed in pregnancy with caution, generally only when other NRTI drug combinations have failed or caused unacceptable toxicity/ side effects. Due to the antagonism between AZT and d4T, they should never be used together as a part of a HAART regimen.

Didanosine (Videx®, ddI)	Wt >60 kg dose: 200 mg po bid or 400 mg po qd (tabs); 400 mg po qd (EC); 250 mg po bid or 500 mg po qd (powder). Wt <60 kg dose: 125 mg po bid or 250 mg po qd (tabs); 250 mg po qd (EC); or 167 mg po bid or 334 mg po qd (powder). Available as 25, 50, 100, 150 200 mg chewable buffered tablets; 100, 167, 250 mg buffered powder for oral solution; 125, 200, 250, or 400 mg enteric coated capsules Take 1/2 hr. before or 2 hr. after meals.	GI intolerance (diarrhea, mouth sores), peripheral neuropathy in (5–12% of patients); pancreatitis (in 1–9% of patients with 6% of cases fatal); transaminase elevation; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	B	Not teratogenic or carcinogenic in rodent studies.	Placental passage approximately 50% PACTG 249 Phase I study showed that ddI was well tolerated by mother and fetus when started at weeks 26–36. (Wang, 1999).	GI side effects may limit use. The pediatric powder and EC tablet formulations are better tolerated (for every 4 g of ddI, mix with 200 cc of Maalox®).
Lamivudine, (Epivir®, 3TC)	150 mg po bid or 300 mg po qd Available as 150 mg, 300 mg tablets; 10 mg/mL oral solution; Combovir (ZDV 300 mg/3TC 150 mg); Trizivir (ZDV 300 mg/3TC 150 mg/ABC 300 mg); Epzicom: 3TC 300 mg/ABC 600 mg	Generally very well tolerated; occasional headache; nausea; diarrhea; abdominal pain; and insomnia; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	C	Not teratogenic or carcinogenic in rodent studies.	Human studies demonstrated 100% placental passage. No increase in birth defects noted in Antiretroviral Pregnancy Registry.	Associated with reduction in perinatal transmission when combined with ZDV (PETRA clinical trial) in later pregnancy or labor plus 1 wk post partum to mother and newborn (see chapter VII Reproduction).
Emtricitabine (Emtriva®, FTC)	200 mg po qd Available as 200 mg capsules Truvada: FTC 200 mg/ TDF 300 mg	Occasional headache, diarrhea, nausea, rash, generally of mild to moderate severity; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	B	No increase in fetal malformations in mice and rabbits. Unknown if placental passage.	No data Placental passage unkown	Similar to 3TC, FTC is active against hepatitis B. Resistance profile is identical to 3TC. Little experience in pregnancy. Not indicated for treatment of chronic HBV infection and safety and efficacy not established in patients with HBV/HIV coinfection.

Table 14-3: Antiretrovirals *(continued)*

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Zalcitabine, (Hivid®, Dideoxy-cytidine, ddC)	0.75 mg po tid Available as 0.375, 0.75 mg tablets.	High incidence of peripheral neuropathy (17–31% of patients); stomatitis, aphthous ulcers; hepatitis; rare cases of pancreatitis reported; rare cases of lactic acidosis and severe hepatomegaly with steatosis.	C	Studies in rhesus monkey demonstrated 30–50% placental passage. Carcinogenic in rodent studies resulting in thymic lymphoma. Teratogenic in rodent studies resulting in hydrocephalus at high dose (see Table 14-6 Drug-Drug Interactions)..	Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses.	ddC is not a component in currently recommended ARV regimens; should not be used with ddI or d4T due to additive peripheral neuropathy and other toxicity.
Nucleotide Reverse Transcriptase Inhibitors (N+RTIs)						
Tenofovir DF (Viread®, TDF)	300 mg po qd Available as 300 mg capsules. Tuvada: TDF 300 mg/FTC 200 mg	Generally well tolerated. Most common side effects: Headache, diarrhea, nausea and vomiting. Asymptomatic elevation of CPK and transaminase levels in 10%. Neutropenia in 7% and increased amylase in 6%. Rare reports of renal insufficiency. Rare lactic acidosis with hepatic steatosis	B	Gravid Rhesus monkeys study showed no fetal malformations, however reduction in body weight, insulin-like growth factor, and fetal bone porosiity was observed (25 times AUC with human therapeutic dosing) (Tarantal, 2004). Placental passage demonstrated in rats and monkeys.	No data Placental passage unknown	Should be taken with food. Data from monkeys support the use of tenofovir DF for post-exposure prophylaxis.
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)						
Efavirenz (Sustiva®, EFV)	600 mg po q hs Available as 50, 100, 200 mg capsules or 600 mg tablets Take on empty stomach.	Morbilliform rash in 15–27% of patients with 1–2% requiring discontinuation; one case of Stevens-Johnson syndrome reported; CNS effects (confusion, depersonalization, abnormal dreams) usually seen in up to 52% of patients and resolve in 2–4 wk; transaminase elevation in 2–3% of patients, hyperlipidemia.	D	Placental passage of 100% seen in cynomolgus monkeys, rats, and rabbits. Teratogenicity demonstrated in cynomolgus monkeys resulting in anencephaly, anophthalmia, microphthalmia. Increase in hepatocellular adenomas and carcinomas and pulmonary alveolar bronchiolar adenomas in female mice at exposures 1.7 times human therapeutic doses.	4 cases of central nervous system defects with 1st trimester exposure; birth defects observed in 3 of 88 live births with 1st trimester exposure and 0 of 11 births with exposure later in pregnancy (Antiretroviral Pregnancy Registry)	Efavirenz should be avoided during pregnancy (particularly early pregnancy) and in women trying to conceive or not using effective contraception.

Nevirapine (Viramune®, NVP)	200 mg po qd for 14 days then 200 mg po bid Available as 200 mg tablets or 50 mg/5mL oral suspension.	Rash in 17% of patients (7% discontinued due to rash, many patients require hospitalization) Stevens-Johnson syndrome reported; transaminase elevation; severe hepatitis; fever; nausea; headache. Women may be at increased risk of rash and liver toxicity, especially with CD4 >250 cells/mm^3 (Mazhude, 2002; Bersoff-Matdra, 2001; Stern, 2002)	C	Not teratogenic in rodent studies. No data on carcinogenicity.	Nevirapine-associated skin rash and hepatotoxicity (including hepatic failure) reported in pregnancy (Knudtson, 2003; Lyons, 2003; Langlet, 2000). These toxicities have not been reported in women or infants receiving HIVNET 012 two-dose regimen for prevention of perinatal transmission.	In HIVNET 012 administration of single-dose nevirapine given to mother during labor and to infants within 72 hr of delivery was compared with administration of AZT during labor and AZT for 7 days to infants. The 18 mo data showed that 26% of infants in the AZT and 16% of infants in the nevirapine arm were infected, a 41% reduction with nevirapine (Jackson, 2003). Monitor LFTs q 2wk x 1st 4 wk, then q mo x 4 mo; then q 1-3 mo. Use with caution as part of combination regimen in pregnant women for purpose of prevention of perinatal transmission. Contraindicated in women with CD4 counts > 250/mm^3.
Delavirdine (Rescriptor®, DLV)	400 mg po tid Available as 100 mg or 200 mg tablets	Rash in 18% of patients (4.3% discontinued due to rash, usually does not require discontinuation unless mucous membrane involvement); rare erythema multiforme or Stevens Johnson syndrome; headache; increased transaminase levels (see Table 14-6 Drug-Drug Interactions)	C	Placental passage of 4–15% in late-term rodent studies. Teratogenic in rodent studies resulting in ventricular septal defects. Maternal toxicity, embryotoxicity and decreased pup survival seen with doses five times the human dose. No data on carcinogenicity.	Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses.	Due to the availability of more potent NNRTIs (e.g., nevirapine) use of delavirdine is generally not recommended.

Table 14-3: Antiretrovirals *(continued)*

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Protease Inhibitors (PIs)						
Lopinavir/ Ritonavir (LPV/r) (Kaletra®)	Lopinavir 400 mg/ritonavir 100 mg (3 capsules or 5 mL) twice daily with food Available as 133.33 mg lopinavir/33.3 mg ritonavir capsules; 80 mg lopinavir/20 mg ritonavir per mL oral solution.	Diarrhea in 13.8–23.8% of patients; nausea, vomiting, abdominal pain, asthenia, headache and rash reported. Class adverse events such as hyperlipidemia, fat redistribution and hyperglycemia are possible.	C	No treatment-related malformations in animal studies. No embryonic or fetal development toxicities seen in rabbits. Delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses.	No human data available. Preliminary data indicate minimal placental passage of ritonavir; unknown for lopinavir	
Ritonavir (Norvir®, RTV)	600 mg po bid (when used as sole PI), but Ritonavir now used at lower doses with other PIs as pharmacologic enhancer or booster. (See Table 14-6) Available as 100 mg capsules; 600 mg/7.5 mL oral solution. Take with food, if possible (may improve tolerability)	Severe GI intolerance (nausea, vomiting, diarrhea; abdominal pain, common with 600 mg bid dosing); taste perversion; asthenia; circumoral and peripheral paresthesias; pancreatitis; lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation (increased incidence seen with hepatitis B and C coinfection); elevated CPK and uric acid.	B	Not teratogenic but slight increase in cryptorchidism reported in rodent studies. Increase in liver adenomas and carcinomas in male mice (4 times human therapeutic dose). No carcinogenic effects in rats.	Minimal transplacental passage.	Use may be limited by GI intolerance at full dose. Better tolerated when used as booster with another PI (RTV 100 mg bid and 2nd PI).
Saquinavir, SQV (Invirase®, INV, hard gel capsules; Fortovase®, FTV soft gel capsules)	INV or FTV 400 mg po bid with ritonavir 400 mg po bid. Invirase not recommended as sole PI; Fortovase 1200 mg po tid when used alone (see Table 14-6) Available as: Invirase 200 mg capsules; Invirase 500 mg tablets; Fortovase 200 mg capsules; take Fortovase with large meal.	GI intolerance (nausea, diarrhea, abdominal pain); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation.	B	Placental passage in rat and rabbit is minimal. No teratogenicity reported in rodent studies. No data on carcinogenicity.	Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. Minimal transplacental passage.	Invirase 1,000 mg RTV/ 100 mg bid is the preferred dosing regimen due to better pharmacokinetics and tolerance.

Indinavir, IDV (Crixivan®)	800 mg po tid (see Table 14-6) 400/400 mg or 800/100 mg or 800/200 mg IDV/RTV bid + EFV 600 mg Available as 200, 333, 400 mg capsules. Take 1 hr before or 2 hr after meals; may take with low fat meals	Nephrolithiasis +/- hematuria in 5–15% of patients (48 oz of fluid recommended to decrease incidence); indirect hyperbilirubinemia (≥ 2.5 mg/dL in 10–15% of patients); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation.	C	Placental passage is significant in rats, but low in rabbits. Not teratogenic in rodent studies (but extra ribs have been reported). Incidence of hyperbilirubinemia in neonatal Rhesus monkeys increased with neonatal but not in utero exposure. No data on carcinogenicity.	Insufficient information to provide reliable and definitive conclusions regarding the risk to pregnant women and their developing fetuses. Minimal transplacental passage.	Due to theoretical concerns of hyperbilirubinemia and nephrolithiasis in newborns, indinavir should be avoided during late pregnancy.
Nelfinavir, NFV (Viracept®)	750 mg po tid or 1250 mg po bid Available as 250 mg tablets; 625 mg tablets; FDA-approved 50 mg/g oral powder. Take with increased fat meal	Diarrhea (treatable with Imodium or pancrealipase); lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation.	B	Not teratogenic in rodent studies. No data on carcinogenicity.	No increase in birth defects noted in Antiretroviral Pregnancy Registry. Minimal transplacental passage.	The combination of AZT, 3TC, and nelfinavir is widely used and has been well tolerated during pregnancy.
Fosamprenavir, fos APV (Lexiva®) (prodrug of amprenavir)	1400 mg po bid with RTV: 1400 mg Lexiva/200 mg RTV po qd (not recommended for PI-experienced patients) or 700 mg Lexiva/100 mg RTV po bid Available as 700 mg tablets	GI intolerance most common (nausea, vomiting, diarrhea); headache; rash (in 19% of patients), usually mild-moderate but Stevens Johnson syndrome reported; lipodystrophy syndrome; hyperglycemia; increased triglycerides and/or cholesterol; transaminase elevation.	C	Increased abortions in rabbits, reduction in pup survival and body weight in rats. Placental passage unknown	No data	Use with caution in patient with sulfa allergy

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Table 14-3: Antiretrovirals *(continued)*

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Amprenavir, APV (Agenerase®)	1400 mg bid (oral solution); <50 kg: APV 20 mg/kg bid (max 2800 mg/day oral solution). APV and RTV oral solutions should not be co-administered due to competition of metabolic pathway of the two vehicles. Available as 15 mg/mL oral solution; also as 50 mg capsules, but capsules and solution NOT interchangeable on mg-per-mg basis. Capsules rarely used because of high pill burden—APV largely replaced by fAPV.	GI intolerance most common (nausea, vomiting, diarrhea); rash (in 20–27% of patients), Stevens Johnson syndrome (in approximately 1%); paresthesias; headache; lipodystrophy syndrome; hyperlipidemia; transaminase elevation	C	Increased incidence benign and malignant liver tumors in male rodents at exposures 2- to 4-fold higher than human dosing. Increased abortions in rabbits and increased incidence of deficient bone ossification in rabbits and rats at exposures lower than recommended human dosing. Reduced body weight in rodent offspring at exposures 2-fold higher than human dosing.	Placental passage unknown. No data in use of APV in pregnant women	Use of oral solution contraindicated in pregnant women, patients with renal or hepatic failure, or those treated with disulfiram or metronidazole because of inability to adequately metabolize propylene glycol base. Use with caution in patients with sulfa allergy.
Atazanavir, ATV (Reyataz®)	400 mg qd with food. With RTV: 300 mg qd/RTV 100 mg qd Available as 100 mg, 150 mg, 200 mg capsules.	Common: Reversible benign hyperbilirubinemia (grade 3-4 occurring in 35–47% of patients), jaundice, and scleral icterus. Occ: nausea, vomiting, abdominal pain, lipodystrophy, rash, headache, and mild transaminase elevation minimal impact on serum lipids.	B	No teratogenic effects in rats or rabbits	No data Placental passage unknown	Avoid near term due to the potential exacerbation of physiologic hyperbilirubinemia in the neonate.

Fusion Inhibitors						
Enfuvirtide (Fuzeon®, T-20)	90 mg (1ml) SQ q12h into upper arm, anterior thigh or abdomen with each injection given at a site different from the preceding injection site Each single-use vial contains 108 mg of enfuvirtide to be reconstituted with 1.1 mL of sterile water for injection with delivery of approx. 90 mg/1mL	Common ADR: local site reaction (grade 3 or 4) including pain (9%), erythema (32%), pruritus (4%), induration (57%), and nodules or cysts (26%) (with 3% requiring d/c). Occ: Bacterial pneumonia (reported in 4.68 events vs. 0.61 events per 100 pts-years. Hypersensitivity reaction (<1%): symptoms may include rash, fever, nausea, vomiting, chills, hypotension, elevated transaminases – may recur on rechallenge.	B	Not teratogenic in animal studies	No data Placental passage unknown	A clear advantage of enfuvirtide is the lack of cross-resistance with currently available antiretrovirals, however, as with other antiretrovirals and as seen in clinical trials, salvage therapy with enfuvirtide is only as good as the background regimen with which it is combined.

Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Trimethoprim-sulfamethoxazole, TMP-SMX (Bactrim®, Septra®, Cotrim®, Sulfatrim®)	PCP prophylaxis: 1 DS po qd, 1 SS po qd, 1 DS po tiw PCP treatment: 5 mg/kg (based on the trimethoprim component) po or IV q 8 h	Fever; leukopenia; rash and/or GI intolerance (in 25–50% of HIV-infected persons, most patients tolerate readministration of lower dose after 2 wk of discontinuation); megaloblastic anemia; neutropenia; thrombocytopenia. Hematologic toxicity increased with folate depletion and high doses-treat with leucovorin 3–15 mg qd x 3 days. Reversible hyperkalemia (with high doses); photosensitivity; renal failure; hemolytic anemia with G6PD deficiency; hepatitis including cholestatic jaundice; thrush; erythema multiforme; Stevens Johnson syndrome.	C	Cleft palate has been observed in some animals.	In a surveillance study of Michigan Medicaid recipients, 2296 exposures to trimethoprim/ sulfamethoxazole in the first trimester resulted in a 5.5% incidence of birth defects. This incidence suggests an association between the drug and congenital defects (cardiovascular); however, other factors such as mother's disease, concurrent drug use, and chance may be involved (Briggs, 1998).	Most authorities consider sulfonamides safe in pregnancy. Theoretical risk of kernicterus in the neonate if administered near term.
Azithromycin (Zithromax®)	MAC prophylaxis: 1200 mg po q week; MAC treatment: 500 mg or 600 mg po qd (in combination with ethambutol +/- rifabutin)	GI intolerance (4%); diarrhea; nausea; abdominal pain; vaginitis; reversible hearing loss (more common with 500 mg x 30–90 days); increased transaminases	B	Animal studies show no harm to the fetus.	Azithromycin and erythromycin were compared for the treatment of chlamydia in pregnancy. The authors recommended using azithromycin due to efficacy and better tolerability. Effect on the fetus was not evaluated (Adair, 1998).	The benefit of azithromycin administration for MAC prophylaxis or treatment outweighs potential risk of congenital malformations.

Clarithromycin (Biaxin®)	MAC prophylaxis: 500 mg po bid MAC treatment: 500 mg po bid (in combination with ethambutol and/or rifabutin.)	GI intolerance (4%); diarrhea; headache; reversible dose-related hearing loss; taste disturbances	C	Studies in monkeys show growth retardation, cleft palate, and embryonic loss	The Teratogen Information Service in Philadelphia reported that the outcome of 34 first or second trimester exposures were similar to those expected in the nonexposed population. The 122 pregnancies exposed to clarithromycin in the 1st trimester did not have increased major or minor malformations when compared with matched controls. Incidence of spontaneous abortion was higher in clarithromycin-exposed group compared with controls (14% vs 7%) (p=.04) (Schick, 1996).	Should be used with caution during pregnancy because of teratogenicity in animals.
Pyrazinamide	15 mg/kg/day for latent TB (2.0 g max); 20–25 mg/kg/day for active TB (2.0 g max); 30–50 mg/kg 2–3 times/wk (3.0–4.0 g max) for intermittent therapy	Nongouty polyarthralgia; asymptomatic hyperuricemia; hepatitis (dose related, frequency not increased when given with INH or rifampin, rarely serious); GI intolerance; gout	C	No animal data available.	No human data available.	Due to insufficient data pyrazinamide should generally be avoided in pregnancy. INH, rifampin, and ethambutol are recommended as first-line agents for treatment of drug-sensitive TB during pregnancy.

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Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients *(continued)*

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Isoniazid (INH, Tubizid®, Nydrazid®)	300 mg po qd	Age-related hepatitis: <20 yr old-nil/35 yr old-6%/45 yr old-11%/ 55 yr old-18%; drug should be discontinued if transaminase levels are >3–5 x normal limits; allergic reactions; fever; peripheral neuropathy (especially with preexisting alcoholism, diabetes, pregnancy, malnutrition); glossitis	C	Animal studies show embryocidal effect, but not teratogenic.	Retrospective analysis of more than 4900 exposures to INH did not show increased fetal malformations. (Snider, 1980).	The American Academy of Pediatrics and the American Thoracic Society recommend that pregnant women with a positive PPD should receive INH if HIV-positive, have had recent TB contact, or have an X-ray showing old TB; start after 1st trimester if possible.
Rifampin (Rifadin)	10 mg/kg/day (600 mg/day max) for TB prophylaxis or active TB; 600 mg 2–3x/wk with DOT	Orange discoloration of urine, tears, sweat; hepatitis—usually cholestatic changes during first month (frequency not increased when given with INH); jaundice (usually reversible with dose reduction and/or continued use); GI intolerance; hypersensitivity reactions; flu-like syndrome with intermittent use characterized by dyspnea, wheezing	C	Animal data show congenital malformations—cleft palate, spina bifida, and embryotoxicity.	Several reviews have evaluated treatment of TB in pregnancy. All concluded that rifampin was not teratogenic and recommended use of the drug with INH and ethambutol if necessary (American Thoracic Society, 1986).	The American Thoracic Society recommends rifampin in combination with INH and ethambutol if treatment for drug-sensitive TB is needed during pregnancy. Many drug interactions. Because of potential increased risk of hemorrhagic disease in neonates, prophylactic vitamin K 10 mg should be administered to the neonate.
Rifabutin (Mycobutin®)	300 mg po qd (dose is decreased to 150 mg qd or 300 mg 3x/wk when used with indinavir, nelfinavir, amprenavir; 150 qod with RTV or LPV/r; 450 mg qd or 600 mg 3x/wk with EFV; 300 mg 3x/wk with NVP; 150 mg 3x/wk with SQV/RTV. Not recommended with DLV or SQV alone (Fortovase).	Orange discoloration of urine, tears, sweat; uveitis with eye pain, photophobia, redness and blurred vision—usually seen with high doses (600 mg/day or concurrent use of fluconazole or clarithromycin); hepatitis; GI intolerance; allergic reactions	B	Animal data showed skeletal abnormalities.	No human data available.	Experience with rifabutin in pregnancy is limited. Many drug interactions with dose modifications recommended. (See Drug Interactions Table 14-6)

Ethambutol (Myambutol®)	15-25 mg/kg po qd (1.6 g max); 35-50 mg/kg 2x/wk (4.0 g max); 25-30 mg/kg 3x/wk (2.4 g max)	Optic neuritis (decreased acuity, reduced color discrimination, constricted fields, scotomata—dose related and infrequent with 15 mg/kg); GI intolerance; confusion; precipitation of acute gout.	C	Teratogenic in animal studies.	No congenital defects have been reported. In 38 patients exposed to ethambutol during pregnancy, no increased risk of birth defects observed (including embryonic optic nerve toxicity). (Brobowitz, 1974).	The CDC considers ethambutol safe in pregnancy.
Atovaquone (Mepron®)	750 mg po bid for PCP treatment or prophylaxis; 1500 mg po qd for PCP prophylaxis; 1500 mg po bid for toxoplasmosis treatment (with pyrimethamine or sulfadiazine)	GI intolerance (nausea, vomiting, diarrhea); headache; rash. 7–9% required discontinuation due to side effects	C	Not teratogenic in rat studies. Maternal and fetal toxicities (decreased fetal weight, early fetal resorption and post-implantation fetal loss) reported in rabbits.	No human data available.	Alternative regimen for PCP prophylaxis and treatment due to high cost, poor GI tolerance, and lack of safety data in pregnancy. Preferred regimens for PCP prophylaxis and treatment include trimethoprim/sulfamethoxazole and dapsone. Third-line treatment and prophylaxis for toxoplasmosis
Hydroxyurea (Hydrea®, Droxia®)	500 mg po bid	Dose-dependent leukopenia, anemia and thrombocytopenia; GI intolerance (N/V/D, constipation), stomatitis; rash; alopecia	D	Hydroxyurea is teratogenic in several animal studies; anomalies include nervous system, palate, skeleton, neural tube and cardiac defects.	Eight case reports of hydroxyurea exposure during pregnancy did not demonstrate teratogenicity, however, the data are too limited to draw any conclusions (Briggs, 1998).	Contraindicated due to high incidence of teratogenicity in animal studies and limited human experience. No longer recommended as part of HAART.

Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients *(continued)*

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Amphotericin B (Fungizone®)	0.5–1.2 mg/kg IV qd depending on specific condition. 0.7 mg/kg for cryptococcal meningitis	40–50% incidence of fever and chills; 30–40% incidence of renal tubular acidosis—dose dependent and reversible in absence of prior renal damage and dose <3 g (reduced with hydration and sodium loading); 20% incidence of hypokalemia; hypomagnesemia; anemia; phlebitis and pain at infusion site; hypotension; nausea; vomiting; metallic taste; headache	B	Animal studies demonstrated amphotericin to be harmless in pregnancy.	The Collaborative Perinatal Project identified 9 1st trimester exposures to amphotericin and found no adverse fetal effect (Briggs, 1998).	Can be used in pregnancy for the treatment of serious fungal infections.
Flucytosine (Ancobon®)	25 mg/kg q 6 h (monitor levels – goal 50–100 mcg/mL at steady state)	GI intolerance (N/V/D); marrow suppression with leukopenia or thrombocytopenia (dose related with renal failure, serum concentration >100 mg/mL or concurrent amphotericin); confusion; rash; hepatitis (dose related); enterocolitis; headache; photosensitivity reaction; peripheral neuropathy	C	Teratogenicity reported in animal studies.	Three case reports of second and third trimester exposure resulted in no defects in the newborns, however, no conclusion can be drawn (Briggs, 1998).	4% of administered dose converts to 5FU in the fungal organism. 5FU has been associated with congenital malformations. Use with amphotericin for the treatment of cryptococcal meningitis may reduce relapse rates but does not reduce mortality or speed recovery (van der Horst, 1997). Use in pregnancy only if benefits outweigh potential risks.
Nystatin	500,000 units 5x/day (oral thrush)	GI intolerance (N/V/D)	B	No animal data	489 first trimester exposures to nystatin were observed in a Michigan Medicaid recipients surveillance study. No association between nystatin and congenital defects was observed (Briggs, 1998).	Due to low systemic absorption nystatin may be used in the management of thrush during pregnancy.

Clotrimazole	10 mg troches 5x/day (oral thrush) 100 mg intravaginal tablets bid x 3 day or qd x 7 day. 1 applicator (5g) vaginal cream q hs x 7–14 day (Candida vaginitis)	GI intolerance (N/V); transaminase elevation. Topical treatment (rare): burning, erythema, pruritus	C	Embryotoxic in rats and mice. Not teratogenic in mice, rabbits, and rats.	2624 exposures to clotrimazole (vaginal use) were observed in the first trimester in a Michigan Medicaid recipients surveillance study. No association between clotrimazole and congenital defects were observed (Briggs,1998)	Due to minimal systemic absorption nystatin is preferred over clotrimazole in the management of thrush during pregnancy. Vaginal use in 1st trimester should be on risk/benefit basis
Fluconazole (Diflucan®)	C. esophagitis: 200–800 mg/day. 150 mg po x 1 for Candida vaginitis; 150 mg po q wk for multiple recurrences Cryptococcal infection: 200–400 mg/day.	Dose-related GI intolerance including bloating, nausea, vomiting, pain, anorexia, weight loss (8–11% with dose <400 mg/day, 30% with dose >400 mg/day); reversible alopecia in 10–20% of patients receiving 400 mg/day for 3 months; transaminase elevation to >8 x normal; rare cases of fatal hepatitis and Stevens Johnson syndrome	C	Teratogenic in animal studies.	Craniofacial, limb and cardiac defects have been reported in 4 infants with 1st trimester exposure to high-dose fluconazole (Pursley, 1996; Aleck, 1997). Anomalies do not appear to be increased among infants born after exposure to single dose fluconazole in the 1st trimester (Mastroiacovo, 1996; Sorenson, 1999).	Contraindicated in the 1st trimester due to potential for teratogenicity. Use topical agents in treatment of C. vaginitis in pregnancy.
Itraconazole (Sporanox®)	100–400 mg po qd, depending on specific condition	Headache; GI intolerance—nausea (10%) and vomiting; rash (8%); hypokalemia reported with high doses (600 mg per day); adrenal insufficiency; impotence; gynecomastia; leg edema; transaminase elevation, rare cases of fatal hepatitis	C	Teratogenic in rats and mice (encephaloceles, macroglossia, and skeletal malformation).	FDA has received 14 case reports of malformations following use of itraconazole, 4 were limb defects. However in another report of 80 exposures to single-dose itraconazole or fluconazole no malformations were reported (Rosa, 1996).	Contraindicated in the 1st trimester due to potential for teratogenicity.

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Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients *(continued)*

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Voriconazole (Vfend®)	IV: 6 mg/kg IV q12h x 2 doses (load), then 3-4 mg/kg IV q12h infused over 1-2 hours. PO: (>40 kg) 200 mg po tid x 1 da (load), then 200-300 mg po bid; (<40 kg) 100 mg po q12h, may be increased to 150 mg po q12h (administer on an empty stomach, avoid high fat food!)	Common: Visual disturbances ("abnormal vision" described as blurriness, color changes, and enhanced vision) seen in 20.6% of pts but less than <1% required discontinuation. Occ: Inc.LFTs (13%) and alk phos required d/c in 4–8%. hallucination (4.3%), rash (6%), nausea/vomiting.	D	Teratogenic in animal studies	No data	Avoid in pregnancy. Do not use with EFV or RTV (400 mg bid)
Pyrimethamine (Daraprim®)	Acute treatment of toxoplasmosis: Pyrimethamine 100–200 mg loading dose, then 50–75 mg po qd, in combination with sulfadiazine 4–6 g po per day in four divided doses for at least 6 wk, plus leucovorin 10–20 mg po qd; Toxoplasmosis maintenance dose: After acute treatment, pyrimethamine 25–50 mg po qd, plus sulfadiazine 2–4 g po per day in four divided doses, plus leucovorin 10–25 mg po qd Toxoplasmosis prophylaxis: Pyrimethamine 50–75 mg po q wk, in combination with dapsone, plus leucovorin 25 mg po q wk	Folic acid deficiency with megaloblastic anemia and pancytopenia (dose-related and reversed with leucovorin); allergic reactions; GI intolerance (nausea, anorexia, vomiting)	C	Teratogenic in animal studies.	No adverse fetal effects were reported in two reviews of treatment of toxoplasmosis in pregnancy (Matsui, 1994; Wong, 1994).	If pyrimethamine is used during pregnancy, concomitant leucovorin (folinic acid) supplementation (25 mg/day) is recommended, especially during the 1st trimester, to prevent hematologic toxicity.

Sulfadiazine	Acute treatment of toxoplasmosis: Sulfadiazine 4–6 g po per day in four divided doses, in combination with pyrimethamine 50–75 mg po qd for at least 6 wk, plus leucovorin 10–20 mg po qd Toxoplasmosis maintenance dose: After acute treatment, sulfadiazine 2–4 g po qd in four divided doses, plus-pyrimethamine 25–50 mg po qd, plus leucovorin 10–25 mg po qd	Allergic reactions—rash, pruritus; crystalluria with renal damage, urolithiasis and oliguria; GI intolerance; photosensitivity; hepatitis; fever; periarteritis nodosum, Stevens Johnson syndrome; serum sickness	C	At high doses, animals developed cleft palate and bone abnormalities.	Extensive use in humans without complication except one case of agranulocytosis that was possibly associated (Briggs, 1998).	Theoretical risk of kernicterus in the neonate if administered near term.
Aerosolized pentamidine	PCP prophylaxis—300 mg nebulized q mo	Asthma reaction reported in 2–5% of patients; cough seen in 30% of patients	C	Systemic pentamidine is embryotoxic but not teratogenic in rats and rabbits	Aerosolized pentamidine given to 15 women during the 2nd and 3rd trimesters did not alter pregnancy outcome or cause fetal harm (Nanda, 1992).	CDC and manufacturer advise against the use of pentamidine during pregnancy due to the lack of data; however, aerosolized pentamidine may be considered safe due to minimal systemic absorption (Kaplan, 1995). Concerns have been raised about adequate drug distribution during pregnancy due to restrictive changes with an enlarged uterus.

Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients *(continued)*

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Intravenous pentamidine	PCP treatment—3–4 mg/kg IV qd	Nephrotoxicity—seen in 25% (usually reversible with discontinuation); hypotension (administer IV over 60 min to decrease risk); hypoglycemia—seen in 5–10% (usually occurs after 5 days of treatment including past treatment, may last days or weeks) may lead to insulin—dependent diabetes; marrow suppression (leukopenia; thrombocytopenia); GI intolerance with nausea, vomiting, abdominal pain, anorexia, and bad taste; transaminase elevation; pancreatitis; toxic epidermal necrolysis; fever	C	Not teratogenic in rat and rabbit studies, however, has been shown to be embryocidal.	Spontaneous abortion reported, but causal relationship has not been established.	Use in pregnancy only if benefits outweigh potential risks. Due to the toxicity profile Bactrim or clindamycin/primaquine is preferred
Primaquine	15–30 mg (base) po qd (in combination with clindamycin for the treatment of PCP)	Hemolytic anemia (G6PD deficiency); methemoglobinemia; GI intolerance; neutropenia	C	No animal studies available.	No human data available.	Theoretical concern is hemolytic anemia in G6PD-deficient fetus. Should screen for G6PD deficiency in mother before use.
Albendazole (Albenza®)	400 mg po bid x 3 weeks for microsporidiosis	Diarrhea; abdominal pain; transaminase elevation; hepatotoxicity; reversible pancytopenia and neutropenia	C	Teratogenic and embryotoxic in rodent and rabbit studies.	No human data available.	Contraindicated in pregnancy.

Dapsone	100 mg po qd (PCP prophylaxis). 100 mg po qd plus trimethoprim x 3 wk (PCP treatment). 50 mg po qd or 200 mg q wk plus leucovorin and pyrimethamine (PCP + toxoplasmosis prophylaxis).	Rash; blood dyscrasias including methemoglobinemia and sulfhemoglobinemia and hemolytic anemia (with or without G6PD deficiency); nephrotic syndrome; fever, nausea, anorexia; blurred vision; photosensitivity; tinnitis; insomnia; irritability; headache (transient); rare "sulfone syndrome"—fever, exfoliative dermatitis, jaundice, adenopathy; methemoglobinemia and anemia	C	No animal teratogenicity studies conducted. Carcinogenic risk in rats.	No adverse effects reported. (Luzzi, 1993).	Dapsone has been used extensively in the treatment of malaria and for chemoprophylaxis of leprosy without producing major fetotoxicity or causing birth defects. Recommend screening for G6PD deficiency in mother before use.
Acyclovir (Zovirax®)	5–10 mg/kg IV q 8 h; 200–800 mg po x 3–5 times per day	GI intolerance (nausea and vomiting; diarrhea); renal toxicity (especially with rapid IV infusion); dizziness; transaminase elevation; itching, headache. Toxicities are infrequent.	C	Not teratogenic but potential to cause chromosomal damage at high doses.	Birth defects reported in 23 of 1002 exposures; however, this was not statistically different from the expected rate. (Glaxo Wellcome, 1996)	Acyclovir is 1st choice for therapy of HSV infections in pregnancy and should be used for VZV if parenteral therapy indicated.
Valacyclovir (Valtrex®)	1000 mg po tid (for zoster); 500 mg po bid (for recurrent HSV); 500–1000 mg po qd (for HSV suppression)	GI intolerance—nausea, vomiting, diarrhea; headache; constipation	B	Not teratogenic in animal studies.	No human data available but likely to be similar to acyclovir.	Recommendation similar to acyclovir since valacyclovir is converted to acyclovir. Valacyclovir is preferred treatment for chicken pox in pregnancy.
Famciclovir (Famvir®)	500 mg po q 8 h (for zoster); 125–250 mg q 12 h (recurrent HSV and HSV suppression)	Headache; nausea; fatigue	B	Carcinogenic, but not embryotoxic or teratogenic in animal studies.	No human data.	Until more data are available, acyclovir is 1st choice in pregnancy.

Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients *(continued)*

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Ganciclovir (Cytovene®)	CMV retinitis Induction: 5 mg/kg IV q12h x 2 wk then Maintenance: 5 mg/kg IV qd	Neutropenia (ANC <500 in 15–20%; usually early in treatment and responds within 3–7 days to drug holiday or to G-CSF); thrombocytopenia (platelet count <20,000 in 10%, reversible). Monitor CBC 2–3 times/wk and discontinue if ANC <500-750 or platelet count <25,000; anemia; fever; rash; CNS—headache, seizures, confusion, changes in mental status; abnormal liver function tests (2–3%)	C	Teratogenic (in concentrations comparable to those achieved in humans) and embryotoxic: cleft palate, anophthalmia, hydrocephalus, aplastic kidney and pancreas (rabbits); growth retardation.	No human data.	Based on limited data and weighing toxicity of the various drugs, ganciclovir is 1st choice for treatment during pregnancy; for retinal disease intraocular implants or intravitreous injections should be considered to limit fetal exposure to systemically administered drugs. Monitor fetus with fetal movement counts in 3rd trimester and periodic ultrasound after 20 wk gestation for evidence of significant anemia, manifest as hydrops fetalis. Evaluate newborn for bone marrow suppression.
Valganciclovir (Valcyte®)	Induction: 900 mg po bid w/ food x 3 weeks; Maintenance: 900 mg po qd.	Diarrhea; nausea; fever; bone marrow suppression; LFT elevation.	C	Teratogenic (in concentrations comparable to those achieved in humans) and embryotoxic: cleft palate, anophthalmia, hydrocephalus, aplastic kidney and pancreas (rabbits); growth retardation.	No data	Concerns expected to be same as with ganciclovir. Monitor fetus with fetal movement counts in 3rd trimester and periodic ultrasounds after 20 wk gestation for evidence of significant anemia, manifest as hydrop fetalis. Evaluate newborn for bone marrow suppression.

Cidofovir (Vistide®)	CMV retinitis Induction: 5 mg/kg q week x 2 weeks then q2 weeks (give concurrently with probenecid and hydration). Probenecid Regimen: 2 g given 3 hours prior to cidofovir and 1 g given at 2 and 8 hours after infusion (total 4 g); >1L normal saline 1 or 2 hrs immediately before cidofovir infusion.	Nephropathy—dose dependent, reduced with hydration and probenecid. (Side effect of probenecid includes chills, fever, headache, rash and nausea in 30–50% of patients); uveitis; GI intolerance; neutropenia; metabolic acidosis	C	Embryotoxic and teratogenic (meningomyelocele, skeletal abnormalties) in rats and rabbits,	No human data available.	Ganciclovir is 1st choice for treatment during pregnancy. Use only if benefits appear to outweigh potential risks.
Foscarnet (Foscavir®)	CMV retinitis Induction: 60 mg/kg IV q 8 hr or 90 mg/kg IV q12hr x 14 day. Maintenance: 90–120 mg/kg IV qd. Acyclovir-resistant HSV or VZV: 40 mg/kg IV q 8 h or 60 mg/kg IV q 12 h x 3 wk	Renal failure (usually reversible; 30% get serum creatine (Cr) >2 mg/dL; (monitor Cr 1–3 times/ wk and discontinue if Cr >2.9 mg/dL); mineral and electrolyte changes—reduced magnesium, phosphorus, ionized calcium, potassium (monitor serum electrolytes 1–2 times/wk and monitor for symptoms of paresthesias); seizures (10%); fever; GI intolerance; anemia; genital ulceration; neuropathy	C	Skeletal malformation or variation in animal studies.	No human data available.	Due to high incidence of nephrotoxicity, monitoring of aminiotic fluid volume by ultrasound weekly after 20 wk gestation to detect oligohydramnios is recommended. Electrolyte and renal function should be evaluated in neonate if therapy given near delivery.
Ribavirin (Rebetrol®)	Treatment of hepatitis C (in combination with interferon): <75 kg—400 mg q am and 600 mg q pm. >75 kg—600 mg bid	Hemolytic anemia (mean hgb decrease is 3 g/dL); leukopenia; hyperbilirubinemia; increased uric acid.	X	Ribavirin has been demonstrated teratogenic in low doses in multiple animal species (limb abnormalties, craniofacial defects, exencephaly, anophthalmia) in rodents (and in all animals tested), but not in primates when given during the first trimester.	No data available.	Use of ribavirin contraindicated during pregnancy and in male partners of pregnant women.

Table 14-4: Commonly Used Antimicrobials for the Treatment and Prevention of Opportunistic Infections in HIV-Infected Patients *(continued)*

Drug Name	*Dosing*	*Adverse Effects*	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Interferon (Roferon®, Intron®)	Treatment of hepatitis C (in combination with ribavirin): 3 million units 3 x/week. IM or SQ. Also used at higher doses for treatment of hepatitis B and Kaposi's sarcoma	Flu-like syndrome; GI intolerance (N/V/D, anorexia); CNS toxicity (delirium; obtundation and depression); neutropenia, anemia, thrombocytopenia, increased transaminase; rash; alopecia; proteinuria	C	Abortifacient in rhesus monkeys when given 20–500 times the human dose.	Limited case reports of interferon exposure during pregnancy do not suggest an association with birth defects; however, data are too limited to draw a conclusion.	Since goal of treatment of HCV is to prevent long-term sequelae, treatment in pregnancy rarely indicated and generally not recommended.
Peg-interferon (Peg-Intron® [alfa-2B]/ Pegasys® [alfa-2A])	Peg-Intron: 1mcg/kg SC q week (with ribavirin). [Dose reduction to 0.5 mcg/kg recommended for ANC<750 or plt<50k and D/C if ANC<500 or plt <25K]. Pegasys: 180mcg SC qweek (with ribavirin)[dose reduce with heme toxicity]. Peg-inteferon alfa-2A or alfa-2B and ribavirin is treatment of choice for HCV.	Common: Flu-like symptoms, headache, dizziness, fatigue, fever, rigor, injection site inflammation, depression (29%), insomnia, alopecia, GI (abd. pain, anorexia, N/V/D.) Occasional: Thrombocytopenia, neutropenia, hypo and hyperthyroidism, LFTs elevation.	C	Abortifacient in rhesus monkeys.	No data	Since goal of treatment of HCV is to prevent long-term sequelae, treatment in pregnancy rarely indicated and generally not recommended.
Caspofungin	70 mg IV load on day 1, then 50 mg IV qd (infuse over 1 hour)	Generally well tolerated. Histamine-mediated symptoms including rash, facial swelling, pruritus and sensation of warmth have been reported. Rare: Fever, phlebitis, nausea, vomiting, headache, eosinophilia, proteinuria, increased alk phos and hypokalemia	C	Animal data with exposure similar to a 70 mg dose in human resulted in incomplete ossification of skull, torso, cervical ribs and talus/calcaneous.	No data	Avoid in pregnancy until more data becomes available.

Thalidomide (Thalomid®)	50–200 mg/da po—used for treatment of aphthous ulcers, wasting	Sedations, rash, neuropathy, constipation, neutropenia found in up to 50%	X	–	High potential for birth defects, including absent or abnormal limbs; cleft lip; absent ears; heart, renal or genital abnormalties. Single dose can be associated with teratogenic effects.	Contraindicated in pregnancy and in women at risk for pregnancy (not using effective contraception or trying to conceive).
ANC, absolute neutrophil count: CBC, complete blood count; CMV, cytomegalovirus; CNS, central nervous system; G-CSF, granulocyte-colony stimulating factor; G6PD, glucose-6-phosphate dehydrogenase; GI, gastronintestinal; INH, isoniazid; MAC, *Mycobacterium avium* complex; N/V/D, nausea/vomiting, diarrhea; PCP, *Pneumocystis carinii* pneumonia.						

Table 14-5: Safety of Commonly Used Antimicrobials

Drug Name	*FDA Class*	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Metronidazole	B	Animal (rodents) data show risk of carcinogenicity.	2 meta-analyses, a population-based case-control study, and a prospective controlled cohort study have not found increased risk in birth defects (Diav-Citrin, 2001; Czeizel, 1998, Caro-Paton, 1997; Burtin 1995)	Most authorities feel metronidazole is safe in the 2nd and 3rd trimester. Use with caution in 1st trimester.
Clindamycin	B	No fetal harm demonstrated in rat studies. Cleft palate observed in one mouse strain.	In a surveillance study of Michigan Medicaid recipients, 647 exposures to clindamycin during the first trimester resulted in a 4.8% incidence of birth defects. Patterns of anomalies do not support an association between clindamycin and congenital effects (Briggs, 1998).	Clindamycin is usually considered safe to use during pregnancy.
Penicillins	B	Carcinogenicity demonstrated in rats after prolonged subcutaneous administration of penicillin in peanut oil.	Several collaborative perinatal project reports involving over 12,000 exposures to penicillin derivatives during the 1st trimester indicated no association between penicillin derivative drugs and birth defects (Briggs,1998).	Penicillins are usually considered safe to use during pregnancy.
Cephalosporins	B	Not teratogenic or fetotoxic.	Extensive pregnancy exposure was not associated with birth defects.	Cephalosporins are usually considered safe to use during pregnancy.
Erythromycin	B	No teratogenic effect in rat studies.	In a surveillance study of Michigan Medicaid recipients, 6972 patients exposed to erythromycin during the first trimester resulted in a 4.6% incidence of birth defects. Patterns of anomalies do not support an association between erythromycin and congenital malformations.	Avoid estolate salt (due to hepatotoxicity in 10% of patients). Other forms are usually considered safe to use during pregnancy.
Tetracyclines	D	Teratogenic in animal studies resulting in retardation of skeletal development and embryotoxicity.	Tetracyclines are contraindicated in pregnancy due to retardation of skeletal development and bone growth, enamel hypoplasia, and discoloration of teeth of fetus. Maternal liver toxicity has also been reported.	Contraindicated.

Fluoroquinolones	C	Animal data demonstrated arthropathy in immature animals resulting in erosions in joint cartilage.	In a prospective follow-up study conducted by the European Network of Teratology Information Services (ENTIS), 666 cases of fluoroquinolone exposure (the majority during the 1st trimester) showed a congenital malformation rate of 4.8%. From previous epidemiologic data, this rate did not exceed the background rate (Schaefer, 1996).	Based on animal data and the availability of alternative antimicrobial agents, the use of fluoroquinolones during pregnancy is contraindicated.
Aminoglycosides	D	Fetotoxicity reported in rodent studies.	Eighth cranial nerve toxicity in the fetus is well documented with exposure to kanamycin and streptomycin and can potentially occur with other aminoglycosides.	Gentamicin is classified by the FDA as "C" (although it has the same potential adverse effects). Use as preferred aminoglycoside if treatment indicated.
Imipenem	C	Animal studies (monkeys) show increased embryogenic loss.	No data in humans.	Due to the lack of human data, use only in life-threatening infections.
Meropenem	B	No risk.	No data in humans.	Due to the lack of human data, use only in life-threatening infections.
Chloramphenicol	C	No animal data.	A collaborative perinatal project monitored 98 exposures during the first trimester and 348 exposures anytime during pregnancy. No relationship between chloramphenicol and malformations were found (Briggs, 1998).	Although apparently nontoxic to the fetus, chloramphenicol should not be used near term due to the potential of cardiovascular collapse (gray baby syndrome).
Aztreonam	B	Animal studies show no harm to the fetus.	No human data available.	Likely to be safe in pregnancy, but due to the lack of data, use only if absolutely needed.
Methenamine	C	No animal data.	In a surveillance study of Michigan Medicaid recipients, 209 exposures to methenamine during the first trimester resulted in a 3.8% incidence of birth defects. This data did not support an association between methenamine and congenital defects.	The benefit of methenamine therapy is not likely to be worth the potential risk of use during pregnancy.
Nitrofurantoin	B	Not teratogenic or fetotoxic in rat and rabbit studies.	In a surveillance study of Michigan Medicaid recipients, 1292 exposures to nitrofurantoin resulted in a 4.0% incidence of birth defects. These data did not support an association between nitrofurantoin and congenital defects (Briggs, 1998).	Most authorities feel that use of nitrofurantoin is safe during pregnancy.
Vancomycin	C	No animal data.	The manufacturer has received reports of vancomycin use during pregnancy without adverse fetal effects.	Consider use only when the benefit outweighs the risk of drug administration.

Table 14-6 Drug Interactions of Antiretrovirals

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
Drug Interactions with Nucleoside Reverse Transcriptase Inhibitors						
AZT (Zidovudine) (Retrovir®)	Ganciclovir/ Valganciclovir	Pharmacodynamic interaction/Additive toxicity.	Enhanced bone marrow toxicity.	Delayed	Moderate	Monitor CBC frequently. May require switch to alternative antiretroviral or use concomitant G-CSF.
AZT	Acetaminophen	Competitive inhibition of glucuronidation	May rarely result in granulocytopenia and hepatotoxicity	Delayed	Minor	Intermittent use of acetaminophen 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	Ribavirin	In vitro ribavirin inhibits phosphorylation of AZT Pharmacodynamic interaction	Antagonism in vitro but not in vivo Additive anemia	Immediate Delayed	 Moderate/ Severe	Avoid combination if possible or closely monotor virologic response. Anemia may be severe. May require treatment or change in drugs.
AZT	Doxorubicin	Pharmacodynamic interaction	Additive bone marrow suppression	Delayed	Moderate	Additive bone marrow suppression. Consider alternative to AZT or support with G-CSF.
AZT	Zalcitabine	Low potency combination	Non-responsive regimen	Delayed	Moderate	Avoid combination.
AZT	Myelosuppressive drugs (e.g., interferon, pyrimethamine)	Pharmacodynamic interaction	Additive bone marrow suppression	Delayed	Moderate	Use with caution. Monitor for bone marrow suppression.
AZT	Atovaquone	Inhibition of AZT glucuronidation	AZT: AUC increased 31% decreased clearance	Immediate	Moderate	Clinical significance unknown. Use standard dose.

ddI (Didanosine) (Videx®)	Ganciclovir/ Valganciclovir	Unknown	ddI AUC increased by >100% with concomitant dosing (or when oral ganciclovir is administered 2 hours after ddI); ganciclovir AUC decreased 21%	Delayed	Moderate	Monitor for ddI toxicity (i.e. peripheral neuropathy, pancreatitis). Appropriate doses for combination of ddI and ganciclovir not established. Dose adjustment may be required.
ddI	Tenofovir	Unknown	ddI AUC increased by 40–60%. Suboptimal response in 91% of patients with ddI/TDF/3TC only	Delayed	Major	May increase rate of peripheral neuropathy and pancreatitis. Lower dose of ddI EC to 250 mg qd with TDF co-administration for pts >60kg. Dose for pts <60kg 200 mg qd.
ddI	Indinavir Ritonavir Delavirdine	Increase in gastric pH due to the buffer in ddI formulation	Decreased absorption of indinavir, ritonavir, and delavirdine	Immediate	Moderate	Separate administration time by at least 2 hours or use ddI EC formulation.
ddI	Dapsone	Increase in gastric pH due to the buffer in ddI formulation	No significant interaction	Immediate	Mild	Use standard dose.
ddI	Itraconazole Ketoconazole	Increase in gastric pH due to the buffer in ddI formulation	Decreased absorption of antifungal agent	Immediate	Major	Separate administration time by at least 2 hours or use ddI EC formulation. Fluconazole may be preferred as an alternative azole antifungal.
ddI	Fluoroquinolones, Tetracyclines	Chelation of fluoroquinolones and tetracyclines by the divalent cation in DDI formulation	Significant decrease in antibiotic absorption resulting in sub-therapeutic levels	Immediate	Major	Administer quinolones or tetracyclines 2 hours before or 6 hours after DDI administration or use ddI EC formulation.
ddI	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.
ddI	Atazanavir	Decreased absorption of ATV due to buffer in ddI formulation	ATV AUC decreased 87% with buffered ddI given simultaneously; no significant interaction expected with ddI EC	Immediate	Severe	buffered ddI: Take ATV with food 2 hr before or 1 hr after ddI (if this timing of dosing not followed, 90% reduction in ATV level); ddI EC: take at different times (ATV with food and ddI on empty stomach).

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
ddI	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.
ddI	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.
ddI	Methadone	Unknown	buffered ddI AUC decreased by 63%, methadone levels remains unchanged. No interaction with ddI EC	Delayed	Moderate	Consider using ddI EC. May consider buffered ddI increase.
ddI	Allopurinol	Unknown	ddI levels increased by 120%	Immediate	Moderate	Avoid co-administration.
ddI	Ribavirin	Inhibition of mitochondrial DNA polymerase gamma	ddI intracellular triphosphate levels increased	Delayed	Major	Increased of risk of pancreatitis and lactic acidosis. Avoid co-administration.
ddC (Zalcitabine) (Hivid®)	ddI, 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-suppresive 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.

ddC	Pentamidine I.V.	Pharmacodynamic interaction	Additive toxicity	Delayed	Moderate	May increase the risk of development of fulminant pancreatitis.
ddC	Probenecid	Inhibition of tubular secretion	May decrease elimination of ddC. ddC AUC increased by 54%	Delayed	Moderate	Monitor signs of toxicity.
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	ddI	Pharmacodynamic interaction/ Additive toxicity	Increased risk lactic acidosis in pregnant women. Peripheral neuropathy and pancreatitis also reported with this combination.	Delayed	Major	Avoid coadministration use 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.
d4T	Ribavirin	In vitro ribavirin interacts with thymidine-phosphorylated nucleoside analogs	Antagonism in vitro but not in vivo	Immediate	Minor	Not clinically significant.
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.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
3TC	Emtricitabine	Overlapping resistance profile	Non-suppressive regimen	Delayed	Major	Avoid use together.
3TC	Tenofovir + didanosine	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Major	Avoid use of this combination without an NNRTI or a PI.
3TC	Zalcitabine	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Moderate	Consider alternative combination.
FTC (Emtricitabine) (Emtriva®)	–					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.
Abacavir	Tenofovir + didanosine	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Major	Avoid us of this combination without an NNRTI or a PI.
Drug Interactions with Nucleotide Reverse Transcriptase Inhibitors						
Tenofovir (Viread®)	Atazanavir	Possible interference with absorption	Atazanavir AUC decreased by 25%; decreased C_{min} by 23%	Immediate	Moderate	Clinical significance unknown. Consider dosing tenofovir 2 hours before atazanavir or "boosting" with RTV dose: (ATV 300 mg + RTV 100 mg).
Tenofovir	ddI	Unknown Low potency combination	ddI AUC increased by 40–60%.	Delayed	Major	May increase rate of peripheral neuropathy and pancreatitis. Lower dose of ddI to 250 mg qd with TDF co-administration for pts >60kg. Dose adjustments for pts <60kg 200 mg qd. Preliminary data shows low potency.

Tenofovir	Cidofovir, ganciclovir, valganciclovir	Possible competition for active tubular secretion	May increase concentration of TDF or these drugs	Immediate	Moderate	Monitor for dose-related toxicities.
Tenofovir	Lamivudine + Abacavir	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Major	Avoid use of this combination without an NNRTI or a PI.
Tenofovir	Lamivudine + didanosine	Pharmacodynamic interaction	Non-suppressive regimen	Delayed	Major	Avoid use of this combination without an NNRTI or a PI.
Tenofovir	Didanosine	Increased ddI serum level	ddI AUC increased by 44% may result in increased toxicity	Immediate	Major	Monitor for ddI associated toxicities for patients ≥ 60 kg, decrease ddI EC dose 250 mg qd for patients < 60 kg.
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 withdraw may occur. May need to increase dose of methadone by 15–25% (some patients may required doses of greater than 150 mg per day).
NVP	Ketoconazole	Induction of hepatic metabolism by nevirapine. Inhibition of hepatic metabolism by ketoconazole	Ketoconazole levels decreased by 72%. Nevirapine levels increased by 15–30%	Delayed	Moderate	Co-administration not recommended. Ketoconazole dose may need to be increased. Fluconazole may be preferred as alternative azole agent.
NVP	Rifampin/ Rifabutin	Induction of hepatic metabolism	Nevirapine levels decreased by 37% with rifampin and 16% with rifabutin	Delayed	Major	Co-administration not recommended with rifampin. Rifabutin is the preferred alternative agent.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
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).
NVP	Clarithromycin	Induction of hepatic metabolism by nevirapine	Clarithromycin AUC decreased by 30%, but active hydroxy-metabolite is increased	Delayed	Minor	No dose modification needed. Use standard doses of nevirapine and clarithromycin.
NVP		Inhibition of hepatic metabolism by clarithromycin	Nevirapine AUC increased by 26%	Immediate	Minor	
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 100 mg q12h) 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_{min} 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	No data				Consider using ATV 300 mg/ RTV 100 mg qd.
NVP	Fluconozole	Inhibition of NVP metabolism	May increase NVP serum level	Immediate	Moderate	Monitor NVP-associated side effects.
NVP	Voriconozole	Potential for bi-directional inhibition	May significantly decrease voriconazole serum level	Delayed	Moderate/ Severe	Monitor frequently for toxicites and voriconazole efficacy. Dose adjustment may be needed.
NVP	Norethindrone	Induction of northindrone metabolism	May decrease norethindrone	Delayed	Major	Use additional method of contraception.
NVP	Rifapentine	Induction of NVP metabolism	May significantly decrease NVP serum level	Delayed	Major	Avoid use together; consider rifabutin.
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_{min} 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_{min} increased by 500%; DLV AUC decreased by 15%.	Delayed	Minor	A beneficial interaction. No dose adjustment necessary. Monitor transaminase levels.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
DLV	Amprenavir	Inhibition of hepatic metabolism by DLV. Induction of hepatic metabolism by APV	Amprenavir AUC increased by 125%. DLV AUC decreased by 60%	Delayed	Major	Co-administration not recommended.
DLV	Lopinavir/r	Inhibition of hepatic metabolism	LPV AUC increased by 8–134%. DLV no change	Immediate	Minor	Limited data. No dose adjustment.
DLV	ddI and antacid	Decreased delavirdine absorption due to antacid content in DDI	Delavirdine AUC decreased by 41%	Immediate	Moderate	Separate administration by at least 1 hour or use ddI EC.
DLV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism	Increased serum levels of simvastatin and lovastatin	Immediate	Moderate	Avoid concurrent administration. Consider alternatives such as atorvastatin, pravastatin, fluvastatin. Monitor for adverse effects due to limited clinical data.
DLV	H2 blockers, Proton pump inhibitors (i.e. omeprazole)	Decreased delavirdine absorption due to antacid content in DDI	May decrease delavirdine concentration	Immediate	Moderate	Concurrent administration contraindicated.
DLV	Terfenadine, Astemizole, Cisapride	Inhibition of hepatic metabolism	Increased levels of terfenadine, astemizole, cisapride	Immediate	Major	Concurrent administration contraindicated due to potential for serious cardiac arrhythmias.
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	Ergot alkaloid	Inhibition of hepatic metabolism	Possible acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.

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	Clarithromycin	Inhibition of hepatic metabolism	Clarithromycin levels increased by 100% and delavirdine levels increased by 44%	Immediate	Minor	May require clarithromycin dose adjustment, based upon CrCl.
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_{min} decreased below the level of detection AUC decreased by 96%	Delayed	Major	Concurrent administration contraindicated due to sub-therapeutic level of delavirdine.
DLV	Rifabutin	Inhibition of hepatic metabolism by delavirdine	Rifabutin AUC increased by 100%	Immediate	Moderate	Concurrent administration contraindicated due to sub-therapeutic level of delavirdine.
DLV	Rifabutin	Induction of hepatic metabolism by rifabutin	Delavirdine AUC decreased by 80%	Delayed	Major	Concurrent administration contraindicated.
DLV	Warfarin	Potential inhibition of warfarin metabolism	May increase warfarin	Immediate	Moderate	Monitor INR.
DLV	Voriconazole	Potential for bi-directional inhibition	May increase voriconazole and DLV serum level	Immediate	Moderate	Monitor frequently for toxicities.
DLV	Bepridil	Potential inhibition of bepridil metabolism	May increase bepridil serum level	Immediate	Moderate	Use with caution; monitor for cardiac arrhythmias.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
DLV	Tadalafil	Potential inhibition of tadalafil metabolism	May substantially increase in tadalafil AUC and half life	Immediate	Moderate	Start tadalafil 5 mg dose; do not exceed a single 10 mg dose of tadalafil in 72 hours.
DLV	Vardenafil	Potential inhibition of vardenafil metabolism	May substantially increase vardenafil AUC			Start with a 2.5 mg dose; do not exceed a single 2.5 mg dose of vardenafil in 72 hours.
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	Amprenavir	Induction of hepatic metabolism	Amprenavir AUC decreased by 36%	Delayed	Moderate	Dose: APV 600 mg/ RTV 100 mg q12h + EFV 600 mg qhs.
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_{min} decreased by 39%	Delayed	Major	Dose: LPV/r 533 mg/133 mg (4 caps) bid + EFV 600 mg qhs.
EFV	Ergot alkaloid	Induction of hepatic metabolism	Potential acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.

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.
EFV	Terfenadine, Astemizole, Cisapride	Induction of hepatic metabolism	Levels of terfenadine, astemizole, cisapride increased	Immediate	Major	Concurrent administration contraindicated due to potential for serious cardiac arrhythmia.
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	Clarithromycin	Induction of hepatic metabolism	Clarithromycin AUC decreased by 39%	Immediate	Moderate	Incidence of rash increased to 46% with concurrent administration. No interaction with azithromycin, a better alternative.
EFV	Ethinyl estradiol	Inhibition of hepatic metabolism	Ethinyl estradiol AUC increased by 37%	Immediate	Minor	No dose changes recommended. Clinical significance of interaction unknown. No data on progestin component of oral contraceptive available. Alternative or additional form of birth control recommended.
EFV	Rifabutin	Inhibition of hepatic metabolism	Rifabutin AUC decreased by 35%. No effect on Efavirenz AUC	Delayed	Moderate	If concurrent administration required, increase dose of rifabutin to 450 mg or 600 mg po qd.
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.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
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	Fosamprenavir	Induction of hepatic metabolism	fAPV Cmin decreases 36% when dosed at fAPV 1400 mg + RTV 250 mg qd	Delayed	Major	Use fAPV 700 mg + RTV 100 mg bid, OR fAPV 1400 mg + RTV 300 mg with EFV co-administration.
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.
EFV	Warfarin	Unknown	Potential increase or decrease in warfarin levels	Delayed	Moderate	Monitor INR.
Drug Interactions with Protease Inhibitors						
Indinavir (Crixivan®) (IDV)	ddI	Impairment of indinavir absorption by DDI buffer	Decreases absorption of indinavir	Immediate	Moderate	Separate indinavir and ddI dosing by at least 2h or use ddI EC formulation.
IDV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism	Increased serum levels of simvastatin and lovastatin	Immediate	Moderate	Avoid concurrent administration. Possible alternative include atorvastatin, pravastatin, fluvastatin. Monitor for adverse effect due to limited clinical data with these agents.
IDV	Rifabutin	Inhibition of hepatic metabolism by indinavir	Rifabutin AUC increased by 2 fold.	Immediate	Moderate	Decrease rifabutin dose by half (150 mg once a day) or 300 mg 3x/week.

IDV	Rifabutin	Induction of hepatic metabolism by rifabutin	Indinavir AUC decreased by 32%	Delayed	Moderate	May need to increase indinavir dose to 1000 mg tid. When IDV "boosted" with RTV, adjust rifabutin 150 mg qod.
IDV	Rifampin	Induction of hepatic metabolism	Indinavir AUC decreased by 90%	Immediate	Major	Concurrent administration contraindicated.
IDV	Terfenadine, Astemizole, Cisapride	Inhibition of hepatic metabolism	Drug levels increased by 3-fold or greater	Immediate	Major	Concurrent administration contraindicated due to potential for cardiac arrhythmias. Alternative antihistamines include loratidine, fexofenadine, or cetirizine. Alternative pro-kinetic agent includes metoclopramide.
IDV	Ergot alkaloid	Inhibition of hepatic metabolism	Potential acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	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.
IDV	Clarithromycin	Inhibition of hepatic metabolism	Clarithromycin AUC increased by 53%	Immediate	Minor	No dose adjustment.
IDV	Oral contraceptives	Inhibition of hepatic metabolism	Ethinyl estradiol AUC increased by 24% and norethindrone AUC increased by 26%.	Immediate	Minor	No dose adjustment.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
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	Sildenafil	Inhibition of hepatic metabolism	Sildenafil AUC increased 3-fold.	Immediate	Moderate	The maximum dose of sildenafil is 25 mg/48h.
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	Amprenavir	Inhibition of hepatic metabolism	Amprenavir AUC increased by 26%. Indinavir AUC increased by 38%.	Immediate	Minor	No dose adjustment recommended. Dose APV 800 mg tid /IDV 800 mg tid.
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 1200 mg/RTV 400 mg qd (limited data).
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 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			No interaction. Use standard dose
IDV	Voriconazole	When IDV is boosted with RTV, potential for bi-directional interaction	Voriconazole levels may be decreased with IDV/RTV	Delayed	Moderate	No interaction with IDV but voriconazole may be decreased with RTV co-administraion. Monitor for toxicities and therapeutic efficacy.
IDV	Tadalafil	Inhibition of hepatic metabolism	May substantially increase tadalafil AUC	Immediate	Moderate	Start with 5 mg dose and do not exceed a single dose of 10 mg in 72 hrs.
IDV	Vardenafil	Inhibition of hepatic metabolism	Vardenafil increases 16-fold IDV unboosted decreases 30%	Immediate	Moderate	For unboosted IDV, consider using sildenafil instead; for IDV + RTV, do not exceed 2.5 mg vardenafil in 72 hrs.
IDV	Atorvastatin	Inhibition of hepatic metabolism	Potential for atorvastatin AUC increase	Immediate	Moderate	Use lowest possible starting dose of atorvastatin with careful monitoring or avoid use together.
Saquinavir (Invirase®) (Fortovase®) (SQV)	Ritonavir	Inhibition of hepatic metabolism	Saquinavir AUC increased by 20-fold.	Immediate	Minor	Dual protease inhibitor combination with the most clinical experience. 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.
SQV	Amprenavir	Induction of hepatic metabolism	Saquinavir level decreased by 18%. Amprenavir level decreased by 36%.	Delayed	Moderate	Limited data: SQV (FTV) 800 mg tid plus APV 800 mg tid.
SQV	Lopinavir/r	Inhibition of hepatic metabolism	Saquinavir C_{min} increased by 3..6-fold	Immediate	Minor	Dose: SQV 800–1000 mg bid plus LPV/r 400/100 mg bid.

Table 14-6 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/da, 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.
SQV	Terfenadine, Astemizole, Cisapride	Inhibition of hepatic metabolism	Drug levels increased by 3-fold or greater.	Immediate	Major	Concurrent administration Contraindicated due to potential for cardiac arrhythmias. Alternative antihistamines include loratidine, fexofenadine, or cetirizine. Alternative pro-kinetic agent includes metoclopramide.
SQV	Dexamethasone	Induction of hepatic metabolism	May decrease SQV serum levels	Delayed	Moderate	Clinical significance unknown.
SQV	Phenobarbital, phenytoin, and carbamazepine	Induction of hepatic metabolism	May decrease serum levels of SQV	Delayed	Moderate	Consider alternative anticonvulsants (i.e valproic acid, levetiracetam, or topiramate). Monitor anticonvulsant level.
SQV	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.
SQV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism.	Simvastatin and lovastatin serum level increased	Immediate	Moderate	Avoid co-administration. Recommended alternatives include atorvastatin, pravastatin (but pravastatin AUC decreased by 50% with SQV/r), fluvastatin. Monitor for adverse effects due to limited clinical data with these agents.

SQV	Clarithromycin	Inhibition of hepatic metabolism	Clarithromycin increases SQV AUC 177% and SQV increases clarithromycin AUC 45%	Immediate	Minor	Beneficial pharmacokinetic interaction. Use standard doses.
SQV	Rifabutin/ Rifampin	Induction of hepatic metabolism	Rifabutin and rifampin decrease AUC of saquinavir by 40% and 80% respectively.	Delayed	Major	Concurrent administration contraindicated unless using RTV/SQV. Consider RTV/SQV 400 mg/400 mg with rifabutin 150 mg 3x/week or rifampin 600 mg qd or 3x/week.
SQV	Sildenafil	Inhibition of hepatic metabolism.	Sildenafil AUC increased by 2-fold.	Immediate	Moderate	Caution with concurrent use, Do not exceed 25 mg of sildenafil in a 48-hour period.
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_{min} 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.
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.
SQV	Warfarin	Unknown	Increases or decreases warfarin	Dealyed	Moderate	Monitor INR.
SQV	Amitryptiline Imipramine	Inhibition of hepatic metabolism	May increase tricyclics	Immediate	Minor	Monitor tricyclic antidepressant concentration.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
SQV	Voricanazole	Potential for bi-directional inhibition	With SQV/RTV voriconazole serum level may be decreased	Delayed	Moderate	Monitor for toxicities and therapeutic efficacy.
SQV	Tadalafil	Inhibition of hepatic metabolism	May substantially increase tadalafil AUC	Immediate	Moderate	Start with a 5 mg dose and do not exceed a single 10 mg dose of tadalafil in 72 hrs.
SQV	Vardenafil	Inhibition of hepatic metabolism	Vardenafil AUC may increase substantially	Immediate	Moderate	Start with a 2.5 mg dose, and do not exceed a single 2.5 mg dose in 72 hrs.
SQV	Atorvastatin	Inhibition of hepatic metabolism	Atorvastatin increases 450% when combined with SQV/RTV	Immediate	Moderate	Use lowest possible starting dose of atorvastatin with careful monitoring.
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	Voriconazole	Hepatic induction	Decreased voriconazole by 82% when administered with RTV 400 mg bid	Delayed	Major	Do not co-administer with standard dose RTV 400 bid; no data with boosting doses of RTV.
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.
RTV	Sildenafil	Inhibition of hepatic metabolism.	Sildenafil AUC increased by 2 to 11-fold.	Immediate	Major	Caution with concurrent use, Do not exceed 25 mg of sildenafil in a 48-hour period.
RTV	Theophylline	Induction of glucuronosyl transferase activity.	Theophylline AUC decreased by 43%	Delayed	Moderate	Monitor theophylline levels; dose may need to be increased if subtherapeutic.
RTV	Ketoconazole	Inhibition of hepatic metabolism	Ketoconazole AUC increased by greater than 3-fold.	Immediate	Moderate	May need to decrease ketoconazole dose.

RTV	Rifabutin	Inhibition of hepatic metabolism	Rifabutin AUC increased 4-fold	Immediate	Moderate	Dose rifabutin 150 mg qod or 150 mg 3x/week with standard ritonavir.
RTV	Rifampin	Induction of hepatic metabolism	Ritonavir AUC decreased by 35%	Delayed	Moderate	There may be an increased risk of liver toxicity. Dose RTV 400 mg/ SQV 400 mg bid with rifampin 600 mg qd.
RTV	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.
RTV	Terfenadine, Astemizole, Cisapride	Inhibition of hepatic metabolism	Drug level increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated due to potential for cardiac arrhythmias. Alternative antihistamines include loratidine, fexofenadine, or cetirizine. Alternative pro-kinetic agent includes metoclopramide.
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%.	Delayed	Moderate	Clinical significance unknown.
RTV	Ketoconazole	Inhibition of hepatic metabolism	Ketoconazole levels increased by 3-fold.	Immediate	Moderate	Use with caution; do not exceed 200 mg ketoconazole per day.
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.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
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	Antipsychotic (Olanzapine)	Induction of hepatic metabolism	Olanzapine AUC decreased by 50%.	Delayed	Moderate	Olanzapine dose may need to be increased.
RTV	Antipsychotic (Pimozide)	Inhibition of hepatic metabolism	May significantly increase pimozide serum level resulting in QTc prolongation	Immediate	Major	Concurrent administration of pimozide is contraindicated.
RTV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism.	Serum levels of simvastatin and lovastatin are increased.	Immediate	Moderate	Avoid co-administration, alternatives that may be used inlcude atorvastatin, pravastatin, fluvastatin. Monitor for adverse effects due to limited clinical data.
RTV	Opioid analgesic	Inhibition of hepatic metabolism.	Prolonged sedation and possible respiratory depression	Immediate	Major	Avoid concurrent administration of meperidine, propoxyphene, and fentanyl. Morphine may be a safer alternative.
RTV	Clarithromycin	Inhibition of hepatic metabolism.	Clarithromycin AUC increased by 77%	Immediate	Minor	Reduce clarithromycin dose for renal failure. Consider using azithromycin.
RTV	Didanosine (buffered)	Interference with absoption	Decreased ritonavir absorption.	Immediate	Major	Consider using ddI EC or separate administration by >2 hours.
RTV	Saquinavir	Inhibition of hepatic metabolism.	Saquinavir AUC increased by 20-fold.	Immediate	Minor	Dual protease inhibitor with the most clinical experience. 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.
RTV	Amprenavir	Inhibition of hepatic metabolism.	Amprenavir AUC increased by 2.5-fold.	Immediate	Minor	Dose: APV 600 mg bid plus RTV 100 mg bid or APV 1200 mg qd plus RTV 200 mg qd.
RTV	Atazanavir	Inhibition of hepatic metabolism	ATV increases AUC by 238%	Immediate	Minor	A beneficial PK interaction, use ATV 300 mg + RTV 100 mg qd.
RTV	Fosamprenavir	Inhibition of hepatic metabolism	fAPV increases AUC by 100%, C_{min} by 400% when combined with 200 mg RTV	Immediate	Minor	A beneficial PK interaction, use RTV-boosted regimen (fAPV 700 mg + RTV 100 mg bid) in ARV-experienced patients.
Nelfinavir (Viracept®) (NFV)	Ketoconazole	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 35%	Immediate	Minor	No dose adjustment needed.
NFV	Fluconazole	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 30%	Immediate	Minor	May be beneficial. No dose adjustment needed.
NFV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism.	Increased serum level of simvastatin and lovastatin	Immediate	Moderate	Avoid co-administration: Alternatives includes pravastatin (but pravastatin AUC decreased by 47%), and fluvastatin. Monitor for adverse effects due to limited clinical data. Atorvastatin levels increased by 74%.
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.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
NFV	Rifabutin	Induction of hepatic metabolism by rifabutin	Nelfinavir AUC decreased by 32%	Delayed	Moderate	If co-administration required, increase nelfinavir to 1000 mg po tid.
NFV		Inhibition of hepatic metabolism by nelfinavir	Rifabutin levels increased by 2-fold	Immediate	Moderate	If co-administration required, decrease rifabutin to 150 mg po qd or 300 mg 3x/week.
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	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.
NFV	Terfenadine, Astemizole, Cisapride	Inhibition of hepatic metabolism	Drug levels increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated due to potential cardiac arrhythmia. Recommended alternative antihistamine: loratidine, fexofenadine, or cetirizine. Alternative pro-kinetic agent: metoclopramide.
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	Sildenafil	Inhibition of hepatic metabolism.	Sildenafil AUC increased by 2-11 fold.	Immediate	Major	Caution with concurrent use. Do not exceed 25 mg of sildenafil in a 48-hour period.

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.
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.
NFV	Delavirdine	Induction of hepatic metabolism	Delavirdine AUC decreased by 50%. NFV AUC increased by 2-fold.	Immediate	Minor	Consider increasing DLV dose to 600 mg tid with standard dose NFV 1250 mg bid (limited data).
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.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
Amprenavir (Agenerase®) (APV)	Rifampin	Induction of hepatic metabolism	Amprenavir AUC decreased by 80%	Delayed	Major	Concurrent administration contraindicated.
APV	Rifabutin	Induction of hepatic metabolism	Amprenavir AUC decreased by 14%. Rifabutin AUC increased by 204%	Delayed	Moderate	Dose rifabutin 150 mg qd or 300 mg 3x/ week. No change in amprenavir dose.
APV	Ketoconazole	Inhibition of hepatic metabolism	Amprenavir AUC increased by 32%. Ketoconazole AUC increased by 44%.	Immediate	Minor	May be beneficial. No dose adjustment needed.
APV	Clarithromycin	Inhibition of hepatic metabolism	Amprenavir AUC increased by 18%	Immediate	Minor	No dose adjustment needed.
APV	Oral contraceptives	Induction of hepatic metabolism	Potential decreases in ethinyl estradiol level.	Delayed	Major	Advise patient of potential risk and the use of an alternative or additional method of contraception.
APV	Sildenafil	Inhibition of hepatic metabolism.	Sildenafil AUC increased by 2-11 fold.	Immediate	Major	Caution with concurrent use, Do not exceed 25 mg of sildenafil in a 48-hour period.
APV	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism.	Simvastatin and lovastatin levels increased.	Immediate	Moderate	Avoid concurrent administration. Alternative agents include atorvastatin, pravastatin, fluvastatin. Monitor for adverse effects due to limited clinical data.
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%. Amprenavir level decreased by 36%.	Delayed	Minor	No dose adjustment. Insufficient data for dose recommendation.
APV	Indinavir	Inhibition of hepatic metabolism	Amprenavir AUC increased by 33%. Indinavir AUC decreased by 38%.	Immediate	Minor	No dose adjustment. IDV 800 mg tid plus APV 800 mg tid.
APV	Nelfinavir	Inhibition of hepatic metabolism	Nelfinavir AUC increased by 15%, Amprenavir AUC increased by 50%.	Immediate	Minor	No dose adjustment. NFV 750 mg tid plus APV 800 mg tid.
APV	Ritonavir	Inhibition of hepatic metabolism	Amprenavir AUC increased by 2.5-fold.	Immediate	Minor	Dose: APV 600 bid/RTV 100 bid or APV 1200 mg qd /RTV 200 mg qd.
APV	Lopinavir/r	Induction of hepatic metabolism by APV. Inhibition of hepatic metabolism by LPV/r	APV C_{min} 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	Amprenavir 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 trough 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.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
APV	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated
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	Terfenadine Astemizole Cisapride	Inhibition of hepatic metabolism	Cardiotoxic drug level increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated due to potential for cardiac arrhythmias. Alternatives include loratidine, fexofenadine, or cetirizine. Alternative pro-kinetic agent includes metoclopramide.
APV	Amiodarone, lidocaine (systemic), quinidine, and bepridil		May increase serum level of antiarrhythmics.	Immediate	Moderate	Use with caution. Monitor antiarrhythmic serum level.
APV	Pimozide		May increase serum level of pimozide.	Immediate	Major	Contraindicated. Potential for life-threatening cardiac arrhythmia.
APV	Calcium channel blocker		May increase serum level of calcium channel blocker	Immediate	Moderate	Use with caution. Close monitoring recommended.
APV	Dexamethasone		May decrease APV serum level.	Delayed	Moderate	Use with caution.
APV	Cyclosporine, tacrolimus, rapamycin		May increase immunosuppressant serum level.	Immediate	Moderate	Therapeutic drug monitoring of immunosuppressant highly recommended.
APV	Amitriptyline, imipramine, and desipramine		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		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.
APV	Warfarin	Unknown	Increase or decrease in warfarin	Immediate	Moderate	INR must be monitored.
APV	Voriconazole	Potential for bi-directional interaction (or induction with RTV co-administration)	Voriconazole may be decreased with RTV co-administration. APV may be increased	Immediate	Moderate	Monitor for toxicities and therapeutic efficacy.
APV	Bepridil	Inhibition of hepatic metabolism	May increase bepridil	Immediate	Moderate	Use with caution.
APV	Tadalafil	Inhibition of hepatic metabolism	May substantially increase tadalafil AUC and half life	Immediate	Moderate	Start with 5 mg dose; do not exceed a single 10 mg dose of tadalafil in 72 hrs.
APV	Vardenafil	Inhibition of hepatic metabolism	May increase vardenafil AUC	Immediate	Moderate	Start with a 2.5 mg dose; do not exceed a 2.5 mg dose of vardenafil in 72 hrs.
APV	Atorvastatin	Inhibition of hepatic metabolism	May increase atorvastatin substantially	Immediate	Moderate	Use lowest possible starting dose of atorvastatin with careful monitoring.
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.						
fAVP	LPV/r	Enzyme induction	Significant decrease in levels of both LPV and APV	Delayed	Major	Boosting with RTV still resulted in significant reduction of APV trough at standard dose. Best PK data with fAPV 1400 mg bid and LPV/r 533 mg/133 mg bid.
fAPV/r	EFV	Enzyme induction	APV Cmin decreased by 17% (90% CI 4–29%) with bid vs. 36% (90% CI 8–56%) with qd fAPV dosing	Delayed	Moderate	Recommended Dose: fAPV 700 mg bid/RTV 100 mg bid or fAPV 1400 mg qd/RTV 300 mg qd.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
fAPV	Atorvastatin	Enzyme inhibition	Atorvastatin AUC increased by 130% (with fAPV 1400 mg bid) and 150% (with fAPV 700 mg/RTV 100 mg bid). No change in APV AUC.	Immediate	Moderate	Close monitoring recommeded. Do not exceed 20 mg per day of atorvastatin.
fAPV/r	Ritonavir	Enzyme inhibition	Amprenavir AUC increased by over 2-fold. C_{min} increased by 4-fold with daily administration and 6-fold with twice daily administration compared to fAPV 1400 mg bid.	Immediate	Minor	Dose: fAPV 700 mg bid/RTV 100 mg bid or fAPV 1400 mg qd/RTV 200 mg qd.
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 with LPV/r.
LPV/r	Rifabutin	Inhibition of hepatic metabolism by LPV/r	Rifabutin serum level increased by 3-fold. LPV serum level not affected	Immediate	Moderate	Dose: LPV/r 3 caps bid plus rifabutin 150 mg qod or 150 mg 3x/week.
LPV/r	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities	Immediate	Major	Concurrent administration contraindicated.

LPV/r	Terfenadine Astemizole Cisapride	Inhibition of hepatic metabolism	Drug level increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated due to potential for cardiac arrhythmias. Alternative antihistamines include loratidine, fexofenadine, or cetirizine. Alternative pro-kinetic agent includes metoclopramide.
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, SSRIs, Bupropion)	See RTV section				
LPV/r	Antiarrhythmics	Inhibition of hepatic metabolism	AUC of antiarrhythmics increased	Immediate	Major	Concurrent administration of propafenone, flecainide, and encainide are contraindicated.
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	Simvastatin/ Lovastatin	Inhibition of hepatic metabolism.	Serum levels of simvastatin and lovastatin are increased.	Immediate	Moderate	Avoid co-administration, alternatives that may be used include pravastatin, fluvastatin. Monitor for adverse effects due to limited clinical data.
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.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
LPV/r	Atorvastatin	Inhibition of hepatic metabolism	Atorvastatin AUC increased by 6-fold.	Immediate	Moderate	Clinical significance unknown. Use with caution. Starting dose atorvastatin 10 mg qd.
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	Amprenavir	Induction of hepatic metabolism by APV. Inhibition of hepatic metabolism by LPV/r	APV C_{min} increased 5-fold. LPV AUC decreased 30–50%.	Delayed	Moderate	Dose: LPV/r 533 mg/133 mg (4 caps) + APV 750 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_{min} 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_{min} 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 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.
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	Voriconazole	Potential for bi-directional inhibition and/or induction	May decrease voriconazole serum level	Immediate	Moderate	Monitor for toxicities and therapeutic efficacy. Co-administration not recommended by manufacturer.
LPV/r	Vardenafil	Inhibition of hepatic metabolism	May substantially increase vardenafil AUC	Immediate	Moderate	Start with a 2.5 mg dose; do not exceed a 2.5 mg dose of vardenafil in 72 hrs.

LPV/r	Ethinyl estradiol	Induction of hepatic metabolism	EE AUC decreases 42%			Use alternative or additional method.
Atazanavir (ATV)	Clarithromycin	Inhibition of hepatic metabolism	ATV AUC increased by 28%. Clarithromycin AUC increased by 94%. Clarithromycin hydroxy-metabolite AUC decreased by 30%	Immediate	Major	QTc prolongation observed with co-administration. 50% of clarithromycin dose recommended.
ATV	ddI (buffered)	Interference with absorption	No effect on ddI serum level. ATV AUC decreased by 87%.	Immediate	Major	Administer ATV 400 mg one hour after ddI (buffered) administration. Consider ddI 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	Diltiazem	Inhibition of hepatic metabolism	Diltiazem AUC increased by 125%. Desacetyl diltiazem (active metabolite) AUC increased by 165%. ATV not affected.	Immediate	Major	Increase in PR interval observed. Use with caution. Start with 50% of diltiazem dose and titrate slowly. Monitor BP and pulse.
ATV	Atenolol	Inhibition of hepatic metabolism	Atenolol AUC increased by 25%. ATV not affected.	Immediate	Moderate	No effect on PR or QTc interval with co-administration. Monitor BP and pulse.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
ATV	Rifabutin	Inhibition of hepatic metabolism	Rifabutin AUC increased. ATV not affected	Immediate	Moderate	Dose: ATV 400 mg qd plus rifabutin 150 mg 3x/week.
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 administration of SQV 1200 mg.
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	Interaction likely to occur due to interference with absorption. ATV dose 300 mg qd + RTV 100 mg qd with co-administration.
ATV	Rifampin	Induction of hepatic metabolism	ATV may be decreased	Delayed	Moderate	Rifabutin may be a safer alternative. Dose: ATV 400 mg qd plus rifabutin 150 mg 3x/week.
ATV	Ergot alkaloid	Inhibition of hepatic metabolism	Acute ergot toxicity characterized by peripheral vasospasm and ischemia of extremities may be observed	Immediate	Major	Concurrent administration contraindicated until more data become available.
ATV	Terfenadine Astemizole Cisapride	Inhibition of hepatic metabolism	Drug level may be increased by 3-fold or greater.	Immediate	Major	Concurrent administration contraindicated until more data become available.
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 benzodiazepine that can be used: Temazepam, oxazepam, and lorazepam.
ATV	Antiarrhythmics	Inhibition of hepatic metabolism	AUC of antiarrhythmics increased	Immediate	Major	Concurrent administration of propafenone, quinidine, flecainide, encainide, amiodarone, and bepridil are contraindicated until more data become available.
ATV	Proton-pump inhibitors	Decreased absorption ATV	Significantly decreases ATV levels	Immediate	Major	Avoid concomitant use.
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.
ATV	Nevirapine	No data				Consider using ATV 300 mg + RTV 100 mg qd.
ATV	Ritonavir	Induction of hepatic metabolism	ATV AUC increases by 238%	Immediate	Minor	Use ATV 300 mg + RTV 100 mg.
ATV	Warfarin	Unknown	May increase in warfarin concentration	Delayed	Moderate	Monitor INR.
ATV	Amitryptiline Imipramine	Inhibition of hepatic metabolism	May increase tricyclic concentration	Immediate	Minor	Monitor tricyclic antidepressant concentration.
ATV	Voriconazole	Potential for bi-directional inhibition and/or induction	May decrease voriconazole serum level with RTV co-administration	Delayed	Moderate	Monitor for toxicities and therapeutic efficacy.
ATV	Sildenafil	Inhibition of hepatic metabolism	May increase sildenafil AUC	Immediate	Moderate	Use with caution; start with reduced dose of 25 mg q48h and monitor for adverse affects.

Table 14-6 Drug Interactions of Antiretrovirals (*continued*)

Primary drug	*Interacting drug*	*Mechanism of interaction*	*Effect*	*Time course*	*Severity*	*Comments/ management recommendation*
ATV	Tadalafil	Inhibition of hepatic metabolism	May substantially increase tadalafil AUC	Immediate	Moderate	Start with 5 mg dose; do not exceed a single 10 mg dose of tadalafil in 72 hrs.
ATV	Vardenafil	Inhibition of hepatic metabolism	May substantially increase vardenafil AUC	Immediate	Moderate	Start with a 2.5 mg dose; do not exceed a 2.5 mg dose of vardenafil in 72 hrs.
ATV	H2 receptor antagonist	Interference with absorption	May significantly decrease ATV concentration	Immediate	Moderate	Separate ATV concentration by 12 hrs.
ATV	Atorvastatin	Inhibition of hepatic metabolism	May increase atorvastatin substantially	Immediate	Moderate	Use lowest possible starting dose (10 mg) of atorvastatin with careful monitoring.
Tipranavir/ ritonavir (currently in Phase III trials)	Efavirenz		No change in EFV PK,. TPV PK (at 500/100 mg dose)			Phase II trials are currently using TPV500/ 200 mg with the co-administration of EFV (Roszko, 2003).
TPV/r	AZT		AZT AUC decreased by 40%. No change in TPV PK.		Minor	Clinical significance unknown.
TPV/r	ddI EC		No Interactions			Separate administration time by 4 hours due to potential interaction of self emulsifying drug delivery system (SEDDS) of TPV and the ddI EC outer coat.
TPV/r	Tenofovir		TPV AUC decreased by 20% (with TPV 500 mg/100 mg)		Minor	Reduction of TPV may be due to decrease in RTV. TPV 500 mg/200 mg should be considered.
TPV/r	LPV/r		LPV AUC decreased by 49%		Major	Do not co-administer.
TPV/r	APV		APV AUC decreased by 45%		Major	Do not co-administer.
TPV/r	SQV		SQV AUC decreased by 70%		Major	Do not co-administer.

Drug Interactions with Fusion Inhibitors						
Fuseon	No significant drug interactions					

AUC= *Area Under the Concentration Time Curve*
Cmax = *Peak serum concentration*
Cmin = *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 = Do not co-administer; contraindicated.
Moderate = Can be co-administered with caution and possible dose adjustment.
Minor = Can be co-administered.

Table 14-7: Clinically Pertinent Food-Drug Interactions
Valganciclovir / Itraconazole Capsule / Ritonavir / Atazanavir: Should be taken with food or within 2 hr of eating.
AZT: Can be taken with food to decrease GI side effects.
Saquinavir[1] (Fortovase® and Invirase®) / Atovaquone / Nelfinavir: Should be administered with a high-fat meal.
Efavirenz / Amprenavir: High-fat meal should be avoided.
Didanosine[2] / Indinavir[3] / Itraconazole Solution / EFV: Should be taken on an empty stomach (1 hr before or 2 hr after meals).
Grapefruit Juice: Increases saquinavir levels 40–100% but decreases indinavir AUC by 26%.

1 No food restriction when saquinavir is co-administered with RTV.
2 No food restriction when ddI is co-administered with TDF.
3 No food restriction when IDV is co-administered with RTV.

Table 14-8: Drugs of Special Consideration in Pregnant Women		
Drug Name	***FDA Class***	***Comments***
Terbutaline	B	Terbutaline has produced significant increases in birth weights (Briggs et al, 1998). Follow-up studies did not show increased adverse fetal outcomes (Svenningsen,1982).
Ritodrine	B	The manufacturer reports that ritodrine administration after the 20th wk of gestation has not been associated with an increase in fetal abnormalities.
Methergine	C	Indicated for postpartum uterine bleeding due to atony. According to the manufacturer, oral methylergonovine .2 mg 3–4 times daily may be administered to nursing mothers for a MAXIMUM of 1 wk postpartum to control uterine bleeding. Should not be given during antenatal period. Should not be used in women with hypertension (including pre-eclampsia) or heart disease.
Pain Medication		
Acetaminophen	B	Acetaminophen is considered safe for shortterm use in all stages of pregnancy.
Aspirin	C	Use of aspirin, especially of chronic or intermittent high doses, should be avoided in pregnancy. May increase risk for maternal or newborn hemorrhage. Full dose aspirin in 3rd trimester may result in premature closure of ductus arteriosus and may prolong gestation and labor. Acetaminophen is preferred analgesic/antipyretic during pregnancy.
Nonsteroidal anti-inflammatory drugs (NSAIDs)	C	Avoid in pregnancy. Due to prostaglandin synthesis inhibition, constriction of ductus arteriosus has been reported. Persistent pulmonary hypertension in the newborn has occurred when NSAIDs were used in 3rd trimester or near term. NSAIDs have been shown to inhibit labor and prolong pregnancy and have been associated with decreases in amniotic fluid volume.
Narcotic analgesic	B	Narcotic analgesics can be used short term in pregnancy. Avoid the use of high doses for prolonged periods near term as neonatal withdrawal can occur.

Table 14-9: Alternative/Complimentary Medication to Avoid in Pregnancy

Drug Name	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Vitamin A	A known teratogen at high doses in animal data.	A double-blind randomized trial of low-dose supplementation with vitamin A or beta-carotene (7000 µg retinol equivalent) in malnourished pregnant women reported a 40% decrease in newborn mortality (West, 1999). In a prospective case-controlled study of 423 exposures to 10,000 IU vitamin A during the first 9 wk an increased risk of major malformations was not reported (Mastroiacovo, 1999).	Until more data are available it is prudent to consume only the recommended dietary allowance of 8000 IU (which can be obtained by a balanced diet).
Vitamin B6 (in doses above 100 mg/day)	None	None	Avoid use of high doses in pregnancy. Possible health hazard: ataxia and peripheral neuropathy. *
Niacin (in doses above 500 mg immediate-release or 750 mg sustained-release)	None	None	Avoid use of high doses in pregnancy. Possible health hazard: GI symptoms (nausea, vomiting, diarrhea, abdominal cramps); liver disease.*
Selenium (in doses of greater than 800–1000 µg per day)	None	None	Avoid use of high doses in pregnancy. Possible health hazard: tissue damage.*
Ma-huang (*Ephedra sinica*)	None	None	Avoid use in pregnancy. The FDA warns against using Ma-huang (*Ephedra sinica*) due to possible health hazards including: high blood pressure, irregular heartbeat, nerve damage, injury, insomnia, tremor, headache, seizure, heart attack, stroke, and death.* Over 500 reports of adverse events including 8 fatalities have been reported to the FDA (CDC, 1996).
St. John's wort (*Hypericum perforatum*)	None	None	Metaanalysis of St. John's wort suggests that it was more effective than placebo and as effective as low-dose tricyclic antidepressants for short-term management of mild to moderately severe depression (Kim, 1999). Due to the lack of data in pregnancy the routine use of St. John's wort cannot be recommended. Major drug interaction: Indinavir trough concentration (C_{min}) decreases by 81% when co-administered with St. John's wort.

Table 14-9: Alternative/Complimentary Medication to Avoid in Pregnancy (*continued*)

Drug Name	*Animal Data*	*Human Experience in Pregnancy*	*Comments*
Chaparral herb (traditional American Indian medicine)	None	None	Avoid use in pregnancy. Possible health hazard: liver disease, possibly irreversible.*
Comfrey herb	None	None	Avoid in pregnancy. Possible health hazard: obstruction of blood flow to liver, possibly leading to death.*
Slimming/dieter's tea	None	None	Avoid in pregnancy. Possible health hazard: nausea, diarrhea, vomiting, stomach cramps, chronic constipation, fainting, possibly death.*
Germander herb	None	None	Avoid in pregnancy. Possible health hazard: liver disease, possibly leading to death.*
Lobelia herb (Indian tobacco)	None	None	Avoid in pregnancy. Possible health hazard: respiratory distress, tachycardia, hypotension, and possibly coma and death at higher doses.*
Magnolia-Stephania herb	None	None	Avoid in pregnancy. Possible health hazard: renal failure which may be irreversible.*
Willow bark herb	None	None	Avoid in pregnancy. Possible health hazard: allergic reaction (marketed as aspirin-free product, although it actually contains a precursor of aspirin with subsequent conversion to aspirin).*
Wormwood herb	None	None	Avoid in pregnancy. Possible health hazard: neurological symptoms, paresthesia, delirium and paralysis.*
Germanium mineral	None	None	Avoid in pregnancy. Possible health hazard: kidney damage, possibly death.*
L-tryptophan amino acid	None	None	Avoid in pregnancy. Possible heath hazard: eosinophilic myalgia syndrome, a potentially fatal blood dyscrasia. (FDA has limited its import into the US).*

** Note: Folic acid deficiency has been associated with increased risk of neural tube defects in the fetus and megaloblastic anemia in the mother. All pregnant women should receive sufficient dietary or supplementary folic acid to maintain normal maternal folate levels. The CDC recommends daily consumption of 0.4 mg of folic acid from diet and/or supplements for all women of childbearing age before the onset of pregnancy.*

Table 14-10: Dosing of Antiretroviral Agents in Renal Insufficiency and/or Hepatic Insufficiency

Drug Name	*Usual adult dose*	*Dosing for GFR > 50 mL/min*	*Dosing for GFR 10-50 mL/min*	*Dosing for GFR < 10 mL/min*	*Dosing in Hemodialysis (HD)*	*Dosing in Peritoneal dialysis (PD)*	*Hepatic clearance/ Comments*
Zidovudine (Retrovir®; AZT)	300 mg bid, or 200 mg tid	300 mg bid	300 mg bid	300 mg qd	300 mg qd	300 mg qd, a very small amount removed in PD (no supplemental dose needed) (Gallicano, 1992)	Extensive with significant first pass liver metabolism to GAZT. Excreted in urine as 14–18% unchanged drug and 60–74% GAZT. With GFR <20 mL/min half life is increased from 1.1–1.4 hr to 0.9 to 8 hours (with high inter patient variation).
Didanosine (Videx®; (Dideoxyinosine, ddI)	Wt >60kg dose: 400 mg qd (tabs) or 500 mg qd (powder). Wt <60kg dose: 250 mg qd (tabs) or 334 mg qd (powder). Dose can also be taken in two divided doses	Usual dose	50% of usual dose	25% of usual dose	25% of usual dose qd, on days of dialysis give post dialysis. 30% removal after a 3-hours session (Knupp, 1996)	25% of usual dose qd. Not removed with PD (Knupp, 1996)	Metabolism not fully evaluated. 20–40% excreted unchanged in the urine.
Stavudine (Zerit®; d4T)	Wt >60kg dose: 40 mg bid. Wt <60kg dose: 30 mg bid	Wt >60kg dose: 40 mg bid. Wt <60kg dose: 30 mg bid	Wt >60kg dose: 20 mg q12–24h. Wt <60kg dose: 15 mg q12–24	Wt >60kg dose: 20 mg q24h. Wt <60kg dose: 15 mg q24h	Wt >60kg dose: 20 mg q24h. Wt <60kg dose: 15 mg q24h, on days of dialysis dose post dialysis. (Grasela, 2000)	No data: Wt >60kg dose: 20 mg q24h. Wt <60kg dose: 15 mg q24h	Some hepatic metabolism and degradation by pyrimidine pathway. 40% of drug excreted unchanged.
Zalcitabine (Hivid®; (Dideoxycytidine, ddC)	0.75 mg tid	0.75 mg tid	0.75 mg bid	0.75 mg qd	No data: 0.75 mg qd, on days of dialysis dose post dialysis (likely to be dialysed out)	No data: 0.75 mg qd, on days of dialysis dose post dialysis	Insignificant liver metabolism. 62–75% excreted unchanged in the urine. 10% excreted unchanged in the feces.

Table 14-10: Dosing of Antiretroviral Agents in Renal Insufficiency and/or Hepatic Insufficiency (*continued*)

Drug Name	*Usual adult dose*	*Dosing for GFR > 50 mL/min*	*Dosing for GFR 10-50 mL/min*	*Dosing for GFR < 10 mL/min*	*Dosing in Hemodialysis (HD)*	*Dosing in Peritoneal dialysis (PD)*	*Hepatic clearance/Comments*
Lamivudine (Epivir®; 3TC)	150 mg bid or 300 mg qd	150 mg bid	150 mg qd	150 mg x1 then 50 mg qd (some recommend 150 mg qd due to good safety profile and convenience)	150 mg x 1 then 25–50 mg qd; Dose after HD	50 mg qd; Limited data	Intermittent hemodialysis does not warrant a further change in dose from that defined by CrCl (Johnson, 1996).
Emtricitabine (Emtriva®) (FTC)	200 mg qd	200 mg qd	30–49 mL/min: 200 mg q 48hr. 15–29 mL/min: 200 mg q 72 hr. < 15 mL/min: 200 mg q 96 hr	200 mg qd	200 mg q 96 hr. (30% of dose removed with 3 hr. HD; on days of dialysis, dose post-HD)		
Abacavir (Ziagen®) ABC	300 mg bid or 600 mg qd	300 mg bid	300 mg bid	300 mg bid	Usual dose [In 4 patients undergoing HD or PD, the pharmacokinetics of abacavir were not altered (Thompson, 1998)	Usual dose [In 4 patients undergoing HD or PD, the pharmacokinetics of abacavir were not altered (Thompson, 1998)	Pharmacokinetics are unchanged in renal failure (Izzedine, 2001b). Animal studies: 12% unchanged Abacavir in the urine. Only 2% metabolized to carbovir. Consider ABC 200 bid with hepatic insufficiency.
Tenofovir (Viread®)	300 mg qd	300 mg qd 30–49 mL/min: 300 mg q48h.	<30 mL/min: 300 mg q72–96h	300 mg q7days	300 mg q 7 days following dialysis (54% removed with 4 hours high flux HD-healthy volunteer PK data) May require more if patient requires more than three 4-hour HD sessions.	No data: Not recommended by manufacturer. Interval adjustment likely.	Note: Dosing recommendations based on single dose PK data in healthy volunteer. HIV infected patients with Cr Clearance less than 60 mL/min were excluded from clinical trials.

Efavirenz (Sustiva®)	600 mg qhs	Usual dose**	Usual dose likely**	Usual dose likely**	600 mg qhs, No significant removal with HD (Izzedine, 2000a)	600 mg qhs, Not removed with PD (Gill, 2000)	Data limited in renal failure. Extensive liver metabolism 14–34% excreted in urine as glucuronide metabolite and 16–61% excreted in stool.
Nevirapine (Viramune®)	200 mg qd x 14 days then 200 mg bid	Usual dose	Usual dose	Usual dose	Usual dose post-HD. Small amount removed (Izzedine, 2001a)	Usual dose post dialysis. 16 mg removed in dialysate in a 24 hour period.	Extensive liver metabolism to hydroxylated metabolites which are renally cleared. Less than 5% excreted unchanged in the urine.
Delavirdine (Rescriptor®)	400 mg tid	Usual dose**	Usual dose likely**	Usual dose likely**	No data: Unlikely to be removed in dialysis due to high protein binding**	No data: Unlikely to be removed in dialysis due to high protein binding**	Extensive liver metabolism.
Nelfinavir (Viracept®)	750 mg tid or 1250 mg bid	Usual dose	Usual dose	Usual dose	Usual dose. Removed with HD, MUST be given post-HD on days of dialysis (Izzedine, 2000a)	Usual dose. Not removed with PD (Tillotson, 2000)	Pharmacokinetics are unchanged in renal failure (Izzedine, 1999). Extensive liver metabolism to active oxidative metabolites. Major biliary excretion with less than 2% renal excretion.
Indinavir (Crixivan®)	800 mg tid* or IDV 800/RTV 100–200 mg bid (increased incidence of kidney stones with RTV 200 mg–generally recommended only in pt also on EFV or NVP)	Usual dose*	Usual dose	Usual dose	Usual dose. Very small amount removed in dialysis (Izzedine, 2000b)	No data: Usual dose likely** (Low probability of significant amount being removed in dialysis due to low protein binding)	Pharmacokinetics are unchanged in renal failure (Izzedine, 2000b). Extensive liver metabolism to glucuronide and oxidative metabolites. Major biliary excretion with approximately 10% renal excretion.

Table 14-10: Dosing of Antiretroviral Agents in Renal Insufficiency and/or Hepatic Insufficiency (*continued*)

Drug Name	*Usual adult dose*	*Dosing for GFR > 50 mL/min*	*Dosing for GFR 10-50 mL/min*	*Dosing for GFR < 10 mL/min*	*Dosing in Hemodialysis (HD)*	*Dosing in Peritoneal dialysis (PD)*	*Hepatic clearance/Comments*
Ritonavir (Norvir®)	600 mg bid (High dose not well tolerated, dose may be lowered if used with another PI)	Usual dose	Usual dose	Usual dose	Small amount dialyzed out, dose post HD (Izzedine, 2001b)	No data: Usual dose likely**, dose post dialysis on days of dialysis. (Unlikely to be removed in dialysis due to high protein binding, however due to low volume of distribution small amount possibly removed)**	Pharmacokinetics are unchanged in renal failure (Izzedine, 2001b). Extensive liver metabolism to isopropylthiazole (active metabolites) and other inactive metabolite. Major biliary excretion with approximately 4–10% renal excretion.
Saquinavir (Invirase® (capsule); Fortovase® (soft gel capsule)	Invirase 600* mg tid (not recommended as sole PI); Fortovase 1200 mg tid or INV 1000 mg/RTV 100 mg q12h.	Usual dose	Usual dose	Usual dose	Not dialyzed out (Izzedine, 2001b)	No data: Usual dose likely** (Unlikely to be removed in dialysis due to high protein binding and large volume of distribution.)	Pharmacokinetics are unchanged in renal failure (Izzedine, 2001b). Extensive first pass metabolism which accounts for saquinavir's low bioavailability. Major biliary excretion with only 1–3% renal excretion.
Amprenavir (Agenarase®)	1,200 mg bid* or APV 600 mg/RTV 100 mg q12h.	Usual dose	Usual dose likely	Usual dose likely	No data: Usual dose likely	No data: Usual dose likely	Impaired hepatic function moderate—consider dose reduction 450 mg bid; severe—300 mg bid.
LPV/RTV (Kaletra®)	400/100 mg bid	Usual dose	Usual dose likely	Usual dose likely	Usual dose. Not removed with HD (Izzedine, 2001c)	No data: Usual dose likely	

Atazanavir (Reyataz®)	400 mg qd* or ATV 300/RTV 100 qd.	Usual dose	Usual dose likely	Usual dose likely	Usual dose. Dose post-HD	Usual dose likely	ATV is not recommended in patients with severe hepatic insufficiency. ATV AUC increased by 45% with mild to moderate hepatic impairment. Consider decreasing ATV to 300 mg/day in subjects with mild to moderate hepatic impairment. Clinical data using the lower dose in hepatic insufficiency has not been assessed.
Fosamprenavir (Lexiva®)	1400 mg* q12h or fAPV 700/100 RTV q12h.	usual dose	usual dose likely	usual dose likely	No data. Usual dose likely.	No data. Usual dose likely.	
Enfuvirtide (Fuzeon®)	90 mg SQ q12h	usual dose	usual dose likely	usual dose likely	No data. Usual dose likely.	No data. Usual dose likely.	

** Approved adult dose, but usually use lower doses with ritonavir boosting for most PIs.*

*** Prediction based on pharmacokinetic principles. Drugs likely to be removed have a Vd <0.7 L/kg, protein binding <80%, and size <1500 Dalton*

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