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Interactions of Antiretroviral Drugs

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Abstract

The rapid expansion of antiretroviral agents in recent years has resulted in a growing potential for drug interactions, either between themselves or with other pharmacologically active compounds commonly used in the management of HIV complications. All protease inhibitors and non-nucleoside reverse transcriptase inhibitors are metabolized by cytochrome P450. At the same time, these drugs have enzyme inducing or inhibiting properties, which explains the high risk of drug interactions that their use proposes. Some of these interactions may lead to undesirable outcomes, such as severe adverse effects or sub-therapeutic drug concentrations which increase the risk of antiretroviral resistance. However, not all is negative; the prior knowledge of antiretroviral interactions can be used for the design of new regimens, optimizing doses or drug intervals in order to ensure adequate drug concentrations, or to obtain synergetic effects. Antiretroviral interactions can be classified in three main groups: Those that require a change in drug dosage, contraindicated combinations, and interactions in which special monitoring is advisable. Comprehensive tables of clinically relevant antiretroviral interactions are provided.

Key words

HIV. Antiretrovirals. Drug interactions. Side effects. Toxicity.

The introduction of highly active antiretroviral therapies (HAART) for the treatment of HIV infection in recent years has raised a growing interest in drug interactions. An increase in the number of available antiretroviral drugs, their wide use in combinations, a greater knowledge about cytochrome P450, and a more qualified information demanded by HIV-infected persons are the main reasons which explain the emergence of this field[1]. However, many issues on drug interactions remain unresolved, and data are scarce in many areas. This fact explains the morbidity associated with the use of antiretroviral therapy is now a major issue.

Information on drug interactions in HIV infection is limited. The rapid approval of many of the new antiretroviral agents, without accurate pharmacokinetic and/or pharmacodynamic studies, mainly in the face of being given with other drugs, explains this fact. Many metabolic studies on drug interactions are performed on human liver microsomes *in vitro*, and results are extrapolated to *in vivo*. Although this approach allows one to build a profile of the expected significant interactions for that compound, discrepancies between *in vitro* and *in vivo* results do exist, mainly for drugs such as ritonavir, which possess both inhibitory and inducer potentials[2].

Another aspect regarding the lack of information on drug interactions is derived from methodological questions. For example, some investigations have been performed as single dose studies, which do not always predict steady-state interactions after multiple doses in clinical practice. In other studies, drug interactions have been examined in healthy volunteers, and not in HIV-infected persons, in whom

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pharmacokinetics are often altered and more complex. Moreover, drug interaction studies often examine the interaction between two drugs, but currently most HIV-infected patients are receiving three or more drugs.

The large number of potential antiretroviral combinations also complicates the execution of investigations of drug interactions. Currently, the number of antiretroviral drugs available in the market or through compassionate protocols has increased considerably. There are six nucleoside reverse transcriptase inhibitors (NRTIs), three non-nucleoside (NNRTIs), and five protease inhibitors (PI). In fact, a solid body of pharmacological information on each of these combinations is not yet available.

Many drug interactions are listed in the product label, but few studies have been performed to evaluate the extent of these interactions in clinical settings not related to the industry. Drug interaction is sometimes defined as potential (could occur on the basis of the pharmacokinetic or pharmacodynamic profile), but clinical experience is lacking. In other instances, despite drug interaction studies have been conducted, no specific recommendations about doses or changes in drug therapy have been made.

They must always face issues related to drug interactions. When clinicians need to switch therapy as a result of immunologic and/or virologic failure, drug intolerance, or toxicity, the most problematic combinations are those including PI. In a retrospective study performed to estimate the potential for drug interactions in HIV-infected patients who add a PI to their previous therapy, the authors found that the probability of interactions were 31% for indinavir, 42% for saquinavir, and 77% for ritonavir[3].

The management of drug interactions in HIV-positive subjects is rapidly evolving and is becoming increasingly complex. However, only a few of them are clinically relevant, and will be the subject of this paper.

Basic concepts on drug interactions

Drug interactions can be classified as pharmacodynamic (synergy or antagonism in toxicity or efficacy) or as pharmacokinetic (alterations in absorption, distribution, metabolism or excretion of a drug as result of another). Most drug interactions in HIV-infected patients are related to alterations in absorption or hepatic metabolism of drugs. The cytochrome P450 system is the major enzyme complex involved in drug liver metabolism. More than thirty isoenzymes have been identified, but CYP3A4, CYP2D6 and CYP2C9/19 are the main ones involved in the metabolism of antiretroviral molecules[4]. Antiviral drugs can behave as substrates, inducers or inhibitors of the CYP450 isoenzymes. Moreover, some drugs can be metabolized by more than one isoenzyme or may inhibit or induce the activity of one or several isoenzymes. Overall, interactions appear when drugs sharing similar metabolic pathways are taken together.

Drugs favoring the metabolism of others are called 'enzyme inducers'. The pharmacological consequence of enzyme induction is a decrease in serum levels of drugs whose metabolism is stimulated. The clinical consequence of this is the higher risk of therapeutic failure, often as consequence of the development of resistance. Examples of drug inducers are rifamycins and anticonvulsant drugs. Among the antiretroviral agents, nevirapine is a potent inducer.

Drugs inhibiting the metabolism of others are called 'enzyme inhibitors'. They produce an increase in serum levels of affected drugs, and the risk of drug toxicity increases substantially. For instance, recent reports have pointed out the higher risk of vascular complications associated to the use of sildenafil (Viagra®) in subjects receiving PI. Overall, PI are inhibitors of the CYP450 system, although there exist differences in potency between them, being ritonavir the most and saquinavir the less potent, respectively. Indinavir and nelfinavir show an intermediate inhibitory potency[5]. Ritonavir is also a significant inhibitor of the 2D6 isoenzyme system. At the same time, PI are substrates for the CYP3A4 isoenzyme.

In respect to reverse transcriptase inhibitors, nucleosides are not substrates, inhibitors or inducers of the CYP450 system and, except for zidovudine, which is metabolized by the glucuronosyltranferase, few metabolic drug interactions occur with them[6]. Among NNRTIs, delavirdine inhibits both CYP3A4 and CYP2C9 isoenzymes and, therefore, indirectly increases the levels of PI. Conversely, nevirapine is a CYP3A4 inducer, and efavirenz is both an inducer and an inhibitor of the CYP3A4 isoenzyme[1].

Drug interactions requiring dosage adjustments

Many drug interactions can be successfully overcome by making appropriate changes to drug doses. In most cases, pharmacokinetic mechanisms are involved. Changes of dosages generally depend on magnitude of the effect in pharmacokinetic parameters (AUC, C_{max} and C_{min}), but no rules are yet defined. In our opinion, changes in AUC above 30% should require a change in dosage. However, when the drug affected has a large therapeutic range (its threshold for toxicity is far from its threshold for antiviral activity), the interaction can be of benefit since drug activity can be increased. This is the case for saquinavir, which has a very low oral bio-availability (4% when administered with food) due to extensive first-pass intestinal metabolism through CYP3A4; however, in combination with ritonavir, a potent inhibitor of this isoenzyme, saquinavir achieves plasma levels 20-fold higher than when is taken alone. Likewise, delavirdine increases saquinavir serum levels by 520%[7], clarithromycin by 177%[1], and ketoconazole by 130%[1].

Many harmful drug interactions can be avoided by appropriate changes in dosages. Table 1 de-

scribe those that clinicians particularly need to know about. Ritonavir causes a 77% increase in the AUC of clarithromycin, a macrolid antibiotic used in the treatment of disseminated *Mycobacterium avium* complex infection, as well as occasionally in community-acquired pneumonias. No dosage adjustment appears necessary in patients with normal renal function, but a 50% reduction in clarithromycin dosage is advisable in patients with creatinine clearance below 60 mL/min[8].

Dual protease inhibitor-based regimens are currently generating great interest, as a result of the benefit provided by their pharmacokinetic interactions and distinct resistance profile. When ritonavir is combined with indinavir, an increase of the AUC of indinavir by up to 475% is seen. Although indinavir has no effect on ritonavir pharmacokinetics, a reduction of both drugs to 400 mg bid (alternatively, ritonavir 100 mg and indinavir 800 mg, both bid) is advisable[9]. We have already mentioned the benefit of the saquinavir-ritonavir combination, which is currently the most widely used PI combination. At doses of 400 mg bid, ritonavir increases the AUC of saquinavir-SGC by 120%, and by 1587% of saquinavir-HCG[10,11].

The interaction between ritonavir and nelfinavir is very complex because both induction and inhibition mechanisms are involved in a bi-directional way. The net effect is an increase of 152% in the plasma concentrations of nelfinavir, while no significant changes are seen in ritonavir levels[12]. Moreover, the levels of nelfinavir metabolite M8 are also increased by ritonavir, suggesting that nelfinavir metabolism might be induced by ritonavir.

The combination of indinavir and nelfinavir allows a reduction in the dose of both drugs, since they act as enzyme inhibitors[13] (Table 1). Likewise, nelfinavir increases saquinavir-SGC levels up to 5-fold, allowing the use of saquinavir twice daily[14].

The metabolism of NNRTIs is also carried out by cytochrome P450. Nevirapine may decrease the plasma concentrations of PI. The AUC of indinavir is affected by nevirapine, and indinavir dosage should be increased[15]. In contrast, nevirapine has no significant effect on ritonavir's AUC. The effect of nevirapine on nelfinavir metabolism is controversial. In one study a mean reduction of 49% in the AUC of nelfinavir was seen[16], while another showed an 8% increase in the AUC of nelfinavir[17]. Lastly, some authors have noted that the observed decrease in nelfinavir concentrations most likely reflects an auto-induction of nelfinavir metabolism[18].

Efavirenz is also an enzyme inducer. It reduces the AUC of indinavir by 35%[19], and consequently the dose of indinavir should be increased to 1000 mg tid. Since efavirenz has also enzyme inhibiting properties, an increase in nelfinavir[20] and ritonavir[21] serum concentrations of 15% and 22%, respectively, has been observed in combination therapy. Although this is a modest increase in the AUC of PI, some authors have considered reducing ritonavir doses to 500 mg twice daily. No changes are recommended for nelfinavir.

Delavirdine is a potent cythocrome P450 inhibitor, and increases serum concentrations of all PI: by 5-fold the AUC of saquinavir[11], by 3-fold for indinavir[22], and 2-fold for nelfinavir[23]. Cases of neutropenia have been described in patients receiving nelfinavir and delavirdine. Therefore, until more data becomes available. This combination must be used with caution. The AUC of ritonavir is increased in 60% by delavirdine[24]; therefore, a reduction in ritonavir doses to 400 mg bid is recommended. Ritonavir has no effect on delavirdine serum levels.

The co-administration of indinavir[27] or nelfinavir[25] with rifabutin results in a 2-fold increase in the AUC of rifabutin. At the same time, the serum levels of both PI are decreased by nearly 30%. The effect results from an induction of CYP3A4 by rifabutin together with an inhibition of the same isoenzyme by PI. Rifabutin should be reduced to 150 mg/day. This lower rifabutin dose may cause less induction of indinavir or nelfinavir metabolism, and allows the use of both drugs with slightly higher doses.

Rifampicin induces nevirapine metabolism, and reduces its AUC by 37%. An increase in nevirapine dosage to 300 mg bid has been recommended[26].

The administration of ketoconazole with indinavir forces the reduction of indinavir dosage to 600 mg tid, since ketoconazole is a CYP3A4 inhibitor, increasing the AUC of indinavir by 68%[27]. As an alternative, fluconazole can be given with indinavir without adjustments of doses[28].

Contraindicated drug combinations

The harmful effect of some drug interactions recommends to avoiding their concomitant use (Table 2). This is the case of cisapride, non-sedating antihistamine drugs, and also ergotamine derivatives, whose plasma levels can be largely increased when combined with PI or some NNRTIs. On the other hand, some drugs acting as enzyme inducers can drastically reduce the level of antiretroviral drugs. For instance, nevirapine decreases the AUC of saquinavir by more than 25%[29], a deleterious effect considering the already low bio-availability of this PI. Even more pronounced effects have been described with efavirenz. Therefore, saquinavir should not be used with NNRTIs[30]. Likewise, saquinavir should not be prescribed together with rifabutin, another hepatic inducer[31]. In respect to rifampicin, which is a potent inducer of the CYP3A4, dramatic reductions in PI serum concentrations are seen[32]. Rifampicin decreases the AUC of saquinavir-SGC by 84%[11], ritonavir by 35%[2], indinavir by 89%[30], and nelfinavir by 82%[30]. Therefore, the concurrent use of PI and rifampicin is not recommended. Delavirdine is also contraindicated, since the interaction with rifampicin results in nearly undetectable delavirdine serum concentrations[33]. On the other hand, rifabutin should be avoided in subjects taking ritonavir, since rifabutin levels increase significantly[34], and related side effects such as uveitis, skin discoloration or arthralgias are common[35].

Table 1. *Drug interactions requiring adjustments of antiretroviral dosages.*

Antiretroviral drug (usual dosage)	Concomitant drug (usual dosage)	New dosage	Explanation	References
Protease inhibitors				
Amprenavir (1200 mg bid)	Rifabutin (300 mg/day)	↓ Rifabutin (150 mg/day)	Rifabutin metabolism inhibition by amprenavir. Risk of rifabutin toxicity	1
	Indinavir (800 mg tid)	↑ Indinavir (1000 mg tid)	Indinavir metabolism induction by amprenavir	1
Indinavir (800 mg tid)	Delavirdine (400 mg tid)	↓ Indinavir (600 mg tid)	Indinavir metabolism inhibition by delavirdine	22
	Efavirenz (600 mg/day)	↑ Indinavir (1000 mg tid)	Indinavir metabolism induction by efavirenz	19
	Ketoconazole (200mg bid)	↓ Indinavir (600 mg tid)	Indinavir metabolism inhibition by ketoconazole	27
	Nelfinavir (750 mg tid)	↓ Indinavir (1000 mg bid) + ↓ Nelfinavir (750 mg bid)	Reciprocal drug metabolism inhibition	13
	Nevirapine (200 mg bid)	↑ Indinavir (1000 mg tid)	Indinavir metabolism induction by nevirapine	15
	Rifabutin (300 mg/day)	↑ Indinavir (1000 mg tid) + ↓ Rifabutin (150 mg/d)	Reciprocal drug metabolism inhibition and induction	27
	Ritonavir (600 mg bid)	↓ Indinavir (400 mg bid) + ↓ Ritonavir (400 mg bid)	Reciprocal drug enzyme inhibition Potential for cross-resistance	9
Nelfinavir (750 mg tid)	Delavirdine (400 mg tid)	Under study. Dosage recommendation not yet available.	Increased risk of neutropenia	23
	Rifabutin (300 mg/day)	↑ Nelfinavir (1000 mg tid) + ↓ Rifabutin (150 mg/day)	Reciprocal drug metabolism inhibition and induction	25
	Saquinavir-SGC (1200 mg tid)	↓ Saquinavir-SGC (800 mg tid)	Saquinavir metabolism inhibition by nelfinavir	14
	Ritonavir (600 mg bid)	↓ Nelfinavir (500 mg bid) + ↓ Ritonavir (400 mg bid)	Reciprocal drug enzyme inhibition	12
Ritonavir (600 mg bid)	Clarithromycin (500 mg bid)	↓ Clarithromycin (250 bid if crCL < 60 mL/min)	Clarithromycin metabolism inhibition by ritonavir	8
	Delavirdine (400 mg tid)	↓ Ritonavir (400 mg bid)	Ritonavir metabolism inhibition by delavirdine	24
	Efavirenz (600 mg/day)	↓ Ritonavir (500 mg bid)	Ritonavir metabolism inhibition by efavirenz	21
	Saquinavir-HGC (600 mg tid) Saquinavir-SGC (1200 mg tid)	↓ Ritonavir (400 mg bid) + ↓ Saquinavir-HGC (400 mg bid)	Reciprocal drug enzyme inhibition	10

Reverse transcriptase inhibitors				
Nevirapine (200 mg bid)	Rifampin (600 mg/day)	↑ Nevirapine (300 mg bid)	Nevirapine enzyme induction metabolism by rifampin	26
Zidovudine (250-300 mg bid)	Interferon β 1a	Decrease 50% in zidovudine dosage	Inhibition of glucuronization by IFN	39
	Probenecid (in cidofovir treatment)	Decrease 50% in zidovudine dosage	Inhibition of hepatic glucuronization and renal secretion by probenecid	39

The metabolism of terfenadine to its pharmacologically active metabolite terfenadine carboxylate is inhibited by PI. A marked increase in terfenadine serum concentrations can result in potentially lethal ventricular arrhythmias. An inhibition of the CYP3A4 isoenzyme by PI explains this harmful interaction[30]. Likewise, symptoms of ergotism such as abdominal pain, dizziness, confusion, somnolence, and tingling of extremities have been described with ergotamine derivatives in patients treated with ritonavir[36].

Interaction between antiretroviral compounds and recreational drugs is also clinically significant. MDMA (Ecstasy) is an amphetamine-like compound metabolized by demethylation by CYP2D6. Drugs inhibiting this cythocrome, such as ritonavir, impair MDMA detoxification, and large increases in serum levels are expected to occur in patients taking these compounds together. A case of death from cardiorespiratory arrest has been described in a patient on ritonavir who took 180 mg of MDMA. Blood concentrations of the drug were 10-fold higher than anticipated[37], and death was consistent with a severe serotoninergic reaction to MDMA.

An excessive sedation occurred in a patient on saquinavir-HGC who received 5 mg of midazolam iv as sedative cover for bronchoscopy[38]. The prolonged sedation was the result of a drug interaction, since both saquinavir and midazolam are metabolised by CYP3A4.

Lastly, the contraindication for some drug combinations depends on the possibility of synergistic toxicity. For instance, zidovudine should be avoided when taking ganciclovir, ribavirin, or trimetoprim-sulfamethoxazole at high doses, as used for the treatment of *Pneumocystis carinii* pneumonia[39], since a high risk of hematologic toxicity exists, mainly anemia and/or granulopenia.

Drug combinations requiring close monitoring

Many drugs, such as benzodiazepines, opiates, oral anticoagulants and oral contraceptives, need special monitoring when they are given concomitantly with antiretroviral agents. Regarding benzodiazepines, the interaction studies are controversial. According to manufacturers, the use of alprazolam is contraindicated with ritonavir[44]. However, the AUC of alprazolam is reduced only by 12% when it is given concomitantly with ritonavir in healthy volunteers[40]. This is an example of the lack of concordance between *in vitro* and *in vivo* studies.

Methadone is widely used in the treatment of opiate addiction. In HIV-infected subjects on methadone programs, drug interactions with anti-retrovirals agents are of concern. There is controversy as to effect of PI on methadone metabolism, since discrepancies results have been collected between *in vitro* and *in vivo* studies. Methadone undergoes extensive biotransformation in the liver via N-demethylation and cyclization. The CYP450 enzymes involved in its metabolism are CYP3A4 and other not yet identified isoenzymes. Human liver microsomes studies have demonstrated that ritonavir inhibits N-demethylation of methadone. Therefore, an increase in methadone levels should be expected[41]. However, the co-administration of ritonavir and methadone in patients results in an unexpected 36% decrease in the AUC of methadone[42]. In another study, the addition of ritonavir or nelfinavir led to a reduction in methadone steady-sate concentrations, in the range of 40-50%, whereas the addition of saquinavir or indinavir had no effect on methadone serum concentrations[43]. Therefore, clinicians must be alert for symptoms of methadone withdrawal (diaphoresis, tachycardia, etc.) in patients receiving PI. Although data on NNRTIs and methadone interactions are still scarce, similar effects of methadone withdrawal are seen with nevirapine and efavirenz.

The information available on interactions between PI and oral anticoagulants is sporadic and contradictory. When ritonavir was approved, the package insert indicated that a moderate increase (1.5-3 times) in the AUC of R-warfarin was observed in patients receiving ritonavir. However, a moderate increase or decrease in the AUC could also occur with S-warfarin, the more potent enantiomer[44]. A report in 1997 described a dramatic decrease in the anticoagulant activity of acenocoumarol after ritonavir onset. The effect was sustained even when the doses of the coumarin derivative were increased[45]. Another more recent report[46] described a decrease in the anticoagulant activity of warfarin in a patient receiving indinavir and ritonavir in combination. This unexpected reduction in warfarin levels has been noted in another recent report, following the addition of ritonavir[47]. Conversely, a case of hypercoagulability has been recorded in a subject being on saquinavir and warfarin[48].

Table 2. *Contraindicated drug combinations.*

Drug	Affected drug	Mechanisms	Alternative options	References
Efavirenz	Saquinavir SGC	Efavirenz decrease saquinavir concentrations in 60%	Do not use saquinavir as the sole protease inhibitor.	30
Nevirapine	Saquinavir HGC	Risk of saquinavir inefficacy	Other protease inhibitors (Table 1)	29
Protease inhibitors	Cisapride	Risk of cisapride cardiotoxicity	Metoclopramide	30
	Astemizol Terfenadine	Risk of antihistamine cardiotoxicity	Loratadine, cetirizine, fexofenadine	30
	Ergotamine	Risk of ergotism (vomiting, nausea, leg ischemia)	Sumatriptan, non opiod analgesics (aspirin, acetominophen)	36
	Rifampicin	Rifampin induces antiretroviral metabolism and reduces serum concentrations in more than 80%, with antiviral inefficacy risk	Rifabutin (Table 1)	32
Delavirdine	Rifabutin	Risk of rifabutin toxicity	Clarithromycin or change to other antiretroviral drug	52
Ritonavir	Rifabutin	Risk of rifabutin toxicity	Clarithromycin or change to other antiretroviral drug	34
	Metronidazole	Disulfiram reaction	Avoid combination	44
	MDMA	Fatal drug interaction	Avoid combination	37
Saquinavir HGC	Rifabutin	Risk of subtherapeutic saquinavir levels	Other protease inhibitors	31
	Midazolam	Prolonged sedation reported	Avoid combination	38
Zalcitabine	Pentamidine	Increases risk of severe pancreatitis	Hold zalcitabine during pentamidine treatment	53
Zidovudine	TMP/SMX	Increased risk of anemia and neutropenia	Hold zidovudine when high-dose of TMT/SMX for *P. Carinii* pneumonia	53
	Ganciclovir	Additive granulocytopenia	Change to other antiretroviral agents such as stavudine or didanosine	39
	Pyrimethamine	Decreased pyrimethamine effect	Hold zidovudine during therapy for toxoplasmosis or use other antiretrovirals	53

Both ritonavir[49] and nelfinavir[12] can induce glucuronosyltransferases, and decrease the AUC of ethinylestradiol by 40%. Although the clinical significance of these changes is unknown, alternative methods of contraception must be recommended when these antiretrovirals are used. On the other hand, indinavir increases serum concentrations of ethynilestradiol by 24%, which does not demand dosage changes.

The measurement of drug serum concentrations is recommended for molecules such as cyclosporine and anticonvulsant drugs, which may be greatly affected by PI. In the case of theophylline, a 43% reduction in AUC has been described with ritonavir[50]. This PI is a CYP1A2 inductor, which explains the reduction of serum theophylline levels are reduced. Therefore, serum concentration monitoring and dosage adjustment of theophylline are recommended in patients receiving ritonavir concomitantly. A case of increasing levothyroxine requirements in a patient that started on ritonavir has been described[51]. Most likely, an increase in the levothyroxine glucuroconidation caused by ritonavir explained this observation.

When evaluating combinations of drugs, the toxicity profile of the agents to be used needs to be considered. Drugs with the same spectrum of toxicity may result in additive or synergistic adverse effects. Some examples are observed in table 3. Peripheral neuropathy is a problem with didanosine, zalcitabine, stavudine and, to a lesser extent, with PI. Patients should be monitored carefully for this complication when these drugs are combined, or when some of them are taken with other potentially neurotoxic agents, such as isoniazid, ethambutol, cisplatin or vincristine.

Table 3. *Drug combinations requiring close monitoring.*

Drug	Concomitant drug	Comments	References
Adefovir	Nephrotoxic drugs: amphotericin B, aminoglycosides, pentamidine, foscarnet, cidofovir, vancomycin	Monitoring renal function thrice weekly Dose of antiretroviral drugs eliminated by glomerular filtration (didanosine, lamivudine, stavudine, zalcitabine) must be adjusted according to the patient's renal function	1
Delavirdine	Saquinavir	Increased hepatotoxicity observed Monitor liver function tests	7
Didanosine	Pentamidine, zalcitabine, valproic acid, ethanol, antimonial compounds	Monitor amylase and lipase monthly because of increased risk of pancreatitis	53
	Ganciclovir	Monitor didanosine toxicity (neuropathy, diarrhea, etc.) since ganciclovir increases serum didanosine concentrations	53
	Neurotoxins: Dapsone, ethionamide, isoniazid, stavudine, zalcitabine	Increases risk of peripheral neuropahty	53
Protease inhibitors	Oral anticoagulants	Monitor INR. A decrease in oral anticoagulant activity is expected	46, 47
Ritonavir	Theophylline	Monitor serum theophylline concentrations and change doses if necessary	50
Ritonavir, Nelfinavir	Methadone	Increases in methadone doses can be required. Indinavir and saquinavir are safer for methadone maintenance therapy	43
	Oral contraceptives	Alternative use methods of contraception Indinavir does not interact	49
Saquinavir-HCG	Cyclosporin	3-fold increase in cyclosporin concentrations Monitor cyclosporin concentrations	54
Stavudine Zalcitabine	Neurotoxins: dapsone, ethionamide, isoniazid, didanosine, vincristine, protease inhibitors	Monitor peripheral neuropathy	53

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