Clin Pharmacokinet 2003; 42 (3): 223-282
0312-5963/03/0003-0223/$30.00/0

Drug Interactions Between Antiretroviral Drugs and Comedicated Agents

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Abstract

HIV-infected individuals usually receive a wide variety of drugs in addition to their antiretroviral drug regimen. Since both non-nucleoside reverse transcriptase inhibitors and protease inhibitors are extensively metabolised by the cytochrome P450 system, there is a considerable potential for pharmacokinetic drug interactions when they are administered concomitantly with other drugs metabolised via the same pathway. In addition, protease inhibitors are substrates as well as inhibitors of the drug transporter P-glycoprotein, which also can result in pharmacokinetic drug interactions. The nucleoside reverse transcriptase inhibitors are predominantly excreted by the renal system and may also give rise to interactions.

This review will discuss the pharmacokinetics of the different classes of antiretroviral drugs and the mechanisms by which drug interactions can occur. Fur-

thermore, a literature overview of drug interactions is given, including the following items when available: coadministered agent and dosage, type of study that is performed to study the drug interaction, the subjects involved and, if specified, the type of subjects (healthy volunteers, HIV-infected individuals, sex), antiretroviral drug(s) and dosage, interaction mechanism, the effect and if possible the magnitude of interaction, comments, advice on what to do when the interaction occurs or how to avoid it, and references.

This discussion of the different mechanisms of drug interactions, and the accompanying overview of data, will assist in providing optimal care to HIV-infected patients.

The treatment of HIV-1 infection has been improved markedly during recent years by the introduction of new classes of antiretroviral drugs, resulting in decreased morbidity and mortality.[1-3] Antiretroviral therapy generally involves combination therapy and consists typically of three or four drugs, in most cases from different drug classes.[4] Although regimens have recently become more convenient after the reduction in dietary restrictions and pill burden due to (i) the implementation of boosting protease inhibitors (PIs) with ritonavir[4,5] and (ii) the introduction of coformulations (lopinavir and ritonavir [Kaletra™**1**]; lamivudine, zidovudine, and abacavir [Trizivir®]; lamivudine and zidovudine [Combivir®]), the treatment still requires much attention.

HIV-infected individuals usually have an impaired immune response. Therefore, they are frequently confronted with opportunistic infections and malignancies. In addition, comorbidity such as drug dependence, psychiatric disorders, neurological manifestations of HIV disease (HIV-1 dementia complex) or hepatic disease may also be present. Due to this comorbidity, a wide variety of drugs (e.g. antidepressives or antibacterials) is used in addition to the antiretroviral regimen. Since both non-nucleoside reverse transcriptase inhibitors (NNRTIs) and PIs are extensively metabolised by the cytochrome P450 (CYP) system,[6,7] there is a considerable potential for pharmacokinetic interactions when these drugs are administered concomitantly with drugs metabolised via the same pathway. Awareness, recognition and management of drug interactions are important in the optimisation of pharmaceutical care to HIV-infected patients, helping to prevent adverse events and/or loss in efficacy of the drugs administered.[8-11] This review presents a tabulated overview of interactions of antiretroviral drugs and comedicated agents based on drug-drug interaction studies, case reports, population pharmacokinetic data, *in vitro* studies and theoretical grounds. Furthermore, a concise review is presented of the pharmacokinetics and mechanisms of interaction of antiretroviral drugs.

1 Use of tradenames is for product identification only and does not imply endorsement.

1. Methods

A Medline search was performed using the keywords 'human immunodeficiency virus', 'pharmacokinetics', 'metabolism', 'drug interactions' and the names of the individual antiretroviral drugs. Information gathered from a review of the literature, including peer-reviewed journals, abstracts from large congresses, review articles and package inserts, has been incorporated in the overview. The drug interactions were tabulated with the comedicated agent (as a single drug or as a specific drug class) in alphabetical order. The following items were described in as much detail as possible: coadministered agent and dosage, type of study that was performed to study the specific drug interaction, the subjects involved and, if specified, the kind of subjects (healthy volunteers, HIV-infected individuals, sex), antiretroviral drug and dosage, mechanism of interaction, the effect, comments, advice on what to do when the interaction occurs

or how to avoid the interaction, and references used to assemble the information. Advice on how to cope with specific interactions will be given as completely and clearly as possible. This review will only focus on drug interactions between antiretroviral drugs and comedicated agents, and not on drug interactions among antiretroviral drugs. For information on this subject, we refer to earlier published reviews.[12-15]

2. Pharmacokinetics of Antiretroviral Drugs

2.1 Nucleoside Reverse Transcriptase Inhibitors

At this moment, six representatives of this class are licensed: zidovudine (AZT), didanosine (DDI), zalcitabine (DDC), stavudine (D4T), lamivudine (3TC), and abacavir (ABC). The NRTIs are prodrugs that require intracellular phosphorylation to the active dideoxynucleoside triphosphates, which compete with the natural substrates for HIV reverse transcriptase (deoxynucleoside triphosphates) for incorporation into newly synthesised proviral DNA. The NRTIs lack a 3′-hydroxyl group, thereby preventing growth of the DNA and resulting in termination of virus replication.[16] As a class, the NRTIs are predominantly excreted by the renal system (tubular secretion) and interactions based upon CYP are not regularly encountered.[17] However, drugs influencing renal clearance or intracellular phosphorylation may cause drug interactions with the NRTIs. Table I presents an overview of the pharmacokinetic parameters of each NRTI.

2.2 Non-Nucleoside Reverse Transcriptase Inhibitors

Currently, three drugs from this class are available: nevirapine (NVP), efavirenz (EFV) and delavirdine (DLV). In contrast to the NRTIs, the NNRTIs are not incorporated in the proviral DNA, but bind directly to the viral reverse transcriptase to block polymerase activity by causing a disruption of the enzyme catalytic site.[6] The NNRTIs are extensively metabolised by the liver via the CYP enzyme system. Besides substrates, NVP and EFV are both inducers of CYP3A4, whereas DLV acts as a potent inhibitor of CYP3A4.[50] In addition, *in vitro* studies showed that EFV inhibits CYP2C9, 2C19 and 3A4.[30] Therefore, drug interactions can be anticipated if the NNRTIs are coadministered with other drugs that are metabolised via the same metabolic pathway. Table I summarises the pharmacokinetic parameters of the different NNRTIs, including the specific enzymes involved in their metabolism.

2.3 Protease Inhibitors

Six PIs are currently commercially available for the treatment of HIV-1-infection: amprenavir (AMP), indinavir (IDV), ritonavir (RTV), lopinavir (LPV) [coformulated with a low dose of RTV], nelfinavir (NFV), and saquinavir (SQV) [formulated as hard or soft gelatin capsules]. The target of these drugs is the viral protease that is a key enzyme in the synthesis of structural proteins and replicative enzymes. Inhibition of the viral protease leads to production of noninfectious virus particles.[51,52] Pharmacokinetic parameters and metabolic pathways of each PI are listed in table I. As can be observed, CYP3A isoenzymes are predominantly responsible for the metabolism of the PIs. In addition, all PIs are inhibitors of CYP3A. Both RTV and LPV have also CYP-inducing properties. Besides being substrates of CYP, PIs are also substrates and can act as inhibitors of P-glycoprotein, a transmembrane glycoprotein that functions as an energy-dependent efflux pump for a wide variety of structurally unrelated compounds.[53-55] Furthermore, the multidrug resistance associated proteins, MRP1 and possibly MRP2, are known to be involved in the disposition of the PIs.[53] These transporter proteins are also involved in drug efflux.

3. Mechanisms of Drug Interaction

Drug interactions are of pharmacokinetic or pharmacodynamic nature or consist of a combination of both. Generally, pharmacokinetic interac-

Table I. Steady-state pharmacokinetics of the antiretroviral drugs

Drug	Typical adult dosage (mg)	F (%)	Protein binding (%)	$t_{1/2\beta}$ (h)	AUC[a] (mg • h/L)	C_{max} (mg/L)	C_{min} (mg/L)	Metabolism	Induction of CYP	Inhibition of CYP
Nucleoside reverse transcriptase inhibitors										
Abacavir[17-19]	300 bid	83	50	1.5	6.02	3.0 ± 0.89[b]	<0.1	ADH, GT		
Didanosine[17,20,21]	200 bid	42	5	1.5	1.2	0.9	<0.01			
Lamivudine[17,22]	150 bid	86	<36%	5–7	12	1.5	0.1			
Stavudine[17,23]	40 bid	86	5	1.4	1.9	0.85	0.02			
Zalcitabine[24]	0.75 tid	>80	5	2	0.07	0.03	<0.005			
Zidovudine[17,25-27]	300 bid	65	34–38	1	2.0[c]	1.2[c]	<0.02	GT		
Non-nucleoside reverse transcriptase inhibitors										
Delavirdine[6,28,29]	400 tid	85[d]	98	2–11	82.2 ± 45.7[b]	16.0 ± 9.1[b]	6.8 ± 4.6[b]	3A4, 2D6, 2C9/19		3A4
Efavirenz[30-32]	600 qd	NA	>99	18–51	54.8 (33.3–66.6)[e]	3.63 (2.61–5.37)[e]	1.55 (0.93–2.04)[e]	3A4, 2B6	3A4	2C9/19, 3A4
Nevirapine[33-35]	200 bid	90	60	12–22	54.5 (48.0–72.0)[e]	5.86 (5.52–7.22)[e]	3.72 (3.07–4.91)[e]	3A4, 2B6	3A4, 2B6	
Protease inhibitors										
Amprenavir[36]	1200 bid	35–90	90	2–10	18.9 ± 6.1[b]	7.55 (54)[f]	0.32 (77)[f]	3A4		3A4
Indinavir[37,38]	800 tid	70	60	1–2	20.2 ± 7.8[b]	8.98 ± 2.87[b]	0.18 ± 0.13[b]	3A4		3A4
Lopinavir[g] [39,40]	400 bid	NA	98–99	5–6	82.8 ± 44.5[b]	9.6 ± 4.4[b]	5.5 ± 4.0[b]	3A4	GT	3A4, 2D6
Nelfinavir[41,42]	750 tid	70–80	>98	3.5–5	15.5	3.0 ±1.6[b]	2.2 ± 1.3[b] (morning) 0.7 ± 0.4[b](evening)	3A4, 2C9 /19, 2D6		3A4
Ritonavir[43,44]	600 bid	60–80	98–99	3–5	78	11.2 ± 3.6[b]	3.7 ± 2.6[b]	3A, 2D6	GT, 1A2, 3A, 2C9	3A, 2D6
Saquinavir HGC[45-47]	600 tid	4	98	1.5	0.9 ± 0.5[b]	0.2	0.04 ± 0.03[b]	3A4		3A4
Saquinavir SGC[46,48,49]	1200 tid	331[h]	97	1.5	7.2 ± 6.2[b]	2.2	0.07	3A4		3A4

a During one administration interval of a typical adult dose.
b Mean ± standard deviation.
c After 200mg single dose.
d Relative to oral solution.
e Median (interquartile range).
f Mean (% coefficient of variation).
g In combination with ritonavir 100mg bid.
h Relative to saquinavir HGC.

ADH = alcohol dehydrogenase; **AUC** = area under the concentration-time curve; **bid** = twice daily; **C_{max}** = maximum drug concentration; **C_{min}** = minimum drug concentration; **CYP** = cytochrome P450; **F** = oral bioavailability; **GT** = glucuronosyltransferase; **HGC** = hard gel capsules; **NA** = data not available; **qd** = once daily; **SGC** = soft gel capsules; **tid** = thrice daily; **$t_{1/2\beta}$** = elimination half-life.

tions involve alterations in absorption, transport, distribution, metabolism or excretion of a drug. The results of these interactions can be a decreased or an increased exposure, which in turn can lead to reduced efficacy or increased toxicity, respectively. Pharmacodynamic interactions are those where the pharmacological response to a drug is directly altered. This can lead to potentiation of effect (including toxicity) in either an additive or synergistic manner, or antagonism.

Table II presents the comedicated drugs (with abbreviations) that are involved in the drug interactions that are displayed in table III. Mechanisms that may be involved in these drug interactions are outlined in the following sections.

3.1 Pharmacokinetic Interactions

3.1.1 Drug Absorption

All currently available antiretroviral drugs are given orally and require absorption through the mucous membranes of the gastrointestinal tract. A dramatic change in plasma concentrations can be the result of incomplete drug absorption. A clear distinction must be made between an effect on the rate of absorption or the total amount absorbed. For drugs used long-term, which is the case in the treatment of HIV-1-infection, the rate of absorption is usually of less importance, provided that the total amount absorbed is not markedly changed. A variety of mechanisms could lead to reduced or increased absorption from the gastrointestinal tract.

Both DLV and IDV need normal gastric (acidic) pH for optimum absorption.[28,37] The concomitant administration of DLV with antacids led to impaired absorption of DLV, yielding a decrease of 41% in the area under the plasma concentration-time curve (AUC) [table III].[28] A similar effect on IDV when coadministered with antacids can be expected.

Originally, DDI tablets were formulated with a buffer (because of instability of DDI in the presence of gastric acid) that contains calcium carbonate and magnesium hydroxide and can influence drug absorption.[20] Coadministration of fluoroquinolones and these tablets results in complexation of the quinolone with the cations in the DDI formulation, leading to a significant decrease in the AUC of the quinolone (table III).[76] This type of drug interaction can easily be avoided by separation of drug administration. Alternatively, the new, enteric-coated formulation of DDI,[21,126] which lacks the buffer, could be used.

Change in gastrointestinal motility can also influence drug absorption. For instance, methadone decreases D4T absorption by decreasing gastrointestinal motility, which results in a 25% reduction in the AUC of D4T (table III).[144]

3.1.2 Metabolism and P-Glycoprotein

Metabolism of most drugs occurs by the liver via phase I reactions (involving oxidation, reduction and hydrolysis) into more polar compounds. In addition, phase II reactions involve conjugation of the drugs. The metabolites formed are usually pharmacologically inactive. Both types of reactions result in more water-soluble compounds that are more easily excreted by the kidneys. The most important enzymes involved in phase I reactions are the CYP enzymes,[228] a family of mixed function oxidases that account for the majority of oxidative biotransformations of xenobiotics and endogenous biochemicals.[229] These metabolic enzymes can both be induced and inhibited. It may take days to up to 2–3 weeks, depending on the drug and its dosage, to fully develop enzyme induction. Enzyme induction can lead to an increased (in case of the use of a prodrug) as well as a decreased drug effect. Another process involves enzyme inhibition, which unlike enzyme induction, can occur almost immediately.

In humans, CYP3A is the largest fraction of the total CYP content.[230] CYP3A4 is responsible for the metabolism of a broad spectrum of drugs, including the PIs and the NNRTIs (table I). Furthermore, CYP3A4 is located in the small bowel and liver and is, therefore, also involved in presystemic (first-pass) metabolism.[229]

As mentioned earlier, P-glycoprotein acts as an energy-dependent efflux pump that exports substrates out of the cell. P-glycoprotein is expressed in the epithelial cells of the gastrointestinal tract,

Table II. Index and abbreviations of the coadministered drugs involved in drug interactions with antiretrovirals

Coadministered drug	Abbreviation	Coadministered drug	Abbreviation	Coadministered drug	Abbreviation	Coadministered drug	Abbreviation	Coadministered drug	Abbreviation
Acenocoumarol	ACE	Clorazepate	CLR	γ-Hydroxybutyrate	GHB	Morphine	MOR	Ranitidine	RAN
Acetylsalicylic acid (aspirin)	ASA	Clozapine	CLZ	Ganciclovir	GAN	Mucosal protectives	MUC	Ribavirin	RIB
Albendazole	ALB	Codeine	COD	Garlic supplements	GAR	Nefazodone	NEF	Rifabutin	RFB
Alendronate	See bisphosphonates	Corticosteroids[a]	COR	Gemfibrozil	GEM	Nicardipine	See calcium channel antagonists	Rifampicin (rifampin)	RIF
Alfentanil	ALF	Cyclobarbital	See barbiturates	Gentamicin	See aminoglycosides	Nifedipine	See calcium channel antagonists	Risperidone	RIS
Alimemazine	ALI	Cyclophosphamide	CYC	Glutethimide	GLU	Nimodipine	See calcium channel antagonists	Roxithromycin	ROX
Allobarbital	See barbiturates	Cyclosporin	CsA	Grapefruit juice	GRJ	Nisoldipine	See calcium channel antagonists	Salicylic acid	SAC
Allopurinol	ALU	Dapsone	DAP	Haloperidol	HAL	Nitrendipine	See calcium channel antagonists	Secobarbital	See barbiturates
Alprazolam	ALP	Daunorubicin	DAU	Heptobarbital	See barbiturates	Nitrofurantoin	NIT	Sertraline	See SSRIs
Amikacin	See aminoglycosides	Demeclocycline	See tetracyclines	Hexobarbital	See barbiturates	Nizatidine	NIZ	SSRIs	SSRI
Aminoglycosides	AMG	Desipramine	DES	Hydralazine	HYD	Norethindrone	See oral contraceptives	Sildenafil	SIL
Amiodarone	AMI	Dexamethasone	DEX	Hydroxycarbamide	HYX	Norfloxacin	See fluoroquinolones	Simvastatin	SIM
Amitriptyline	See tricyclic antidepressants	Dextropropoxyphene	DRX	Ifosfamide	IFS	Nortriptyline	See tricyclic antidepressants	Sirolimus	SIR
Amlodipine	See calcium channel antagonists	Diazepam	DIA	Imipramine	See tricyclic antidepressants	Ofloxacin	See fluoroquinolones	Sparfloxacin	See fluoroquinolones
Amobarbital	See barbiturates	Digoxin	DIX	Interferon-α	INFα	Olanzapine	OLE	St Johns wort	SJW

Amphotericin B	AMB	Dihydroergotamine	See ergot derivatives	Interleukin-2	IL-2	Omeprazole	OME	Streptomycin	See amino-glycosides
Antacids	ANT	Diltiazem	DIL	Iodoquinol	IDO	Oral contraceptives	OC	Sulfadiazine	SUF
Aprobarbital	See barbiturates	Disopyramide	DSP	Isoniazid	INH	Oxazepam	OXE	Sulfamethoxazole	SUL
Astemizole	AST	Disulfiram	DIS	Isotretinoin	ISO	Oxytetracycline	See tetracyclines	Tacrolimus	TAC
Atorvastatin	ATR	Dothiepin	See tricyclic antidepressants	Isradipine	See calcium channel antagonists	Pamidronate	See bisphosphonates	Tamoxifen	TAM
Atovaquone	ATO	Doxepin	See tricyclic antidepressants	Itraconazole	ITR	Paclitaxel	PAC	Terfenadine	TER
Aurothioglucose	AUR	Doxorubicin	DOX	Ketoconazole	KET	Paroxetine	See SSRIs	Tetracycline	See tetra-cyclines
Azithromycin	AZI	Doxycycline	See tetracyclines	Lacidipine	See calcium channel antagonists	Pefloxacin	See fluoroquinolones	Tetracyclines	TET
Barbital	See barbiturates	Encainide	ENC	Lansoprazole	LAN	Pentamidine	PET	Thalidomide	THA
Barbiturates	BAR	Etidronate	See bisphosphonates	Levodopa	DOP	Pentobarbital	See barbiturates	Theophylline	THE
Bepridil	BEP	Ergotamine	See ergot derivatives	Levofloxacin	See fluoroquinolones	Perazine	PER	Thioridazine	THI
Bisphosphonates	BIP	Ergonovine	See ergot derivatives	Levomepromazine	LEP	Periciazine	PEC	Tiludronate	See bisphos-phonates
Brallobarbital	See barbiturates	Ergot derivatives	ERD	Levothyroxine	LEV	Perphenazine	PEZ	Timolol	TIM
Bupropion	BUP	Erythromycin	ERY	Lidocaine	LID	Phenobarbital	PHB, see barbiturates	Tiotixene	TIO
Butalbital	See barbiturates	Ethambutol	ETH	Lomefloxacin	See fluoroquinolones	Phenytoin	PHT	Tramadol	TRM
Butobarbital	See barbiturates	Ethanol	ETN	Loperamide	LOP	Pimozide	PIM	Trazodone	TRA
Calcium channel antagonists	CAC	Ethinylestradiol	See oral contraceptives	Loratadine	LOR	Pipotiazine	PIP	Triazolam	TRI

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Table II. Contd

Coadministered drug	Abbreviation	Coadministered drug	Abbreviation	Coadministered drug	Abbreviation	Coadministered drug	Abbreviation	Coadministered drug	Abbreviation
Carbamazepine	CAR	Ethionamide	ETI	Lovastatin	LOV	Piroxicam	PIR	Tricyclic antidepressants	TRC
Chloramphenicol	CHA	Ethosuximide	ETX	Maprotiline	See tricyclic antidepressants	Pravastatin	PRA	Trifluoperazine	TRF
Chlordiazepoxide	CHL	Famotidine	FAM	MDMA	MDMA	Prazepam	PRZ	Triflupromazine	TRP
Chlorpromazine	CHP	Felodipine	See calcium channel antagonists	Mebendazole	MEB	Prednisone	PRE	Trimethoprim	TMP
Chlortetracycline	See tetracyclines	Fentanyl	FEN	Medroxypro-gesterone	MED	Prednisolone	PRD	Trimipramine	See tricyclic antidepressants
Cimetidine	CIM	Flecainide	FLE	Mefloquine	MEF	Primaquine	PRQ	Tobramycin	See amino-glycosides
Ciprofloxacin	CIP	Fluconazole	FLC	Meperidine (pethidine)	MEP	Primidone	PRI	Trovafloxacin	See fluoro-quinolones
Cisapride	CIS	Flucytosine	FLY	Methadone	MET	Probenecid	PRO	Valproic acid	VAL
Cisplatin	CIT	Fluticasone	See corticosteroids	Methylergonovine	See ergot derivatives	Prochlorperazine	PRC	Verapamil	VER
Citalopram	See SSRIs	Fluoroquinolones	FLQ	Methylpheno-barbital	See barbiturates	Promethazine	PRM	Vincristine	VIN
Clarithromycin	CLA	Fluoxetine	FLX, see SSRIs	Metoprolol	MEO	Propafenone	PRP	Warfarin	WAR
Clindamycin	CLI	Flurazepam	FLU	Metronidazole	MEN	Pyrazinamide	PYR	Zolpidem	ZOL
Clodronate	See bisphosphonates	Fluvoxamine	See SSRIs	Mexiletine	MEX	Pyrimethamine	PYM		
Clomipramine	See tricyclic antidepressants	Foscarnet	FOS	Midazolam	MID	Quinidine	QUI		
Clonazepam	CLO	Fusidic acid	FUA	Minocycline	See tetracyclines	Quinine	QUN		

a Inhaled or rectal.

MDMA = methylenedioxymethamphetamine; **SSRI** = selective serotonin reuptake inhibitor.

Table III. Overview of drug interactions of antiretrovirals drugs and coadministered drugs

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Acenocoumarol (ACE)	T		AMP, DLV, EFV, IDV, LPV/RTV, NFV, NVP, SQV	Inhibition CYP3A? by PI; inhibition CYP2C9/2C19 by DLV/NFV?; induction CYP3A? by EFV/NVP	Conc. ACE ↑ (PI/DLV) or ↓ (EFV/NVP)	Based on case report with RTV	Monitor INR	28
	T		RTV	Induction CYP2C9, 3A? by RTV	Conc. ACE ↓		Monitor INR	43,56
	Case report	1 HIV+, female	RTV		Anticoagulant activity ↓, prothrombin test ↑			
Acetylsalicylic acid (ASA)	*In vitro* (human liver microsomes)		AZT	Inhibition of glucuronidation by ASA	0.5 mmol/L 97.8% enzyme activity remained; 10 mmol/L 43.9% emzyme activity remained	Conc. AZT probably ↑; significance?	Monitor blood counts regularly	57
Albendazole (ALB)	T		RTV	Inhibition/induction CYP3A by RTV	Conc. ALB ↑ or ↓	Influence on first pass, hepatic elimination?	Monitor efficacy ALB, monitor leucocytes and LEs regularly	58
Alfentanil (ALF) [see also fentanyl]	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. ALF ↑	Based on study with fentanyl	Monitor for increased respiratory depression	
Alimemazine (ALI)	T		RTV	Inhibition CYP2D6 by RTV, ALI	Conc. ALI ↑; conc. RTV ↑	Based on interaction with perphenazine	Monitor for ↑ sedation. Dosage reduction ALI, RTV may be needed. TDM RTV recommended.	
Allopurinol (ALU) 300mg/day	S	2 HIV+	DDI single dose 200mg	Inhibition tubular secretion by ALU?	AUC, C_{max} DDI ↑ 312%, 232%, resp.		Coadministration not recommended	20,21
ALU 7 days 300mg/day	S	14 vol	Single dose 400mg		AUC, C_{max} DDI ↑ 113%, 69%, resp.			
Alprazolam (ALP)	T		AMP, DLV, EFV, IDV, LPV/RTV, NFV, NVP, SQV	Inhibition CYP3A by PI/DLV, induction CYP3A by EFV/NVP	Conc. ALP ↑ (PI/DLV) or ↓ (EFV/NVP)	Risk for ↑ (PI/DLV) or ↓ (EFV/NVP) sedation.	Coadministration not recommended; A = oxazepam, lorazepam	28,36

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
ALP single dose 1mg	Open-label crossover	12 vol	RTV 10 days 500mg bid (escalation scheme)	Induction CYP3A4 by RTV	AUC ALP ↓ 12%, C_{max} ↓ 15.7%	During initial exposure inhibition may predominate, while during extended exposure induction may offset inhibition	Coadministration not recommended; A = oxazepam, lorazepam	43,59-61
ALP single dose 1mg	Double-blind, randomised, 2-way crossover	10 vol	RTV 200mg bid (4 doses)	Inhibition hepatic CYP3A4 by RTV	CL ALP ↓ 41%, ↑ sedation			
Aminoglycosides (AMG)	T		DDC	Inhibition of renal elimination by AMG	Increased risk for peripheral neuropathy, other AE		Frequent clinical/laboratory monitoring. Adjust dosage DDC based on renal function	24
Amiodarone (AMI)	T		AMP, DLV, EFV, LPV/RTV, NFV, NVP, RTV, SQV	Inhibition CYP3A by PI/DLV, induction CYP3A by EFV/NVP	Conc. AMI ↑ (PI/DLV) or ↓ (EFV/NVP)	May result in potential serious or life-threatening AEs.	CI (NFV, RTV), dose increase (+NVP/EFV), reduction (+PI/DLV) AMI may be needed, TDM AMI recommended	28,36,39, 41,43
AMI 200mg/day ss	Case report	1 HIV+	IDV 800mg tid	Inhibition hepatic CYP3A by IDV	Conc. AMI 0.9 → 1.3 mg/L (↑ 44%)	Not above therapeutic window in this case, but higher baseline conc. AMI → toxic values	TDM AMI recommended	62
Amphotericin B (AMB)	T		AZT, DDC	Similar toxicity profile, inhibition renal elimination by AMB (DDC)	Increased risk haematological toxicity (AZT), peripheral neuropathy (DDC)		Avoid where possible. Monitor blood counts regularly (AZT)	24,25
Antacids containing magnesium + aluminium or carbonates (ANT)	S (30ml Maalox®)	12 HIV+	DDC single dose 1.5mg	Gastric pH ↑ by ANT	BA/absorption DDC ↓ 25%	Not recommended to ingest simultaneously	DDC >2h before ANT	24

ANT	T		DDI	Similar ingredients in formulation	↑ risk AEs related to ingredients DDI		Monitor toxicity; A = DDI EC	20
ANT	Single-dose	12 vol	DLV single dose 300mg	Gastric pH ↑ by ANT	AUC DLV ↓ 41 ± 19%		DLV >1h before or after ANT	28
ANT	T		AMP, IDV	Gastric pH ↑ by ANT	Absorption AMP/IDV ↓	Normal (acidic) pH necessary for optimum absorption IDV	AMP/IDV >1h before or after ANT	36,37
Astemizole (AST)	T, *in vitro* (AMP)		AMP, DLV, EFV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. AST ↑	Risk for cardiac arrhythmias (↑ QT interval)	CI; A = cetirizine, acrivastine	28,30,36,37, 39,41,43,45, 48,63
Atorvastatin (ATR)	T		AMP, IDV	Inhibition CYP3A by PI	Conc. ATR ↑	Risk of myopathy including rhabdomyolysis	Combination not recommended; A = pravastatin, fluvastatin	36,37
ATR 20mg qd	Case report	1 HIV+, male	DLV 400mg tid	Inhibition CYP3A4 by DLV	Generalised malaise with muscle pain in legs and lower back, nausea, vomiting, dark urine: acute renal failure		Combination not recommended; A = pravastatin, fluvastatin	64
ATR 4 days 20mg qd	S	12 vol	LPV/RTV 14 days 400/100mg bid	Inhibition CYP3A by LPV/RTV	AUC, C_{max} ATR ↑ 5–6-fold; no effect on LPV	Risk of myopathy including rhabdomyolysis	Combination not recommended; A = pravastatin, fluvastatin	65
ATR 14 days 10mg qd	Open-label, sequential, multiple-dose	15 vol	NFV 14 days 1250mg bid	Inhibition CYP3A4 by NFV	AUC ATR ↑ 74%; C_{max} ATR ↑ 122%	Risk of myopathy including rhabdomyolysis	Combination not recommended; A = pravastatin	41,66,67
ATR 5 days 40mg qd	3-way crossover	8 vol	NFV 5 days 750mg tid		AUC ATR ↑ 31.7%; C_{max} ATR↑ 209%			
ATR 4 days 40mg qd	Randomised, open-label, multiple dose	14 vol	RTV/SQV-SGC 4 days 400/400mg bid	Inhibition CYP3A by RTV/SQV	AUC ATR ↑ 347%; AUC total active ATR ↑ 79%	Risk of myopathy including rhabdomyolysis	Combination not recommended; A = pravastatin, fluvastatin	43,45,48,68
Atovaquone (ATO) 12 days 750mg bid	Crossover	14 HIV+ male	AZT 12 days 200mg tid	Inhibition glucuronidation by ATO	AUC AZT ↑ 33%; CL AZT ↓ 34%; ratio GAZT : AZT ↓ 31%; PK ATO ↔	Clinical significance unknown	Monitor blood counts regularly	25,69
ATO	T		LPV/RTV, RTV	Induction glucuronidation by LPV/RTV	Conc. ATO ↓	Clinical significance unknown	Dose increase ATO may be needed	39,43

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Aurothioglucose (AUR)	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor closely for peripheral neuropathy	20,21,24
Azithromycin (AZI) single dose 1200mg	Open-label, 2-way crossover	12 vol	NFV 11 days 750mg tid	Inhibition P-gp by NFV	AUC, C_{max} AZI ↑ 107%, 107%, resp.; AUC, CL_{oral} M8 ↓ 24%, ↑ 30%, resp.; AUC, $t_{½β}$ NFV ↓ 28%, 24%	No increase in AEs	TDM NFV recommended	70
Barbiturates (BAR) [see also phenobarbital]	T		AMP, DLV, EFV, IDV, LPV/RTV, NFV, NVP, RTV, SQV	Induction CYP3A by BAR/EFV/NVP, inhibition CYP3A by PI/DLV	Conc. PI/NNRTI ↓; conc. BAR ↑ (PI/DLV) or ↓ (EFV/NVP)	Based on predicted interaction with PHB	TDM PI/NNRTI/BAR recommended; A = valproic acid (anticonvulsant)	
Bepridil (BEP)	T		AMP, DLV, IDV, NFV, LPV/RTV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. BEP ↑	Risk for cardiac arrhythmias	Avoid where possible or CI (AMP, RTV used as sole PI)	4,36,39,43
Bisphosphonates (BIP)	T		DDI	Chelation with cations in DDI tablets	↓ absorption BIP		BIP >2h before DDI; A = DDI EC	
Bupropion (BUP) 10 μmol/L	*In vitro* (human liver microsomes)		NFV, RTV 0–50 μmol/L	Inhibition CYP2B6 by NFV/RTV	NFV: IC_{50} 2.5 ± 0.4 μmol/L	IC_{50} < clinical plasma concentration → *in vivo* interaction possible: ↑ risk for convulsions.	Dose increase (EFV/NVP), reduction (>50%) [PI] BUP may be needed.	30,43,71
BUP	T		EFV, NVP	Induction CYP2B6 by EFV/NVP	RTV: IC_{50} 2.2 ± 0.1μmol/L; conc. BUP ↓			
Calcium channel antagonists (dihydropyridines) [CAC]	T		AMP, DLV, IDV, NFV, LPV/RTV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. CAC ↑	↑ risk for hypotension	Dosage reduction CAC may be needed	28,36,37,39, 41,43,45

Carbamazepine (CAR)	T		AMP, EFV, LPV/RTV, NFV, NVP, SQV	Induction CYP3A by CAR/NVP/EFV, inhibition CYP3A by PI	Conc. PI/NNRTI ↓, conc. CAR ↑ (PI), conc. CAR ↓ (EFV/NVP)	Potentially significant	TDM PI/NNRTI, CAR recommended; A = amitriptyline/gabapentin (PHN); valproic acid/lamotrigine (anticonvulsant)	12,36,39,41, 45,48,72
CAR	Population PK data	8 HIV+	DLV	Induction CYP3A by CAR, inhibition CYP3A by DLV (T)	Substantial reduction C_{min} DLV; conc. CAR ↑			28
CAR 200mg qd	Case report	1 HIV+	IDV 800mg tid (ss) [incl. AZT/3TC]	Induction CYP3A4 by CAR; inhibition CYP3A4 by IDV	Plasma conc. IDV ↓; plasma conc. CAR high in contrast to low dose used			37,73
CAR (ss)	Case report	2 HIV+	RTV 400mg bid (incl. SQV 400 bid or SQV 600mg bid and EFV 600mg qd)	Inhibition CYP3A4 (possibly CYP2C8) by ARV drugs	Conc. CAR ↑ 3-4-fold	Possibly conc. PI/NNRTI ↓		12,30,43, 74,75
Chloramphenicol (CHA)	*In vitro* (human liver microsomes)		AZT	Inhibition glucuronidation by CHA	0.5 mmol/L 63.3% enzyme activity remained; 10 mmol/L 11.3% emzyme activity remained	Conc. AZT probably ↑. Significance?	Monitor blood counts regularly	57
CHA	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
Chlordiazepoxide (CHL)	T		RTV	Inhibition CYP3A by RTV	Conc. CHL ↑	Metabolism CHL via CYP3A. Risk for ↑ sedation.	Dosage reduction CHL may be needed; A = oxazepam, lorazepam	
Chlorpromazine (CHP)	T		RTV	Inhibition CYP2D6 by RTV, CHP	Conc. CHP ↑, conc. RTV ↑	Based on interaction with perphenazine	Dose reduction CHP, RTV may be needed. TDM RTV recommended	
Cimetidine (CIM) single dose 800mg	Single dose	12 HIV+	DDC single dose 1.5mg	Inhibition renal tubular secretion by CIM	AUC DDC ↑ 36%; CL_R DDC ↓ 24%		Monitor for peripheral neuropathy; decrease dose DDC if warranted	24

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
CIM	T		DLV	↑ gastric pH by CIM	↓ absorption DLV	Clinical significance unknown	Long-term use CIM with DLV not recommended. TDM DLV recommended	28
CIM	S	11 HIV+	NVP (ss)	Inhibition CYP3A by CIM	C_{min} NVP ↑ 21%	Significance?	TDM NVP recommended	33
Ciprofloxacin (CIP) 3 days 750mg bid, 2h prior to DDI	Open-label, multiple-dose	16 HIV+	DDI 3 days 200mg bid	Formation of chelation complex CIP and Mg/Al in DDI tablets	AUC DDI ↓ 21%; C_{max} DDI ↓ 33%; AUC CIP ↓ 26%	DDI EC single dose 400mg + CIP single dose 750mg → no effect	CIP 2h prior to DDI or 6h after DDI; A = DDI EC	20,76-78
CIP single dose 750mg, concomitant administration (see also fluoroquinolones)	Randomised, 2-treatment crossover	12 vol	DDI-placebo tablets bid		AUC CIP ↓ 98%; C_{max} CIP ↓ 93%; t_{max} CIP ↓ 52%			
Cisapride (CIS)	T		AMP, DLV, EFV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A4 by PI/NNRTI	Conc. CIS ↑	Risk for cardiac arrhythmias	CI; A = metoclopramide	28,30,36,37, 39,41,43, 45,48
Cisplatin (CIT)	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
Clarithromycin (CLA) 4 days 500mg bid	Open-label, randomised, multiple-dose, 3-period crossover	12 vol, male	AMP 4 days 1200mg bid	Inhibition CYP3A4 (P-gp?) by CLA	AUC AMP ↑ 18%; C_{max}, C_{min} AMP ↑ 15% and 39%, resp.; CL AMP ↓ 15%; C_{max} CLA ↓ 10%	Dose adjustment CLA not necessary	TDM AMP recommended	36,79
CLA 7 days 500–3000mg bid	Crossover	15 HIV+, male	AZT 3 days 100mg 6×d	↓ absorption by CLA	AUC, C_{max}, t_{max} AZT ↓ 25%, 41%, ↑ 84%	Possibly not clinically relevant	Separate administration >2h is recommended	80
CLA 7 days 500mg bid (see also fluconazole + D4T and rifabutin + D4T)	Sequential, eight-part, multiple-dose, non-blinded, randomised	10 HIV+	D4T 7 days 40mg bid	↓ absorption by CLA?	C_{max} D4T ↓ 35% when combined with CLA + RFB + FLU	Significance?		81

CLA 500mg bid	S	6 HIV+	DLV 300mg tid	Inhibition CYP3A by DLV, CLA	AUC DLV ↑ 44%; AUC CLA ↑ 100%; AUC 14OH-CLA ↓ 75%	CLA PK compared with HCs	Maximum dosage CLA 1 g/day; A = azithromycin; reduce dosage CLA by 50–75% in patients with CL_{CR} <60ml/min; TDM DLV recommended	28
CLA 7 days 500mg bid	Multiple-dose	12 vol	EFV 7 days 400mg qd	Induction CYP3A4 by EFV, inhibition CYP3A4 by CLA	AUC CLA ↓ 26%; C_{max} CLA ↓ 39%; AUC, C_{max} 14OH-CLA ↑ 34% and 49%, resp.; C_{max} EFV ↑ 11%	Clinical significance unknown for CLA, effect on EFV not relevant; 46% developed rash	Maximum dosage CLA 1 g/day; A = azithromycin; monitor for rash	30,82
CLA 7 days 500mg bid	S	?	IDV 7 days 800mg tid	Inhibition CYP3A4 by IDV, CLA	AUC IDV ↑ 29%; AUC CLA ↑ 53%		Maximum dosage CLA 1g/day; A = azithromcyin	37,83
CLA 7 days 500mg bid	Multiple-dose, randomised, 3-period, crossover, placebo-controlled	14 vol, male	7 days 800mg tid	Inhibition hepatic CYP3A4 by CLA, inhibition CYP3A4 by IDV	C_{min} IDV ↑ 52%; AUC, C_{max} CLA ↑ 47%, 19%; AUC, C_{max} 14OH-CLA ↓ 49%, 48%	CLA wide safety margin, AE IDV associated with C_{max}/AUC rather than C_{min}	Reduce dosage CLA by 50–75% in patients with CL_{CR} <60ml/min; TDM IDV recommended	
CLA	T		LPV/RTV, NFV	Inhibition CYP3A by PI, CLA	Conc. CLA and/or PI ↑		Maximum dosage CLA 1g/day; A = azithromycin; reduce dosage CLA by 50–75% in patients with CL_{CR} <60ml/min; TDM PI recommended	39,41
CLA ss 500mg bid	Multiple dose	15 HIV+	NVP 14 days 200mg qd, thereafter 200mg bid	Induction CYP3A by NVP, inhibition CYP3A by CLA	AUC CLA ↓ 30%, C_{max}, C_{min} CLA ↓ 46% and 21%, resp.; AUC NVP ↑ 26%	Total exposure to CLA (incl. metabolite) not changed	TDM NVP recommended	84-86

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
CLA 10 days 500mg bid	Case report	1 HIV+, male	2 months 200mg bid	Accumulation of active 14-OH metabolite of CLA by NVP	Hyperactivity: pressure of speech, poor concentration, extreme anxiety, suicidal/homicidal ideation			
CLA 4 days 500mg bid	Open-label, randomised, 3-period, crossover	22 vol	RTV 4 days 200mg tid	Inhibition hepatic CYP3A4 by RTV, CLA	AUC RTV ↑ 13%; C_{max} RTV ↑ 15%; C_{min} RTV ↑ 15%; AUC CLA (14OH-CLA) ↑ 77% (↓ 100%); C_{max} CLA (14OH-CLA) ↑ 31% (↓ 99%); C_{min} CLA ↑182%	CLA → 14OH-CLA completely inhibited by RTV	Maximum dosage CLA 1g/day; A = azithromycin; reduce dosage of CLA by 50–75% in patients with CL_{CR} <60ml/min; TDM RTV recommended	43,87
CLA 7 days 500mg bid	Multiple dose	12 vol	SQV-SGC 7 days 1200mg tid	Inhibition CYP3A4 by CLA and SQV	AUC CLA (14OH-CLA) ↑ 45% (↓ 24%); C_{max} CLA (14OH-CLA) ↑ 39% (↓ 34%); AUC SQV ↑ 177%; C_{max} SQV ↑187%		Maximum dosage CLA 1g/day; A = azithromycin; reduce dosage of CLA by 50–75% in patients with CL_{CR} <60ml/min; TDM SQV recommended	88,89
Clindamycin (CLI)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. CLI ↑		Combination not recommended; A = azithromycin, (flu)-cloxacillin	45
Clonazepam (CLO)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. CLO ↑		Monitor for increased sedation, dose reduction CLO may be needed	43
Clorazepate (CLR)	T		AMP, RTV	Inhibition CYP by RTV	Conc. CLR ↑	Sedation, respiratory depression	CI; A = lorazepam, oxazepam	7,12,36,43
Clozapine (CLZ)	T		RTV	Induction CYP1A2 by RTV	Conc. CLZ ↓		CI	4,7

Codeine (COD)	T		RTV	Inhibition CYP by RTV	COD → morphine ↓	Analgesic efficacy ↓		72
Corticosteroids (COR) [see also fluticasone]	T		DLV, IDV, LPV/RTV, NFV, SQV	Inhibition (presystemic) CYP by PI/DLV	Systemic conc. COR ↑		Monitor for symptoms of hypercorticism	
Cyclosporin (CsA)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV	Inhibition CYP3A by PI/DLV, CsA	Conc. CsA, PI/NNRTI ↑		TDM CsA, PI/NNRTI recommended	36,39,41,43
CsA ss 175mg bid	Case report	1 HIV+, male	EFV 600mg qd	Induction CYP3A4 by EFV, inhibition CYP3A by CsA (?)	Conc. CsA ↓ 75% 1 month after start EFV		Frequent TDM CsA, EFV recommended	90
CsA	T		NVP	Inhibition CYP3A by CsA, induction CYP3A by NVP	Conc. CsA ↓, conc. NVP ↑	Based on interaction with EFV	TDM CsA, PI/NNRTI recommended	
CsA ss 150mg bid	Case report	1 HIV+	SQV 1200mg tid (added to CsA)	Similar metabolism via CYP3A, P-gp	Conc. CsA ↑ 3-fold, fatigue, headache, GI discomfort, AUC SQV ↑		TDM CsA, SQV recommended	91
Cyclophosphamide (CYC)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV, induction CYP by CYC	Conc. CYC ↑; metabolism to active metabolite ↓; conc. PI/NNRTI ↓		TDM PI/NNRTI recommended; monitor blood counts regularly	
Dapsone (DAP)	T		AZT	Similar toxicity profile	Haematological toxicity		Monitor blood counts regularly	25
DAP	T		DDC, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	23,24
DAP single dose 100mg	S	6 HIV+	DDI EC 14 days 200mg bid		No change AUC / C_{max}	Multiple dose studies show no clinically significant PK interaction, but conflicting reports	DAP should be administered > 1h before or 2h after DDI tablets. A = DDI EC	20,21,92,93
DAP	Multiple dose, case reports	?	DDI	↓ absorption by DDI	DDI		Avoid where possible, monitor for peripheral neuropathy	
DAP	T		DDI	Similar toxicity profile	Peripheral neuropathy			
DAP	T		DLV, SQV	Inhibition CYP3A by DLV/SQV	Conc. DAP ↑		Monitor blood counts regularly	28,45

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Daunorubicin (DAU)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. DAU ↑	Consider ↑ risk for cardiotoxicity	Monitor blood counts regularly, dosage reduction DAU may be needed.	
Desipramine (DES) 0–300 μmol/L	*In vitro* (human liver microsomes)		RTV 5–25, IDV 10–25, SQV 25–50, NFV 25–50 μmol/L	Mixed competitive and noncompetitive inhibition CYP2D6 by PI	K_i: RTV (4.84) > IDV (15.6) > SQV (24.0) > NFV (51.9) [μmol/L]		Dosage reduction DES may be needed, TDM DES recommended	43,94,95
DES single dose 100mg (see also tricyclic antidepressant*s*)	S	14 vol	RTV 12 days escalating to 500mg bid		AUC DES (2OH-DES) ↑ 145% (↓ 15%); C_{max} DES (2OH-DES) ↑ 22% (↓ 67%)			
Dexamethasone (DEX)	T		AMP, DLV, EFV, IDV, LPV/RTV, NFV, NVP, RTV, SQV	Induction CYP3A4 by DEX, EFV/NVP, inhibition CYP3A4 by PI/DLV	Conc. PI/NNRTI ↓, conc. DEX ↑ (PI/DLV) or ↓ (EFV/NVP)		TDM PI/NNRTI recommended, dosage increase (EFV/NVP), reduction (PI/DLV) DEX may be needed	28,30,36,37, 39,43,45,48
Dextropropoxyphene (DRX)	T		RTV	Inhibition CYP3A/2D6 by RTV	Conc. DRX ↑	↑ risk for sedation, CNS toxicity	CI	43
Diazepam (DIA)	T		AMP, DLV, IDV, NFV, LPV/RTV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. DIA ↑	Risk for ↑ sedation.	CI (RTV); A = lorazepam, oxazepam	36,39,43,72
Digoxin (DIX)	Case report	1 HIV+, female	IDV/RTV 800/200mg bid	Inhibition P-gp in the small intestine or proximal renal tubules by RTV	Nausea, vomiting, mildly dehydrated. Conc. DIX (5h post ingestion) 7.2 nmol/L (± 2.5 × normal upper level)		TDM DIX recommended	96
Diltiazem (DIL)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. DIL ↑		Dosage reduction DIL may be needed	36,43
Disopyramide (DSP)	T		RTV	Inhibition CYP3A by RTV	Conc. DSP ↑	Cardiac events have been reported with this combination	Avoid where possible, dosage reduction DSP >50% may be needed	43

Disulfiram (DIS)	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
DIS	T		LPV/RTV liquid, RTV liquid	Irreversible inhibition ADH by DIS	Disulfiram-like reactions by ↑ conc. acetaldehyde	LPV/RTV and RTV liquids contain alcohol	A = LPV/RTV or RTV capsules	39,43
Doxorubicin (DOX)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. DOX ↑	Consider ↑ risk for cardiotoxicity	Monitor blood counts regularly, dosage reduction DOX may be needed	
DOX	*In vitro*		DDC	Inhibition of phosphorylation by DOX	>50% inhibition of phosphorylation	Clinical relevance unknown		24
Encainide (ENC)	T		LPV/RTV, RTV	Inhibition CYP2D6 by LPV/RTV, RTV	Conc. ENC ↑	Based on CI for FLE	CI	
Ergot derivatives (ERD)	T		AMP, DLV, EFV, LPV/RTV, SQV	Inhibition CYP3A4 by PI/DLV	Conc. ERD ↑	Ergotism = vasospasm	CI; A = paracetamol (acetaminophen)/ sumatriptan	28,30,36,39, 45,48
ERD	T		IDV	Inhibition hepatic CYP3A4 by IDV	Conc. ERD ↑	Ergotism = vasospasm	CI; A = paracetamol/suma triptan	37,97
Ergotamine 1mg bid	Case report	1 HIV+	IDV 800mg tid (incl. 3TC 150mg/D4T 40mg bid)		Conc. ERD not determined, ergotism			
ERD	T		NFV	Inhibition CYP3A by NFV	Conc. ERD ↑	Ergotism = vasospasm	CI; A = paracetamol/suma triptan	41,98
Ergotamine single dose 2 mg	Case report	1 HIV+, female			Pain, oedema, cyanosis feet and hands. Symptoms resolved after 6–15 days			
ERD	T		RTV	Inhibition CYP3A4 by RTV	Conc. ERD ↑	Ergotism = vasospasm	CI; A = paracetamol/suma triptan	43,99,100
Ergotamine single dose 1mg (n = 1) or 5 days 3mg (n = 1)	Case report	2 HIV+	RTV 600mg bid		Ergotism	Toxicity of ERD linked to peak serum conc.		

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Erythromycin (ERY)	T		AMP, DLV, IDV, NFV, LPV/RTV, RTV	Inhibition CYP3A by ERY or PI/DLV	Conc. ERY ↑ or PI/NNRTI ↑	Based on interaction of ERY + SQV	TDM PI/NNRTI recommended, dosage reduction ERY may be needed. Monitor for GI toxicity	
ERY	Monitoring plasma conc.	24 HIV+	NVP	Inhibition CYP3A by macrolides (ERY)	C_{min} ss NVP ↑ 12%	Probably not significant	TDM NVP recommended	33
ERY 7 days 250mg qid	Open-label, substudy	11 HIV+	SQV-SGC 7 days 1200mg tid (ss)	Inhibition CYP3A4 by ERY	AUC, C_{max} SQV ↑ 99%, 106%, resp.		No dosage adjustment necessary	101
Ethambutol (ETH)	T		DDI	Similar toxicity profile	Peripheral neuropathy, ocular effects		Avoid where possible, monitor for peripheral neuropathy, neuritis optica	4,92
Ethanol (ETN) 0.7mg/kg	Open-label, randomised, 3-way-crossover	25 HIV+ male	ABC single dose 600mg	Competition for metabolism by ADH	AUC ABC ↑ 41%, $t_{½\beta}$ ↑ 26%, C_{max} ↑ 15%	Not considered clinically significant		18,102,103
Ethionamide (ETI)	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
Ethosuximide (ETX)	T		RTV	Inhibition CYP3A by RTV	Conc. ETX ↑	Risk for ↑ sedation	TDM ETX recommended. Dosage reduction ETX (>50%) may be needed	43
Famotidine (FAM)	T		DLV, IDV	↑ gastric pH by FAM	↓ absorption DLV, IDV	Clinical significance unknown	Long-term use FAM with DLV, IDV not recommended	28
Fentanyl (FEN) single dose 5 μg/kg IV 2min	Double-blind, placebo-controlled, crossover, 2 phases	11 vol	RTV 3 days 300mg tid	Inhibition CYP3A4 by RTV	AUC FEN ↑ 170%, CL FEN ↓ 67%	Fatal respiratory depression	Small bolus FEN: no dose adjustment. Continuous administration FEN: reduce dosage FEN	104

Flecainide (FLE)	T		LPV/RTV, RTV	Inhibition CYP2D6 by LPV/RTV, RTV	Conc. FLE ↑	Risk for cardiac arrhythmias	CI	39,43
Fluconazole (FLC) 7 days 400mg qd	Randomised, 2-period, 2-treatment crossover	12 HIV+	AZT 200mg bid ss	Inhibition CYP3A4 by FLC, substrate competition for UDPGT binding sites	AUC AZT ↑ 74%, C_{max} AZT ↑ 84%, $t_{½β}$ AZT ↑ 128%		Monitor blood counts regularly	25,105
FLC 7 days 200mg qd (see also clarithromycin + D4T and rifabutin + D4T)	Sequential, eight-part, multiple-dose, non-blinded, randomised	10 HIV+	D4T 7 days 40mg bid	Inhibition absorption by FLC?	C_{max} D4T ↓ 35% when combined with CLA + RFB + FLC	Significance?		81
FLC 7 days 200mg qd	S	10 vol	EFV 7 days 400mg qd	Inhibition CYP3A by FLC, induction CYP3A by EFV	AUC EFV ↑ 16%, PK FLC?		TDM EFV recommended	30
FLC 8 days 400mg qd	Multiple-dose 3-period, placebo-controlled, crossover	11 HIV+	IDV 7¾ days 1000mg tid	Induction CYP?, inhibition absorption by FLC	AUC IDV ↓ 24%, C_{max} IDV ↓ 13%, C_{min} IDV ↓ 10%	Probably not clinically significant	TDM IDV recommended	106
FLC	Population pharmacokinetic data	23 HIV+ (n = 174)	NFV 500 or 750mg tid	Inhibition CYP2C19 by FLC	CL NFV ↓ 26–27%	Probably not clinically significant	TDM NFV recommended	107
FLC 4 days 200mg	Open-label, randomised, 2-period crossover	8 vol	RTV (liquid) 4 days 200mg 4dd	Inhibition CYP3A4 in gut wall by FLC	AUC RTV ↑ 12%, C_{max} RTV ↑ 15%	Probably not clinically significant	TDM RTV recommended	43,108
FLC day 1 400mg, then 5 days 200mg qd	Open-label, crossover	5 HIV+	SQV 6 days 1200mg tid	Inhibition CYP3A4 and/or P-gp in gut wall by FLC	AUC, C_{max}, CL SQV ↑ 50%, 56%, ↓ 50%, respectively		TDM SQV recommended	109
Flucytosine (FLY)	T		AZT	Similar toxicity profile	Haematological toxicity		Monitor blood counts regularly	25
Fluoroquinolones (FLQ) [see also ciprofloxacin]	T		DDI	Formation of chelation complex FLQ and Mg/Al in DDI tablets	Probably ↓ absorption both drugs		FLQ 2h prior to DDI or 6h after DDI; A = DDI EC	20,21
Fluoxetine (FLX)	Population PK data	36 HIV+	DLV	Inhibition CYP2D6 by FLX	C_{trough} DLV ↑ ± 50%		TDM DLV recommended	28
FLX 20-40mg/day	Case study	5 HIV+	EFV, IDV, RTV, SQV	Inhibition CYP by PI/EFV	Development serotonin syndrome after introduction PI/NNRTI	One case also used GRJ	Dose reduction FLX >50–60%, then adjustment as necessary (RTV)	43,110,111

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
FLX 8 days 30mg bid (see also selective serotonin reuptake inhibitors)	Phase I, open-label	16 vol	RTV (liquid) single dose 600mg	Inhibition CYP2D6 (postabsorption) by FLX	AUC RTV ↑ 19%	ss RTV: ↓ impact CYP2D6 with multiple doses, induction 3A by RTV		
Fluticasone (FLT) 500mg bid inhaled (see also corticosteroids)	Case report	1 HIV+	AMP/RTV 600/100mg bid	Inhibition CYP by RTV	Hypercorticism (moon facies, acute weight gain, diffuse acne, candidal oesophagitis). Undetectable cortisol, ACTH plasma conc.			112
Flurazepam (FLU)	T		AMP, RTV	Inhibition CYP3A by AMP, RTV	Conc. FLU ↑	Risk for ↑ sedation, respiratory depression	CI; A = oxazepam, lorazepam	36,43
Foscarnet (FOS)	T		DDC	Inhibition renal elimination by FOS	Increased risk for peripheral neuropathy, other AE		Monitor for peripheral neuropathy. Adjust dosage DDC based on renal function	24
Fusidic acid (FUA) 500mg tid	Case report	1 HIV+	RTV/SQV 400/400mg bid	Inhibition CYP3A4 by FUA and RTV/SQV	RTV↑ 19.3 → 43.4 mg/L; SQV↑ 11.2 → 16.3 mg/L; FUA high conc. and decreased elimination. Acute onset of nausea, fatigue, arthralgias, vertigo, jaundice		Avoid where possible, TDM RTV/SQV recommended	113
γ-Hydroxybutyrate (GHB) [+ MDMA] ±10 mg/kg	Case report	1 HIV+	RTV/SQV 400/400mg bid	Inhibition (presystemic) metabolism by RTV/SQV	GHB intoxication: loss of consciousness, seizurelike activity, respiratory depression, rapid/complete recovery		Discourage coadministration of illicit substances	114
Ganciclovir (GAN)	S	8 HIV+	AZT	Induction enzymes by GAN; related to CMV disease?	CL AZT ↑	Effect < usual inter- and intraindividual variability	Monitor blood counts regularly, dosage reduction AZT may be needed	4,25,115, 116

GAN 7 days 1000mg tid PO	Multicentre, open-label, randomised, crossover	12 HIV+	AZT 7 days 100mg 5 times/day	↑ absorption by GAN	AUC AZT ↓ ±30%; $AUC_{0\text{-}4}$ AZT ↑ 20%; C_{max} AZT ↑ 62%			
GAN	T		AZT	Similar toxicity profile	Haematological toxicity			
GAN 4 days 1000mg tid	Open-label, multidose, 3-way crossover	10 HIV+ and CMV+	DDC 4 days 0.75mg tid	↑ absorption by DDC	AUC GAN ↑ 22.2%		Monitor blood counts regularly	117
GAN 13 days 1000mg tid PO	Multicentre, open-label, randomised, crossover	12 HIV+	DDI 13 days 200mg bid	↓ intestinal absorption by DDI; alteration absorption, metabolism DDI by GAN (?)	(sim) AUC DDI ↑ 108%; (seq) AUC DDI ↑ 115%; (sim) GAN ↔; (seq) AUC GAN ↓ 21%	Note: neuropathy, pancreatitis DDI conc. dependent	Administer GAN and DDI simultaneously, monitor for peripheral neuropathy, pancreatitis	20,21,116, 118
GAN 3 days 2000mg tid PO	Open-label, randomised, 3-period crossover	16 HIV+	DDI 3 days 200mg bid	↑ extent of absorption by GAN	GAN→DDI: AUC, C_{max} DDI ↑ 124%, 87%, resp.; DDI→GAN: AUC, C_{max} DDI ↑ 87%, 59%, resp.	n = 12 DDI PK; n = 9 GAN PK		
Garlic supplements (GAR): allicin/allin 4.64/11.2mg caplet 20 days bid	2-treatment, 3-period, single-sequence, longitudinal	9 vol (4 male, 5 female)	SQV 3 days 1200mg tid	Induction intestinal CYP (P-gp?) by GAR	AUC SQV ↓ 51%; C_{max} SQV ↓ 54%; C_{min} SQV ↓ 49%	After 10-day washout AUC, C_{min}, C_{max} returned to 60–70% of baseline	Use GAR with caution when SQV is used as sole PI. TDM SQV recommended	119
GAR	T		AMP, DLV, EFV, IDV, LPV/RTV, NFV, NVP	Induction CYP (P-gp) by GAR	Conc. PI/NNRTI ↓	Based on interaction with SQV	TDM PI/NNRTI recommended	
Gemfibrozil (GEM) 600mg bid	Placebo-controlled (interim analysis)	14 HIV+	RTV/SQV both 400 or 600mg bid; RTV 600mg bid	?	C_{min} RTV ↑ 45%; effect on SQV?		TDM RTV/SQV recommended	120
Glutethimide (GLU)	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
Grapefruit juice (GRJ) single dose 240ml	Single-dose	Vol	IDV single dose 400mg	Inhibition intestinal CYP3A4, induction P-gp by GRJ	AUC IDV ↓ 26%		TDM IDV recommended	29,37,121

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
GRJ double-strength 180ml	Randomised, crossover, open-label	14 HIV+	IDV ss 800mg tid	+ ↑ gastric pH by GRJ	AUC IDV ↔; t_{max} ↑ 39%; gastric pH ↑ 130%	Effect GRJ on BA IDV is variable		
GRJ single dose 150(1)/300(2)ml	Single-dose	12 vol	SQV single dose 600mg	Inhibition CYP3A by GRJ	(1) AUC SQV ↑ 39%; (1) C_{max} SQV ↑ 63%; (2) AUC SQV ↑ 121%; (2) C_{max} SQV ↑ 120%	'Boosting' BA	TDM SQV recommended	122,123
GRJ 2 x 200ml single-strength	Open crossover	8 vol	SQV single dose 600mg PO (1); single dose 12mg IV (2)	Inhibition intestinal CYP3A4 by GRJ	(1) AUC SQV ↑ 50%; (1) F SQV ↑ 100%; (2) PK SQV ↔			
Haloperidol (HAL)	T		RTV	Inhibition CYP2D6 by RTV	Conc. HAL ↑	Risk for extrapyramidal symptoms	Dosage reduction HAL may be needed	12
Hydralazine (HYD)	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
Hydroxycarbamide (HYX)	T		AZT	Similar toxicity profile	Haematological toxicity		Avoid where possible, monitor blood counts regularly	4,25
Ifosfamide (IFS)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. IFS ↑; metabolism to active metabolite ↓		Monitor blood counts regularly	
Interferon-α (INFα)	T		AZT	Similar toxicity profile	Haematological toxicity		Dose reduction or interruption of one or both agents. Monitor blood counts regularly	4,25
Interleukin-2 (IL-2) 5 days 3-12 MIU/day, continuous infusion	Prospective, open-label, nonrandomised	9 HIV+	IDV 800mg tid, for at least 4 weeks	Inhibition CYP by IL-2	AUC IDV ↑ 88%	Cytokines suppress mRNA of CYP isoenzymes by ↓ transcriptional rate of corresponding gene	TDM IDV recommended	124

Iodoquinol (IDO)	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
Isoniazid (INH)	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
Isotretinoin (ISO) 50mg qd	Case report	1 HIV+, male	RTV/IDV 400/400mg bid (incl AZT/3TC)	Inhibition CYP3A by RTV/IDV, intracellular blockage of CRABP-1 by RTV/IDV	Dry skin, cheilitis with painful fissures lips, growth, dull curly hair, 'sticky skin'	Syndrome disappeared after 50mg minocycline	Avoid where possible	125
Itraconazole (ITR)	T		AMP, DLV, EFV, LPV/RTV, NFV, NVP, RTV, SQV	Inhibition CYP3A by PI/DLV and/or ITR, induction CYP3A by EFV/NVP	Conc. ↑ ITR and/or PI/DLV; conc. ITR ↓ (EFV/NVP)	Based on interaction study with KET	Avoid dosages ITR >200mg/day (PI/DLV). TDM PI/NNRTI recommended. A = fluconazole	36,39,43,45, 48
ITR	S		DDI	↑ gastric pH by DDI	↓ absorption ITR	Based on interaction with KET	Administer ITR >2h prior to DDI, or >2h after DDI. A = DDI EC or itraconazole liquid	20,21,126
ITR 200mg bid	Multiple-dose		IDV 600mg tid	Inhibition CYP3A4 by ITR	AUC IDV ↑	AUC ≈ AUC IDV 800mg tid administered alone for 1 week	TDM IDV recommended, dosage reduction IDV may be needed. A = fluconazole	37
Ketoconazole (KET) single dose 400mg	Open-label, randomised, balanced, single-dose, 3-period crossover	12 vol, male	AMP single dose 1200mg	Inhibition CYP3A by KET, AMP	AUC, C_{max} AMP ↑ 31%, ↓ 16%, resp. AUC, C_{max} KET ↑ 44%, ↑ 19%, resp.	↑ BA AMP by KET, may alter both BA and CL of KET	Dose reduction KET may be needed when KET >400mg/day. A = fluconazole	36,127,128
KET	Concurrently/ historically controlled trials		AMP	Inhibition CYP3A by KET	AUC AMP ↑ 32%, C_{max} AMP ↓ 16%			
KET 4 days 200mg qd, 2h before DDI	Open-label, randomised, 3-way crossover	12 HIV+, male	DDI (buffered powder for oral solution)	↑ gastric pH by DDI	AUC DDI ↓ 8%, C_{max} DDI ↓ 12%, no effect on KET	Effect is within variability	Administer KET >2h prior to DDI. A = DDI EC	20,21,78, 129

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
KET	Population PK data	26 HIV+	DLV	Inhibition CYP3A by KET	C_{trough} DLV ↑ ± 50%		TDM DLV recommended	28
KET single dose 400mg	Single dose		IDV single dose 400mg	Inhibition CYP3A by KET	AUC IDV ↑ 68%		Reduce dose IDV to 600mg tid, TDM IDV recommended	37
KET 400mg qd	Multiple dose		IDV 600mg tid		AUC IDV ↓ 18% (compared with 800mg tid)			
KET single dose 200mg	S	12	LPV/RTV 16 days 400/100mg bid	Inhibition CYP3A by LPV/RTV	AUC KET ↑ 3-fold, no effect on LPV		Avoid dosages KET > 200 mg/day. A = fluconazole	39
KET 7 days 400mg qd	Randomised, crossover	12 vol	NFV 6 days 500mg tid	Inhibition CYP3A by KET	AUC NFV ↑ 35%, C_{max} NFV ↑ 25%	Not clinically significant. *In vitro* data: KET may cause modest elevation in NFV conc.	No dosage adjustment (TDM NFV recommended)	41,130,131
KET 32 days 400mg qd	Open-label single arm	22 HIV+	NVP 28 days 200mg bid (1st 2 weeks 200mg qd)	Induction CYP3A by NVP, inhibition CYP3A by KET	AUC KET ↓ 63%, C_{max} KET ↓ 40%, C_{max}, C_{min} NVP ↑ ± 15–20% (HC)		CI; A = fluconazole	33,132
KET 7 days 200mg qd	S	12 HIV+	RTV 10 days 500mg bid	Inhibition CYP3A by RTV and KET	AUC, C_{max} RTV ↑ 18, 10%, resp., AUC, C_{max} KET ↑ 3.4-fold, 55%, resp.		Avoid dosages KET > 200mg/day. A = fluconazole	43
KET 10 days 200 or 400mg qd	Two-period, 3-group, dose-escalation, longitudinal PK	12 HIV+, male	RTV/SQV 400/400mg bid	Inhibition hepatic CYP3A by KET, (RTV/SQV?), inhibition CSF-to-plasma active transport by KET	AUC, $t_{½\,\beta}$, C_{min}, CL/F SQV ↑ 37%, 38%, 94%,↓ 27%, resp. AUC, $t_{½\beta}$, C_{min}, CL/F RTV ↑ 29%, 31%, 62%, ↓ 22%, resp. CSF RTV conc. ↑ 2.8-fold. CSF SQV conc. ↑ 3.6-fold		No dosage adjustment, TDM RTV/SQV recommended	133
KET 6 days 200mg qd	Multiple dose study	12 vol	SQV-HGC 6 days 600mg tid	Inhibition hepatic CYP3A by KET	AUC SQV ↑ 130%, C_{max} SQV ↑ 147%		No dosage adjustment, TDM SQV recommended	45,88,101

KET 7 days 400mg qd	Retrospective review	?	SQV-SGC single dose 1200mg		AUC SQV ↑ 190%, C_{max} SQV ↑ 171%			
KET 7 days 200mg qd	Open-label, substudy	11 HIV+	SQV-SGC 1200mg tid (ss)		AUC SQC ↑ 69%, C_{max} SQV ↑ 36%			
Lansoprazole (LAN)	T		DLV, IDV	↑ gastric pH by LAN	↓ absorption DLV, IDV	Normal acidic pH necessary for optimum absorption	TDM DLV/IDV recommended	28,37,134
LAN 15mg qd (a)/15mg bid (b) [n = 2] (see also omeprazole)	Case reports	4 HIV+	(a) DLV 600mg bid, (b) DLV 800mg bid, IDV 1200mg bid		(a) low trough conc. DLV, (b) no effect on DLV, low trough conc. IDV			
Levodopa (DOP) 700–750 mg/day + DOPA decarboxylase inhibitor	Case report	1 HIV+	IDV 800mg tid	Inhibition oxidative reactions by IDV, or delayed dopaminergic receptor hypersensitivity by IDV	After 4 weeks: severe dyskinesias occurring at peak dose periods, on-periods lasted the whole day without fluctuations	Potentially be used to potentiate DOP?	Dosage reduction DOP may be necessary	135
Levomepromazine (LEP)	T		RTV	Inhibition CYP2D6 by RTV, LEP	Conc. LEP ↑, conc. RTV ↑	Based on interaction with perphenazine	Dosage reduction LEP, RTV may be needed. TDM RTV recommended	
Levothyroxine (LEV) 0.125mg qd	Case report	1 HIV+, female	IDV 800mg tid followed by NFV 1250mg bid (PEP regimen +AZT/3TC)	Competition glucuronidation by AZT/IDV (?)	Hypercholesterolaemia within 1–2 weeks, headache, nausea, which resolved with switch to NFV, and fatigue		High cholesterol during PEP may be reversible, may not require intervention	136
LEV 0.125mg qd	Case report	1 HIV+, male	RTV/SQV 400/600mg bid	Induction glucuronosyl-transferase by RTV	TSH levels↑		Adjust dosage LEV based on thyroid function testing	137
Lidocaine (LID)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. LID ↑	Risk for cardiac arrhythmias	Use with caution, TDM LID recommended	28,36,39,43
Loperamide (LOP) single dose 16mg	Randomized, double-blind, 2-way crossover	12 vol	RTV single dose 600mg	Inhibition CYP3A by RTV	AUC, C_{max}, CL_{oral} LOP ↑ 223%, 17%, ↓ 70%, resp.	Lack of central effects when combined with RTV → no P-gp involvement	No dosage adjustment necessary	138

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Loratadine (LOR)	T		RTV	Inhibition CYP3A (2D6) by RTV	Conc. LOR ↑	Risk for tachycardia, headache	A = cetirizine, acrivastine	58
Lovastatin (LOV)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A4 by PI/DLV	Conc. LOV ↑	Risk of myopathy including rhabdomyolysis	Combination not recommended. A = pravastatin, fluvastatin (not with NFV)	36,37,39,41, 43,45,48
Mebendazole (MEB)	T		RTV	Inhibition CYP? by RTV	Conc. MEB ↑		Risk for ↑ diarrhoea, suggest supportive care	
Medroxyprogesterone (MED)	T		RTV	Inhibition CYP3A by RTV	Conc. MED↑			
Mefloquine (MEF) 3 days 250mg qd, then 250 mg/week (I). 3 days 250mg qd, then 250mg/4 weeks (II)	Open-label, nonfasting, 3-treatment, 3-period, longitudinal	12 vol (I), 11 vol (II)	RTV 7 days 200mg bid (I), single dose 200mg (II)	Reduction bile production by MEF → ↓ solubility/absorption RTV in small intestine	I: CL, AUC, C_{max} RTV ↑ 45%, ↓ 31%, 36%. II: no effect	Despite strong inhibition CYP3A4 from single 200mg dose RTV, no effect on MEF PK	TDM RTV recommended	139
Meperidine (MEP) [= pethidine], single oral dose 50mg	Open-label	8 vol	RTV 10 days 500mg bid	Induction CYP1A2 by RTV, concomitant induction/inhibition competing metabolic pathways, inhibition P-gp in gut wall	AUC MEP ↓ 62%, C_{max} MEP ↓ 59%. n = 6: AUC N-MEP ↑ 47%, C_{max} N-MEP ↑ 87%	N-MEP = normeperidine	Dosage increase and long-term use of MEP not recommended due to ↑ conc. N-MEP which has both analgesic and CNS activity (seizures)	43,140
Methadone (MET) maintenance 12.5–112.5mg/day	S	16 vol	AMP 10 days 1200mg bid	Both metabolised via CYP3A4	AUC_{24} (*R*)-MET, (*S*)-MET ↓ 12%, 37%, resp. C_{max} (*R*)-MET, (*S*)-MET ↓ 24%, 45%, resp. AMP PK no change	Interim analysis (12 subjects): opioid PD measures did not change	Adjustment dosage MET may be necessary	141,142
MET	Prospective, cross-over	5 HIV+	AMP (+ ABC 600mg/day) 14 days 1200mg bid	Induction CYP3A4 by AMP (effect of ABC cannot be excluded)	Conc. MET ↓ 35%	n = 2 nausea		

MET	Prospective	5 HIV+	AZT morning dose 100–500mg	Inhibition glucuronidation by MET (*in vitro*)	CL AZT ↓ 45%		Monitor blood counts regularly, consider dosage reduction to 400/500mg AZT daily when symptoms suggestive of AZT toxicity are observed	25,115,143
MET maintenance 30–90mg daily	S	9 HIV+	AZT 200mg every 4h		n = 4 AUC AZT ↑ 2-fold; n = 5 AUC AZT = AUC control			
MET maintenance	Within-subject	8 HIV+	AZT 200mg tid	Inhibition Type 2 UDPGT by MET	Acute effect: PO AUC AZT ↑ 41%; IV AUC AZT ↑ 19%. Long-term effect: PO AUC AZT ↑ 29%; IV AUC AZT ↑ 41%	Higher MET conc. in long-term phase (IV); ↑ first pass metabolism (PO)		
MET maintenance	Open-label, intersubject (parallel design)	17, 10 (9, 5 HIV+)	D4T 40mg bid	↓ GI motility by MET → ↓ absorption d4T	AUC d4T ↓ 25%, C_{max} d4T ↓ 44%, t_{max} d4T ↑ 2-fold, C_{trough} MET ↓	Effect on MET not clinically significant		144
MET chronic maintenance	Parallel design	16, 10	DDI EC single dose 200mg	↓ GI motility by MET → ↓ absorption DDI	AUC DDI ↓ 41%, C_{max} DDI ↓ 59%	Appropriate dosages DDI have not been established		20,21,144
MET maintenance	Open-label, intersubject (parallel design)	17, 10 (9, 5 HIV+)	DDI 200mg bid		AUC DDI ↓ 60%, C_{max} DDI ↓ 66%, C_{trough} MET ↓	Effect on MET not clinically significant		
MET 100mg maintenance	Case report	1 HIV+	EFV600mg qd	Induction CYP3A4 by EFV	Typical withdrawal symptoms: tiredness, headache, cold sweats and shivering. Conc. (*R*)-MET ↓ ±46%, (*S*)-MET ↓ ±72%	Regimen + D4T 40mg bid, 3TC 150mg bid	Dosage increments MET of 10mg with daily supervision of dosage and clinical evaluation	145-147
MET 30mg maintenance	Case report	1 HIV+, male	EFV 600mg qd		Withdrawal symptoms after 2 days	Regimen + D4T, DDI		
MET 35–100mg maintenance	Crossover	11 HIV+	EFV 14 or 21 days 600mg qd		C_{max}, AUC_{24} MET↓ 48%, 57%, MET dose ↑ 22%	Dose increase not as large as would be expected by individual's PK. Higher initial dose = higher increase		

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
MET 7 days 20–60mg daily	S	?	IDV 7 days 800mg tid	Inhibition CYP3A by IDV	No change AUC MET, little or no change AUC IDV		TDM IDV recommended	37
MET single dose 5mg	S	11 vol	LPV/RTV 10 days 400/100mg bid	Induction CYP by LPV/RTV	AUC MET ↓ 53%, C_{max} MET ↓ 45%		Dosage increase MET may be needed	39
MET	Part of case series	2 HIV+	NFV	Induction isoenzymes of CYP other than 3A4 by NFV	Conc. ss MET ↓ ± 55%		Dosage increase MET may be needed, TDM NFV/M8 may be recommended	148-150
MET maintenance 10–140mg/daily	Prospective	14 HIV+	NFV 1250mg bid		Plasma concentration (+)-MET, (–)-MET ↓ 47%, 39%, respectively	No withdrawal symptoms, no dosage adjustment		
MET maintenance 20–110mg/daily	Retrospective case series	36 HIV+	NFV 750mg tid and 1250mg bid		34/36 unchanged dose, 1/36 dose increase, 1/36 dose reduction			
MET 40–120mg/day	Non-crossover	16 vol	NFV 5 days 1250mg bid	Inhibition metabolism NFV to M8 by MET	AUC, C_{max} M8 ↓ 47%, 53%, respectively	MET PK not determined		
MET chronic maintenance	Retrospective chart review	7 HIV+	NVP	Induction CYP3A4 by NVP	Withdrawal symptoms 4–8 days after start NVP. Trough conc. MET ↓	Use MET trough conc. at baseline and titrate	Dosage increments MET of 10mg with daily supervision of dosage and clinical evaluation	33,146, 151-153
MET 80mg	Case report	1 HIV+, female	NVP		Withdrawal symptoms, dose to 130mg	Twice daily MET may be needed		
MET	Case series	5 HIV+	NVP		4/5 mild–severe withdrawal symptoms			
MET 40mg maintenance	Case report	1 HIV+, male	NVP (+D4T and DDI)		Withdrawal symptoms after 2 days	Rechallenge: recurrence symptoms		

MET	Part of case series	1 HIV+	RTV	Induction CYP3A as well as GT, 1A2, possibly 2C9 by RTV	Conc. ss MET ↓ ± 56%		Dosage increments MET of 10mg with daily supervision of dosage and clinical evaluation	43,148, 154-156
MET single dose 5mg C = single dose 20mg	Crossover study, dose-normalised	11 vol	RTV 15 days 500mg bid		AUC MET ↓ 36%, C_{max} MET ↓ 38%			
MET 90mg/day	Case report	1 HIV+, male	RTV/SQV 400/400mg bid	Induction CYP3A4, may be that 2C9 induction offsets 3A4/2D6	Shakiness, blurred vision, anxiety, hypotension etc			
MET maintenance	Crossover	12 HIV+	15 days RTV/SQV 400/400mg bid (RTV liquid)	Induction CYP2C19, CYP2B6 by RTV	AUC_{total} (*R*)-MET ↓ 32%, AUC_{free} (*R*)-MET ↓ 20%, 37% of ↓ in total (*R*)-MET conc. = protein displacement	PD evaluations showed no difference		
MET	T		SQV (sole PI) [see also combination with RTV]	Induction/inhibition (?) CYP3A by SQV	Conc. MET ↑ or ↓	Based on similar metabolism via CYP3A	Dosage adjustment may be needed	
Methylenedioxy metamphetamine (MDMA) ±180mg	Case report	1 HIV+, male	RTV 600mg bid	Hepatic inhibition CYP2D6 by RTV, deficiency in CYP2D6, impaired hepatic function	Conc. MDMA 4.56 mg/L (normally 0.5 mg/L); hypertonic, sweating profusely, tachypnoeic, tachycardia, cyanosed	Patient deficiency in CYP2D6, impaired hepatic function? Patient died	Discourage coadministration illicit substances	114,157,158
MDMA (+ GHB)	Case report	1 HIV+, male	RTV/SQV 400/400mg bid	Inhibition metabolism by RTV	Sustained effect MDMA: repetitive, clonic contractions of legs, and left side body			
MDMA + amyl nitrate	Case report	1 HIV+, male	RTV/SQV 400/400mg bid	Inhibition CYP by NO (metabolite amyl nitrate), inhibition CYP2D6 by RTV	Autopsy: moderate atheroma, up to 40% occlusion; MDMA plasma conc. 0.5 mg/L, traces DIA/nor-DIA in blood			
Metoprolol (MEO)	T		RTV	Inhibition CYP2D6 by RTV	Conc. MEO ↑		Dosage reduction (>50%) MEO may be needed	43

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Metronidazole (MEN)	T		AMP, DLV, IDV, NFV, SQV	Inhibition CYP3A by PI/DLV	Conc. MEN ↑	↑ risk for convulsions	Dose reduction MEN may be necessary	
MEN	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
MEN	T		LPV/RTV(-liquid), RTV(-liquid)	Irreversible inhibition ADH by MEN, inhibition CYP3A by RTV	Disulfiram-like reactions by ↑ conc. acetaldehyde, conc. MEN ↑	LPV/RTV and RTV liquids contain alcohol, ↑ risk for convulsions	CI (liquid). A = LPV/RTV, RTV capsules. Dosage reduction MEN may be necessary	39
Mexiletine (MEX)	T		RTV	Inhibition CYP2D6 by RTV	Cardiac events have been reported with this combination		Use with caution. Dosage reduction (>50%) MEX may be needed	43
Midazolam (MID)	T		AMP, DLV, EFV, IDV, LPV/RTV, NFV, RTV	Inhibition CYP3A by PI/DLV/EFV	Conc. MID ↑	Risk for prolonged or ↑ sedation, respiratory depression	CI	28,30,36,37, 39,41,43,159
MID 2–15mg IV bolus form	Outpatient bronchoscopies	73 HIV+	PI		No change in oxygenation or procedure time	↑ Sedation?	A = oxazepam, lorazepam	
MID 5mg IV	Case report	1 HIV+, male	SQV-HGC 600mg tid	Inhibition CYP3A4 by SQV	Flumazenil 300µg IV necessary, >5h free of sedative effects	Control: awaking spontaneously, >2h free of sedative effects	Combination not recommended	45,48,160, 161
MID 7.5mg PO 0.05mg/kg IV	Double-blind, randomised, 2-phase crossover	12 vol	SQV-SGC 5 days 1200mg tid	Inhibition CYP3A4 in gut wall, liver by SQV	PO: AUC, C_{max} MID ↑ 2.3-, 5-fold, resp.; C_{max} αOH-MID ↓ 38%. IV: AUC, CL MID ↑ 2.4-fold, ↓56%, resp.; C_{max} αOH-MID ↓ 43%		Initial dosage reduction of 50%; careful titration	
Morphine (MOR)	T		RTV	Induction CYP3A, incl. GT, CYP1A2, and possibly CYP2C9 by RTV	Conc. MOR ↓		Dose increase MOR may be needed to get desired effect	43,72

Mucosal protectives containing bismuth (MUC)	T		DDC, DLV, IDV	↑ gastric pH by MUC	↓ absorption DDC, DLV, IDV		DDC, DLV, IDV >1h before or after MUC	
Nefazodone (NEF)	T		AMP, DLV, IDV, LPV/RTV, NFV, SQV	Inhibition CYP3A by PI/DLV	Conc. NEF ↑		Dosage reduction NEF may be needed.	12,43
NEF 7 days 75mg bid, 2 days 150mg bid	Case report	1 HIV+	RTV ss	Inhibition CYP3A4 by RTV	Headache, confusion, dizziness, nausea, intense anxiety, agitation		Start with ≤50–100mg qd and increase slowly if necessary	162
Nitrofurantoin (NIT)	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
Nizatidine (NIZ)	T		DLV, IDV	↑ gastric pH by NIZ	↓ absorption DLV, IDV	Clinical significance unknown	Long-term use NIZ with DLV, IDV not recommended. TDM DLV/IDV recommended	28
Olanzapine (OLE) single dose 10mg	Crossover	14 vol	RTV 12 days escalated to 500mg bid	Induction CYP1A2 and GT by RTV	AUC, $t_{½β}$, CL/F OLE ↓ 53%, 50%, ↑ 115%, resp.	All had wild type CYP1A2 genotype	Dosage increase OLE may be needed to get desired effect	163
Omeprazole (OME)	T		DLV	↑ gastric pH by OME	↓ absorption DLV	Clinical significance unknown	Long-term use OME with DLV not recommended	28,134
OME 20mg bid (n = 1) [rabeprazole 20mg qd (n = 1)] (see also lansoprazole)	Case reports	4 HIV+	DLV ss		↓ trough conc. DLV	1/4 used rabeprazole 20mg qd → ↓ trough conc. DLV		
OME 20–40mg daily	Retrospective case series	9 HIV+	IDV 800mg tid	Induction 3A by OME; pH ↑ by OME → ↓ solubility IDV	n = 4 <95% confidence interval of ref., n = 4 within 95% confidence interval, n = 1 > 95% confidence interval of ref.	Variable effect: interindividual variability IDV PK?	A = ranitidine (only pH ↑), IDV 1000mg tid	164,165
OME 14 days 40mg qd	Multiple dose OME	8 vol, male	IDV single dose 800mg	Hepatic induction, ↓ absorption by OME	d5: AUC IDV ↓ 2.4%. d14: AUC IDV ↓ 9.5% (n = 4: >25% ↓)		TDM IDV recommended	

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Oral contraceptives (OC), ethinylestradiol (EE) component	*In vitro* (human liver microsomes)		AZT	Inhibition glucuronidation by EE	0.5 mmol/L 46.8% enzyme activity remained; 10 mmol/L 21.0% enzyme activity remained	Conc. AZT probably ↑. Significance?	Monitor blood counts regularly	57
OC-EE	T	-	AMP	?	Effect on EE not known, probably conc. EE ↓		Use additional methods of birth control	36
OC-EE single dose	S	13 vol	EFV 10 days 400mg qd	Not fully characterised: CYP-mediated, glucuronidation	AUC EFV ↑ 2%, C_{max} EFV ↑ 5%, AUC EE ↑ 37%, C_{max} EE ↑ 8%	Clinical significance unknown	Use additional methods of birth control	30,166
OC-EE 7 days 35µg (Ortho Novum®)	S	12 vol	LPV/RTV 400/100mg bid	Induction CYP by LPV/RTV	AUC EE ↓ 42%, C_{max} EE ↓ 41%, C_{min} EE ↓ 58%		Use additional methods of birth control	39,167
OC-EE 15 days 35µg	S	12	NFV 7 days 750mg tid	Induction of estrogen glucuronidation by NFV	AUC EE ↓ 47%, C_{max} EE ↓ 28%		Use additional methods of birth control	14,41
OC-EE single dose 50µg	Open-label, multiple-dose	23 vol	RTV 16 days escalating dose to 500mg bid	Induction glucuronidation, and CYP-mediated pathway	AUC EE ↓ 41%, C_{max} EE ↓ 32%		Use additional methods of birth control	43,168
OC, norethindrone (NET) component, 21 days 1mg qd (Ortho Novum®)	S	12 vol	LPV/RTV 14 days 400/100mg bid	Induction metabolism by LPV/RTV	AUC, C_{max}, C_{min} NET ↓ 17%, 16%, 32%		Use additional methods of birth control	39,167
OC-NET 15 days 0.4mg qd	S	12 vol	NFV 7 days 750mg tid	Induction metabolism by NFV	AUC NET ↓ 18%, C_{max} NET ↔	Clinical significance unknown	Use additional methods of birth control	41
OC-NET/EE 7 days 1mg NET/35µg EE qd (Ortho Novum®)	S	?	IDV 7 days 800mg tid	Inhibition CYP3A4 by IDV	AUC EE ↑ 24%, AUC NET ↑ 26%	Clinical significance unknown	Use additional methods of birth control	37
OC-NET/EE single dose (Ortho Novum®)	Open-label, crossover	14 HIV+	NVP 14 days 200mg, qd, thereafter 200mg bid	Induction CYP3A4 by NVP	AUC NET/EE ↓ 18/29%, $t_{½β}$ EE ↓ 26%, no effect on NVP PK	PK analysis on 10 subjects	Use additional methods of birth control	169

Oxazepam (OXE)	*In vitro* (human liver microsomes)		AZT	Inhibition glucuronidation by OXE	0.5 mmol/L 89.5% enzyme activity remained, 10 mmol/L 67.9% enzyme activity remained	Probably conc. AZT ↑. Significance?		57,170
OXE 2 days 15mg tid	3-phase, crossover	6 HIV+	AZT 2 days 100mg every 4h			Frequency headache ↑		
Paclitaxel (PAC) 100mg/m^2 3h infusion	Case report	1 HIV+, male	Different ARV drugs (RTV/SQV or IDV, NVP)	Similar metabolism: CYP, P-gp	AUC, C_{max} PAC ↓		Modify dose PAC when necessary. Monitor leucocytes regularly	171,172
PAC 100mg/m^2 3h infusion	Case report	2 HIV+, male/ female	DLV + SQV	Inhibition CYP3A by DLV, SQV	Mucositis, febrile neutropenia, total alopecia (n = 1), respiratory distress (n = 1)	1 PAC dose biweekly 60mg/m^2 3h infusion = tolerable AE		
Pentamidine (PET)	T		DDI, 3TC, D4T	Similar toxicity profile	Pancreatitis		Avoid where possible, monitor for pancreatitis	4
Perazine (PER)	T		RTV	Inhibition CYP2D6 by RTV, PER	Conc. PER ↑. Conc. RTV ↑	Based on interaction with perphenazine	Dosage reduction PER, RTV may be needed. TDM RTV recommended	
Periciazine (PEC)	T		RTV	Inhibition CYP2D6 by RTV, PEC	Conc. PEC ↑. Conc. RTV ↑	Based on interaction with perphenazine	Dosage reduction PEC, RTV may be needed. TDM RTV recommended	
Perphenazine (PEZ)	T		RTV	Inhibition CYP2D6 by RTV, PEZ	Conc. PEZ ↑. Conc. RTV ↑		Dosage reduction PEZ, RTV may be needed	12,43
Phenobarbital (PHB) [see also barbiturates]	Population PK data	8 HIV+	DLV	Induction CYP3A by PHB, inhibition CYP3A by DLV (T)	C_{trough} DLV ↓. Conc. PHB ↑		TDM DLV/PHB recommended. A = valproic acid	28
Phenytoin (PHT)	T		AMP, EFV, IDV, LPV/RTV, NVP, RTV, SQV	Induction CYP3A by PHT/EFV/ NVP, inhibition CYP3A by PI	Conc. PI/NNRTI ↓. Conc. PHT ↑ (PI) or ↓ (EFV/NVP)		TDM PI/NNRTI/ PHT recommended. A = valproic acid	30,36,37,39, 43,45,48
PHT single dose 300mg	S	12 HIV+	AZT 200mg 4dd, ss conditions	?	CL AZT ↓ 30%. PK PHT ↔		Monitor blood counts regularly	25

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
PHT	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
PHT	Population PK data	8 HIV+	DLV	Induction CYP3A by PHT, inhibition CYP3A by DLV (T)	C_{trough} DLV ↓. Conc. PHT ↑		TDM PHT/DLV recommended. A = valproic acid	28
PHT 7 days 300mg qd	Parallel design	15, 12 vol	NFV 7 days 1250mg bid	Induction CYP3A by NFV	AUC_{24}, C_{max}, C_{min} PHT ↓ 30%, 21%, 39%, resp.; NFV/M8 not determined	Possibly conc. NFV ↓	TDM PHT/NFV recommended. A = valproic acid	41,173,174
PHT ss 300mg/day	Case report	1 HIV+, male	NFV 750mg tid	Induction CYP by NFV ? (or interaction with AZT/ D4T)	Numbness left upper limb followed by generalised tonic-clonic seizure; serum conc. PHT ↓	Interaction via CYP2C9, 2C19?		
Pimozide (PIM)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. PIM ↑	Risk for cardiac toxicity	Combination not recommended. CI (AMP, IDV, LPV/RTV)	36,37,39,43
Pipotiazine (PIP)	T		RTV	Inhibition CYP2D6 by RTV, PIP	Conc. PIP ↑. Conc. RTV ↑	Based on interaction with perphenazine	Dosage reduction PIP, RTV may be needed. TDM RTV recommended.	
Piroxicam (PIR)	T		RTV	Inhibition metabolism by RTV	Conc. PIR ↑	Risk for ↑ GI and CNS toxicity	CI. A = diclofenac, ibuprofen	7,44
Pravastatin (PRA) 4 days 20mg qd	S	12 vol	LPV/RTV 14 days 400/100mg bid	Inhibition CYP3A by LPV/RTV	AUC, C_{max} PRA ↑ 33%, 26%, resp. AUC, C_{max}, C_{min} LPV ↓ 5%, 2%, 12%, resp.	PRA is to minor extent metabolised by CYP3A	No dosage adjustment required	65
PRA 4 days 40mg qd	Randomised, open label, multiple dose	14 vol	RTV/SGQ-SGC 4 days 400/400mg bid	Induction glucuronidation by RTV	AUC PRA ↓ 50%		Higher doses PRA may be needed	68
Prazepam (PRZ)	T		RTV	Inhibition CYP3A by RTV	Conc. PRZ ↑	Based on similar metabolism via CYP3A	A = oxazepam, lorazepam	

Prednisone (PRE)	T		RTV	Inhibition CYP3A by RTV	Conc. PRE ↑		Monitor toxicity PRE, dosage reduction (>50%) may be necessary	43
Prednisolone (PRD)	T		RTV	Inhibition CYP3A by RTV	Conc. PRD ↑	Based on interaction with PRE	Monitor toxicity PRD, dosage reduction may be necessary	43
Primaquine (PRQ)	T		AZT	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor blood counts regularly	4,25
Primidone (PRI)	T		AMP, EFV, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Induction CYP3A by PRI	Conc. PI/NNRTI ↓	Chemically related to barbiturates	TDM PI/NNRTI recommended. A = valproic acid	28,30,36,37, 39,41,43,45, 48
Probenecid (PRO) 3 days 500mg tid	2-part, open-label	8 HIV+	AZT 3 days 200mg every 4h	Inhibition hepatic glucuronidation, renal organic anion secretory mechanism by PRO	AUC AZT ↑ 80%. CL_R GAZT ↓ 58%		Avoid combination where possible, reduce dosage AZT. Monitor blood counts regularly.	25,175-178
PRO 28 days 500mg tid	S	8 vol, male	AZT 200mg tid		n = 4: completed study, n = 4: discontinuation PRO because of rash	3/4 severe rash and constitutional symptoms		
PRO 3 days 500mg every 6h, >3h prior to AZT	S	2 vol, male	AZT single dose 200mg		AUC AZT ↑ 115%, CL AZT ↓ 51%, AUC GAZT ↑ >3.5-fold			
PRO 500mg every 6h, separated >2h from AZT dose	Balanced, crossover	7 HIV+	AZT 2mg/kg tid (oral solution)		AUC AZT, CL ↑ 106%, ↓ 45%, resp. GAZT/AZT urine ↓58%			
PRO 500mg >2h prior and >4h after DDC	Randomised 2-way crossover	12 HIV+	DDC single dose 1.5mg	Inhibition tubular secretion by PRO	AUC DDC ↑54%, CL DDC ↓ 37%, CL_R DDC ↓ 42%	Specific nucleoside transport system?	Monitor for peripheral neuropathy, dosage reduction DDC may be needed	24,179
Prochlorperazine (PRC)	T		RTV	Inhibition CYP2D6 by RTV, PRC	Conc. PRC ↑. Conc. RTV ↑	Based on interaction with perphenazine	Dosage reduction PRC, RTV may be needed. TDM RTV recommended	

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Promethazine (PRM)	T		RTV	Inhibition CYP2D6 by RTV, PRM	Conc. PRM ↑. Conc. RTV ↑	Based on interaction with perphenazine	Dosage reduction PRM, RTV may be needed. TDM RTV recommended	
Propafenone (PRP)	T		LPV/RTV, RTV	Inhibition CYP2D6 by PI	Conc. PRP ↑	Risk for cardiac arrhythmias	CI	39,43
Pyrazinamide (PYR)	Prospective, observational	4 HIV+/ TBC+, 7 HIV+/ TBC+ (controls)	AZT	?	n = 4: very low PYR conc.	2h serum concentrations were drawn	Avoid combination	180
Pyrimethamine (PYM)	T		AZT	Similar toxicity profile	Haematological toxicity		Avoid where possible, monitor blood counts regularly	4,25
PYM	T		RTV	Inhibition/induction CYP3A by RTV	Variable or unknown effect		Monitor blood counts and efficacy PYM regularly	14
Quinidine (QUI)	T		AMP, DLV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. QUI ↑	Risk for cardiac toxicity	CI (RTV, NFV). A = indinavir, TDM QUI recommended	28,36,39,41, 43,45
Quinine (QUN)	T		RTV	Inhibition CYP3A by RTV	Conc. QUN ↑	Risk for cardiac toxicity	Monitor toxicity QUN, dose reduction QUN may be needed	43
Ranitidine (RAN) single dose 150mg, 2h prior to DDI	Open, randomised, 3-way crossover	12 HIV+	DDI single dose 375mg	↑ BA by ↑ gastric pH by RAN, ↓ absorption RAN in presence of antacid	AUC, C_{max} DDI ↑ 14%, 13%, resp. AUC, C_{max} RAN ↓ 16%, ↔, resp.	No dosage modification; buffer formulation DDI adequate protection	RAN 2h prior to DDI. A = DDI EC	20,181
RAN	T		DLV, IDV	↑ gastric pH by RAN	↓ absorption DLV, IDV	Clinical significance unknown	Long-term use RAN with DLV, IDV not recommended. TDM DLV/IDV recommended	28

RAN 150mg 2 doses	S	12 vol	SQV-HGC single dose 600mg	?	AUC, C_{max} SQV ↑ 67%, 74%, resp.		TDM SQV recommended	45,48
Ribavirin (RIB)	T		AZT	Interference with phosphorylation by RIB	Conc. triphosphate anabolite-AZT ↓ (active)		Avoid where possible, monitor blood counts regularly	25,182
RIB 2, 20 μmol/L	*In vitro*		AZT 10, 100 μmol/L	↑ formation dTTP by RIB → ↓ activity thymidine kinase	↓ phosphorylation AZT; effect primarily on AZT-MP rather than active AZT-TP	Concentration dependent; ↓ AZT-MP, thus ↓ toxicity		
RIB	T		DDC, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	24
RIB 6 months 800–1200 mg/day	Case reports	3 HIV+, male	DDI 400mg qd	RIB promotes phosphorylation by inhibition of IMP	Moderate hyperlactacidaemia, severe clinical symptoms; ↑ intracellular/mitochondrial conc. of ddATP (suggested)		Avoid where possible, dosage reduction DDI may be needed	20,21,183
RIB	T		DDI	Similar toxicity profile	Peripheral neuropathy			
Rifabutin (RFB) 10 days 300mg qd	Open-label, randomised, parallel-group, 3-period	12 vol	AMP 10 days 1200mg bid	Inhibition CYP3A4 by AMP	AUC, C_{max}, C_{min} RFB ↑ 2.9-, 2.2-, 3.7-fold, resp. AUC, C_{max}, C_{min} 25-*O*-desacetyl-RFB ↑ 13.35-, 7.39-, 32.9-fold, resp.	Combination poorly tolerated: only 6 evaluable, PK AMP?	Monitor neutrophil counts regularly, dosage reduction RFB >50%. TDM AMP recommended	36,184
RFB	T		AZT	Similar toxicity profile	Haematological toxicity		Avoid where possible, monitor blood counts regularly	4,25
RFB 14 days 300mg qd	Open-label, parallel-group, multiple-dose, randomised	7, 5 HIV+ (controls)	DLV 30 days 400mg tid	Induction CYP3A by RFB, inhibition CYP3A by DLV	CL DLV ↑ 445%, C_{min}, C_{max} DLV ↓ 95%, 75%, resp. C_{max} RFB ↑ 20%, C_{trough}, CL RFB ↓ 40%, 20%, resp.		Avoid where possible, monitor neutrophil counts regularly. TDM DLV recommended, DLV 600mg tid	28,185,186
RFB 30 days 300mg	S	6 HIV+	DLV 14 days 400mg tid	Inhibition hepatic CYP3A by DLV	AUC, C_{min} RFB ↑ 242%, 455%, resp. AUC DLV ↓ 80%	RFB compared with historical data		
RFB 300mg qd	S	7 HIV+	DLV 400mg tid		AUC RFB ↑ 100%			

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
RFB 7 days 300mg qd (see also clarithromycin + D4T and fluconazole + D4T)	Sequential, 8-part, multiple-dose, non-blinded, randomised	10 HIV+	D4T 7 days 40mg bid	Inhibition absorption by RFB?	C_{max} D4T ↓ 35% when combined with CLA + RFB + FLU	Significance?		81
RFB 14 days 300mg qd	S		EFV 14 days 600mg qd	Induction CYP3A by EFV	Conc. RFB ↓, PK EFV?		Increase dose RFB to 450–600mg/day. TDM EFV recommended	30,187
RFB (1) 300mg qd, (2) 150mg qd	S		IDV 800mg tid	Inhibition CYP3A by IDV, induction CYP3A by RFB	(1) AUC IDV ↓ 32%, AUC RFB ↑ 204%. (2) AUC IDV ↓ 31%, AUC RFB ↑ 60%	AUCs compared with RFB 300mg qd without IDV	Reduce dosage RFB >50% (300mg qd 2–3 times/week), monitor neutrophil counts regularly	37,188
RFB 150mg qd when + IDV, 300mg qd when alone	A: multiple-dose, 3-period, randomised crossover. B: multiple-dose, 2-period sequential	?	1000mg tid when + RFB, 800mg tid when alone		A: AUC RFB 150mg qd + IDV 1000mg tid = 60% ↑ than AUC RFB 300mg qd. B: AUC IDV 1000mg tid + RFB 150mg qd = AUC IDV 800mg tid	Sequential administration = simultaneous administration when RFB PK were compared	IDV 1000mg tid, TDM IDV recommended	
RFB 10 days 150mg qd	S	14 vol	LPV/RTV 20 days 400/100mg bid	Inhibition CYP3A by LPV/RTV	AUC RFB + 25-*O*-desacetyl-RFB ↑ 5.7-fold. AUC LPV ↑ 17%		Maximum dose RFB 150mg every other day or 3× per week. Monitor neutrophil counts regularly. TDM LPV/RTV recommended	39
RFB 8 days 150mg qd	S	12 vol	NFV 7/8 days 750mg tid	Inhibition CYP3A by NFV, induction CYP3A by RFB	AUC, C_{max} RFB ↑ 83%, 19%, resp. AUC, C_{min} NFV ↓ 23%, 18%, resp.	NFV 1250mg bid shows no change in PK when combined with RFB 150mg qd	Reduce dosage RFB >50% (300mg qd 2–3 times/week), monitor neutrophil counts regularly	41

RFB 8 days 300mg qd	S	10 vol	NFV 7/8 days 750mg tid		AUC, C_{max} RFB ↑ 207%, 146%, resp. AUC, C_{min} NFV ↓ 32%, 25%, resp.		TDM NFV recommended, preferred dosage NFV 1250mg bid	
RFB	S	19	NVP	Induction CYP3A by RFB	C_{trough} ss NVP ↓ 16%		Avoid where possible, TDM NVP recommended	33
RFB 24 days 150mg qd	Multiple-dose, randomised, parallel-group, double-blind	5, 11 (control) vol	RTV 10 days 500mg bid (escalation scheme)	Inhibition CYP3A (intestinal, hepatic, or combi) by RTV	AUC, C_{max}, C_{min} RFB ↑ 4-, 2.5-, 6-fold, resp. AUC, C_{max}, C_{min} 25-*O*-desacetyl-RFB ↑ 35-, 16-, 200-fold, resp.	8 patients discontinued because of AE (1 control, 7 case).	RTV/SQV 400/400mg bid + RFB 300mg/week or 150mg every 3 days, monitor neutrophil counts regularly. TDM RTV/SQV recommended	189,190
RFB	S		SQV		AUC SQV ↓ 45%		RTV/SQV 400/400mg bid + RFB 300mg/week or 150mg every 3 days, monitor neutrophil counts regularly.	45,48,190
RFB 14 days 300mg qd	Preliminary data	12 HIV+	SQV-HGC 14 days 600mg tid	Induction CYP3A by RFB	AUC, C_{max} SQV ↓ 43%, 30%, resp.		TDM RTV/SQV recommended	
Rifampicin (RIF) 10 days 600mg qd	Open-label, randomised, parallel-group, 3-period	12 vol	AMP 10 days 1200mg bid	Induction hepatic/intestinal CYP3A4 by RIF	AUC, C_{max}, C_{min}, CL AMP ↓ 82%, 70%, 92%, ↑ 5.45-fold resp.	Combination poorly tolerated: only 6 evaluable	CI; A = AMP + RFB reduced dose > 50%	36,184
RIF 14 days 600mg qd	2-treatment, 3-period, single sequence, repeated measures	8 HIV+	AZT 14 days 200mg tid	Induction glucuronidation, amination by RIF; induction AMT formation	AUC, C_{max} AZT ↓ 47%, 43%, resp. AUC: GAZT/AZT ↑ 99%; AMT/AZT ↑ 36%		No dosage adjustment necessary	25,191,192
RIF 600mg qd	S	10	AZT 200mg qd		AUC AZT ↓ 48%			
RIF 600mg qd		4 HIV+, male	AZT 200–500mg bid/tid		AUC normalised AZT ↓ > 50%; $t_{½\beta}$ ↔ for n = 3	AUC AZT compared with AUC AZT of population not using RIF		

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
RIF 600mg qd	S	7 HIV+	DLV 400mg tid	Induction CYP3A by RIF, inhibition CYP3A by DLV	AUC DLV ↓ 96%; CL DLV ↑ 27-fold	Conc. RIF ↑ (T)	CI; A = NVP + RFB	28,193
RIF 15 days 600mg qd	S	7, 5 HIV+	DLV 30 days 400mg tid		Metabolite formation/metabolite elimination ↑ 16-fold	Virtually negligible ss C_{trough} DLV		
RIF 7 days 600mg qd	S	12 vol	EFV 14 days 600mg qd	Induction CYP3A by RIF, induction CYP3A by EFV	AUC, C_{max} EFV ↓ 13%, 14%, resp. n = 10: AUC, C_{max} EFV ↓ 33%, 23%, resp.	2 patients had ↑ AUC, C_{max} EFV. Clinical significance unknown	A = RFB 450–600mg/day. Increase dose EFV to 800mg qd. TDM EFV recommended.	30,194,195
RIF 7 days	Randomised, 3-group	24 HIV+	EFV 600mg qd/800mg qd		7/8 (600mg qd) C_{max}, C_{min}, AUC EFV ↓ 30%, 24%, 22%, resp. EFV 800mg qd: conc. in therapeutic range	Conc. RIF ↓ (T)		
RIF 7 days 600mg qd	S		IDV 7 days 800mg tid	Induction CYP3A4 by RIF, inhibition CYP3A4 by IDV	AUC IDV ↓ 89%		Avoid combination; IDV 1000mg tid + reduced dose RFB (>50%), TDM IDV recommended	14,37,196
RIF single dose 600mg	S	11 HIV+	IDV 14 days 800mg tid		AUC_{24} RIF ↑ 73%		A = 9-month streptomycin-based regimen	
RIF 10 days 600mg qd	S	22 vol	LPV/RTV 20 days 400/100mg bid	Induction CYP3A by RIF, inhibition CYP3A by LPV/RTV	AUC, C_{max}, C_{min} LPV ↓ 75%, 55%, 99%, resp.	Conc. RIF ↑ (T)	CI. A = RFB maximum dosage 150mg every other day or 3× per week. TDM LPV/RTV recommended	39,167
RIF 7 days 600mg qd	Randomised crossover	12 vol	NFV 6 days 750mg tid ss	Induction CYP3A by RIF, inhibition CYP3A by NFV	AUC_8, C_{max} NFV ↓ 82%, 76%	Conc. RIF ↑ (T)	CI; A = RFB reduced dosage >50% + NFV 1250mg bid	130,197

RIF 7 days 600mg qd	Case report	1 HIV+ infant	NFV ss 27 mg/kg bid (+ 380mg/m^2 RTV bid)	Blocking RIF-induced metabolism NFV by addition RTV	AUC_{24} (NFV + M8), C_{min} (NFV + M8) ↑ 130%, 142% compared with population values	Addition of RTV resulted in highly elevated M8 conc.	TDM NFV (+ M8) recommended	
RIF 43 days 600mg qd	Open-label, single arm	22 HIV+	NVP 28 days 200mg bid	Induction CYP3A4 by RIF, NVP	Average conc., C_{min} NVP ↓ 58%, 68%, resp. n= 3: C_{trough} ss NVP ↓ 37%	RIF 600mg twice weekly less marked drug interaction than with daily RIF. Conc. RIF ↓ (T)	Consider NVP 300mg bid, TDM NVP recommended. A = RFB	33,198,199
RIF 10 days 600mg/300mg qd	Parallel design	7 / 9	RTV 20 days 500mg bid	Induction CYP3A by RIF, inhibition CYP3A by RTV	AUC, C_{max} RTV ↓ 35%, 25%, resp.	Conc. RIF ↑ (T)	A = RFB 150mg every other day. TDM RTV recommended	43,200
RIF 28 weeks 600mg qd	Pilot, non-randomised, open-label	18 HIV+	RTV 28 weeks 600mg bid		n = 8: median C_{min} RTV 2.22 mg/L, > IC_{90} at most time-points. RIF level within normal limits	6 discontinued because of intolerance to RTV liquid		
RIF 7 days 600mg qd	S	12 vol	SQV-HGC 14 days 600mg tid	Induction CYP3A by RIF, inhibition CYP3A by SQV	AUC, C_{max} SQV ↓ 84%, 79%, resp.	Conc. RIF ↑ (T)	Avoid combination or use SQV combined with RTV, TDM RTV/SQV recommended	45,48,88, 101,201
RIF	Retrospective review				AUC, C_{max} SQV ↓ 70%, 65%, resp.			
RIF 14 days 600mg qd	Open-label, randomised, 2-way crossover	14 vol	SQV-SGC 1200mg tid ss		AUC, C_{max} SQV ↓ 70%, 65%, resp.	SQV plasma concentrations < EC_{50} SQV		
RIF 14 days 600mg qd	Open-label, substudy	11 HIV+	SQV-SGC 1200mg tid ss		AUC, C_{max} SQV ↓ 46%, 43%, resp.			
Risperidone (RIS) 1.5mg daily	Case report	1 HIV+, female	RTV/IDV	Inhibition CYP2D6 by RTV and CYP3A4 by RTV/IDV	Neuroleptic malignant syndrome: persistent fever, rigidity, tremor, autonomic instability, ↑ CPK. AUC RIS ↑ 1. 5–3-fold by RTV		Avoid combination	12,43,202

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Roxithromycin (ROX) 300 or 600mg/day	Open-label, randomised	6 HIV+	NFV	Protein (AAG) binding displacement by ROX?	3/6 no baseline resistance to NFV: median ↑ HIV-RNA 0.96 log after 1 week. 3/6 baseline resistance to NFV: transient/no virological response		TDM NFV recommended	203
Salicylic acid (SAC)	*In vitro* (human liver microsomes)		AZT	Inhibition glucuronidation by SAC	0.5 mmol/L 99.7% enzyme activity remained; 10 mmol/L 52.2% emzyme activity remained	Conc. AZT probably ↑. Significance?	Monitor blood counts regularly	57
Selective serotonin reuptake inhibitors (SSRI) [see also fluoxetine]	T		RTV	Inhibition CYP3A and/or CYP2D6 by RTV	Conc. SSRI ↑		Use lowest dose SSRI possible and titrate	12,43
Sildenafil (SIL)	T		AMP, DLV, LPV/RTV, NFV	Inhibition CYP3A by PI/DLV	Conc. SIL ↑	Based on studies with other PIs	Starting dose SIL 25mg in 48h, monitor for AEs	28,36,39,41
SIL single dose 25mg	S	6 HIV+	IDV 800mg tid ss	Inhibition CYP3A4 IDV/SIL	AUC_8, C_{max} IDV ↑ 11%, 48%, resp. Headache, flushing, dyspepsia, rhinitis, blood pressure ↓	PD effect >72h post ingestion	Starting dose SIL 25mg in 48h	204
SIL 25mg	Case report	1 HIV +, male	RTV/SQV 400/400mg bid	Inhibition CYP3A4 (first-pass)/2C9 (systemic CL) by RTV	Severe central chest pain		Starting dose SIL 25mg in 48h	43,205,206
SIL single dose 100mg	Independent, open, randomised, placebo-controlled, parallel-group	28 vol	RTV 8 days 500mg bid (escalation scheme)		AUC, C_{max} SIL ↑ 11-, 3.9-fold			
SIL 100mg	Independent, open, randomised, placebo-controlled, parallel-group	27 vol	SQV-SGC 7 days 1200mg tid	Inhibition CYP3A4 (both intestinal and hepatic) by SQV	AUC, C_{max} SIL ↑ 3.1-, 2.4-fold	See also case report RTV/SQV	Starting dose SIL 25mg in 48h	45,48,206

Simvastatin (SIM)	T		AMP, DLV, IDV, LPV/RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. SIM ↑	Based on interaction with atorvastatin, risk for myopathy	Combination not recommended. CI (AMP), A = fluvastatin, pravastatin	36,37,39,45, 48,207
SIM	Case report	1 HIV+, male	IDV/RTV	Inhibition CYP3A by PI/DLV	RTV was added to IDV and SIM → rhabdomyolysis, renal failure			
SIM 14 days 20mg qd	Open-label, sequential, multiple-dose	16 vol	NFV 14 days 1250mg bid	Inhibition CYP3A by NFV	AUC, C_{max} SIM ↑ 505%, 517%, resp.	Risk for myopathy, including rhabdomyolysis	CI; A = pravastatin	41,66
SIM 4 days 40mg qd	Randomised, open label, multiple dose	14 vol	RTV/SQV-SGC 14 days 400/400mg bid	Inhibition CYP3A by RTV/SQV	AUC SIM ↑ 30-fold	Risk for myopathy, including rhabdomyolysis	CI; A = fluvastatin, pravastatin	43,68
Sirolimus (SIR)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. SIR ↑	TDM SIR recommended. Risk for anaemia, thrombo-cytopenia	Monitor blood counts regularly. TDM SIR recommended	36,39
St John's wort (SJW)	T		AMP, DLV, EFV, LPV/RTV, NFV, RTV, SQV	Induction CYP3A by SJW	Conc. PI/NNRTI ↓		Coadministration not recommended. TDM PI/NNRTI recommended	36,39,41,43
SJW 14 days 300mg tid	Open-label	8 vol, male	IDV 800mg tid	Induction CYP3A4 by SJW, maybe effect on P-gp	AUC_8, C_{min}, C_{max} IDV ↓ 57%, 49–99%, 28%, resp.	After 4th dose IDV PK	Coadministration not recommended. TDM IDV recommended	37,208
SJW	Population PK data	5 HIV+ (n = 176)	NVP	Induction CYP3A4 by SJW	CL NVP ↑ 35%		Coadministration not recommended. TDM NVP recommended	33,209
Sulfadiazine (SUF)	T		AZT	Similar toxicity profile	Haematological toxicity		Avoid where possible, monitor blood counts regularly	4,25

Continued over page

Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Tacrolimus (TAC)	T		AMP, DLV, IDV, LPV/RTV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. TAC ↑		Monitor blood counts regularly. TDM TAC recommended	36,39,41,43
TAC 0.5mg weekly	Case report	1 HIV+, male	NFV 500mg tid	Inhibition CYP3A by NFV	Conc. TAC 5–15μg/L. Conc. NFV slightly ↑ than normal		Monitor blood counts regularly. TDM TAC recommended	41,210
TAC	Case report	1 HIV+, female	(1) RTV/SQV 400/400mg bid. (2) NFV	Inhibition CYP3A by PI	(1) Conc. TAC ↑ 120 μg/L, severe prolonged toxicity. (2) Confusion, lethargy, delusional		Monitor blood counts regularly. TDM TAC recommended	41,43,211
Tamoxifen (TAM)	T		RTV	Inhibition CYP3A by RTV	Conc. TAM ↑		Monitor for neurotoxicity, dosage reduction TAM may be needed	
Terfenadine (TER)	T, *in vitro* (AMP)		AMP, DLV, EFV, IDV, LPV/RTV, RTV, SQV-HGC (see also TER + SQV-SGC)	Inhibition CYP3A4 by PI/NNRTI	Conc. TER ↑	Risk for cardiac arrhythmias	CI; A = cetirizine, acrivastine	28,36,37,39, 43,63
TER single dose 60mg	S	12 vol	NFV 7 days 750mg tid	Inhibition CYP3A4 by NFV	Conc. TER alone <5 μg/L. C_{max} TER + NFV 5–15 μg/L	Risk for cardiac arrhythmias	CI; A = cetirizine, acrivastine	130
TER 11 days 60mg bid	S	12 vol	SQV-SGC 4 days 1200mg tid	Inhibition CYP3A4 by SQV	AUC, C_{max} TER ↑ 368%, 253%, resp. AUC, C_{max} TER acid metabolite ↑ 120%, 93%, resp.	Risk for cardiac arrhythmias	CI; A = cetirizine, acrivastine	45,48,89
Tetracyclines (TET)	T		DDI	Chelation with cations in DDI tablets	↓ absorption TET		TET > 2h prior to DDI or 6h after DDI; A = DDI EC	92
Thalidomide (THA)	T		RTV	Inhibition CYP by RTV	Conc. THA ↑		Monitor for neurotoxicity THA, dosage reduction THA may be needed	

Theophylline (THE) 5 days 3 mg/kg tid	Placebo-controlled	13, 11 (control)	RTV 10 days 500mg bid (escalation scheme)	Induction CYP1A2 by RTV?	AUC, C_{max}, C_{min} THE ↓ 43%, 32%, 57%, resp.		TDM THE recommended	43,212
Thioridazine (THI)	T		RTV	Inhibition CYP2D6 by RTV, THI	Conc. THI potential ↑. Conc. RTV potential ↑	Based on interaction with perphenazine	Dosage reduction THI may be needed	12,43
Timolol (TIM)	T		RTV	Inhibition CYP2D6 by RTV	Conc. TIM ↑	↑ risk for bradycardia and hypotension	Dosage reduction TIM (>50%) may be needed	43
Tiotixene (TIO)	T		RTV	Inhibition CYP2D6 by RTV	Conc. TIO ↑	↑ risk for sedation	Dosage reduction TIO may be needed	
Tramadol (TRM)	T		RTV	Inhibition CYP3A by RTV	Conc. TRM ↑	↑ risk for GI toxicity	Dosage reduction TRM (>50%) may be needed	43
Trazodone (TRA)	T, *in vitro* (human liver microsomes)		IDV, RTV	Inhibition CYP3A (2D6) by IDV, RTV	IC_{50} IDV 0.63 µmol/L, IC_{50} RTV 0.30 µmol/L, conc. TRA potential ↑		Monitor for increased sedation. Dosage reduction may be needed	12,213
Triazolam (TRI)	T		AMP, DLV, EFV, IDV, LPV/RTV, NFV, SQV	Inhibition CYP3A by PI/NNRTI	Conc. TRI ↑	Risk for prolonged or ↑ sedation, respiratory depression	CI; A = oxazepam, lorazepam	28,30,36,37, 39,41,45,48
TRI Single dose 0.125mg	Double-blind, randomised, 5-way crossover	6 vol, male	RTV 200mg bid (4 doses)	Initial inhibition of CYP3A by RTV (presystemic)	AUC, $t_{½β}$, C_{max} TRI ↑ 19-, 13-fold, 87%, resp. CL TRI ↓ 96%. PD: ↑ sedation	Probably induction from long-term exposure will offset inhibition due to short-term exposure	CI; A = oxazepam, lorazepam	43,59,60
Tricyclic antidepressants (TRC) [see also desipramine]	T		AMP, RTV	Inhibition CYP2D6 and/or CYP3A by PI	Conc. TRC ↑		TDM TRC recommended, dosage reduction TRC may be needed	12,36,43

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
Trifluoperazine (TRF)	T		RTV	Inhibition CYP2D6 by RTV. TRF	Conc. TRF ↑. Conc. RTV ↑	Based on interaction with perphenazine	Dosage reduction TRF, RTV may be needed. TDM RTV recommended	
Triflupromazine (TRP)	T		RTV	Inhibition CYP2D6 by RTV. TRP	Conc. TRP ↑. Conc. RTV ↑	Based on interaction with perphenazine	Dosage reduction TRP, RTV may be needed. TDM RTV recommended	
Trimethoprim (TMP) 8 days 200mg bid	Open, randomised, crossover	8 HIV+	AZT single dose 200mg	Competition by TMP at the renal tubular site	CL_R AZT ↓ 58%	Only 20% of CL/F AZT by CL_R, thus probably not significant	Monitor blood counts regularly	4,25,214
TMP/sulfamethoxazole (SUL) [cotrimoxazole]	T		AZT	Similar toxicity profile	Haematological toxicity			
TMP	S	? HIV+	DDC	Inhibition renal tubular secretion	CL_R DDC ↓	Clinical significance unknown		215
TMP/SUL 5 days 800/160mg qd	Randomised, 2-way crossover	14 HIV+	3TC single dose 300mg	Competitive inhibition renal tubular secretion by TMP	AUC 3TC ↑ 44%, CL_R 3TC ↓ 30%, CL 3TC ↓ 29%	No intervention when TMP/SUL is used to prevent PCP (480mg qd)	Stop 3TC during high dose therapy with TMP/SUL (>960 mg/day)	4,22, 216-218
TMP/SUL	T		3TC	Similar toxicity profile	Pancreatitis		Monitor for pancreatitis	
TMP/SUL	T		DDI, D4T	Similar toxicity profile	Pancreatitis		Monitor for pancreatitis	4
TMP/SUL 7 days 400/80mg bid	S	?	IDV 400mg qid	Inhibition CYP by IDV	AUC TMP ↑ 19%		No dosage adjustment necessary	37

TMP/SUL single dose 800/160mg	Open-label	15 vol	RTV 12 days 500mg bid (escalation scheme)	Induction *N*-glucuronidation, inhibition CYP by RTV	AUC, C_{max} SUL ↓ 20%, ↔, resp. AUC, C_{max} TMP ↑ 20%, ↔, resp.	Not clinically relevant	No dosage adjustment necessary	43,219
Valproic acid (VAL) 4 days 250mg tid	S	6 HIV+	AZT 4 days 100mg tid	Inhibition glucuronidation, first-pass metabolism by VAL	AUC, C_{max}, CL AZT ↑ 80%, 41%, ↓ 38%, resp. AUC, C_{max} GAZT ↓ 22%, 36%, resp. GAZT/AZT urinary excretion ratio ↓ 58%	Clinical significance unknown	Monitor blood counts regularly	25,220
VAL	Case report	1 HIV+, male	RTV/SQV 400/400mg bid, followed by NVP 200mg bid	↑ risk carnitine depletion, accumulation toxic VAL metabolites by CYP-inducing agents RTV, NVP	Headache, nausea, vomiting, anorexia, fevers etc. → hepatitis	Levocarnitine 1g tid administered	Replacement of carnitine is recommended	221
Verapamil (VER)	T		AMP, DLV, IDV, LPV/RTV, NFV, RTV, SQV	Inhibition CYP3A by PI/DLV	Conc. VER ↑	Risk for hypotension, bradycardia etc.	Dosage reduction VER may be needed	36,43
Vincristine (VIN)	T		DDC, DDI, D4T	Similar toxicity profile	Peripheral neuropathy		Avoid where possible, monitor for peripheral neuropathy	20,21,24
Warfarin (WAR)	T		AMP, DLV, EFV, LPV/RTV, NFV	Inhibition CYP3A by PI/DLV, induction CYP3A by EFV	Conc. WAR ↑ (or ↓ in case of EFV)		Monitor INR	28,30,36,39
WAR 5mg/day	Case report	1 HIV+, male	IDV 800mg tid, followed by RTV 600mg bid	Induction metabolism by RTV/IDV	Both regimens ↑ PCA → dosage WAR ↑ 8.75mg/day		Monitor INR	43,222
WAR	Case reports	3 HIV+	NVP 200mg bid	Induction of CYP by NVP	Dosage increase WAR was needed to stabilise Quick time and INR within therapeutic range		Monitor INR	223

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Table III. Contd

Coadministered agent and dosage	Type of study	Subjects involved (n)	Antiretroviral agent and dosage	Interaction mechanism	Effect of interaction	Comments	Advice	References
WAR 12.5mg qd	Case report	1 HIV+, female	RTV 400mg bid	↓ anticoagulant effect, results of RTV effect on TMP-SUL interaction/RTV affected WAR directly	Paradoxical effect: INR↓, WAR dosage ↑, RTV discontinued: INR ↑ 3-fold	Comedication CLA, TMP/SUL	Monitor INR	43,224,225
WAR 10mg/day	Case report	1 HIV+, male	RTV 400mg bid, NFV 750mg tid (switch from EFV 600mg qd)	Inhibition CYP2C9 by RTV	INR ↑ 4-fold			
WAR	Case report	1 HIV+, male	SQV 600mg tid	Inhibition CYP3A4 by SQV	INR ↑ slowly → hypoprothrombinaemia		Monitor INR	226
Zolpidem (ZOL)	T		AMP, DLV, IDV, LPV/RTV, NFV, SQV	Inhibition CYP3A by PI/DLV	Conc. ZOL ↑	Based on interaction with RTV	Dosage reduction ZOL may be needed. A = oxazepam, lorazepam	
ZOL single dose 5mg	Double-blind, randomised, 5-way crossover	6 HIV+	RTV 200mg bid (4 doses)	Initial inhibition CYP3A by RTV	AUC, $t_{½\beta}$, C_{max} ZOL ↑ 28%, 20%, 22%, resp. CL ZOL ↓ 26%	Probably induction from long-term exposure will overcome inhibition due to short-term exposure	Dosage reduction ZOL may be needed. A = oxazepam, lorazepam	43,227

A = alternative; **AAG** = α_1-acid glycoprotein; **ABC** = abacavir; **ADH** = alcohol dehydrogenase; **AE** = adverse events; **AMP** = amprenavir; **AMT** = 3 -amino-3 -deoxythymidine; **ARV** = antiretroviral; **AUC** = area under the plasma concentration-time curve; **AZT** = zidovudine; **BA** = bioavailability; **bid** = twice daily; **C** = controls; **CI** = contraindicated; **CL** = apparent ('oral') systemic clearance; $\mathbf{CL_{CR}}$ = creatinine clearance; $\mathbf{CL_R}$ = renal clearance; $\mathbf{C_{max}}$ = maximum plasma concentration; $\mathbf{C_{min}}$ = minimum plasma concentration; **CNS** = central nervous system; **Conc**. = plasma concentration; **CPK** = creatinine phosphokinase; **CRABP-1** = cellular retinoic acid-binding protein-1; **CSF** = cerebrospinal fluid; $\mathbf{C_{trough}}$ = trough plasma concentration; **CYP** = cytochrome P450; **dd** = times per day; **DDC** = zalcitabine; **DDI** = didanosine; **DLV** = delavirdine; **dTTP** = deoxythymidine triphosphate; **D4T** = stavudine; **EC** = enteric coated; **EFV** = efavirenz; **F** = oral bioavailability; **GAZT** = 3 -azido-3 -deoxy-5 -O-β-D-glucopyranuronosylthymidine; **GI** = gastrointestinal; **HC** = historical controls; **HGC** = hard gel capsule; $\mathbf{IC_{50}}$ = concentration giving 50% inhibition; **IDV** = indinavir; **IMP** = inosine monophosphate dehydrogenase; **INR** = international normalised ratio; **IV** = intravenous; $\mathbf{K_i}$ = inhibitory constant; **LEs** = liver enzymes; **LPV/RTV** = lopinavir/ritonavir; **NFV** = nelfinavir; **NNRTI** = non-nucleoside reverse transcriptase inhibitors; **NO** = nitric oxide; **NVP** = nevirapine; **PCA** = prothrombin complex activity; **PCP** = *Pneumocystis carinii* pneumonia; **PD** = pharmacodynamic; **PEP** = post-exposure prophylaxis; **PHN** = postherpetic neuralgia; **PI** = protease inhibitor; **PK** = pharmacokinetic; **PO** = oral; **P-gp** = P-glycoprotein; **qd** = once daily; **qid** = four times daily; **ref.** = reference population; **resp.** = respectively; **RTV** = ritonavir; **S** = study, design not specified; **seq** = sequential; **SGC** = soft gel capsule; **sim** = simultaneous; **SQV** = saquinavir; **ss** = steady state; **T** = theoretical; **TDM** = therapeutic drug monitoring; **tid** = three times daily; $\mathbf{t_{max}}$ = time to C_{max}; **TSH** = thyroid stimulating hormone; $\mathbf{t_{½\beta}}$ = elimination half-life; **UDPGT** = uridine diphosphate glucuronosyltransferase; **vol** = healthy volunteers; **3TC** = lamivudine;↑ indicates increase; ↓ indicates decrease.

the liver, the kidney, the blood-brain barrier and in CD4+ lymphocytes. Kim et al. demonstrated in *Mdr1a* knockout mice that P-glycoprotein has a role in the absorption, distribution and elimination of PIs,[231] indicating that P-glycoprotein may affect these processes in humans too. Moreover, data indicate that modulation of P-glycoprotein function plays an important role in drug interactions.[54,232] Many substrates metabolised by CYP3A4 are also substrates for P-glycoprotein. The spatial relationship of P-glycoprotein traversing the plasma membrane and CYP3A inside the cell on the endoplasmic reticulum suggests that P-glycoprotein may act to control exposure of substrates to metabolism by CYP3A enzymes.[233]

Induction of CYP3A and/or P-glycoprotein was suggested in the interaction of St John's wort and IDV, in which St John's wort reduced the AUC of IDV by 57% (table III).[208,234] That herbal agents are not as harmless as generally thought is also illustrated by clinically important interactions observed with garlic supplements and grapefruit juice (table III). In a study in healthy volunteers, garlic supplements administered twice daily for 20 days resulted in a 51% reduction in the AUC of SQV, probably by induction of CYP enzymes.[119] After a 10-day washout the AUC of SQV was still only 60–70% of the AUC at baseline. The effect of grapefruit juice on the pharmacokinetics of protease inhibitors appears unpredictable. Grapefruit juice reduced the AUC of IDV by 26%, while the AUC of SQV increased, depending on the dose of grapefruit juice, by 39–121%.[122,123] Grapefruit juice was thought to exert these effects by modulation of the function of P-glycoprotein and/or CYP3A. Based on these results and the fact that the interacting potential for most of these herbal agents has not been completely elucidated, one should always be aware of possible interactions with herbal agents.

Modulation of P-glycoprotein function was also suggested in an HIV-infected patient who received digoxin and started with IDV and RTV as part of the antiretroviral regimen. This patient experienced nausea, vomiting and mild dehydration. The digoxin plasma concentration was 2.5 times the upper limit of normal and inhibition of P-glycoprotein in the small intestine or renal proximal tubules by RTV was suspected as the cause of this drug interaction (table III).[96]

PIs and NNRTIs are substrates of CYP3A4 and P-glycoprotein and can modulate their function. Therefore, these drugs are expected to have considerable effects on coadministered agents that are also using this metabolic pathway. Coadministered drugs may, however, also influence the pharmacokinetics of PIs and NNRTIs by modulation of CYP enzymes or drug transporters. Furthermore, besides the influence of drug-drug interactions on the pharmacokinetics of the antiretroviral drugs and comedicated agents, polymorphism of several CYP enzymes (e.g. CYP3A4/5, CYP2D6 and CYP2C19) and P-glycoprotein may also result in large interindividual differences in plasma concentrations.[235]

3.1.3 Protein Binding

Following absorption, drugs are rapidly distributed by the body circulation. Most drugs are partly protein-bound, particularly to albumins and α_1-acid glycoprotein (AAG). In contrast to the NNRTIs, which are predominantly bound to albumin, PIs are mostly bound to AAG.[6,7] Only the unbound fraction is considered to have pharmacological activity. Variations in plasma albumin and/or AAG levels may alter free drug fractions and may, therefore, influence activity. On the other hand, changes in unbound fraction will generally not lead to changes in free drug concentrations due to other equilibrium processes. Protein binding displacement of one drug by another may increase the free plasma concentration of the former drug, and hence the effect of that drug. For drugs with a high hepatic extraction ratio, the free plasma concentration determines the elimination rate. However, for drugs with a low hepatic extraction ratio, an increase in the free plasma concentration will not lead to a proportional increase in clearance. This type of interaction mostly has minor effects on drug exposure and is, therefore, in general not clinically relevant.[236]

3.1.4 Excretion

Drug interactions based on alterations in renal elimination mainly involve changes in tubular secretion or changes in kidney function. Drugs that use the same active transport system in the kidney tubules can compete for this excretory system. Probenecid and trimethoprim are known inhibitors of tubular secretion,[237] and the observation that the AUC of AZT increased 80–115% when concomitantly used with probenecid can partly be explained by this effect (table III).[175-177] Aminoglycosides are nephrotoxic drugs[238] and the use of this class of drugs might lead to a decreased renal clearance, as demonstrated for DDC (table III).[24]

3.2 Pharmacodynamic Interactions

3.2.1 Efficacy

An example of a synergistic pharmacodynamic interaction is combination treatment with hydroxycarbamide (hydroxyurea) and DDI. By adding hydroxycarbamide to the regimen, levels of deoxyadenosine triphosphate (dATP; cellular competitor) decrease, favouring incorporation of dideoxyadenosine triphosphate (ddATP; DDI is the precursor of ddATP) into proviral DNA.[239] This combination provides a simultaneous inhibition of a cellular protein (by hydroxycarbamide) and a viral protein (by DDI), which should result in a sustained suppression of HIV-1. However, in practice it appears that a higher rate of toxicity was encountered without increased efficacy.[240,241]

3.2.2 Toxicity

Combinations of drugs may lead to an increased toxicity compared with administration of the single drugs. For example, both AZT and ganciclovir used as single agents show bone marrow suppression.[25,242] When these drugs are used concomitantly, this toxic effect is enhanced and increased incidence of severe neutropenia and anaemia are found. DDI, D4T and DDC are associated with the development of peripheral neuropathy,[20,21,23,24] and DDI and 3TC are associated with the development of pancreatitis.[20-22] Patients using these drugs and other agents with a similar toxicity profile should be monitored closely and frequently for signs of these adverse effects. In addition, drugs with adverse events similar to those of PIs and NNRTIs should be added with caution to a PI- or NNRTI-containing antiretroviral regimen.

4. Practical Issues for Use of Interactions Table

In table III we have defined nine areas that are considered essential for overviewing drug interactions between antiretroviral drugs and comedicated agents:

1. The first column ('Co-administered agent and dosage') is presented in alphabetical order, either for the individual drug or the drug class (see table II). The dosage of the coadministered drug is given when available from the cited interaction study.

2. The second column describes 'Type of study'. As can be observed from the table, most drug interactions are based on theoretical considerations (= T), e.g. because it is known that the drugs are metabolised by the same CYP isoenzymes.

3. In the third column, the 'Number of subjects' involved in the interaction study is mentioned. In case of an interaction based on theoretical grounds, this field is empty. Whenever possible, the type of subjects (healthy volunteers, HIV-infected patients, gender) is presented.

4. The fourth column includes 'Antiretroviral agent and dosage'. For one comedicated agent, more than one row can be presented. This occurs when information on a drug interaction with one specific drug or drug group includes more than just theoretical information. Antiretroviral drugs are then presented in different rows for that comedicated agent. The antiretroviral drugs are in alphabetical order per row and per comedicated agent.

5. In the section 'Interaction mechanism', the most plausible mechanism is given. When a question mark is given, it is possible, but not completely certain, that the interaction is caused by the mentioned mechanism.

6. The column 'Effect of interaction' includes the effect of the increase or decrease in plasma con-

centration of the antiretroviral drug and/or comedicated agent. In addition, other observations made during the observation of drug interaction (increase in adverse events, change in International Normalised Ratio) are presented.

7. In the column 'Comments', additional information on the drug interaction that cannot be classified into another category is presented.

8. The section 'Advice' suggests how to deal with the interaction. Therapeutic drug monitoring (TDM) of PIs and NNRTIs is currently valued as an additional clinical tool in HIV care, since relationships have been described between plasma concentrations and efficacy and/or toxicity.[4,8-11] When TDM of drugs is suggested, the plasma concentration needs to be quantified with a validated method and interpretation of the result should be performed by a qualified person (e.g. clinical pharmacologist). When TDM of RTV is recommended, this only refers to RTV used as an antiviral rather than a pharmacoenhancer. Management of interactions with drugs that have a similar toxicity profile will include regular monitoring of the most frequent and prominent toxicity, although other adverse events may occur. The frequency of monitoring is dependent on hospital procedures and needs to be judged by the treating physician.

9. The last column ('Reference') provides the literature source that describes the drug interaction. It could be that a presented drug interaction is not supported by a literature reference. In this case, an interaction can be based on another drug interaction with a comedicated agent that is structurally similar. In addition, the drug interaction can be based on knowledge of the metabolic pathway of the drugs involved and/or the capacity to inhibit or induce this metabolic pathway by one of the implicated drugs.

5. Conclusions

When using this overview in the management of drug interactions, it should be kept in mind that most information is based on theoretical considerations and *in vitro* data. Extrapolating *in vitro* data to the *in vivo* situation requires consideration of a number of factors such as the role of metabolites and interindividual differences in clearance.[58] Case reports should also be interpreted with caution as they usually provide limited information and can be outliers in a population.

For some drug combinations, well-designed drug interaction studies have been performed, but not all involve HIV-infected patients. Pharmacokinetic studies are often performed in healthy volunteers who are exposed to two-drug combinations, whereas in the treatment of HIV infection more complex multidrug regimens are used. In addition, CYP3A4 activity appears to be more variable in HIV-positive patients than in non-infected subjects.[243] Moreover, Lee et al. demonstrated that AIDS patients with acute illnesses had altered patterns of drug metabolism.[244] Data collected from studies performed in healthy volunteers should thus be extrapolated carefully to HIV-infected individuals.

The use of a single dose in some studies is also an important factor to consider. Some drugs must be administered for longer times before the effect of an interaction can be observed. An example is the interaction between RTV and alprazolam, in which opposite effects of RTV on alprazolam clearance were found with short and extended administration of RTV.[59,60] During initial exposure to RTV, inhibition of CYP3A may predominate, while during extended exposure induction may offset this inhibition.

Special care should also be addressed to the effect of a drug interaction when an enzyme-inducing agent is discontinued. Toxicity may then occur due to continuation of the high dose of the drug that was formerly needed to offset the inducing effect.

In this overview, the aim was to provide a complete overview about drug interactions between antiretroviral drugs and comedicated agents. New information in this field, however, emerges rapidly. An excellent review on drug interactions among drugs for HIV and opportunistic infections was published in 2001 in which some web sites

were suggested for the most recent information on this subject.[15]

Overall, this overview may be a further aid in understanding and addressing drug interactions that can be encountered in the treatment of HIV-infected persons. Awareness of the mechanisms of drug interactions and clinical consequences, as well as interventions to minimise these interactions, are pivotal in the optimisation of treatment of HIV-infected individuals.

Acknowledgements

No sources of funding were used to assist in the preparation of this manuscript. There are no conflicts of interest directly relevant to the content of this review.

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