

Review

Adverse effects and drug interactions of medications commonly used in the treatment of adult HIV positive patients: Part 2

Rachel Heylen, Robert Miller

Introduction

In this part 2 drug interactions occurring with the recently licensed anti retrovirals: lamivudine, saquinavir, indinavir and ritonavir are examined.

Pharmacodynamic interactions (table 5)

Additive toxicity One or a number of the main side effects of the two drugs overlap and can lead to increased toxicity. The classification of this toxicity is denoted by a letter:

- M—Myelotoxicity
- P—Pancreatitis
- N—Peripheral neuropathy
- K—Nephrotoxicity
- L—Hepatotoxicity

The clinical significance of this interaction is as below.

Increased Serum Levels This is usually due to inhibition of metabolism by the liver or excretion via the kidneys, and can lead to increased toxicity. The drug that has been affected is indicated by the direction of the arrow (table 5). The clinical significance of this interaction is described below.

Decreased Serum Levels This is often caused by an increase in metabolism by the liver as a result of the use of drugs which induce liver enzymes such as rifampicin, or by a decrease in the absorption of the drug from the gastrointestinal tract such as the bioavailability of ketoconazole is reduced by the administration of drugs which increase gastric pH. The clinical significance of this interaction is as below.

Miscellaneous

Interactions that have been reported but which do not fall under the above headings.

Clinical significance

The interactions have been allocated to one of four categories as follows:

?—unknown clinical significance This category is used when there have been reports in the literature of an interaction but which are only case reports or in vitro work, or the conclusions of these reports are conflicting. It also includes drugs where an interaction may be expected (from those reported with other members of the same class drug etc) but no reports have been found, this may be important for drugs that have been recently released on the market.

!—take note This category is used when there is evidence of an interaction but it is of

theoretical interest rather than clinical importance or it involves the fine tuning of dosing, such as reducing the dose of a relatively non toxic medication in renal failure.

!!—use with caution This category is used when there is evidence of an interaction, and it is of clinical importance. Adjustments may have to be made in doses of toxic medications etc.

Skull and cross—contraindicated The combination of drugs should be avoided where possible. This includes well documented interactions that are clinically significant, combinations that are precluded by the manufacturer or combinations which share potentially very serious side effects, for example nephrotoxicity with co-administration of IV amphotericin and IV pentamidine.

Clock—delay administration Administration of the two medications should be separated as specified in the text.

Lamivudine

Lamivudine is a nucleoside analogue reverse transcriptase inhibitor of HIV-1, HIV-2 and hepatitis B.⁷² It has recently been licensed in the UK for the treatment of adults and children > 12 years of age with progressive immunodeficiency (CD4+ lymphocyte count < 500 cells/mm³) in combination with other anti retroviral agents.⁷³ Only the combination of lamivudine and zidovudine has been studied extensively with improvement in surrogate marker data (HIV viraemia and CD4 + lymphocyte count)⁷⁴ and survival at 52 weeks being reported.⁷⁵

Pharmacokinetic interactions

Lamivudine is well absorbed from the gastrointestinal tract, with an absolute bioavailability of the tablet formulation of over 80%.⁷⁶ Dosing with food delays the rate of absorption but does not effect the area under the concentration-time curve (AUC), and it may therefore be taken at any time in relation to food.⁷⁷

Lamivudine is excreted mainly unchanged in the urine by renal clearance and active tubular secretion.⁷⁶ Dose reductions are recommended in pre-existing renal impairment and in renal impairment due to concurrent administration of nephrotoxic drugs such as intravenous foscarnet, pentamidine, amphotericin, cidofovir.⁷³ In addition other drugs which are actively secreted by the organic cationic transport system, eg trimethoprim, may inhibit the excretion of lamivudine.

Pharmacy
Department,
University College
London Hospitals
(NHS) Trust,
Middlesex Hospital
Site, London, UK
R Heylen

Department of
Sexually Transmitted
Diseases, Division of
Pathology and
Infectious Diseases,
University College
London Medical
School and Camden &
Islington Community
Health Services (NHS)
Trust, London UK
R Miller

Address correspondence to:
Dr R F Miller, 4th Floor,
Mortimer Market Centre,
Mortimer Market, (off
Capper Street), London
WC1E 6AU, UK.

Accepted for publication
2 December 1996

ANTIRETROVIRALS 2	Lamivudine	Saquinavir	Indinavir	Ritonavir
Alcohol				!!
Aminoglycosides	⊕I		⊕I K?	K?
Amphotericin (IV)	⊕I		⊕I K?	K?
Antacids		⊕?	⊕⊖?	
Astemizole, terfenadine, cisapride		⊖⊗	⊖⊗	⊖⊗
Atovaquone				⊖II
Azithromycin				⊖?
Carbamazepine		⊖⊗ ⊕	⊖II ⊕II	⊖II ⊕II
Cidofovir + probenecid	⊕I		K?	K?
Ciprofloxacin				
Corticosteroids		⊖? ⊕I	⊖? ⊕I	⊖II ⊕I
Clarithromycin		⊕?	⊕?	⊕II
Dapsone		⊖?	⊖?	⊖?
Didanosine (ddl)			⊕II ⊖	⊖?
Doxo/Daunorubicin (liposomal)	M!			⊖?
Fluconazole		⊕I		
Flucytosine	M!			
Food		⊕II	⊕II ⊖	⊕II
Foscarnet	⊕I		⊕I K?	K?
Ganciclovir	M!			
Isoniazid				
Itra/Ketoconazole		⊕I	⊕II	⊕II
Methadone			⊖I	⊖II
Metronidazole				⊖II
Oral Contraceptive				⊖⊗/II
Pentamidine (IV)	⊕I		⊕I K?	K?
Phenytoin		⊖⊗ ⊕	⊖II ⊕II	⊖II ⊕II
Pyrimethamine	M!			
Rifabutin		⊕⊗	⊖II ⊕I	⊖⊗
Rifampicin		⊕⊗	⊕⊗	⊕⊗
Ritonavir		⊕II	⊕II	
Sulphonamides (high dose)	M!		K?	K?
Thalidomide	M!			
Trimethoprim (high dose)	⊕⊗ M			
Vinblastine / Vincristine	M!	⊖?	⊖?	⊖I
Zalcitabine (ddC)				
Zidovudine (AZT)	M!!			⊖?

- Additive Toxicity
- Increased Serum Levels
- Decreased Serum Levels
- Miscellaneous

- M - Myelotoxicity
- P - Pancreatitis
- N - Peripheral Neuropathy
- K - Nephrotoxicity
- L - Hepatotoxicity

? ! !! ☠ → Increasing Clinical Significance



Separate Doses

Administration of co-trimoxazole at doses used for prophylaxis of *Pneumocystis carinii* pneumonia result in a 40% increase in lamivudine levels which is caused by the trimethoprim component. However, unless the patient has renal impairment no dosage adjustment of lamivudine is necessary. Co-administration of lamivudine with high-dose trimethoprim (for example when co-trimoxazole, or dapsone and trimethoprim, are used to treat *P carinii* pneumonia), should be avoided.⁷³

Pharmacodynamic interactions

Lamivudine is well tolerated. In a study which compared lamivudine monotherapy with combinations of zidovudine + lamivudine (two groups) and to zidovudine monotherapy adverse events occurred more rapidly in the three groups who received zidovudine than in the lamivudine monotherapy group.⁷⁴ The mostly commonly reported adverse effects are: headache, malaise, fatigue, nausea and vomiting, abdominal pain or cramps, cough, nasal symptoms and musculoskeletal pain. Cases of pancreatitis and peripheral neuropathy have been reported; these are not thought to be dose-related. Neutropenia and anaemia (both occasionally severe) have occurred when the combination of lamivudine and zidovudine has been used. Care should be taken when lamivudine is used with other myelosuppressive drugs. Thrombocytopenia, transient elevations in liver enzymes, and increases in serum amylase have been reported.^{73 78 79}

Saquinavir, indinavir and ritonavir

Saquinavir, indinavir and ritonavir have all recently been licensed in the UK for treatment, in combination with anti retroviral analogues, of HIV-1 infected patients with advanced or progressive immunodeficiency. The compounds are collectively known as protease inhibitors and share a common mechanism of action. They bind reversibly to the active site of HIV protease and competitively inhibit the enzyme thereby preventing cleavage of viral precursor polyproteins that occurs during maturation of newly formed viral particles. The resulting immature particles are non-infectious and are incapable of establishing new cycles of infection. In vivo emergence of HIV-1 variants resistant to multiple protease inhibitors has been reported.⁸⁰ Sub-therapeutic plasma concentrations of protease inhibitors are thought to increase the potential for development of resistance. It is therefore important that they are taken regularly and that sub-therapeutic plasma concentrations resulting from drug interactions are avoided (see below).

Saquinavir in combination with zalcitabine has been shown to reduce HIV-1 replication, increase CD4 + lymphocyte counts⁸¹ and delay clinical progression.⁸² Ritonavir has been shown to potently inhibit HIV replication^{83 84} and when added to existing anti retroviral therapy in patients with low CD4 + lymphocyte counts delays clinical progression and improves survival.⁸⁵ Indinavir has been shown

to bring about improvements in surrogate markers,⁸⁶ but data confirming clinical efficacy has not yet been published.

International guidelines outlining the role of protease inhibitors in the treatment of HIV positive patients have been published,⁸⁷ and the British HIV Association guidelines will be published shortly.

Pharmacokinetic interactions

Saquinavir

The bioavailability of saquinavir is substantially increased by administering the drug with food, but remains low at 4%. The low bioavailability is thought to be caused by a combination of incomplete absorption and extensive first-pass metabolism. The possibility of inadequate absorption should be considered in patients with diarrhoea or those taking agents that increase gut motility eg cisapride or metoclopramide. Patients should be advised to take saquinavir with a meal or substantial snack.⁸⁸

Saquinavir is highly protein bound (approximately 98%), leading to negligible concentrations being found in cerebrospinal fluid. It is extensively metabolised in the liver by the specific cytochrome P450 isoenzyme CYP3A4 to a variety of mono and dihydroxylated metabolites of very low antiviral activity.⁸⁸ Elimination of saquinavir is mostly non-renal, with only 1.1% appearing in urine after oral radioactive dosing.⁸⁹

Saquinavir is a weak inhibitor of the CYP3A4 isoenzyme and therefore has the potential to increase plasma concentrations of drugs which share this method of elimination. Saquinavir should be not administered in combination with astemizole, terfenadine or cisapride until pharmacokinetic data are available to show that no significant interactions occur. Care should be taken with the use of calcium channel antagonists such as nifedipine, and other drugs including clindamycin, dapsone, quinidine, triazolam and midazolam which are also metabolised by the CYP3A4 isoenzyme.⁸⁸

Plasma concentrations of saquinavir may be increased by concurrent use of inhibitors of CYP3A4 isoenzyme system, these include; cimetidine, clarithromycin, erythromycin, fluconazole, fluoxetine, itraconazole, ketoconazole and ritonavir. Grapefruit juice also has been shown to increase the serum levels of saquinavir but the mechanism has not been fully elucidated. There was an increase in the AUC of saquinavir when saquinavir was given with food and ranitidine compared with when saquinavir was given with food alone. The increases in plasma concentrations of saquinavir seen when it is co-administered with the above compounds are not considered to be clinically significant, do not necessitate dose reduction⁸⁸ and it is postulated, may improve efficacy. The exception to this is ritonavir. Studies are presently underway to assess the safety and efficacy of the combination of ritonavir and saquinavir.⁹⁰

Sub-therapeutic plasma concentrations of saquinavir may be caused by compounds that

induce the CYP3A4 isoenzyme these include; carbamazepine, dexamethasone, phenobarbitone, phenytoin, rifabutin and rifampicin. Where possible these agents should be avoided and alternative agents should be used.⁸⁸ As mentioned previously prokinetic drugs such as metoclopramide and cisapride may also lead to decreased saquinavir plasma concentrations.⁸⁸

Indinavir

In trials the AUC of indinavir was reduced by 70–80% when indinavir was administered with a standard meal.⁹⁰ It is therefore recommended that indinavir is taken without food, that is, one hour before or two hours after a meal. Alternatively it may be administered with a low fat light meal such as dry toast with jam, cereal with skimmed milk, coffee, tea, fruit juice etc.⁹¹ It should be emphasised to patients that this does *not* mean that they need a low fat diet and they should be encouraged to eat normally at all other times.

If indinavir and didanosine are used as combination anti retroviral therapy then indinavir should be administered at least one hour before the didanosine. This is because the buffer contained in the didanosine formulation increases the gastric pH and a normal gastric pH may be necessary for optimum absorption of indinavir.⁹¹ This interaction may also be relevant if other antacids are used.

Indinavir is not highly bound to plasma proteins (39% unbound); there are no data on the penetration of indinavir to the central nervous system of humans.⁹¹

Indinavir is hepatically metabolised, specifically by the isoenzyme CYP3A4, to inactive metabolites. The AUC of indinavir had been found to be 60% higher in patients with mild to moderate hepatic insufficiency; a dose reduction is recommended in these patients. There are insufficient data to recommend a dose of indinavir in patients with severe hepatic insufficiency. Less than 20% of a dose of indinavir undergoes renal excretion, of which the main component is intact parent drug (approximately 10% of the initial dose). The safety of indinavir in patients with impaired renal function has not been studied.⁹¹

Indinavir has a similar drug interaction profile as saquinavir; however it is a more potent enzyme inhibitor. The result is that indinavir increases plasma concentrations of drugs metabolised by the CYP3A4 isoenzyme by a greater degree than saquinavir and in turn the plasma concentrations of indinavir are reduced to a lesser extent by enzyme inducers compared with saquinavir. Therefore, like saquinavir the concomitant use of indinavir with terfenadine, astemizole, or cisapride is contraindicated because of the potential for life threatening cardiac toxicity. In addition, concomitant administration with alprazolam, triazolam and midazolam (not shown in table 5) are also contraindicated because of the potential for prolonged sedation.⁹¹ Rifabutin should be not used in combination with

saquinavir because sub-therapeutic plasma concentrations of saquinavir occur. However, when used in combination with indinavir the plasma concentrations of indinavir are marginally decreased, in addition the plasma levels of rifabutin are increased to a clinically significant degree, and a reduction in the dose of rifabutin is necessary.⁹² Care should be taken with drugs with narrow therapeutic windows such as carbamazepine, phenytoin and phenobarbitone as indinavir may increase their plasma concentrations. Indinavir may also increase plasma levels of methadone, the clinical significance of this is unknown.⁹¹

Clinically significant increases in plasma concentrations of indinavir have been observed when indinavir was administered with ketoconazole at a dose of 400 mg. A dose reduction of indinavir has been recommended.⁹¹ Concomitant administration of indinavir with itraconazole has not been studied but the same interaction should be assumed to occur and the same dose reduction made. The efficacy and safety of indinavir in combination with other protease inhibitors has not been established. However, co-administration with ritonavir is likely to lead to clinically significant increases in plasma concentrations of indinavir.⁹¹

Plasma concentrations of indinavir may be reduced with concomitant use of drugs that induce the CYP3A4 isoenzyme, for example carbamazepine, dexamethasone, phenytoin and phenobarbitone. Although no formal studies have been carried out rifampicin should not be used in combination with indinavir because of the potential for sub-therapeutic levels of indinavir to occur.

Specific drug interaction studies have been performed with indinavir and the following drugs: zidovudine, zidovudine/lamivudine, stavudine, co-trimoxazole, fluconazole, isoniazid, clarithromycin, quinidine, cimetidine and an oral contraceptive (norethisterone 1 mg/ethinyloestradiol 35 mcg). No clinically significant interactions have been observed with these drugs.^{91 92}

Ritonavir

Ritonavir shares some of the pharmacokinetic properties of saquinavir; the AUC of ritonavir is increased if it is ingested with food, it is highly protein bound with minimal penetration into the cerebrospinal fluid, it undergoes hepatic metabolism and renal excretion is not a major route of elimination.⁹³ However, ritonavir is a far more potent enzyme inhibitor than either saquinavir or indinavir. In addition to greater inhibition of the cytochrome P450 isoenzyme CYP3A4, it also inhibits isoenzymes CYP2D6 and CYP2C9 thus increasing the potential for drug interactions. Based mainly on literature review it has been recommended that the following substances are not co-administered with ritonavir because large increases in their plasma concentrations may lead to cardiac toxicity, haematological toxicity, profound sedation, seizures or other serious adverse effects; alprazolam, amiodarone, astemizole,

bepidil, bupropion, cisapride, clorazepate, clozapine, dextropropoxyphene (in co-proxamol), diazepam, encainide, estazolam, flecainide (flecainide), flurazepam, midazolam, pethidine, pimozone, piroxicam, propafenone, quinidine, terfenadine, triazolam and zolpidem (some of these medications are not available in the UK).⁹³ The combination of ritonavir and rifabutin is also contraindicated. Co-administration has shown to increase the incidence of arthralgia, joint stiffness, uveitis and leukopenia.⁹⁴ These have been attributed to the significant increases in the AUC of rifabutin and its 25-O-deacetyl metabolite caused by ritonavir.⁹⁵ Ritonavir produces increases in the plasma concentration of saquinavir and this combination is currently evaluated (see under saquinavir).

In addition to the medications given above the following drugs or drug classes are known (or suspected) to undergo metabolism by the same cytochrome P450 isoenzymes: alfentanil, azithromycin, amitriptyline, azithromycin, calcium channel antagonists, carbamazepine, chloroquine, clarithromycin, clindamycin, cyclosporin, desipramine, dexamethasone, erythromycin, fentanyl, fluoxetine, haloperidol, imipramine, itraconazole, ketoconazole, loratadine, methadone, metronidazole, nortriptyline, paroxetine, prednisolone, risperidone, sertraline, tacrolimus, thioridazine, tinidazole, tolbutamide, trazodone, vincristine, vinblastine and warfarin.⁹³ Doses of these drugs should be monitored closely and adjusted either prior to the patient starting on ritonavir or if the patient experiences adverse effects. If these drugs are to be introduced into a patient's medication regimen a reduced starting dose should be considered.

Conversely plasma concentrations of the following drugs were found to be decreased when co-administered with ritonavir: atovaquone (this may be clinically significant in patients with low plasma concentrations of atovaquone) didanosine (not clinically significant), ethinyloestradiol (AUC decreased by 41%, either increased doses of contraceptive, or alternative methods of contraception should be used), morphine, diamorphine, codeine (monitor for decreased efficacy), sulphamethoxazole (not clinically significant), theophylline (monitor serum levels), zidovudine (not clinically significant).⁹³ In a manner similar to saquinavir and indinavir, plasma concentrations of ritonavir may be decreased by enzyme inducers such as carbamazepine, dexamethasone, phenytoin, phenobarbitone and rifampicin. If possible alternative agents should be employed.

Pharmacodynamic interactions

The Summaries of Product Characteristics for saquinavir, indinavir and ritonavir all contain a warning about the increased incidence of bleeding, including spontaneous skin haematomas and haemarthrosis, which has been reported to occur in patients with haemophilia types A and B who are treated with protease inhibitors. In some patients additional factor VIII has been given. In more

than half of the reported cases, treatment with protease inhibitors was continued or reintroduced if treatment had been discontinued. A causal relationship has been evoked, although the mechanism of action has not been elucidated. It is recommended that patients with haemophilia are made aware of the possibility of increased bleeding.^{88 91 93}

Saquinavir

Saquinavir is well tolerated, the main toxicities are: rash (4%), headache (4%), peripheral neuropathy (4%), diarrhoea (16%), abdominal discomfort (6%), buccal mucosa ulceration (6%), nausea (4%) and asthenia (4%).⁸⁸ There are no pharmacodynamic interactions of note.

Indinavir

Notable side effects of indinavir are nephrolithiasis and renal stones and hyperbilirubinaemia. In one study manifestations of nephrolithiasis including flank pain with or without haematuria (including microscopic haematuria) were reported in 2.6% (55/2077) of patients receiving the recommended dose of indinavir (2.4 g/day) and in 7% of all patients receiving indinavir doses above 2.4 g/day.⁹¹ In general these events were not associated with renal dysfunction and resolved with hydration and temporary interruption of therapy (typically between one and three days). Following the acute episode 9.2% of these patients discontinued therapy. Of the patients who continued indinavir approximately 8% had a recurrence.⁹⁶ To reduce the incidence of nephrolithiasis it is recommended that patients should maintain adequate hydration of at least 1.5 litres of fluid/24 hours.⁹¹ There are no obvious predisposing factors for development of nephrolithiasis. Specifically, nephrolithiasis does not appear to correlate with use of any concomitant medication,⁹⁶ but caution should be employed with use of other drugs that may also cause crystalluria, such as suphadiazine and aciclovir. Of note patients on chronic aciclovir therapy have been excluded from clinical trials.⁹¹

Isolated asymptomatic hyperbilirubinaemia (total bilirubin > 43 micromol/l), reported predominantly as an elevated indirect bilirubin and rarely associated with elevations in ALT, AST or alkaline phosphatase enzymes has occurred in approximately 10% of patients treated with indinavir alone or in combination with other anti retroviral agents. Most patients have continued treatment with indinavir without dosage reduction and bilirubin values gradually declined towards baseline. Hyperbilirubinaemia has occurred more frequently when doses of > 2.4/day were used.

Additional side effects that have been attributed to indinavir include dry skin (16.2%), rash (19.1%) and taste perversion (19.1%). The laboratory abnormalities reported by investigators as possibly, probably, or definitely drug related in > 10% of patients alone or in combination were: increases in MCV,

ALT, AST, indirect bilirubin, total serum bilirubin; a decrease in neutrophils; haematuria; proteinuria and cystalluria.

Ritonavir

Ritonavir is often badly tolerated by patients at the start of therapy with a high incidence of nausea (47.5%), diarrhoea (44.9%), vomiting (23.6%), abdominal pain (11.6%), taste perversion (11.4%), circumoral (26.6%) and peripheral (15.4%) paraesthesia, asthenia (22.3%) and headache (15.5%) being reported. These side effects have been attributed to high plasma concentrations of ritonavir. When patients start therapy at a dose of 600 mg twice a day, average ritonavir trough concentrations are in the region of 10 mcg/ml. After two weeks these have diminished to approximately 4 mcg/ml. This is thought to be caused by ritonavir inducing its own metabolism. The high incidence of side effects at the start of therapy has been attributed to the high plasma concentrations that are seen.⁹⁷ To reduce these plasma concentrations and so increase patient tolerance of ritonavir treatment is started at a low dose of 300 mg twice a day and increased over 10 to 14 days to the recommended dose of 600 mg twice a day.

Other side effects which are felt to be directly attributable to ritonavir are; hypertriglyceridaemia, hypercholesterolaemia and hyperuricaemia.⁹³ Renal toxicity has been reported in three patients and it is recommended that renal function is monitored closely especially in patients on concomitant nephrotoxic drugs including foscarnet, amphotericin, didanosine.⁹⁸

Miscellaneous

Ritonavir and alcohol, metronidazole, tinidazole and disulfiram

Ritonavir oral solution contains 43% ethanol therefore concomitant administration of ritonavir with disulfiram or drugs with disulfiram-like reactions (for example metronidazole and tinidazole) should be avoided. Ritonavir capsules also contain ethanol, but in small quantities, patients should be warned that disulfiram-like reactions may occur but are less likely than with the oral solution. Caution should be employed if ritonavir oral solution is used in patients who have a history of alcohol misuse.

Interactions with investigational drugs

Both of the nonnucleoside reverse transcriptase inhibitors (NNRTI) delavirdine and nevirapine are metabolised by hepatic CYP 3A and thus there is potential for significant interaction with other medications that are metabolised by this route.⁹⁹

There are limited data, obtained from studies in HIV negative volunteers on interactions between the NNRTI delavirdine and the protease inhibitors.¹⁰⁰ When saquinavir, at a dose of 600 mg three times daily is given with delavirdine, at a dose of 400 mg three times daily, the mean trough plasma concentration of delavirdine is reduced; in contrast that of

saquinavir is increased almost six-fold. Of note elevations of hepatic transaminase enzyme (ALT) occurred in 13% of subjects.¹⁰⁰

Ritonavir, given at half standard dose (ie 300 mg twice daily) when given with delavirdine (400 mg three times daily) resulted in slight reductions in delavirdine levels; ritonavir levels were unaffected.¹⁰⁰ There are no data on co-administration of delavirdine and full-dose ritonavir.

In subjects already receiving delavirdine 400 mg three times daily, the addition of single doses of 400 mg or 600 mg of indinavir resulted in an almost doubling of predicted indinavir levels.¹⁰⁰ This is an important interaction as elevated indinavir levels are associated with an increased likelihood of nephrolithiasis.⁹¹

Nevirapine is an inducer of hepatic CYP 3A and so potentially could increase the rate of metabolism, and thus reduce the plasma levels of, saquinavir, indinavir and ritonavir.¹⁰¹ Preliminary data confirm that this occurs with saquinavir and indinavir.^{102 103} Data on the interaction between nevirapine and ritonavir are awaited.

We acknowledge the help of Ms Sally Hibbert, Senior Computer Services Technician, Pharmacy Department, UCL Hospitals for her help in the design and compilation of the interaction chart and Jane Rutherford for help with the typing of this manuscript.

- 72 Dienstag JL, Perrillo RP, Schiff ER, Bartholomew M, Vicary C, Rubin M. A preliminary trial of lamivudine for chronic Hepatitis B infection. *N Eng J Med* 1995; 333:1657-61.
- 73 EPIVER (Lamivudine, 3TC) Tablets. Summary of product characteristics Glaxo-Wellcome, August 1996.
- 74 Erron JJ, Benoit S, Jemsek J, MacArthur RD, Santana J, Quinn JB, *et al.* Treatment with lamivudine, zidovudine or both in HIV-positive patients with 200 to 500 CD4 + cells per cubic millimeter. *N Eng J Med* 1995;333: 1662-9.
- 75 The CAESAR Trial (Protocol NUCB3007). Executive summary: preliminary results based on data up to 31 05 95.
- 76 Van Leeuwen R, Lange JMA, Hussey EK, *et al.* *AIDS* 1992;6:1471-5.
- 77 Angel JB, Hussey EK, Hall ST, Donn KH, Hall ST, Harker AJ, *et al.* Pharmacokinetics of 3TC (GR 109714X) administered with and without food to HIV infected patients. *Drug Invest* 1993;6:70-4.
- 78 Katlama C, Ingrand D, Loveday C, Clumech N, Malloley J, Straszewski S, *et al.* Safety and efficacy of lamivudine-zidovudine combination therapy in anti retroviral-naive patients: a randomised controlled comparison with zidovudine monotherapy. *JAMA* 1996;276:118-25.
- 79 Straszewski S, Loveday C, Picazo JJ, Dellamonica P, Skinhoj P, Johnson MA, *et al.* Safety and efficacy of lamivudine-zidovudine combination therapy in zidovudine-experienced patients: a randomised controlled comparison with zidovudine monotherapy. *JAMA* 1996;276:111-7.
- 80 Condra JH, Schleif WA, Blahy OM, Gabreska LJ, Graham DJ, Quintero JC, *et al.* In vivo emergence of HIV-1 variants resistant to multiple protease inhibitors. *Nature* 1995;374:569-71 (letter).
- 81 Collier A, Coombs RW, Schoenfeld DA, Bassett RL, Timgone J, Baruch A, *et al.* AIDS Clinical Trials Group. Treatment of human immunodeficiency virus infection with saquinavir, zidovudine and zalcitabine. *N Eng J Med* 1996;334:1011-7.
- 82 Salgo MP, Beattie D, Bragman K, Donatucci L, Jones M, Montgomery L, NV14256 Study Team. Saquinavir (Invirase SQV) vs Hivid (zalcitabine, ddC) vs combination as treatment for advanced HIV infection in patients discontinuing/unable to take Retrovir (zidovudine, ZDV). Abstract MoB 410, 11th International Conference on AIDS, Vancouver, Canada, 7-12 July 1996.
- 83 Markowitz M, Saag M, Powderly WG, Murley AM, Hsu A, Valdec JM, *et al.* A preliminary study of ritonavir an inhibitor of HIV-1 protease to treat HIV-1 infection. *N Eng J Med* 1995;333:1543-9.
- 84 Danner SA, Carr A, Leonard JM, Lekman LM, Gudiol F, Gonzales J, *et al.* A short term study of the safety, pharmacokinetics and efficacy of ritonavir an inhibitor of HIV-1 protease. *N Eng J Med* 1995;333:1528-33.
- 85 Cameron B, Heath-Chiozi M, Kravciks S, Mills R, Potthoff A, Henry D. Prolongation of life and prevention of AIDS in advanced HIV immunodeficiency with riton-

- avir: Update. MoB 411, 11th International Conference on AIDS, Vancouver, Canada, 7-12 July 1996.
- 86 Deutch P, Tepler H, Squires K. Antiviral activity of L-735,524 an HIV protease inhibitor in infected patients. Paper presented at the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy, Orlando, Florida 60-60, October 4-7 1994.
 - 87 Carpenter CC, Fischl MA, Hammer SM, Hirsh MS, Jacobsen DM, Katzenstein DA, *et al.* Anti retroviral therapy for HIV infection in 1996: recommendations of an international panel. *JAMA* 1996;276:146-54.
 - 88 Invirase: summary of product characteristics. Roche. September 1996.
 - 89 Moyle G. Saquinavir: a review of its development pharmacological properties and clinical use. *Exp Opin Invest Drugs* 1996;5:155-67.
 - 90 Cameron W, Sun E, Markowitz M, Karavcik S, Mills R, Potthoff A, *et al.* Combination use of ritonavir and saquinavir in HIV infected patients: preliminary safety and activity data. Th B 934 11th International Conference on AIDS, Vancouver, Canada, 7-12 July 1996.
 - 91 Crixivan: Summary of product characteristics. Merck Sharp and Dohme Ltd, October 1996.
 - 92 The Indinavir (MK 639) Pharmacokinetic Study Group, Merck Laboratories Indinavir MK 639. Drug interaction studies. MoB 174, 11th International Conference on AIDS Vancouver, Canada, 7-12 July 1996.
 - 93 Norvir: summary of product characteristics. Abbott Laboratories Ltd, August 1996.
 - 94 Sun E, Heath-Chiozzi M, Cameron DW, Hsu A, Grannemann RG, Mawath CJ, *et al.* Concurrent ritonavir and rifabutin increases risk of rifabutin associated adverse effects. MoB 171, 11th International Conference on AIDS, Vancouver, Canada, 7-12 July 1996.
 - 95 Cato A, Cavanaugh JH, Shi H, Grannemann RG, Leonard J. Assessment of multiple doses of ritonavir on the pharmacokinetics of rifabutin. MoB 1199, 11th International Conference on AIDS, Vancouver, Canada, 7-12 July 1996.
 - 96 Personal Communication. Merck Sharp and Dohme 09 10 96.
 - 97 Personal Communication. Abbot Laboratories, September 1996.
 - 98 Duong M, Sgro C, Grappin M, Birou F, Boibieux A. Renal failure after ritonavir. *Lancet* 1996;348:693-4.
 - 99 Morse GD, Hu J, Ingalls E, Bartos L, D'Ambrosio R. In vitro studies of drug-drug protein binding displacement with delavirdine mesylate. XI International Conference on AIDS 1996, Vancouver, Canada: Abstract We.B. 3132.
 - 100 Gilden D. Delavirdine/Protease Inhibitor interactions. *Treatment Issues* 1996;10:11-2.
 - 101 Murphy RL, Montaner J. Nevirapine: a review of its development, pharmacological profile and potential for clinical use. *Exp Opin Invest Drugs* 1996;5:1183-99.
 - 102 Personal Communication: Boehringer Ingleheim, 23 September 1996.
 - 103 Personal Communication: Boehringer Ingleheim, 20 November 1996.