

Clinical issues

in HIV/AIDS

This is the third in a series of bulletins focusing on advances in therapy for HIV/AIDS, particularly developments in triple therapy employing protease inhibitors.

This bulletin looks at drug interaction in HIV therapy and

provides an at-a-glance guide to known clinically significant interactions. There is also the second part of our website review for those working in the HIV/AIDS field.

Watch out for further update bulletins in the coming months.

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Commentary

Thus far, there seem to have been three phases in the history of HIV. First there was a period (probably following transmission from its animal host) when the virus and its effects, aided by a long incubation period, went unnoticed. Second there was an era of clinical observation of the effects of the virus, which involved its identification and the charting of its prevalence and distribution. Third, there is the present period, when enormous efforts in terms of money, research and clinical intervention appear to have allowed us to at least modify the virus and its effects. The virus itself, however, has yet to respond to our efforts, as one day it surely will. This is in the nature of microbial disease.

Continued over

Commentary continued

Man appears to be very good at engineering the demise of species higher up the evolutionary tree than the agents of infectious disease; however, with the notable exception of smallpox, our powers of eradication do not seem to reach these agents. Vaccination may eventually offer a prospect of this, but for the present we must look to containing clinical effects upon the individual by using various drugs. This makes all the more important our responsibility to do the least harm possible to our patients when using powerful chemotherapeutic inventions.

The triple therapy and polypharmacy interventions presently used to manage HIV consist of a number of drugs, old and new, well-known and under-researched, toxic and benign. It is their anticipated effects that we wish to exploit but we must be aware that many drugs and drug combinations are novel, and thus relatively unpredictable, particularly when longer-term effects are considered.

More and more useful chemical interventions will be developed with time and we must anticipate unexpected problems to emerge with these new drugs and with existing drugs. Early reports from the USA suggest that individuals on long-term triple therapy (lasting more than two years) may have a higher risk of cardiovascular problems relating to hypercholesterolaemia. The exact mechanism is unknown, the effect cannot yet be quantified and the other factors that influence this increased risk (eg, diet or genetics), are the subject of much speculation.

We are not yet even at the point where we can determine whether there are gender-related differences in the metabolism of antiretroviral drugs. It is reasonable to assume, therefore, that as the majority of HIV-infected women are in the reproductive age group, we are yet to discover the complex drug interactions between new and established antiretroviral drugs with exogenous and endogenous sex steroids.

Researchers and pharmaceutical companies must construct trials of drugs used in HIV disease to permit the disclosure of side-effects as soon as practicable. Even with these measures, some long-term adverse events of HIV therapy will come as an unwelcome surprise. The pressure to 'fast-track' compounds to exploit their therapeutic effects will have to be tempered

by the need to allow respectable time to elapse for proper evaluation.

Equally, it is irresponsible to present the risks from unpredictable drug side-effects in an ill-considered and dramatic way, particularly when this is done via the mass media, who disseminate this information to large numbers of relatively uninformed people, some of whom will also be our patients.

Dissemination of information about the adverse effects of drugs can be done in a considered, intelligent, informative and reassuring manner. Compare the way in which the information that some brands of the oral contraceptive pill were linked with an increased risk of venous thromboembolism was handled in October 1995, and the way the information about the connection between the contraceptive pill and breast cancer was handled in June 1996.

The first case led to panic among consumers, indecision among prescribers and, ultimately, unwanted pregnancies. The latter case was a message that was first evaluated then released to the mass media in a controlled fashion, resulting in a much more reassuring outcome. The language used by the press, in particular, was totally different and the effects opposite.

Some adverse effects from potent drugs such as those used in HIV are already known and others have yet to be recognised. Careful risk-analysis and proper evaluation of the benefit-versus-risk ratios, with considerate management of the dissemination of this information to health professionals first, has to be the best policy. An organised cascade of information to the mass media and consumers can then flow.

It is our policy in this publication to offer what we consider to be authoritative voices with clear messages backed up with up-to-date, intelligent information. The article in this issue by Professor Back and his colleagues on drug interactions in HIV infection is a perfect example of this, and, with new drugs being evaluated and others about to enter the market, it is perfectly timed.

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Drug interactions in HIV infection

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The ultimate goal of antiretroviral therapy in HIV-positive patients is the total eradication of the virus. Current treatment strategies are aimed at maximising suppression of viral replication using a combination of nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs).¹ The drugs available in the UK are shown in Table 1. The NRTIs and NNRTIs have the same site of action – that is, the enzyme reverse transcriptase.¹ The protease inhibitors act on the protease enzyme, thereby preventing cleavage of *gag* and *gag-pol* protein precursors to the structural and enzymatic proteins essential for HIV maturation and the production of infectious virus particles (Figure 1).³

Our approach to the treatment of patients infected with HIV has changed significantly over the past two years. This follows a number of recent advances, including a better understanding of HIV pathogenesis, the development of more sensitive and accurate quantification of HIV-1 RNA in plasma and the availability of newer antiretroviral agents. The use of PIs in combination with reverse transcriptase inhibitors has been associated with sustained suppression of viral replication, reduced morbidity and prolonged life in patients with HIV infection. Recent guidelines have recommended that initial treatment of all HIV-infected patients includes the administration of a PI.⁴

However, with the advent of PIs and NNRTIs, the importance of drug–drug interaction with antiretrovirals is becoming increasingly recognised. The potential for clinically significant interactions between drugs used to treat HIV infection, and between these drugs and other therapies used in HIV patients, is immense. It is vital that clinicians, pharmacists and others involved in the care of HIV-infected people should have a good knowledge of these

drug–drug interactions. The most important aspect to focus on is the disposition of the drug in the body (that is, its absorption, metabolism and elimination).

TABLE 1. Antiretroviral therapies 1998

NRTIs	NNRTIs	PIs
Abacavir (1592)*	Delavirdine*	Amprenavir (141W94)*
Didanosine (ddl)	Efavirenz (DMP266)*	Indinavir
Lamivudine (3TC)	Nevirapine	Nelfinavir
Stavudine (d4T)		Ritonavir
Zalcitabine (ddC)		Saquinavir hard gel capsule
Zidovudine (ZDV)		Saquinavir soft gel capsule*

* Available only as part of clinical trials or within expanded-access programmes.

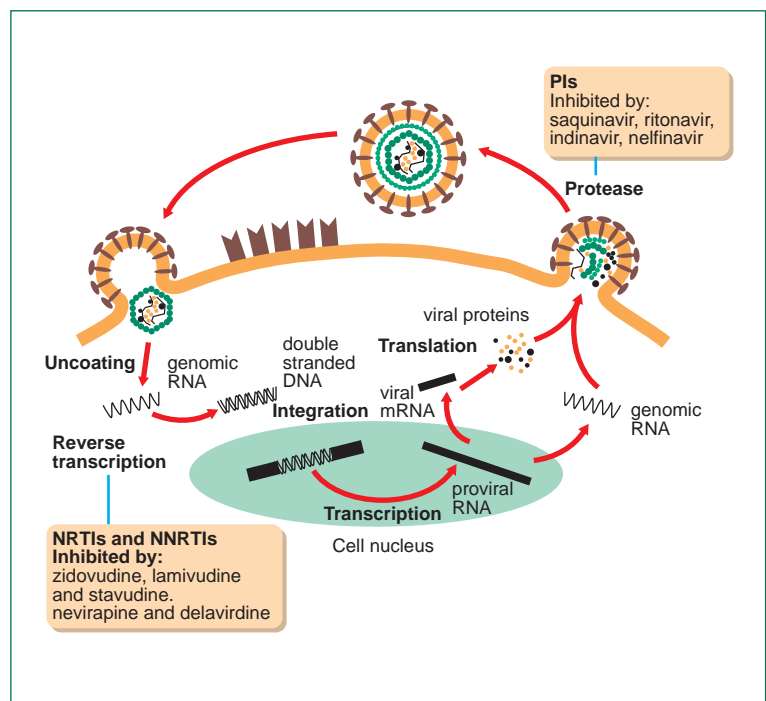


Figure 1. Site of action of anti-HIV drugs
Modified from Barry *et al.*²

TABLE 2. Recommendations for taking anti-HIV drugs with/without food

Without food	With or without food	With food
Didanosine (ddl)	Zidovudine	Ritonavir
Indinavir (1 h apart from ddl)	Zalcitabine	Saquinavir
	Stavudine	Nelfinavir
	Lamivudine	
	Abacavir	
	Amprenavir	
	Nevirapine	
	Delavirdine (2 h apart from antacids/ddl)	

Drug disposition

Absorption from the gastrointestinal tract

Drug absorption may be altered by changes in the pH of the gastrointestinal tract, the presence (or absence) of food and the influence of, for example, calcium and magnesium ions in buffers.

Some drugs, such as ketoconazole and itraconazole, require an acidic environment to be absorbed. If the pH of the stomach is increased – by antacids, buffers found in the formulation of some drugs, H₂ antagonists (such as cimetidine), or proton pump inhibitors (such as omeprazole) – absorption will be reduced. Such an interaction can be minimised by separating administration of the drugs by at least two hours.

Food–drug interactions are often difficult to predict because food can inhibit the absorption of some drugs and increase it in others. Table 2 summarises the advice for the anti-HIV drugs. Note that it is essential to take didanosine (ddl) on an empty stomach (30 minutes before or two hours after eating) to maximise absorption. It is also essential to avoid large or fatty meals for two hours before and one hour after taking indinavir.

Metabolism

The majority of clinically important drug interactions in HIV patients have a metabolic basis (mostly in the liver but also in the gut wall). The main enzymes involved are from the cytochrome P₄₅₀ superfamily (CYPs).

There are at least 15 human CYPs involved in drug metabolism, but the isozymes CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4

are responsible for the metabolism of the majority of drugs. The single most important enzyme in relation to the metabolism of antiretrovirals is CYP3A4.²

All the PIs are metabolised by CYP3A4 (with contributions from other isozymes), but in addition they can prevent other co-administered drugs being metabolised by their enzymes. The poor systemic availability of saquinavir is largely a consequence of rapid and extensive metabolism in both the gut wall and liver.⁵ Although ritonavir has a much better oral availability (about 70%),⁶ it is an incredibly potent inhibitor of CYP3A4 and to a lesser extent CYP2D6 and CYP2C9, leading to elevated plasma concentrations of other drugs and exaggerated pharmacological effects; it is consequently implicated in many drug interactions.⁷ Indinavir and nelfinavir also inhibit CYP3A4. Unfortunately, the plot becomes more complicated because ritonavir and nelfinavir are also able to induce some liver enzymes, which means reduced plasma concentrations and compromised therapeutic effect.

Although the NRTIs are involved in very few metabolic drug interactions, the NNRTIs are known to both inhibit and induce some liver enzymes.⁸

Elimination

Elimination interactions involve drugs which are excreted via the kidney, and occur either by inhibition of active tubular secretion of drug or by decreased elimination as a consequence of a decline in renal function. Since a number of potentially nephrotoxic drugs are used in the treatment of patients with HIV/AIDS, monitoring of renal function is important.

Drugs involved in interactions

So, with a knowledge of the underlying principles of drug disposition and a realisation of the potential for interactions in the gut, liver and kidney, we can look at those drugs that are most likely to be involved in drug interactions. They can be subdivided into five main categories:

Drugs with specific requirements for absorption

Examples include:

- Didanosine (Table 2).
- Itraconazole (take at least two hours apart from ddI or antacids).
- Fluoroquinolones (eg, ciprofloxacin; take four hours apart from ddI, antacids or mineral supplements).

TABLE 3. Interactions between protease inhibitors

Acting drug	Affected drug				
	<i>Indinavir</i>	<i>Ritonavir</i>	<i>Saquinavir</i>	<i>Nelfinavir</i>	<i>Amprenavir</i>
<i>Indinavir</i>		No PK interaction	↑↑↑ AUC (<i>hgc, sgc</i>)	↑ AUC	↑ AUC
<i>Ritonavir</i>	↑↑ AUC		↑↑↑↑ AUC (<i>hgc, sgc</i>)	↑↑ AUC	No reported data
<i>Saquinavir</i>	No reported data	No PK interaction		↑ AUC (<i>sgc</i>)	No reported data
<i>Nelfinavir</i>	↑ AUC	No PK interaction	↑↑ AUC (<i>hgc, sgc</i>)		No reported data
<i>Amprenavir</i>	No PK interaction	No reported data	No reported data	No reported data	

PK, Pharmacokinetic; AUC, area under the plasma concentration–time curve; *hgc*, hard gel capsule; *sgc*, soft gel capsule; ↑ increase (up to 100%); ↑↑ Increase (up to 500%); ↑↑↑ increase (up to 1000%); ↑↑↑↑ Increase (more than 2000%).

TABLE 4. Interactions between non-nucleoside reverse transcriptase inhibitors and protease inhibitors

Acting drug	Affected drug				
	<i>Indinavir</i>	<i>Ritonavir</i>	<i>Saquinavir</i>	<i>Nelfinavir</i>	<i>Amprenavir</i>
<i>Nevirapine</i>	↓↓ AUC	↓ AUC	↓↓ AUC (<i>hgc</i>)	No PK interaction* ↓↓ AUC*	No reported data
<i>Delavirdine</i>	↑↑ Cmax	↑ AUC	↑↑ AUC (<i>hgc</i>)	↑ AUC	No reported data
<i>Efavirenz</i>	↓↓ Cmax	No reported data	No reported data	↑ AUC	↓↓ AUC

PK, Pharmacokinetic; AUC, area under the plasma concentration–time curve; Cmax, maximum plasma concentration; *hgc*, hard gel capsule; *sgc*, soft gel capsule; ↑ increase (up to 100%); ↑ increase (up to 500%); ↓ decrease (up to 10%); ↓↓ decrease (up to 35%)

*awaits clarification (conflicting results from two studies).

Inhibitors of cytochrome P₄₅₀ enzymes

Examples include:

- All protease inhibitors (Table 3 and Table 5).
- Some non-nucleoside reverse transcriptase inhibitors (eg, delavirdine, efavirenz; Table 4).
- Macrolide antibiotics (eg, clarithromycin, erythromycin).
- Azole antifungals (ketoconazole, itraconazole and to a lesser extent fluconazole).

Table 3 summarises interactions between PIs.

Cytochrome P₄₅₀ pharmacokinetic interactions may be beneficial when two PIs are given simultaneously: ritonavir inhibits the hepatic first-pass metabolism of saquinavir, increasing the steady-state concentration or area under the curve (AUC) by more than 20 times;⁹ nelfinavir increases the AUC of saquinavir by 4–5 times¹⁰ and that of indinavir by 51%;¹¹ and indinavir increases the AUC of saquinavir by over 500%.¹² Thus treatment with two PIs takes advantage of this pharmacokinetic enhancement and gives increased antiviral activity. This strategy has been important for the use of saquinavir (low systemic availability enhanced) and should also prove important in reducing three times daily to twice daily dosing for some PIs.

Table 4 summarises the published data on the effects of NNRTIs on protease inhibitor pharmacokinetic profiles. Delavirdine causes elevated plasma concentrations of saquinavir, ritonavir, indinavir and nelfinavir.^{13–15} However, efavirenz apparently increases nelfinavir plasma concentrations but reduces concentrations of indinavir and amprenavir; ie, efavirenz can both inhibit and induce metabolism.^{16,17}

Concurrent administration of ketoconazole increases the AUC by 62% with indinavir, by 35% with nelfinavir and by 300% with saquinavir.⁶ Again, because the bioavailability of saquinavir is poor this interaction may be advantageous, increasing the amount of drug in the circulation.

Inducers of cytochrome P₄₅₀ and/or glucuronyl transferase

Examples include:

- Some protease inhibitors (eg, ritonavir, nelfinavir).
- Some non-nucleoside reverse transcriptase inhibitors (eg, nevirapine).
- Rifamycin antibiotics.

Ritonavir induces its own metabolism and also induces the metabolism of a few other drugs.¹⁸

TABLE 5. Protease inhibitor drug interactions

Class	Drug	Indinavir	Ritonavir	Saquinavir	Nelfinavir
<i>Analgesic</i>					
	Aspirin	▲	▲	▲	▲
	Paracetamol	▲	▲	▲	▲
<i>NSAID</i>					
	Ibuprofen	▲	■	▲	▲
	Piroxicam	▲	●	▲	▲
<i>Narcotic/morphino-mimetic</i>					
	Dextropropoxyphene	■	●	■	■
	Diamorphine	▲	■	▲	▲
	Fentanyl	■	■	■	■
	Meperidine (pethidine)	■	●	■	■
	Methadone	■	■	■	■
	Morphine	▲	■	▲	▲
<i>Antiarrhythmic</i>					
	Amiodarone	■	●	■	●
	Disopyramide	■	■	■	■
	Encainide	■	●	■	■
	Flecainide	■	●	■	■
	Lignocaine	■	■	■	■
	Propafenone	■	●	■	■
	Quinidine	■	●	■	●
<i>Antihistamine</i>					
	Astemizole	●	●	●	●
	Certirizine	▲	▲	▲	▲
	Loratadine	■	■	■	■
	Terfenadine	●	●	●	●
<i>Hypnotic/sedative</i>					
	Flurazepam	■	●	■	■
	Lorazepam	▲	■*	▲	▲
	Midazolam	●	●	■	●
	Temazepam	▲	■*	▲	▲
	Triazolam	●	●	■	●
	Zolpidem	■	●	■	■

● These drugs should not be co-administered. Drug levels may be significantly altered. See specific SPC for more details.
 ■ Potential interaction which may require close monitoring, alteration of drug dosage, or timing of administration. See specific SPC for details.
 ■* Increased dose of lorazepam/temazepam may be required.
 ▲ No clinically significant interaction.

The following interactions are important: ethinyloestradiol (reduced efficacy of the oral contraceptive pill); morphine/methadone (monitor for decreased efficacy); theophylline (monitor serum levels). Nevirapine induces the metabolism of indinavir, saquinavir and probably nelfinavir – dosage increases may therefore be necessary because of enhanced drug metabolism.^{19,20}

An important concern is the effect of concurrent therapy with rifampicin and rifabutin, both of which accelerate the clearance of PIs.⁶ Because of the magnitude of the enzyme-inducing effects, rifampicin should not be given to patients who require treatment with PIs.⁶ For patients

taking indinavir or nelfinavir who require rifabutin, the dose of rifabutin should be reduced. Concurrent administration of rifabutin with ritonavir or saquinavir is not recommended.⁶

Extensively metabolised drugs with narrow therapeutic index

These are affected particularly by protease inhibitors. Some examples are:

- Antiarrhythmics.
- Non-sedating antihistamines.
- Antimigraine drugs.
- Some benzodiazepines.

To help those involved in the care of HIV-positive patients, we have produced a chart which

provides a summary of drug interactions between protease inhibitors and other drugs that may be prescribed to the HIV-infected patient. It provides a simple method of scanning at a glance the level of interaction. Part of the chart is reproduced in Table 5. Copies of the chart may be obtained from the authors (email: sgibbons@liverpool.ac.uk). Clinicians must be aware of the potentially toxic drug interactions involving PIs and avoid prescribing such drugs as terfenadine, cisapride, ergotamine and potent benzodiazepines.

Renally cleared drugs with narrow therapeutic index

Examples include:

- Aminoglycosides.
- Ganciclovir.

Nephrotoxic drugs used in the treatment of patients with HIV/AIDS include aminoglycosides, amphotericin B, foscarnet and high-dose sulphonamides. Good hydration is important and can reduce renal deterioration caused by some of those drugs. If a renally cleared drug (especially a potentially toxic one such as ganciclovir) is used with one of the above drugs, the patient's renal function should be closely monitored and, if necessary, dose adjustments should be made.

Conclusion

It is clear that HIV-infected patients treated with antiretroviral agents have a high likelihood of receiving other concurrent medication. It is essential that information on drug-drug interactions is both available and understood so that the appropriate therapeutic strategy can be devised for each individual patient.

However, simply because an interaction has not been described for a particular drug does not mean that there is no interaction. The advent of new antiretroviral drugs means that physicians should constantly be on the alert for drug

interactions of new therapies with existing therapies. Reports of all potential new adverse reactions and suspected drug interactions should be made to both the manufacturers and the CSM/MRC Reporting Scheme.

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Website review

If you use the Worldwide Web in your clinic for patients to obtain health information, or if you want to advise them on how to gain access to information on STDs, then there are three sites that I would recommend.

- med-www.bu.edu/people/sycamore/std/std.htm is aimed at teenagers in Boston, USA, and the language is 'appropriate' but never patronising. There are a number of (graphic) illustrations of diseases from urethral discharge to oral thrush; since a picture is worth a thousand words, this may help people to recognise their problem more easily than they would from a written description. This site would appeal most to the young of heart and strong of stomach. One of its main attractions is that there is a reminder at the end of each page to seek medical help where appropriate. Mention of drugs is limited and possibly dated – a one-dose treatment for Chlamydia is not mentioned.

- www.sexhealth.org/infocenter/oldtips/htm purports to be one of the top 1,000 world sites. It is very professional and

includes topics such as a sexual survey of readers, sexuality and ageing, and a sex tip of the day (just in case you are wondering, on the day I visited it was 'brush your partner's hair during intercourse').

The section on STDs is very comprehensive and obviously aimed at patients. However, some of the treatments again seem a little dated, and the language used here is not quite appropriate, or designed it seemed, for the general reader. In the section on AIDS, for example, Kaposi's sarcoma is described as 'ecchymoses'.

- www.getwired.co.uk is very accessible, accurate and up-to-date, and promises to provide information without medical terminology and jargon. The 'What's on' page lists mostly gay events, and seems to concentrate mainly on the homosexual and bisexual community. The internet directory to other sites was particularly useful.

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