

# An update on HAART: part 2

In part 2 of an article on antiretroviral therapy for patients with HIV, Rosy Weston, Simon Portsmouth and Andrew Benzie look at protease inhibitors and entry inhibitors, as well as further issues related to drug therapy

Since 1996, the care of individuals living with HIV has been transformed by highly active antiretroviral therapy (HAART), where a combination of three or more antiretrovirals is used as treatment. There are now four classes of antiretrovirals. The introduction of protease inhibitors in 1996 had a dramatic effect on altering morbidity and mortality in HIV-infected individuals.

**Protease inhibitors** Protease inhibitors selectively bind and inhibit HIV protease. By blocking this enzyme, deformed HIV particles are formed and these have a reduced infectious capacity.

Protease inhibitors are metabolised via the cytochrome (CYP) P450 enzyme system so inhibition or induction of CYP 450 enzymes by other drugs can alter protease inhibitor levels.

Most protease inhibitors are now administered with low dose ritonavir (an early protease inhibitor which is poorly tolerated at high doses), which is a potent inhibitor of CYP3A4, resulting in increased levels of most protease inhibitors. This effect is known as "boosting". In some circumstances, boosting has the added advantage of reducing dosage frequency and food restrictions.

Traditionally protease inhibitors had to be taken three times a day, with food restrictions or requirements and often with a high pill burden. More recently, the protease inhibitor atazanavir (boosted with ritonavir) has been developed, which can be taken once daily.

Protease inhibitors are associated with metabolic effects (eg, dyslipidaemia and insulin resistance) and lipodystrophy (see Panel 1, p694).

Further information about individual protease inhibitors is given in Panel 2 (p695).

**Entry inhibitors** Entry inhibitors are mainly used by heavily "treatment-experienced" patients who may have multi-drug resistant HIV or by patients who are intolerant of other antiretrovirals.

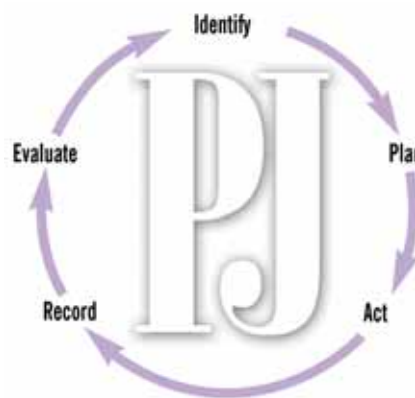
Currently, enfuvirtide (also known as T-20 [Fuzeon]) is the only entry inhibitor approved for the management of HIV. This drug binds to a segment of the HIV gp41 co-receptor and prevents the conformational changes required for the fusion of viral and cellular membranes (see *PJ*, 27 May, p631).

The main disadvantage of enfuvirtide is that it must be administered by subcutaneous injection twice daily and is associated with injection site reactions. Patients should receive training in administration (usually from a nurse specialist) to reduce the chance



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The HIV virus replicates inside T-lymphocytes and infects other cells. The aim of HAART is to suppress viral replication



## Identify knowledge gaps

1. Why do protease inhibitors need to be "boosted"?
2. What are the challenges in treating HIV in the UK?
3. Do you know about post-exposure prophylaxis of HIV infection?

Before reading on, think about how this article may help you to do your job better. The Royal Pharmaceutical Society's areas of competence for pharmacists are listed in "Plan and record", (available at: [www.rpsgb.org/education](http://www.rpsgb.org/education)). This article relates to "drug therapies".

of injection site reactions, as well as in the safe disposal and handling of syringes. Pharmacists should check that patients have received a sharps box and advice on the disposal of used needles.

Special packs are available from the manufacturers for patients to carry the drug and injecting equipment when travelling abroad.

## Drug-drug interactions

HIV-positive patients can take many medicines that have the potential to interact with each other and pharmacists are often asked for advice on the likelihood and significance of these interactions.

Several of the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors are substrates, inducers or inhibitors of the cytochrome P450 enzyme system. Ritonavir is known to be a potent inhibitor of CYP3A4, an enzyme responsible for metabolising many drugs, some of which can be toxic at increased levels (eg, sildenafil and 3,4-methylenedioxymethamphetamine [MDMA]).

Enzyme inducers, such as rifampicin (used for tuberculosis), can reduce antiretroviral levels and, therefore, compromise clinical effect.

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## Panel 1: Lipodystrophy

Lipodystrophy is the term used to describe changes in body shape due to fat redistribution, with or without changes in blood lipids. Changes in body shape, such as lipoatrophy, (see *PJ*, 27 May, p631) and increase in abdominal girth or breast size, are sometimes reversible on altering the drug combination.

Originally, lipodystrophy was thought to be solely associated with the use of protease inhibitors but it has also been reported in HIV-positive individuals not taking antiretroviral therapy and those taking combinations not including protease inhibitors. The mechanism of this syndrome is not fully understood. Drug treatment of hyperlipidaemia (raised cholesterol and triglycerides) may also be required — to reduce the risk of developing cardiovascular disease — along with other lifestyle adjustments, such as smoking cessation. It is important to note that there are significant drug-drug interactions between the protease inhibitors and NNRTIs, and statins. The statins differ in their interaction profiles so caution should be used when selecting one.

Only a minority of patients develop lipodystrophy but, in some cases, the changes are marked and distressing. Inert substances, such as polylactic acid injected into areas of the skin affected by subcutaneous fat loss can significantly improve appearance.

Similarly, when atazanavir is co-prescribed with the NNRTI efavirenz, enzyme induction can decrease atazanavir levels and a higher dose of atazanavir is recommended, even when boosted with ritonavir.

There are other mechanisms whereby drug levels can be altered. The drug transport protein P-glycoprotein (P-gp) found in the intestinal mucosa pumps some drugs out of the cell and back into the lumen of the gastrointestinal tract, therefore decreasing absorption of the drug. A number of antiretroviral drugs are substrates for P-gp, and some (eg, ritonavir) are inhibitors of P-gp. In theory, inhibition of P-gp by this mechanism, would increase intracellular drug concentrations.

Some drug interactions require modification of dose, timing of administration or frequency. When a histamine-2 receptor antagonist is prescribed for a patient on atazanavir, dosing must be well separated and this must be explained. Caution is needed for patients requiring treatment for *Helicobacter pylori*, gastrointestinal reflux disease or indigestion to ensure that potential drug-drug interactions are taken into account. Atazanavir must not be taken with proton pump inhibitors.

Patients may not always voluntarily disclose the fact they are taking antiretroviral therapy or other drugs to their clinic doctor, GP or community pharmacist. For this reason, pharmacists should always ask patients about additional medicines they may be taking, including over-the-counter medicines, herbal prepara-



Storage, administration and possible side effects should be discussed with the patient

## Caution is needed for patients requiring treatment for *Helicobacter pylori*, gastrointestinal reflux disease or indigestion

tions, recreational drugs and medicines purchased through the internet.

The British National Formulary provides good basic information on some of the important drug interactions. Useful internet reference sources for drug interactions include:

- [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org) (This site, run by Liverpool University is updated regularly. It contains drug interaction charts for protease inhibitors and NNRTIs, which can be printed out. It also includes some information on interactions with herbal products.)
- [www.tthhivclinic.com](http://www.tthhivclinic.com) (This site is run by a clinic in Toronto. Drug interaction charts are updated regularly.)

## Role of therapeutic drug monitoring

For protease inhibitors and NNRTIs there is wide inter-patient variation in plasma drug levels, which vary with gender, ethnicity and body weight. The measurement of plasma drug concentrations can be used to make decisions about dose adjustments, either to ensure that levels are adequate for viral suppression or to avoid drug-related side effects.

To date, there are no well-established methods for correlating plasma drug levels to activity of the nucleoside (or nucleotide) reverse transcriptase inhibitors (NRTIs) because intracellular levels cannot be measured. In most cases, plasma trough levels are used (ie, a sample is taken just before the next dose is due). Occasionally, a sample is taken after drug ingestion (peak level) to investigate whether or not dose reduction is needed to avoid toxicity.

## Changing therapy and treatment failure

A patient may need to change therapy for a number of reasons. In the event of the viral load failing to drop to below the limit of detection of the available assay or a patient experiencing “viral rebound” (two consecutive viral loads >400copies/ml at least one month apart and where viral load was previously undetectable), treatment failure is assumed and a complete change should be instituted. If the CD4 T-cell count fails to increase or decreases to below 200cells/mm<sup>3</sup> (“immunological failure”) while on therapy, a change should also be considered.

Selection of a new regimen should take into account results of all resistance tests, previous exposure to individual antiretroviral agents and the patient's ability to adhere to and tolerate the new regimen. For patients failing therapy, simply swapping a new antiretroviral agent with another in a specific regimen is not recommended because the potential for drug resistance developing is increased — the whole regimen should be changed.

Other reasons for considering a change in treatment may include the development of antiretroviral drug resistance.

Many HIV-positive patients in the UK are currently managed on either their first or sec-

ond drug combinations. However, there are a minority who are heavily treatment-experienced and require drugs from all four classes, sometimes in higher doses. This is sometimes referred to as "salvage therapy" or "mega HAART". In devising a suitable regimen for this group of patients, decisions are often

## Panel 2: Protease inhibitors: additional information\*

### Atazanavir (Reyataz)

- Atazanavir must be taken with food to ensure adequate drug plasma levels.
- Hyperbilirubinaemia can occur in up to 30 per cent of patients (and, rarely, jaundice) but this is unlikely to lead to discontinuation of treatment.
- Atazanavir appears to have less adverse effects on serum lipids compared with other protease inhibitors.

### Fosamprenavir (Telzir)

- Fosamprenavir can be taken any time in relation to food but some patients find that taking the ritonavir tablets with food reduces the incidence of nausea.
- Hypersensitivity reactions have been reported in patients with a previous reaction to sulphonamides.

### Nelfinavir (Viracept)

- Nelfinavir must be taken with or after a full meal.
- Diarrhoea is common in all patients so loperamide should be co-prescribed and the reason for the supply explained.

### Lopinavir with ritonavir (Kaletra)

- Kaletra capsules must be taken with or just after food.
- The most common side effect is diarrhoea so patients should be co-prescribed loperamide. Other gastrointestinal effects are common but usually mild.
- The combination of lopinavir with ritonavir is commonly associated with abnormalities in serum lipids.
- Kaletra capsules should be refrigerated. At room temperature (<25C) they are stable for 42 days.
- A new tablet formulation will be licensed shortly which allows the "pill burden" to be reduced — two tablets twice a day, as opposed to three capsules twice a day. Kaletra tablets do not have to be taken with food and do not need to be kept in a refrigerator.

### Saquinavir (Invirase)

- St John's wort preparations have been found to lower saquinavir levels.

### Tipranavir (Aptivus)

- When taken with boosted ritonavir, tipranavir should be taken with food to help reduce nausea.
- Tipranavir should be stored in a refrigerator.
- Tipranavir interacts with a number of medicines, including St John's wort. The summary of product characteristics for tipranavir includes details of drug interactions so should be consulted carefully when tipranavir is prescribed. In particular, tipranavir formulation can interact with the nucleoside reverse transcriptase inhibitor didanosine so the interval between taking the two in a regimen should be at least two hours.

\* See British National Formulary for standard adult doses

## Panel 3: New drugs for HIV

Drug	Class	Status
Darunavir (TMC114)	Protease inhibitor (to be boosted with ritonavir)	Unlicensed (clinical trials* and expanded access programme)
Etravirine (TMC 125)	NNRTI	Unlicensed (clinical trials*)
Maraviroc	CCR-5 antagonist†	Unlicensed (clinical trials*)

\* Clinical trials are in process and are the only way that patients can currently access these drugs

† This is a chemokine receptor on the surface of CD4 lymphocytes (See *PJ*, 27 May, p631)

made with the multidisciplinary team, and take into account patient factors, such as previous and current genotypic resistance test results and antiretroviral history, as well as adherence.

In some cases, a treatment-experienced patient may be eligible for recruitment to a clinical trial where a new agent is being investigated.

For a small, but growing percentage of patients who have been exposed to antiretrovirals over many years and who continue to have a persistent viraemia, the development of new agents and drug classes is essential.

At present, research is being focused on producing drugs with unique resistance profiles and agents that act at different phases in the HIV replication cycle (eg, chemokine receptor antagonists). Some drugs currently undergoing evaluation are listed in Panel 3.

### Treatment support

Much research has been undertaken in the area of adherence to HIV medicines. High levels of adherence are crucial to the success of highly active antiretroviral therapy (HAART) and in order to prevent resistance, which can develop rapidly (within days for some drugs). The reasons patients find taking HIV medicines difficult are multifaceted and include:

- Fear of disclosure of HIV status
- Intolerance to side effects, such as nausea and vomiting
- Perceived harm from taking antiretrovirals
- Forgetting to take them

Because drug therapy for patients living with HIV is a life-long commitment, adherence support and medication counselling are fundamental to ensure the best patient outcomes. Pharmacists can play an important role in addressing such issues and Panel 4 (p696) lists some key counselling points for antiretroviral therapy.

Predicting side effects and co-prescribing drugs to deal with them can help. It is common for patients to experience initial short-term side effects, such as nausea and vomiting, as well as headache and fatigue. Patients often require anti-emetics, such as domperidone 20mg *tds*, for the first six to eight weeks of therapy. Loperamide can be prescribed to counter diarrhoea.

At present, most HIV-positive patients are cared for as outpatients. Although HIV clinics provide most HIV care, patients are strongly encouraged to register with a GP and inform them of their HIV diagnosis. It is suggested that patients show their patient information leaflets to their GPs and community pharmacists to alert them to potential drug interactions with other drugs and antiretrovirals.

### Clinical trials and unlicensed doses

When treating any new or rapidly evolving disease, fast access to new drugs and doses is imperative. This is sometimes facilitated through clinical trials or compassionate pro-

## Panel 4: Key counselling points for antiretroviral therapy

- Explain that therapy is lifelong and must not be stopped unless advised by the clinic doctor. (If a patient needs to stop taking his or her antiretrovirals for any reason, he or she should be encouraged to seek advice from the HIV clinic on the best way to do so.)
- Explain that doses must not be missed and must be taken on time.
- Ensure the patient is familiar with the appearance of the prescribed antiretrovirals and how to take them with regard to specific timing for the individual's lifestyle and other medicines they may be taking.
- Explain which drugs can be taken together and which need to be taken apart, with or without food.
- Ensure that the patient knows how to manage common side effects such as nausea and diarrhoea. Anti-emetics should be supplied with the first prescription and the patient should be advised to take an anti-emetic half an hour before each dose. If the patient vomits within one hour of taking antiretrovirals and the tablets or capsules are visible, an anti-emetic should be taken. The patient should wait 30 minutes and then take another dose of antiretroviral.
- Discuss the potential for drug interactions occurring with other medicines, herbal preparations and recreational drugs.
- Patients should be advised about how to store their medicines, including ensuring that medicines are kept out of children's reach.

grammes that widen access to a drug (eg, expanded access programmes and named patient programmes). These permit the use of an unlicensed drug in a controlled setting.

Often, unlicensed doses of antiretrovirals are prescribed following therapeutic drug monitoring, when drug levels are found to be lower than required for clinical effect and the dose needs to be adjusted.

### Post exposure prophylaxis

People may be exposed to HIV through their occupation (eg, health care workers and needle-stick injuries) as well as through high-risk sexual activity. Although drugs for post exposure prophylaxis (PEP) are currently unlicensed, there is evidence to support their role in clinical practice. The Department of Health Expert Advisory Group on AIDS recommends that prophylaxis with combination antiretroviral therapy is initiated immediately (ideally within 72 hours) of occupational exposure and continued for one month.

In February, the British Association of Sexual Health and HIV produced guidance on sexual exposure (post exposure prophylaxis sexual exposure or PEPSE) recommending prophylaxis with 28 days of combination antiretroviral therapy following a significant risk



Dr Vo Trong / Science Photo Library

The development of new agents and drug classes for HIV is essential

exposure. The Chief Medical Officer has recently (*PJ*, 15 April p432) recommended that provision of 24-hour advice and starter packs for emergency treatment is made available as part of sexual health services.

### Conclusion

HAART has significantly improved the prognosis of HIV infection, reducing the severity and range of opportunistic infections and resulting in fewer hospital admissions. The use of HAART has shifted the standard of care from managing acutely unwell patients to long-term care provided through an out-patient setting. The new drugs and combinations are, however, associated with side effects and toxicities and all therapy should be initiated with the patient's full understanding of the importance of maintaining high levels of adherence.

With the increasing numbers of patients with HIV, pharmacists and pharmacy staff should be aware of the principles of HIV treatment as well as the potential for drug-drug interaction with antiretrovirals and other medicines.

### Resources

- Useful slides on UK figures for HIV and sexually transmitted infections can be found at: [www.hpa.org.uk](http://www.hpa.org.uk)
- European treatment guidelines for children and adolescents are available at: [www.ctu.mrc.ac.uk/penta/guidelines.htm](http://www.ctu.mrc.ac.uk/penta/guidelines.htm)
- Essential information for specialist HIV pharmacists providing abstracts from conferences and medical journals can be found at: [www.hivpharmacology.com/](http://www.hivpharmacology.com/)
- [www.aidsmap.com](http://www.aidsmap.com) provides UK-based information on HIV for clinicians and HIV-positive individuals.
- [www.naturaldatabase.com](http://www.naturaldatabase.com) contains useful information on herbal and complementary medicines. A subscription required, but most medicines information centres have a password.
- HIV post-exposure prophylaxis: guidance from the UK Chief Medical Officer's Expert Advisory Group on AIDS. February 2004. Available at: [www.dh.gov.uk](http://www.dh.gov.uk) (accessed 10 May 2006)
- Johns Hopkins AIDS service ([www.hopkins-aids.edu](http://www.hopkins-aids.edu)) is a website containing conference feedback, case rounds and TB management guidelines as well information on drug interactions.

Ideally, post exposure prophylaxis should be initiated within 72 hours

### Action: practice points

Reading is only one way to undertake CPD and the Society will expect to see various approaches in a pharmacist's CPD portfolio.

1. Where would you direct someone who requires post-exposure prophylaxis? Find out.
2. Talk to a colleague about what special considerations HIV-positive patients might require in community pharmacy.
3. Revise your knowledge of dyslipidaemia.

### Evaluate

For your work to be presented as CPD, you need to evaluate your reading and any other activities. Answer the following questions:

What have you learnt? How has it added value to your practice? (Have you applied this learning or had any feedback?) What will you do now and how will this be achieved?