

Drug treatment of

By E. DAVIES, BSC, MRPHARMS, J. F. MORLESE, BSC, MBBS,
M. BOWER, PHD, MRCP and A. POZNIAK, MD, FRCP

The second part of our special feature focuses on the drug treatments used in HIV infected adults.

The rapid changes occurring in the treatment of human immunodeficiency virus (HIV) infection mean that articles and guidelines on the subject soon become obsolete.

This article provides an overview of current practice and is divided into two parts:

- The use of antiretroviral drugs to control viral replication
- The treatment of HIV-associated opportunistic infections

Ms Davies is principal pharmacist, HIV and GUM, Dr Morlese is research registrar, HIV and GUM, Dr Bower is consultant physician, medical and HIV oncology and Dr Pozniak is consultant physician, HIV and GUM, all at the Chelsea and Westminster Hospital Healthcare NHS Trust

ANTIRETROVIRAL THERAPY

The goal of antiretroviral therapy in HIV infection is to increase the length and quality of life by improving immune function. This is achieved by reducing the amount of replicating virus to as low a level as possible, for as long as possible, in all sites where HIV-infected cells are present, thereby preventing infection of new cells and further damage to the immune system. The amount of replicating virus in the plasma can be assayed by measuring the concentration of HIV ribonucleic acid (RNA), referred to as the viral load. In practical terms, the aim of antiretroviral therapy is to lower the viral load to a value below the level of detection of the assay used. The lower limit of detection of any of the currently available licensed assays is 50 copies per ml.¹ Achieving this with the currently available antiretroviral agents involves appro-

appropriate selection of combination regimens to obtain an optimal antiviral response and excellent adherence to the regimen by the patient. In addition, consideration of a plan for a salvage or second line regimen is required if initial therapy fails.

There are 14 antiretroviral drugs currently licensed in the UK. These can be divided into three classes (nucleoside reverse transcriptase inhibitors [NRTIs], protease inhibitors [PIs] and non-nucleoside reverse transcriptase inhibitors [NNRTIs]) as shown in Panel 1 (p97). These drugs act at different stages in the HIV replication cycle (see Figure 1 on p91). The first antiretroviral agent to become commercially available was zidovudine in 1987, followed by didanosine and zalcitabine in 1993. Initially, these drugs were used alone as monotherapy (often sequentially, as each agent became available). It is now realised that rapid resistance develops to antiretroviral drugs if they are not

Panel 1: Classes of antiretroviral drugs

Nucleoside reverse transcriptase inhibitors

Abacavir
Didanosine (ddI)
Lamivudine (3TC)
Stavudine (d4T)
Zalcitabine (ddC)
Zidovudine (AZT)

Non-nucleoside reverse transcriptase inhibitors

Delavirdine*
Efavirenz (liquid form is unlicensed)
Nevirapine

Protease inhibitors

Amprenavir
Indinavir
Lopinavir + ritonavir (Kaletra)
Nelfinavir
Ritonavir
Saquinavir

*Unlicensed in the UK, available on a named-patient basis

Table 1: Doses and side effects of antiretroviral drugs

Drug	Dose	Side effects
Abacavir (Ziagen)	300mg twice daily	Possibility of a hypersensitivity reaction in about 6 per cent of patients (symptoms can include fever, rash, cough, nausea). If hypersensitivity is confirmed abacavir must never be restarted
Zidovudine + lamivudine (Combivir)	One tablet twice daily after food	Nausea, malaise, anaemia (side effects mainly attributable to zidovudine)
Didanosine (Videx)	400mg once daily (in patients 60kg and over), 250mg once daily (in patients under 60kg). Must be taken on an empty stomach*	Nausea, diarrhoea, peripheral neuropathy, pancreatitis
Lamivudine (EpiVir)	150mg twice daily	Few side effects. Headache and peripheral neuropathy have been reported
Stavudine (Zerit)	40mg twice daily (in patients 60kg and over) 30mg twice daily (in patients under 60kg)	Peripheral neuropathy. If severe, the dose can be halved
Zidovudine + lamivudine + abacavir (Trizivir)	One tablet twice daily	As for the individual drugs
Zalcitabine (Hivid)	0.75mg three times daily	Peripheral neuropathy, mouth ulceration
Zidovudine (Retrovir)	200mg three times daily, 250mg twice daily or 300mg twice daily depending on the preparation. Should be taken after food to minimise nausea	Nausea, malaise, myopathy, anaemia
Tenofovir DF†	300mg once daily after food	Diarrhoea, hypophosphataemia, potential for renal toxicity
Nevirapine (Viramune)	200mg once daily for 14 days, then 200mg twice daily	Skin rash, raised liver function tests, hepatitis
Efavirenz (Sustiva)	600mg once daily. The liquid form has reduced bioavailability, therefore a 600mg tablet = 720mg liquid (24ml)	Drowsiness and dizziness, hence should be taken at night. Vivid dreams and hallucinations. Low dose haloperidol may help. Due to reported animal toxicity, efavirenz must not be taken by pregnant women, therefore avoid in women of child-bearing age
Delavirdine (Rescriptor)†	400mg three times daily or 600mg twice daily. Can be swallowed whole or dispersed in water or a soft drink	Rash (usually mild), headache
Amprenavir (Agenerase)	1,200mg twice daily (more commonly used at lower doses in combination with ritonavir)	Nausea, diarrhoea, perioral tingling, headache
Indinavir (Crixivan)	800mg three times daily. Must be taken on an empty stomach with plenty of water	Renal stones, crystalluria, dry skin, hyperbilirubinaemia
Nelfinavir (Viracept)	750mg three times daily or 1.25g twice daily after food	Mild to moderate diarrhoea
Ritonavir (Norvir)	600mg twice daily (more commonly used at lower doses in combination with other PIs)	Taste perversion, nausea, diarrhoea, perioral tingling
Saquinavir soft gel (Fortovase)	1,200mg three times daily or 1600mg twice daily after food‡. (Invirase, the hard gel form is still available but should only be used in combination with ritonavir)	Nausea, diarrhoea

*Didanosine tablets must be taken on an empty stomach 30 minutes before or two hours after food. Didanosine enteric coated (EC) capsules must be taken on an empty stomach at least two hours after food. There is currently no recommendation for the administration of didanosine EC capsules before food consumption

†Not licensed in the UK

used in combination. Effective combination therapy, or highly active antiretroviral therapy (HAART), is now the accepted standard of care for HIV-infected individuals requiring treatment in the developed world.

Strict adherence to HAART is vital to its success. It has been demonstrated that, even at 95 per cent adherence levels, there are some patients who will not achieve an undetectable plasma viral load.² Since each class of antiretroviral drugs currently available exhibit cross resistance (within the class), development of resistance to a drug often means resistance to the entire class of drugs, thus limiting future treatment options. It is fair to say that HIV infection is no longer considered the terminal illness it was five to 10 years ago, but is now regarded as more of a chronic infection, manageable with antiviral therapy. However, current knowledge indicates that the therapy should be for life, a situation that makes the issue of adherence a real obstacle for some patients.

NRTIs These were the first drugs to be licensed for the treatment of HIV infection. They are generally considered the backbone of antiretroviral therapy when combined with PIs or NNRTIs. These drugs are similar in structure to nucleosides present in HIV RNA. During viral replication, they become incorporated into the genome, competing with cellular nucleosides. Upon incorporation into the HIV RNA, they bring about chain termination and incomplete replication of the viral genome. NRTIs require triphosphorylation within the cell before they become active.

PIs A dramatic decline in the clinical progression of HIV disease and HIV-related deaths followed the introduction of protease inhibitors in 1996.³ These compounds act on the HIV protease enzyme, preventing the production of essential proteins. The main drawback to PIs is the number of dose units that patients have to take, the need for food restrictions, and the potential for long-term metabolic complications.

NNRTIs The non-nucleoside reverse transcriptase inhibitors (NNRTIs) are the third class of drugs currently available to treat HIV infection. These also act on the reverse transcriptase enzyme, thus inducing conformational changes that prevent HIV RNA from being processed. However, the NNRTIs differ in structure from the NRTIs. They are generally considered simpler to take than PIs, but are hampered by the fact that resistance develops quickly, and patients are usually resistant to all drugs within this class once resistance appears. The side effects appear more immediately, for example, skin rash and hepatitis, whereas the PIs are beginning to demonstrate delayed toxicities. It is not known whether the NNRTIs exhibit delayed toxicity, because

Table 2: Guidelines on initiating treatment in HIV infection

Disease state	Surrogate marker*	Action
Primary HIV infection		Start within six months
Asymptomatic HIV infection	CD4 count higher than 500 cells per μl .	Defer treatment
	CD4 count 350 to 500 cells per mm^3	Defer treatment and monitor every three months
	CD4 count 0 to 350 cells per mm^3	Treat
Symptomatic HIV infection		Treat

* Surrogate markers are parameters used to assess disease progression. In HIV infection, the surrogate markers used are the CD4 count and viral load

they are still too new for this to be detected. In the UK, the trend now is to use these drugs as first line therapy in preference to PIs, because of their simplicity (that is, no food restrictions, fewer tablets and less frequency of dosing compared to PIs) and the fact that they have been shown to be equally as potent in randomised controlled clinical trials.^{4,5} The doses and common side effects of the antiretroviral agents in use are outlined in Table 1 (p97).

— BHIVA GUIDELINES

The main issues surrounding treatment with antiretroviral therapy have been addressed in the British HIV Association (BHIVA) guidelines.⁶

When to start therapy The decision of when to start therapy with antiretroviral drugs depends on the following:

- HIV disease state
- Surrogate markers (that is, CD4 count and viral load)
- Assessment of compliance and risk of drug toxicities

Antiretroviral therapy can be started within six months of seroconversion (primary HIV infection, PHI) or during the chronic HIV infection stage. With regard to treating PHI, this is still experimental. Treatment is instituted to prevent immune damage and to reduce the risk of forming HIV reservoirs, which make eradication of the virus difficult. However, these theoretical advantages must be weighed against the potential loss of adherence and development of drug toxicities with increased duration of HAART. Furthermore, if therapy is not instituted as soon as possible after seroconversion, the potential benefits of HAART can be lost. Those patients with chronic asymptomatic disease should be started on therapy if their CD4 count falls below 350 cells per mm^3 (see Table 2). Those patients with symptomatic chronic HIV infection should be treated without delay.

Starting treatment early (when the CD4 count is above 350 cells per mm^3) can result in the earlier development of drug toxicities

and drug resistance. Early treatment can also limit future drug options if drug resistance develops. In addition, it can facilitate the transmission of drug-resistant virus. However, all these factors must be counterbalanced by the evidence that delayed treatment results in disease progression due to impaired immunity and can also limit the overall capacity for immune restoration.⁷

What therapy to use In deciding which type of antiretroviral therapy to use, several factors must be considered, including:

- Likelihood of adherence
- Initial viral load or CD4
- Probability of toxicity
- Co-morbid conditions, such as hepatitis B infection

Table 3 (p99) shows the main types of combination antiretroviral therapy used as initial therapy. Most data are available from studies of two NRTIs and one PI, which have demonstrated a reduced morbidity and mortality in patients treated with a combination containing these two classes of drugs. However, this combination is associated with significant toxicity, especially dyslipidaemia and lipodystrophy. On the other hand, two NRTIs and one NNRTI are associated with less dyslipidaemia, but not as much long-term survival data are available yet. Furthermore, efavirenz has been associated with foetal abnormalities and thus might not be appropriate in women of child-bearing age. The use of three NRTIs is increasingly in vogue because the patient does not have the burden of taking too many tablets. Trizivir is a combination of abacavir, lamivudine and zidovudine in a single tablet. In addition, use of three NRTIs reserves the NNRTI and PI classes for later use. However, there is some debate as to whether three NRTIs are effective in patients with viral loads greater than 100,000 copies per ml .⁸

The bioavailability of current PIs can be increased by the concomitant use of ritonavir. This factor can be used in overcoming drug resistance and in treating patients with a high initial viral load. The additive or synergistic antiviral effects of PIs in combination might improve potency, rela-

Table 3: *Types of combination antiretroviral therapy*

Combination	Advantage	Disadvantage
Two NRTIs + one PI*	Randomised controlled trial evidence with clinical end points Evidence of efficacy in late disease Long term follow-up data	Toxicity common Patient takes a large number of tablets Drug interactions
Two NRTIs + two PIs†	Easier adherence Better pharmacokinetic profile	No clinical end point data Less comparative surrogate marker data Possible increased toxicity and drug interactions
Two NRTIs + one NNRTI‡	Equivalent or superior efficacy in surrogate marker trials at 72 weeks Easier adherence Less known long-term toxicity than PI-containing regimens	No clinical end point data Lack of surrogate marker data in late disease Shorter follow-up data
Three NRTIs§	Reserves PIs and NNRTIs Fewer drug interactions	Single mutations may lead to cross-class resistance No clinical end point data Short term surrogate marker data only Less effective at high viral loads

*Hard gel saquinavir should not be used as a sole PI. There are fewer data concerning the use of saquinavir soft gel in this context than for other PIs

†The primary reason for combining PIs is to improve pharmacokinetics. Suggested regimens: low dose ritonavir (that is, 100 to 400 mg) with saquinavir, indinavir or amprenavir

‡Recommended NNRTIs are efavirenz or nevirapine. In one controlled trial,⁴ efavirenz was more effective compared with indinavir in patients at all viral loads. There are fewer data from controlled trials to address this issue for nevirapine

§Might be suitable for patients with viral load lower than 100,000 copies per ml in whom adherence can be problematic. Two regimens have been studied: abacavir + lamivudine + zidovudine and stavudine + didanosine + lamivudine

tive to a regimen using a single PI. However, the dual PI combination has the disadvantages of increased risk of lipodystrophy, lipid abnormalities and unfavourable drug interactions.

VIROLOGICAL FAILURE

Virological failure is defined as a viral load of more than 50 copies per ml on two occasions, at least one month apart. This is important because HIV patients may show disease progression unless the viral load is re-suppressed. Those patients who fail to attain a viral load of lower than 50 copies per ml on HAART, or patients who achieve a viral load of lower than 50 copies per ml who then have a sustained viral load of more than 50 copies per ml, should be considered for a change in therapy. Patient adherence to antiretroviral therapy should always be considered and pharmacological issues, such as drug interactions, should be investigated as a potential cause. A resistance test should be performed and therapy altered accordingly. If no HIV resistance is found then the current antiretroviral regimen can be intensified by adding another agent, if the viral load is low.

Clearly, it is important to assess adherence in detail. If adherence is poor, then the regimen can be simplified in an attempt to reduce the number of tablets or frequency of dosing.

The causes of antiretroviral failure include lack of adherence, intolerance and resistance. Resistance can be attributable to drug factors, including:

- Lack of potency
- Poor pharmacokinetics (poor absorption,

tion, increased metabolism, poor penetration of CSF and seminal fluid, effect of p-glycoprotein, plasma protein binding, drug interactions)

- Host factors, such as non adherence

HIV resistance Resistance is said to occur when there is a reduced susceptibility of the virus to antiretroviral drugs.

The virus replicates in the presence of drugs, resulting in the development of specific mutations within the protease and reverse transcriptase genes. These mutations result in changes in the structure or function of the protease and reverse transcriptase enzymes which render them less susceptible to inhibition by drugs. The net effect is a reduction in the effectiveness of the antiretroviral drugs and a consequent increase in the HIV viral load.

HIV resistance testing There are two types of resistance testing, each requiring a viral load of at least 1,000 copies per ml.

Phenotypic assays A phenotypic assay measures the ability of a reconstructed HIV isolate from the patient to grow in the presence of specific antiretroviral drugs.

This type of assay is complex and time consuming.

Genotypic assays In a genotypic assay the reverse transcriptase and protease genes from the patient's virus are sequenced to determine the presence of mutations within these genes known to be associated with reduced activity of antiretroviral drugs.

Table 4 (p100) shows the advantages and disadvantages of phenotypic and genotypic assays.

Treatment of virological failure The aim of treatment of virological failure is to alter the combination so that the effectiveness is restored and the viral load is resuppressed below 50 copies per ml.

Failure of first regimen Viral rebound is usually associated with clinical progression in patients on treatment whose viral load continues to rise above 50 copies per ml. If the viral load is higher than 50 copies per ml then it should be repeated two to four weeks later because transient viral "blips" are common with concurrent illnesses, vaccination or transient non-adherence. Persistent viraemia should be considered as virological failure.

Table 5 (p100) shows the treatment options based on failure of the first regimen. The choice should be guided by the resistance test.

Salvage therapy Salvage therapy means treatment following exposure to multiple drugs, usually of all three classes. The goal of therapy is to maintain a healthy CD4 count as it is unlikely that a viral load lower than 50 copies per ml will be obtained. However, small reductions in viral load are associated with clinical benefit. The greatest likelihood of success with a salvage regimen occurs if patients are naive to one class of drugs and use of drugs to which the patient has either not been exposed or to which resistance is unlikely or proven to be absent. In addition, the new regimen will be more successful when started at a lower viral load (eg, lower than 5,000 copies per ml).

If the chance of a good response is minimal, treatment should be deferred until newer drugs are available.

Table 4: Comparing phenotypic and genotypic assays

	Advantages	Disadvantages
Phenotypic	Determines the overall impact of the array of drug-resistance associated mutations on virus phenotype Provides information on cross resistance	Time-consuming and expensive Might not reflect early emergence of resistance
Genotypic	Rapid and commercially available Detection of genetic mutations before phenotypic changes Detection of a wide range of mutations associated with resistance	Insensitive to the presence of minor variants Interpretation requires specialist knowledge

Discontinuation of therapy is controversial. In most patients, stopping HAART results in a rapid rise in the viral load to pre-treatment levels and a fall in the CD4 count. This option must be considered with caution but is an option if the side effects are pronounced.

— DRUG INTERACTIONS

Understanding the potential for drug interactions is very important in patients taking HAART.

Both PIs and NNRTIs are metabolised exclusively in the liver by the cytochrome P450 (CYP) isoenzyme system. The nucleoside analogues are mainly cleared renally and so do not pose as many metabolic drug interaction problems. Identification is now possible in early drug development of the dominant cytochrome P450 isoforms responsible for metabolising a particular drug. In addition, there is the ability to detect whether a drug is capable of inhibiting or inducing a specific CYP isoform.

The major isoforms involved in human drug metabolism are CYP3A, CYP2D6, CYP2C, CYP1A2 and CYP2E1.⁹ Patients who are HIV-positive often take many drugs concurrently, hence an assessment of potential drug interactions is imperative.

CYP3A is the major isoform responsible for all PI and NNRTI metabolism. Co-administration of enzyme inducers leads to a danger of lowered drug levels of the PIs and NNRTIs, thus increasing the risk of development of drug resistance. Conversely, co-administration of enzyme inhibitors could lead to increased toxicity.

Treatment of tuberculosis (TB) in HIV-positive patients taking HAART poses complications because rifampicin, the main component of any anti-TB regimen, is probably one of the most potent enzyme inducers known. Rifampicin is therefore not to be taken with most of the PIs and NNRTIs, although rifabutin can be used as an alternative in some cases, with careful dose adjustment. It

is essential that the product literature is consulted if rifampicin or rifabutin are co-prescribed with anti-HIV drugs.

All the PIs inhibit the isoenzyme CYP3A4, which makes co-administration of drugs such as astemizole and terfenadine contraindicated, owing to the risk of arrhythmias. Some PIs and NNRTIs are also capable of inducing isoenzymes, making co-administration of the combined oral contraceptive pill inadvisable as a sole method of contraception.

The potential for enzyme induction and inhibition with all the PIs and NNRTIs causes complications when constructing a HAART regimen using combinations of both classes of drugs. Referral to the product literature is vital to ensure that any dose modifications required are applied.

Of all the PIs, ritonavir is the most potent inhibitor of the CYP3A isoenzyme. It also inhibits P-glycoprotein, a transport protein responsible for pumping out certain drugs from the gut lining, thereby preventing their absorption. Since the full dose of ritonavir is associated with several side effects, it is now more commonly used in combination with other PIs, mainly for its enzyme inhibition properties. It acts to optimise the pharmacokinetic profile of co-administered PIs, either by reducing first pass metabolism, or by increasing their half lives. Co-administration of low dose ritonavir can therefore often simplify the HAART regimen. For example, the conventional dose of indinavir is 800mg eight-hourly, but by adding low dose ritonavir twice daily, the indinavir can be reduced to twice daily dosing. The food restrictions

associated with indinavir disappear with this regimen and patients are more easily able to comply.

— EMERGING TOXICITIES

Previously unknown toxicities of anti-retroviral drugs are being discovered as more experience is gained in their use. These include mitochondrial toxicity, lactic acidosis and lipodystrophy.

Mitochondrial toxicity Mitochondrial toxicity is a relatively new term used to describe a host of disorders thought to be attributable to nucleoside analogues. NRTIs are thought to inhibit the human mitochondrial enzyme, deoxyribonucleic acid (DNA) polymerase gamma in a similar way to their action against HIV, resulting in the production of dysfunctional mitochondria.¹⁰ Pancreatitis and peripheral neuropathy (which are well known side effects of some of the NRTIs) are now thought potentially to result from mitochondrial toxicity. In addition, the Committee on Safety of Medicines issued a summary in June, 1999, of eight cases of mitochondrial dysfunction in infants exposed antenatally to zidovudine with or without lamivudine. However, the committee concluded that there were insufficient data to establish a causal relationship between nucleoside analogue exposure and mitochondrial dysfunction.¹¹

Lactic acidosis Lactic acidosis is also emerging as a new toxicity in patients taking HAART. It is postulated that antiretroviral-associated lactic acidosis is also a manifestation of mitochondrial toxicity arising from the use of nucleoside analogues. Lactic acidosis is a known toxicity of NRTIs, thus the summaries of product characteristics (SPCs) of all the nucleoside analogues warn of the risk of lactic acidosis. Although no causal relationship has been formally linked to any of the NRTIs in particular, it is postulated that the incidence is more likely with the use of stavudine and didanosine.

Although patients can be asymptomatic, prominent symptoms include weight loss, fatigue, nausea, bloating, vomiting and abdominal pain

Table 5: Dealing with failure of first regimen

Initial regimen	Options to consider		
Two NRTIs + one PI	Two NRTIs + one NNRTI	Two NRTIs + two PIs	Two NRTIs + one NNRTI + one PI (or two PIs)
Two NRTIs + one NNRTI	Two NRTIs + one PI (or two PIs)		
Three NRTIs	Two NRTIs + one NNRTI	Two NRTIs + one PI (or two PIs)	Two NRTIs + one NNRTI + one PI

Associated examination and laboratory abnormalities can include:

- Tachycardia and hypotension
- Abnormal liver function tests (both transaminases and alkaline phosphatase)
- Low chloride, low bicarbonate, raised anion gap
- Raised glucose
- Raised creatine kinase
- Raised amylase

The European Medicines Evaluation Agency has been made aware of seven cases of lactic acidosis in women treated during pregnancy with the combination of stavudine and didanosine. At present, there is insufficient information to decide whether pregnancy is an additional risk factor for lactic acidosis. It is also uncertain whether any increased risk of lactic acidosis is specific to stavudine and didanosine or whether it might be increased with all combinations of NRTIs.¹² However, the use of these two drugs during pregnancy should be avoided, and indeed, where possible, zidovudine should be used as a component of the NRTI portion of the regimen to prevent HIV vertical transmission.

Lipodystrophy One of the main drawbacks to protease inhibitor therapy is the risk of lipodystrophy. This syndrome is now well described with PIs and encompasses a range of manifestations, such as body fat redistribution, hyperlipidaemia, insulin resistance and diabetes mellitus. Many patients are reluctant to take PIs because of the changes in body shape that they can induce. These changes sometimes make it obvious that a patient is on anti-HIV therapy.

The characteristic signs are loss of fat from the face and limbs, accumulation of visceral fat around the abdomen and occasional formation of a "buffalo hump". It is postulated that this syndrome is caused by PIs somehow interfering with the process of fat metabolism, as a result of their effect on the cytochrome P450 enzyme system in the liver. However, more than one theory has been put forward and the exact mechanism is still unknown.

It has been suggested that inhibition of mitochondrial DNA synthesis (hence mitochondrial toxicity) might play some role in the development of lipodystrophy, following case reports in patients not taking PIs, but taking NRTIs.¹³ Lipoatrophy (loss of fat from the face and limbs) has been linked, anecdotally, to the use of NRTIs, especially stavudine, although there is no strong evidence to support this at present. To most patients, the fat redistribution syndrome on the whole is still strongly thought of as being related to protease inhibitor therapy.

Abnormalities of lipid metabolism in patients infected with HIV were described prior to the advent of HAART, including

elevated triglycerides and a reduction in the levels of high density lipoprotein (HDL) cholesterol.¹⁴ Additional significant increases in triglyceride and both low density lipoprotein (LDL) and very low density lipoprotein (VLDL) cholesterol concentrations have been associated with all the available protease inhibitors. However, lipid elevations have also been reported in patients receiving NNRTIs, albeit less frequently. It is not yet known if the lipid elevations that exist during HAART represent a significant risk factor for cardiovascular disease. These observations are a reason for increased concern for the eventual increase in cardiovascular complications as mortality associated with AIDS falls due to HAART.

Treatment of hypercholesterolaemia is usually with 3-hydroxy-3-methylglutaryl co-enzyme A (HMG CoA) reductase inhibitors. However, in HIV-infected patients taking HAART, careful consideration needs to be given to potential drug interactions with the statins. Simvastatin is now contraindicated with protease inhibitors due to the risk of myalgia, myositis and myopathy, caused by an increase in simvastatin levels brought about by enzyme inhibition. Low dose atorvastatin can be used — its metabolism is also inhibited by protease inhibitors, but to a lesser extent. Pravastatin can be used as it is not metabolised by the CYP isoenzyme system, although high doses are often required to achieve adequate response. In the treatment of hypertriglyceridaemia there are no drug-drug interactions with the co-administration of fibrates and HAART.

One published study suggests that patients established on PIs with an undetectable viral load can achieve some resolution of their dyslipidaemia by switching to a nevirapine-based regimen, without losing viral control.¹⁵ Other such "switch" studies have been reported in which efavirenz or abacavir were used as the drugs of choice, although efavirenz has failed to demonstrate a consistent benefit.¹⁶

NEW THERAPIES

Lopinavir is the latest addition to the PIs. It is co-formulated with ritonavir (as Kaletra, recently launched in the UK), and the latter acts as a pharmacokinetic enhancer, substantially increasing lopinavir drug exposure. The area under the plasma

concentration-time curve (AUC) is increased 100-fold compared with that for lopinavir alone. This provides a pharmacological barrier to the emergence of viral resistance and the degree of drug exposure attained is sufficient to suppress the replication of viral strains that are genotypically or phenotypically resistant to the drug.¹⁷ The benefits of elevated drug concentrations have to be weighed against the risks of short or long-term toxicity. At the dose selected for phase III clinical trials (400mg lopinavir and 100mg ritonavir twice daily), it appears to be well tolerated and has been shown, at least in the short-term, not to have many major side effects.

Fusion inhibitors T20 belongs to an entirely new class of antiretrovirals called fusion inhibitors and is derived from a protein called gp41, the HIV protein which penetrates uninfected cells as the first step in viral entry. T20 is believed to interfere with this cell entry process. It is administered subcutaneously twice daily as part of a HAART regimen. At present, in the UK, it is only available in clinical trials for patients whose treatment options have been limited by drug resistance.

Tenofovir Tenofovir, a nucleotide reverse transcriptase inhibitor, has recently been made available on a named-patient basis in the UK. It acts in exactly the same way as NRTIs. However, its structure contains an extra phosphate group, so it does not require triphosphorylation in order to become active within the cell. It has the advantage that it is administered as a single tablet once a day, and is thought to remain active against viruses that have become resistant to many of the NRTIs.

Nucleotide analogues such as tenofovir have the potential to cause renal toxicity, hence co-administration of renally toxic drugs is currently contraindicated with them. Renally toxic drugs, including foscarnet, cidofovir, aminoglycosides, and amphotericin, are used quite commonly in HIV-infected patients and therefore could be a potential problem.

Immunomodulatory agents Immuno-modulatory agents include interleukin-2 and interferon-alpha.

Interleukin-2 (IL-2) The cytokine IL-2 is administered in cycles of twice-daily subcutaneous injections for five days every eight weeks. IL-2 has been shown to increase the CD4 count with improved lymphocyte responses.

Currently, a large multicentre trial is being conducted to determine whether there is an improvement in morbidity or mortality with the use of IL-2.

There is a possible role for IL-2 in patients who have achieved an undetectable viral load with HAART, but whose CD4 count is still low, thus putting them at risk of opportunistic infections.

Interferon-alpha Interferon-alpha is a cytokine whose use is being investigated as adjuvant therapy in salvage HAART regimens.

— OPPORTUNISTIC INFECTIONS

Drug research has tended to concentrate on new antiretrovirals over recent years. Research into new drugs for the treatment of opportunistic infections (OIs) has become less attractive to pharmaceutical companies, with the introduction of HAART seeing a reduction in incidence. There are two main elements to the management of OIs — prevention and treatment.

HIV-infected patients with a CD4 count less than 200 cells per mm³ are at greatest risk of OIs. Table 6 shows the recommended agents for prophylaxis against the common HIV-associated infections. Prophylaxis can be stopped for several of the OIs once the CD4 count has risen in a sustained manner. For example *Pneumocystis carinii* pneumonia (PCP) prophylaxis is commonly discontinued after the CD4 count has been above 200 cells per mm³ for three to six months.¹⁸

The treatments available for different OIs are outlined below.

PCP Several agents have been successfully used in the treatment of PCP (Table 7).

Co-trimoxazole is the “gold standard” for the treatment of PCP. It should be used first line unless there has been any previous allergy to the drug.

Clindamycin-primaquine should be considered in those patients with co-trimoxazole allergy. This regimen cannot be used in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Atovaquone can be used, but it is not as effective as other regimens in treating severe PCP, thus it should only be used in mild to moderate infection.

Pentamidine tends to be reserved for cases where other treatment has failed or where there are no other options. Patients should

Table 6: Prophylaxis of opportunistic infections

Infection	Prophylactic treatment
<i>Pneumocystis carinii</i> pneumonia (primary and secondary prophylaxis)	Co-trimoxazole 960mg once daily or three times weekly Dapsone 100mg once daily Atovaquone 750mg twice daily Inhaled pentamidine 300mg every two weeks Fluconazole 400mg twice daily
Cryptococcosis (secondary prophylaxis only)	
Toxoplasmosis (primary prophylaxis)	Primary prophylaxis is not recommended in the UK, although some PCP prophylaxis regimens, eg, co-trimoxazole, atovaquone also appear to be effective agents for the prophylaxis of toxoplasmosis
(secondary prophylaxis)	Sulphadiazine 1g twice daily and pyrimethamine 25mg once daily (with folinic acid) or Clindamycin 600mg twice daily and pyrimethamine 25mg once daily (with folinic acid) Azithromycin 1.25g once weekly
<i>Mycobacterium avium</i> complex (primary and secondary prophylaxis)	Isoniazid 300mg once daily in patients with a positive Mantoux test greater than 5mm. Occasionally used in patients thought to be at risk of TB, eg, if on long term corticosteroids (controversial)
<i>Mycobacterium tuberculosis</i> (primary prophylaxis)	Aciclovir, valaciclovir, famciclovir
Herpes simplex	

have inhaled pentamidine administered in conjunction with IV therapy for the initial three days as it takes time to achieve adequate plasma levels of the drug.

Use of trimetrexate should be considered as salvage therapy when patients have failed to respond to conventional treatment. It is highly toxic to the bone marrow and therefore requires high doses of folinic acid rescue therapy.

Corticosteroids should be used as adjuvant therapy to PCP treatment in patients with PaO₂ lower than 8kPa because they accelerate the recovery process and prevent the development of respiratory failure and death.¹⁹ A typical regimen is methylpred-

nisolone IV given initially every six hours, which is then converted to an equivalent oral prednisolone dose and reduced slowly over the treatment period.

***Toxoplasma gondii* encephalitis** Treatment of *T. gondii* encephalitis involves pyrimethamine plus sulphadiazine or clindamycin. The regimens are:

- Sulphadiazine 2g IV or orally four times a day + pyrimethamine 75mg once daily (+ folinic acid)
- Clindamycin 600mg IV or orally four times a day + pyrimethamine 75mg once daily (+ folinic acid)

Table 7: Treatment of *Pneumocystis carinii* pneumonia

Drug	Dose
Co-trimoxazole	120mg per kg intravenously (IV) in divided doses or 1.92g orally four times a day for 14 to 21 days
Clindamycin + primaquine	Clindamycin 600mg IV or orally four times a day Primaquine 30mg orally once daily
Dapsone + trimethoprim	Dapsone 100mg once daily Trimethoprim orally or IV 20mg per kg per day in divided doses
Pentamidine	4mg per kg IV once daily for three days then on alternate days to a total of 14 to 21 days and nebulised pentamidine 600mg once daily for the first three days
Atovaquone	750mg twice daily (mild to moderate PCP only)
Trimetrexate + folinic acid (salvage therapy)	Trimetrexate 45mg per m ² body surface IV once daily for 21 days and folinic acid IV or orally 20mg per m ² body surface four times a day (first dose should be given before administration of trimetrexate and continued for a full three days after trimetrexate therapy has been completed)

Both these regimens exhibit a high incidence of adverse events and involve large quantities of tablets. Atovaquone has activity against toxoplasmosis and can be used if side effects or compliance are an issue. Corticosteroids can be used in patients who have evidence of cerebral oedema and increased intracranial pressure. Initial treatment of toxoplasmosis should be for six weeks, after which continuous maintenance therapy is required (secondary prophylaxis).

Cytomegalovirus (CMV) infection

CMV infections are still significant problems in HIV disease, specially in the more severely immunocompromised patients (with CD4 counts lower than 50 cells per mm³).²⁰ The antiviral agents used to treat CMV infection are ganciclovir, foscarnet or cidofovir, intravenously. All three of these antiviral agents are licensed for the treatment of CMV retinitis, although not all are licensed for the treatment of CMV infection elsewhere in the body. First line therapy is usually intravenous ganciclovir, administered twice daily for a period of 14 to 21 days, depending on the site of infection. In CMV retinitis, a maintenance regimen must then be chosen for the patient, to prevent reactivation of disease and risk of blindness. (This is not normally required for infection in other sites.) The maintenance phase for CMV retinitis is indefinite or until an adequate CD4 count rise has been achieved with HAART.²¹ Maintenance treatment can often be safely discontinued once the CD4 count has risen above 100 cells per mm³. Systemic maintenance therapy should be used where possible, usually oral ganciclovir. If additional local therapy is required, intravitreal injections of ganciclovir or foscarnet or a ganciclovir ocular implant may be used. Fomivirsen is a novel antiviral drug that is only available as an injection for intravitreal administration. Cidofovir is an antiviral agent that is active against ganciclovir-resistant CMV. It is administered intravenously once a week for two consecutive weeks as a loading dose, then once every fortnight. This is licensed for second line treatment of CMV retinitis. However, it is sometimes used as an alternative maintenance therapy if adherence to oral ganciclovir is an issue. Cidofovir has high renal toxicity, therefore patients must be kept well hydrated with normal saline. Probenecid is administered to delay renal excretion of cidofovir, so preventing renal tubular damage. Patients receiving cidofovir are also at risk of uveitis and hypotony, which means that they need to be monitored regularly. Cidofovir is not administered intravitreally because of the risk of irreversible hypotony.

Mycobacterium avium complex (MAC)

MAC is common in AIDS and is associated with an accelerated rate of disease progression.²² As MAC is prone to develop drug

Panel 2: Treatment of other OIs

Cryptococcosis	Amphotericin, with/without flucytosine Fluconazole
Cryptosporidiosis	Antiretrovirals Paromomycin
Microsporidiosis	Antiretrovirals Albendazole Thalidomide
Herpes varicellazoster	Aciclovir Valaciclovir Famciclovir
Herpes simplex	Aciclovir Valaciclovir Famciclovir Foscarnet (in aciclovir resistance)

resistance, combination therapy is mandatory. Regimens should consist of a macrolide antibiotic (clarithromycin or azithromycin) with at least one other antimicrobial agent, usually ethambutol. Rifabutin is sometimes used in addition, although less so nowadays due to the risk of drug interactions with the antiretrovirals agents, and a combination of two drugs is usually adequate. Other drugs with activity against MAC include amikacin and ciprofloxacin. Table 8 shows the doses at which these drugs are used.

Mycobacterium tuberculosis The standard antituberculous therapy for HIV-infected individuals with fully sensitive tuberculosis (TB) consists of isoniazid, rifampicin, pyrazinamide and ethambutol for two months, followed by isoniazid and rifampicin for four months.

Treatment of TB in HIV-infected patients is always a complicated issue due to the risk of drug interactions with rifamycins and HAART. Rifampicin is not currently recommended to be used in combination with any of the PIs or NNRTIs, with the exception of efavirenz. There are some pharmacokinetic data to support the use of rifampicin with a raised dose of efavirenz (800mg daily instead of the usual 600mg daily dose).²³ Rifabutin is commonly used to treat TB in HIV patients taking HAART as it may be used with some of the PIs and NNRTIs, providing dose adjustments are applied. It is important to refer to the antiretroviral product liter-

ature before initiating rifamycin therapy.

Drugs used in the treatment of other HIV-related OIs are listed in Panel 2.

MALIGNANCIES

Since the introduction of HAART, the incidence of AIDS-related malignancies such as Kaposi's sarcoma and primary cerebral lymphoma have declined³ while that of non-Hodgkin's lymphoma has remained unchanged.²⁴ The need for effective treatments for these malignancies remains.

Kaposi's sarcoma First line therapy involves starting HAART. HAART alone can achieve complete remission of Kaposi's sarcoma (KS) lesions in up to 50 per cent of patients.²⁵ In some patients, the KS lesions can worsen initially as part of an immune restoration illness. If after three to four months the KS has not improved, or a more rapid response is needed, for example, in the presence of oedema, visceral disease or extensive disfiguring lesions, then systemic chemotherapy should be considered. The first line treatment is liposomal anthracyclines and salvage therapy is with paclitaxel. An alternative is interferon-alpha if the CD4 count is above 400 cells per mm³.

Primary cerebral lymphoma Primary cerebral lymphoma is associated with advanced immunosuppression. It can be difficult to diagnose and the patient has a median survival of only two to four months. There are no curative therapies and so many patients opt for symptom palliation alone. Standard therapy is whole brain irradiation, although one cohort study supports the use of high dose intravenous methotrexate in patients with good performance status.²⁶

Non-Hodgkin's lymphoma Early treatment (pre-HAART) of non-Hodgkin's lymphoma was badly tolerated and had poor results. The use of haemopoietic growth factors, intrathecal chemotherapy prophylaxis, prophylaxis of OIs and HAART have led to improved outcomes. Many centres stratify chemotherapy for patients with preserved immune systems. Regimens used include mBACOD (bleomycin, doxorubicin, vincristine, dexamethasone methotrexate and folinic acid), BEMOP-CA (bleomycin, etoposide, methotrexate, vincristine prednisolone and folinic acid with

Table 8: Doses of drugs used against MAC

Drug	Dose
Ethambutol	15mg per kg daily
Clarithromycin	500mg twice daily
Azithromycin	500mg once daily
Ciprofloxacin	500 to 750mg twice daily
Amikacin	15mg per kg intravenously once daily

cyclophosphamide and doxorubicin) and CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone), although recent experience with cyclophosphamide, doxorubicin, and etoposide infusions (CDE) administered continuously over 96 hours has been promising.²⁷ Drug interactions between chemotherapy and HAART should be considered and doses modified as appropriate. Intrathecal chemoprophylaxis and OI prophylaxis are vital parts of therapy; the management of HIV patients infected with non-Hodgkin's lymphoma should only be undertaken by a team of clinicians experienced in both medical oncology and HIV clinical care.

SUMMARY

The treatment of HIV disease remains complex and is rapidly changing, requiring the input of specialist health care professionals. New antiretroviral drugs are being continually developed and the use of currently available drugs are being refined. There have been fewer drug developments in the treatment of OIs over the last few years but these still remain an important aspect of HIV treatment.

REFERENCES

- Pozniak A. Surrogacy in HIV-1 clinical trials. *Lancet* 1998; 351:536-7.
- Paterson D, Swindells S, Mohr J, Brester M, Vergis E, Squier C, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000; 133:21-30.
- Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998; 338:853-60.
- Staszewski S, Morales-Ramirez J, Tashima KT, Rachlis A, Skiost D, Stanford J, et al (for the study 006 team). Efavirenz plus zidovudine and lamivudine, efavirenz plus didanosine, and didanosine plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med* 1999; 341:1865-73.
- Squires K. The Atlantic Study: a randomised, open-label trial comparing two protease inhibitor (PI)-sparing antiretroviral strategies versus a standard PI-containing regimen, 48-week data [abstract]. Proceedings of the Thirteenth International AIDS conference on antimicrobial agents and chemotherapy; 2000 Jul 9-14; Durban. Abstract no L6PeB7046.
- British HIV Association. Guidelines for the treatment of HIV-infected adults with antiretroviral therapy. *HIV Medicine*. 2000; 1:76-100.
- Pontesilli O, Kerkhof-Garde S, Notermans DW, Foudraïne NA, Roos M, Klein MR, et al. Functional T-cell reconstitution and human immunodeficiency virus-1-specific cell-mediated immunity during highly active antiretroviral therapy. *J Infect Dis* 1999; 180:76-86.
- Staszewski S, Keiser P, Montaner J, Raffi F, Gathe J, Brotas V, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naïve HIV-infected adults: a randomised equivalence trial. *JAMA*; 2001 285:1155-63.
- Bertz R, Granneman G. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. *Clin Pharmacokinet* 1997; 32: 210-58.
- Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral therapy-related lipodystrophy. *Lancet* 1999; 354:1112-5.
- Breckenridge A. Antiretroviral drugs to reduce vertical transmission of HIV infection. *CSM/CMO/99/5*. June 25, 1999.
- EMEA public statement. Reports of lactic acidosis in pregnant women treated with Zerit and Videx. January 26, 2001.
- Madge S, Kinloch-de-Loes S, Mercey D, Johnson MA, Weller IV. Lipodystrophy in patients naive to HIV protease inhibitors. *AIDS* 1999; 13:735-7.
- Grunfield, Pang M, Doerrler, Shigenaga JK, Jensen P, Fenigold KR. Lipids, lipoproteins, triglyceride clearance and cytokines in HIV infection and AIDS. *J Clin Endocrinol Metab* 1992; 74:1045-52.
- Ruiz L, Bonjoch A, Paredes R, Johnson S, Arno A, Roneu J, et al. A multi-centre, randomised, open-label comparative trial of the clinical benefit of switching the protease inhibitor by nevirapine in HAART-experienced patients suffering lipodystrophy [abstract]. Proceedings of the Sixth Conference on retroviruses and opportunistic infections; 1999 Feb; Chicago. Abstract no LB-14.
- Moyle G, Baldwin C. Switching From a PI-based to a PI-sparing regimen for management of metabolic or clinical fat redistribution. *AIDS Reader* 2000; 10:479-85.
- Bertz R, Lam W, Brun S, Kumar G, Fields C, Orth K, et al. Multiple-dose pharmacokinetics (PK) of ABT-378/ritonavir (ABT-378/r) in HIV positive subjects [abstract]. Proceedings of the Thirty-ninth Interscience conference on antimicrobial agents and chemotherapy; 1999 Sept; San Francisco. Abstract no 0327.
- Furrer H, Egger M, Opravil M, Bernasconi E, Hirschel B, Battegay M, et al. Discontinuation of primary prophylaxis against *Pneumocystis carinii* pneumonia in HIV-1-infected adults treated with combination antiretroviral therapy. *N Engl J Med* 1999; 340:1301-6.
- Montaner J, Lawson L, Levitt N, Belzberg A, Schechter MT, Ruedy J. Corticosteroids prevent early deterioration in patients with moderately severe *Pneumocystis carinii* pneumonia and the acquired immunodeficiency syndrome. *Ann Intern Med* 1990; 113:14-20.
- Kuppermann BD, Petty JG, Richman DD, Matthews WC, Fullerton SC, Rickman LS et al. Correlation between CD4 counts and prevalence of cytomegalovirus retinitis and human immunodeficiency virus-related non-infectious retinal vasculopathy in patients with acquired immunodeficiency syndrome. *Am J Ophthalmol* 1993; 115:575-82.
- Studies of the ocular complications of AIDS Research Group, in collaboration with the AIDS Clinical Trials Group. Foscarnet-ganciclovir cytomegalovirus retinitis trial 4: visual outcomes. *Ophthalmology* 1994; 101:1250-61.
- Chaisson RE, Moore RD, Richman DD, Kerly J, Creagh T. Incidence and natural history of *Mycobacterium avium*-complex infections in patients with advanced human immunodeficiency virus disease treated with zidovudine. *Am Rev Respir Dis* 1992; 146:285-9.
- DuPont Pharma. Efavirenz summary of product characteristics. Stevenage: DuPont; 1999
- Matthews G, Bower M, Mandalia S, Powles T, Nelson M, Gazzard B. Changes in acquired immunodeficiency syndrome-related lymphoma since the introduction of highly active antiretroviral therapy. *Blood* 2000; 96:2730-4.
- Martinelli C, Zazzi M, Ambu DS, Bartolozzi D, Corsi P, Leoncini F. Complete regression of AIDS-related Kaposi's sarcoma associated human herpes virus-8 during therapy with indinavir. *AIDS* 1998; 12:1717-9.
- Jacomot C, Girard PM, Lebrétte MG, Farese VL, Monfort L, Rozenbaum W. Intravenous methotrexate for primary central nervous system non-Hodgkin's lymphoma in AIDS. *AIDS* 1997; 11:1725-30.
- Sparano JA, Wiernik PH, Hu X, Sarta C, Schwartz EL, Soeiro R, et al. Pilot trial of infusional cyclophosphamide, doxorubicin, and etoposide plus didanosine and filgrastim in patients with HIV-associated non-Hodgkin's lymphoma. *J Clin Oncol* 1996; 14:3026-35.