New developments in antiretroviral therapy for HIV infection

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Summary

Health professionals need to be aware of the current approach to the treatment of HIV infection as more Australians are living with HIV/AIDS. Approximately half of these patients are taking combination antiretroviral therapy. These regimens have a wide range of adverse effects and interactions. The prevalence of HIV infection is expected to increase, not only because the incidence is increasing, but also because effective antiretroviral therapy is prolonging survival. People living with HIV/AIDS are increasingly likely to seek care from doctors without a special interest in HIV because of increasing comorbidities including cardiovascular disease.

Key words: cardiovascular disease, drug interactions.

(Aust Prescr 2005;28:146–9)

Introduction

Treatment with a combination of antiretroviral drugs prevents the progression of human immunodeficiency virus (HIV) disease by inhibiting viral replication.[1] It also stops the associated immunological deterioration associated with the depletion of CD4 lymphocytes. Effective inhibition of HIV replication may even restore the patient's immune system.

Principles of management

Combination antiretroviral therapy is indicated in patients with symptomatic HIV infection as it reduces the risk of disease progression. The decision to treat asymptomatic patients is made by balancing the benefits and harms of therapy. Current guidelines recommend starting antiretroviral therapy when the risk of disease progression is significant. Treatment is recommended once the CD4 lymphocyte count is below 350/microlitre, but before it falls to 200/microlitre, when there is a significant risk of the development of the acquired immune deficiency syndrome (AIDS). Starting treatment at a lower CD4 count is associated with an impaired immunological response to therapy. The Australasian Society for HIV Medicine has developed locally relevant antiretroviral therapy guidelines* that adapt the detailed guidelines of the US Department of Human Services and Health.

Combination therapy

Treatment usually starts with two nucleoside(tide) analogue reverse transcriptase inhibitors plus either a non-nucleoside reverse transcriptase inhibitor or a 'ritonavir-boosted' protease inhibitor. Ritonavir is a protease inhibitor that also inhibits the cytochrome P450 enzyme system. This inhibits the metabolism of other protease inhibitors, boosting their concentrations. By favourably altering the pharmacokinetics, a low dose of ritonavir enables less frequent dosing of other protease inhibitors.

Since the last review of antiretroviral therapy in *Australian Prescriber*[1] several new drugs have been approved, including one drug (enfuvirtide) with a new target of action (see Fig. 1 and Tables 1 and 2). The availability of new drugs provides options in the management of patients who have exhausted existing treatment options due to either drug toxicity or resistance. Therapy with three nucleoside/tide reverse transcriptase inhibitors in combination has now been shown to be inferior and this approach is not recommended. Similarly, despite the potency of the individual drugs, certain combinations (such as tenofovir with didanosine and efavirenz or nevirapine) are associated with a significant risk of treatment failure and the development of significant drug resistance and cross resistance to many other antiretroviral drugs. Where possible, it is important that clinicians prescribe the specific combinations that have been studied in clinical trials.*

Some combination formulations are now available. As well as reducing the number of pills patients have to take, most combinations can now be taken twice or even once daily. Adherence to twice-daily doses is better than to thrice-daily doses, although adherence to twice-daily and once-daily doses appears equivalent.

Many HIV-infected women are now contemplating pregnancy given the improved prognosis of HIV infection and the increased capacity to prevent mother-to-child transmission of HIV infection. There is increasing experience regarding the safety of antiretroviral drugs in pregnancy. However, efavirenz is a proven teratogen.

* http://www.ashm.org.au

Fig. 1

Simplified lifecycle of HIV showing sites of action of new drugs

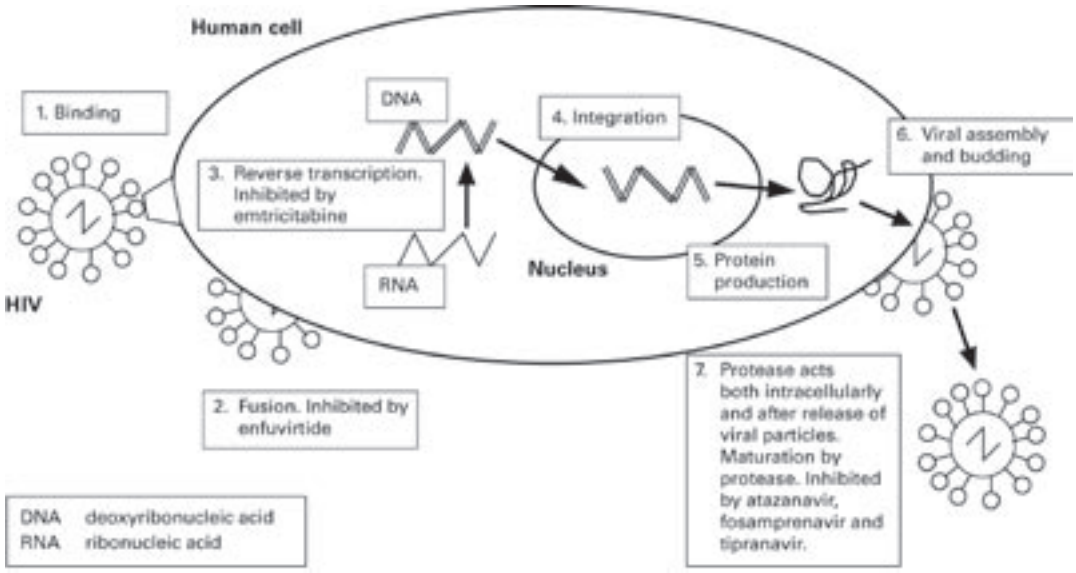

Table 1

Antiretroviral drugs available in Australia

Generic name	Trade name	Abbreviation
Nucleoside reverse transcriptase inhibitors		
abacavir	Ziagen	ABC
didanosine	Videx	DDI
emtricitabine	Emtriva	FTC
lamivudine	3TC	3TC
stavudine	Zerit	D4T
zalcitabine	Hivid	DDC
zidovudine	Retrovir	AZT, ZDV
Nucleotide reverse transcriptase inhibitors		
tenofovir	Viread	TFV
Nucleoside analogue combination preparations		
abacavir/lamivudine	Kivexa	ABC/3TC
zidovudine/lamivudine	Combivir	AZT/3TC
zidovudine/lamivudine/ abacavir	Trizivir	AZT/3TC/ABC
Non-nucleoside reverse transcriptase inhibitors		
delavirdine	Rescriptor	DLV
efavirenz	Stocrin	EFV, EFZ
nevirapine	Viramune	NVP
Protease inhibitors		
amprenavir	Agenerase	APV
fosamprenavir	Telzir	FPV
indinavir	Crixivan	IDV
lopinavir/ritonavir	Kaletra	LPV/r
nelfinavir	Viracept	NLV
ritonavir	Norvir	RTV
saquinavir	Invirase/Fortovase	SQV
tipranavir (currently available on Special Access Scheme)		
Fusion inhibitors		
enfuvirtide	Fuzeon	T20

Table 2

Summary of important features of new antiretroviral drugs

New drug	Usual dose	Common adverse events
atazanavir	400 mg daily OR 300 mg + 100 mg ritonavir daily	Jaundice Gastrointestinal disturbance
fosamprenavir	700 mg twice a day + 100 mg ritonavir twice a day OR 1400 mg daily + 200 mg ritonavir daily in antiretroviral therapy naive patients	Abdominal pain, diarrhoea, flatulence and vomiting
tipranavir	500 mg twice a day + 200 mg ritonavir twice a day	Gastrointestinal disturbance
emtricitabine	200 mg daily	Headache, dizziness, insomnia and rash
enfuvirtide	90 mg subcutaneously twice a day	Injection site reaction, hypersensitivity reactions

Drug interactions

Drug interactions involving antiretroviral drugs are significant. All Australian prescribers should be aware that these interactions can potentially result in increased toxicity or decreased efficacy. These interactions may be unexpected, but the effects can be severe. For example, there have been many reports of Cushing's syndrome in patients who have taken inhaled fluticasone while being treated with antiretroviral

combinations including ritonavir.[2] Consider potential interactions before prescribing any new medication for patients taking antiretroviral drugs. Consultation with a practitioner who is experienced in managing HIV is recommended, but there are also numerous information sources to assist clinicians. The University of Liverpool hosts a useful website.[†]

Comorbidities

People infected by HIV experience significant comorbidities that may lead them to seek care from health professionals with little experience of treating HIV. These comorbidities include smoking-related disorders, hypertension, drug-related dyslipidaemia, osteoporosis and liver disease associated with chronic viral hepatitis.

The care of HIV-infected patients is increasingly shared between multiple clinicians. This shared care should include a clinician who is experienced in treating HIV, as most practitioners will not be familiar with antiretroviral therapy. All treatment decisions should be made with consideration of potential antiretroviral drug interactions and toxicities. Minor clinical problems can be drug related and may be difficult to manage if the association is not recognised and the offending drug withdrawn. For example, ingrowing toenails have been associated with indinavir.

Cardiovascular disease

Antiretroviral therapy appears to be an independent risk factor for ischaemic coronary events. In a prospective observational multicentre study with more than 30 000 patient years of follow-up, each year of therapy was associated with a 26% increased risk of myocardial infarction.[3] This has resulted in a greater focus on strategies to reduce risk factors for ischaemic heart disease. Approximately 50% of people living with HIV/AIDS are smokers and 40% of those treated with antiretroviral therapy have hyperlipidaemia. Strategies to manage antiretroviral-induced hyperlipidaemia include ceasing the offending drug, dietary modification and the addition of lipid-lowering drugs. However, drug treatment has only a modest effect on lipids.[4] There are also significant interactions between antiretroviral and lipid-lowering drugs, and the risks of adverse events may well be higher than when lipid-lowering drugs are used alone. In the absence of clinical endpoint trials to date, the relative risk of treating versus not treating antiretroviral-associated hyperlipidaemia remains undetermined.

New protease inhibitors

These drugs prevent viral replication by inhibiting the proteases in HIV.

Atazanavir

Atazanavir has efficacy in previously untreated patients and in those who have previously taken protease inhibitors.[5] The recommended dose is either 400 mg daily, or 300 mg daily when boosted with ritonavir 100 mg daily. Atazanavir must be boosted with ritonavir when used in protease inhibitor-experienced patients or when used in combination with tenofovir, as tenofovir decreases atazanavir concentrations. Atazanavir is approved for once-daily dosing.

The main advantage of atazanavir over other protease inhibitors is that it is not associated with significant insulin resistance or elevation in serum lipid levels. However, it can cause unconjugated hyperbilirubinaemia. Some patients develop scleral icterus that may be cosmetically unpleasant, but less than 1% of patients in clinical trials ceased atazanavir because of this adverse effect.

Atazanavir should be taken with food. Its absorption is significantly decreased by reductions in gastric acidity. Drugs that reduce gastric acidity may decrease the concentrations of atazanavir. Proton pump inhibitors should therefore not be given to patients taking atazanavir.

Fosamprenavir

Fosamprenavir is the most recently approved protease inhibitor in Australia. When boosted with ritonavir it has efficacy in treated and previously untreated patients.[6] The recommended dose is 700 mg twice a day administered with 100 mg ritonavir twice a day. A once-daily dose of 1400 mg fosamprenavir with 200 mg ritonavir can be used in patients who have not previously received antiretroviral drugs. Fosamprenavir can be taken either with or without food although taking the medication with food is likely to reduce the nausea which is the most common adverse effect of fosamprenavir.

Other adverse effects of fosamprenavir include abdominal pain, diarrhoea, flatulence and vomiting. Rare adverse effects include depression, mood changes, perioral paraesthesia and rash. Drug interactions are significant with fosamprenavir, so it should not be combined with other protease inhibitors (apart from ritonavir).

Tipranavir

Tipranavir is a 'second-generation' protease inhibitor. It is active against a wide variety of isolates which are resistant to the other currently available protease inhibitors. Tipranavir is only available on the Special Access Scheme in Australia.

Emtricitabine

Emtricitabine (FTC) is a potent cytidine nucleoside analogue with a long plasma half-life. It has efficacy as part of a once-daily regimen for previously untreated patients.[7] The recommended dose is 200 mg once daily, but dose adjustments are required for patients with renal impairment. Common adverse effects include headache, dizziness, insomnia and rash. Lactic acidosis, hepatomegaly and liver failure have also been reported.

Like tenofovir and lamivudine, emtricitabine has activity against both HIV and hepatitis B virus. Patients should therefore be tested for hepatitis B infection before treatment to enable the

[†] http://www.hiv-druginteractions.org

strategic use of this drug in patients infected with both viruses. In general, drugs with activity against both hepatitis B virus and HIV are recommended for patients who need treatment for both viral diseases to reduce the risk of emergence of viral resistance. However, clinical endpoint data are not available to support this approach.

Enfuvirtide

Enfuvirtide (T20) is the first HIV fusion inhibitor to be licensed for use in clinical practice. It inhibits the fusion of the viral and human cell membranes following viral attachment (see Fig. 1). Given its novel site of action enfuvirtide has significant antiviral activity against isolates which have resistance to other drug classes. Its benefit is maximised if used with other active drugs, however its role in contemporary practice is limited by the fact that it needs to be injected subcutaneously twice daily.

Injection site reactions are common, but not usually dose limiting. Hypersensitivity reactions can occur.

Conclusion

The therapy of HIV infection continues to change. Clinicians need to be aware of developments in this field, as they are increasingly likely to need to provide care to people living with HIV/AIDS.

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Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 159)

3. Inhaled corticosteroids may interact with ritonavir to cause Cushing's syndrome.
4. Patients treated for HIV have an increased risk of cardiovascular disease.

Dental notes

Prepared by Dr M. McCullough of the Australian Dental Association

Antiretroviral therapy for HIV infection

The prevalence of people living with HIV infection is expected to rise and these people are increasingly likely to seek care from practitioners who are not specialists in managing HIV. Dental clinicians need to be aware of changes occurring in the management of HIV infection, the increase in number and complexity of antiretroviral regimens and the potential for drug interactions with commonly prescribed drugs. For example, erythromycin, metronidazole and miconazole have potential interactions with some antiretroviral drugs that may require close monitoring, alteration of drug dosage or timing of administration. Consultation with an HIV expert is strongly recommended before starting any new medication in patients taking antiretroviral drugs. Furthermore, unusual and rare adverse effects such as peri-oral paraesthesia can occur with antiretroviral drugs.

Dental clinicians should be aware that approximately 50% of patients living with HIV/AIDS are smokers. These patients therefore have an increased likelihood of oral diseases such as periodontal disease, leucoplakia and oral squamous cell carcinoma so thorough dental examination, treatment and monitoring is required.