

Primary care management of HIV disease

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Introduction

The course of HIV infection has been altered significantly in developed countries by the use of potent antiretroviral therapy and treatments for HIV-related opportunistic illnesses. In the era of combination antiretroviral therapy, many patients with HIV infection remain well ten years after their first AIDS-related illness. Nevertheless, HIV disease management remains a complex and evolving area of medicine which is constantly reshaped as new, scientific evidence emerges.

This chapter aims to provide the HIV non-specialist clinician with an update on the management of HIV disease and to describe the role of the primary care clinician in the shared management of patients with HIV infection. When managing patients with HIV disease, the primary care clinician often works in conjunction with a clinician, either a general practitioner or physician, who is able to prescribe antiretroviral drugs under Section 100 of the Pharmaceutical Benefits Scheme (PBS), as well as other services and agencies.

The challenges of managing patients with HIV infection

Management of HIV as a chronic disease

There are many challenges in the management of patients with HIV infection, some of which are common to the management of other chronic conditions. For example, the patient needs to be informed about the nature of the disease and potential treatments. Assistance in adherence to medication is particularly relevant in the management of HIV disease given the potential for drug resistance if doses are missed. The clinician also has a role in exploring a range of psychosocial and sexuality issues, and in encouraging a sense of hope through discussion of treatment options. Management of HIV infection as a chronic disease is shaped by the stigmatisation attached to HIV and the fear or anxiety patients may exhibit following diagnosis.

Key points

- HIV infection remains a complex disease and its management continues to evolve.
- The period of assessment and management of people living with HIV after diagnosis and before anti-HIV treatment is active for both patient and doctor. The role of the primary care clinician during this time is one of support, education, monitoring and referral.
- Knowledge of the conditions and illnesses associated with the stages of HIV immunodeficiency is necessary in the clinical monitoring of patients with HIV infection. Signs and symptoms of HIV disease are discussed in Chapter 6.
- Combination antiretroviral therapy is available for the treatment of HIV infection. Long-term suppression of HIV replication occurs in approximately 80% of people who commence triple combination therapy. Viral suppression produces strong immune recovery in most patients. Specialists and general practitioners who have completed HIV prescriber courses may prescribe antiretroviral therapy through Section 100 of the Pharmaceutical Benefits Scheme (PBS).
- The primary care clinician has a role in supporting adherence with patients who are taking antiretroviral therapy, as well as monitoring for adverse events and drug interactions.
- A focus on general health maintenance, psychosocial issues and support remains central to the care of patients with HIV infection in the era of combination antiretroviral therapy.

The quality of the doctor-patient relationship is central to the successful long-term management of HIV. Nurturing this long-term therapeutic relationship is a major task for the primary care clinician. The key characteristics of this relationship are honesty, accessibility, a demonstrated commitment to confidentiality and the privacy of the patient, and medical expertise. Offering frequent and long

consultations may be appropriate and provision of an after-hours contact number may be considered. The therapeutic relationship may be enhanced if the clinician demonstrates that he or she is comfortable with patients with HIV infection (e.g. by taking blood) and gay or bisexual patients (e.g. by openly discussing sexual matters).

The goals of the therapeutic relationship specifically in relation to patients with HIV include:

- Maintenance of an effective, collaborative, therapeutic relationship
- Thorough, ongoing assessment
- Education of the patient with regard to HIV infection, natural history, transmission and the effects of therapy
- Provision of information and referral regarding medical and psychosocial resources and services
- Facilitation of effective medical intervention to maximise the patient's health prior to and during treatment

Natural history and treatments

Following acute infection with HIV (Chapter 4), there is a stage of clinical stability where immunological and virological markers remain relatively stable. During this period, homeostasis exists between the amount of HIV produced and cleared each day, and the number of CD4 T-lymphocytes (CD4 cells) produced and destroyed each day. Subsequently, clinical stability may continue despite deterioration in laboratory markers as the immune system fails to control the amount of HIV produced (Chapter 1). At this time, the amount of HIV measurable in plasma (the viral load) may increase as the number of CD4 cells falls. The average time to progression to AIDS is about ten years but progression rates vary widely at the individual level. Determinants of the rate of disease progression include age and virological and host factors.

Constitutional symptoms (lethargy, fatigue, diarrhoea, weight loss and night sweats) may occur in the presence of a high viral load at any stage of the disease. Early symptoms of immune deficiency begin to appear when the CD4 cell count falls below normal levels (Figure 1.1, Chapter 1). As the CD4 cell count decreases to levels below 200 cells/ μ L, the patient is at greater risk of opportunistic infections.

An understanding of the natural history of HIV disease provides the basis for treatment decisions. Experts generally recommend commencement of therapy as surrogate markers deteriorate prior to onset of symptomatic disease, certainly prior to severe immune deficiency. However, the best time to commence antiretroviral therapy is yet to be established. See 'HIV treatment issues' on page 105 for more information.

Assessment and monitoring

Assessment and monitoring of the patient with HIV infection relates to general physical health, psychosocial wellbeing, as well as immune and virological status.

Initial assessment

During the initial consultations with a patient with HIV infection, a comprehensive medical and psychosocial assessment should be conducted. General discussion should include the impact of HIV on the patient and the availability of social support systems, as well as a discussion on issues of sexuality and transmission prevention. The patient's priorities with regard to HIV disease and his or her knowledge of HIV need to be established prior to discussion of the treatment options and transmission prevention. Ascertaining whether or not the patient sees an HIV specialist and whether a referral is sought may shape the consultation.

TABLE 10.1 Checklist: Initial assessment of the patient with HIV infection

<ul style="list-style-type: none"> • General assessment including medical history, family history, drug and alcohol history, smoking history, sexual history.
<ul style="list-style-type: none"> • Full psychosocial assessment.
<ul style="list-style-type: none"> • Targeted physical examination including weight, cardiovascular status, oral and dental health, skin, pelvic/anogenital examination and general systems examination.
<ul style="list-style-type: none"> • Sexual health review – tests for gonorrhoea and chlamydia (see Chapter 8 for sampling techniques), syphilis (RPR and a specific test e.g. TPPA), and hepatitis A, B and C (HAV IgG, HBsAg, anti-HBs, anti-HBc, HCV Ab [and HCV RNA if CD4 cells < 200 cells/μL]*). Consider HSV type specific serology and anal smear tests (for detecting dysplasia); the role of regular anal Papanicolaou cytology tests and management of abnormal tests is currently unclear (see Chapter 8).
<ul style="list-style-type: none"> • Screens for infections such as toxoplasmosis (Toxoplasma IgG), tuberculosis (Quantiferon Gold or Mantoux test and chest X-ray), cytomegalovirus (CMV IgG).
<ul style="list-style-type: none"> • Blood tests, including HIV RNA viral load, CD4 cell count, CD4 cell percentage, fasting cholesterol, triglycerides and glucose, liver function tests, serum amylase, creatinine phosphokinase, urea and electrolytes and a full blood count (FBC).
<ul style="list-style-type: none"> • HIV resistance genotyping (can be conducted in consultation with a HIV-experienced clinician).
<ul style="list-style-type: none"> • Vaccination history needs to be noted and future vaccinations discussed. The patient should be offered HBV and HAV vaccination in the absence of established immunity or infection. Live vaccination should not be given to patients with HIV infection. Both Fluvax and Pneumovax are recommended as per NHMRC guidelines¹ (available at http://immunise.health.gov.au/internet/immunise/publishing.nsf/Content/home).

*Patients with advanced HIV may lose anti-HCV reactivity, see page 112.

Initial medical assessment involves the establishment of the stage of HIV disease and assessment of potential co-morbidities. A comprehensive range of blood tests, serological tests and clinical examination should be conducted (Table 10.1).

Chapter 9 addresses how to deliver a positive HIV result to a patient and conduct early follow-up. In the context of a HIV diagnosis, the 'initial assessment' may take place over several weeks or months and psychosocial issues may take priority for the patient at this time.

Coinfection with viral hepatitis

Chronic liver disease commonly affects people with HIV infection and screening for viral hepatitis is recommended. Coinfection with either hepatitis B virus (HBV) or hepatitis C virus (HCV) is associated with greater risk of chronic liver disease and cirrhosis, increased hepatotoxicity from antiretroviral drugs and may affect survival. Viral hepatitis coinfections can impact on antiretroviral regimen choices as well as other lifestyle and health issues. The avoidance of alcohol and other potential hepatotoxins is important, as is the prevention of other hepatic infections. Vaccination against hepatitis A and hepatitis B is recommended for those who are not immune (Chapters 1, 5 and 11).

Markers of HIV disease: immunological and virological status

Immunological and virological status is evaluated by a general physical examination, T-cell subsets and viral load testing every three months. The CD4 cell count is the main measure of immune damage in people with HIV infection. The HIV RNA viral load (the number of viral copies per millilitre of blood plasma) is the key virological assay. In the absence of treatment, higher viral load is associated with faster CD4 cell decline and the development of AIDS-related conditions.

Data from the Multicenter AIDS Cohort Study (MACS) of HIV-infected men confirmed that both the CD4 cell count and HIV viral load are prognostic markers of likely disease progression and clinical illness in HIV disease.² As can be seen from Table 10.2, the proportion of men who progressed to an AIDS-defining illness was greatest for those with the highest viral loads and lowest CD4 cell counts. Within each stratum of CD4 cell count, prognosis was best for those with the lowest viral load.

CD4 cell count

In untreated HIV infection, progressive immune damage will occur, expressed as a loss of CD4 cells at an average rate of 60–80 cells/ μ L per year. Some patients may have a more rapid course, while others will remain stable for longer. There are levels of immune deficiency that are associated with greater risk of HIV-related conditions and opportunistic illnesses (Figure 1.1, Chapter 1). For example, when

Table 10.2 Surrogate markers and risk of progression to AIDS

CD4 cell count %	Viral load	% AIDS progression in men	
		over 3 years	over 9 years
<200 CELLS/ML	<10 000	14%	64%
	10 000 – 30 000	50%	90%
	>30 000	86%	100%
200-350 CELLS/ML	10 000	7%	66%
	10 000 – 30 000	36%	85%
	>30 000	64%	93%
>350 CELLS/ML	<10 000	7%	54%
	10 000 – 30 000	15%	74%
	>30 000	40%	85%

Adapted from multicenter aids cohort study^{2,3}

the CD4 cell count falls to between 200 and 500 cells/ μ L, oral hairy leukoplakia, skin conditions such as seborrhoeic dermatitis and psoriasis, recurrent varicella-zoster virus infection (shingles), and bacterial pneumonia may occur. CD4 cell counts below 200 cells/ μ L are associated with an increased risk of Pneumocystis jiroveci pneumonia (formally Pneumocystis carinii or PCP), cerebral toxoplasmosis, oesophageal candidiasis, Kaposi's sarcoma and cryptococcosis. Advanced immunodeficiency occurs at CD4 cell counts below 50 cells/ μ L, at which stage the individual is at risk of cytomegalovirus (CMV) retinitis, disseminated mycobacterium avium complex (MAC) infection, cryptosporidiosis and microsporidiosis, primary central nervous system lymphoma and HIV-associated dementia, and non-Hodgkin's lymphoma. Opportunistic infections are discussed in greater detail in Chapter 6.

The CD4 cell count is calculated by the percentage of CD4 cells in the lymphocyte component of the white cell count. The total number of CD4 cells will vary according to the white cell count and lymphocyte count. It is important to assess changes in the total CD4 cell count in the context of the percentage of CD4 cells and variability of the lymphocyte number secondary to intercurrent illnesses. A single measurement may be misleading because factors such as intercurrent infection, vaccination, menstrual cycle, and the time of day blood is taken can impact on results. Consequently, evaluation should focus on the trend in CD4 cell levels rather than a single result. A number of tests need to be performed over a period of time to provide an accurate picture of the patient's immune function. These test results enable the clinician to form an assessment of the course of a person's HIV disease and the rate of disease progression.

Viral load

Plasma viral load estimates provide the strongest long-term prognostic information for HIV patients. The plasma viral load is a measure of the balance between the amount of HIV produced each day and the amount of HIV cleared by the immune system.

Viral load (the amount of HIV RNA in the plasma) is measured by reverse transcriptase polymerase chain reaction (RT PCR). The laboratory will give results in both log number of copies/mL and absolute number of copies/mL. A significant change in viral load is an increase or decrease of greater than 0.5 log. Changes of less than 0.3 log are considered to be within the variability of the laboratory test performance (Table 10.3 and Case Study 1). The lower limit of detection of the assay is currently 50 copies/mL, and viral loads below this level are reported as undetectable; however this does not mean that there is no HIV present.⁴

Viral load is used to assist in making the decision to initiate antiretroviral therapy (along with the presence or absence of symptoms and the level of CD4 cells), to monitor the response to antiretroviral therapy and to identify treatment failure.

Monitoring HIV infection

There are a number of Models of Care for the clinical management of HIV infection from the USA, the UK and Europe. Online access to Models of Care can be obtained by consulting the ASHM website at: <http://www.ashm.org.au/moc/>.⁵ Another source is *Clinical practice: Management of newly diagnosed HIV infection* by Hammer (2005).⁶

Patients will require more regular review and monitoring if they are immunocompromised (CD4 cells <350/μL) or receiving antiretroviral therapy. In general, the untreated, immunocompetent patient (CD4 cells >350/μL) should be reviewed every 3–6 months, while the patient with less than 350 CD4 cells/μL or receiving antiretroviral therapy needs review every 2–3 months (Table 10.4).⁷

Psychosocial assessment

Effective management of people with HIV infection involves an approach which addresses psychosocial as well as biomedical factors. In addition to psychosocial issues related directly to HIV infection, the social stigma and marginalisation experienced by groups most affected by HIV may compound the psychological, social and emotional impact of HIV infection.

Social, emotional and educational support is available through AIDS Councils and HIV-positive people's groups in each State and Territory (Chapter 15).

Psychosocial assessment and management involves consideration of the following issues:

- Self-esteem and body image
- Stigmatisation and discrimination
- Family and social relationships and supports
- Sexual relationships and related issues of disclosure and safe sex
- Depression and emotional issues (e.g. anger, denial, anxiety)
- Drug and alcohol use
- Issues around pregnancy and motherhood for women
- Compliance with drug therapy and related lifestyle issues
- Financial and employment situation
- Health care satisfaction

Most of these evaluations will take a number of consultations to complete, and ongoing assessment is recommended.

Key relationships and support systems are pivotal to the wellbeing of the patient. One of the most important support systems for many people is their biological family, therefore assessment of family relationships and social support should be conducted. Issues to consider include whether the family is aware of the patient's sexuality and HIV status, their reaction to this information and the patient's reasons for not telling them. Friends may also provide an invaluable support network.

TABLE 10.3 Significance of viral load changes

Biologically relevant changes in viral load (>0.5 log) and changes considered within the variability of the laboratory assay (>0.3 log)

Copy number	Log ¹⁰	Log ¹⁰ change from 10,000 copies/mL	Fold change	Significant change from 10,000 copies/mL
5000	3.7	-0.3	0.5	No
10,000	4.0	0	1.0	–
20,000	4.3	+0.3	2.0	No
50,000	4.7	+0.7	5.0	Yes
100,000	5.0	+1.0	10	Yes

Other questions to ask are: is the patient in a relationship and what is the quality of that relationship? Does the partner know of the person's HIV status? How does the person's HIV status affect the relationship sexually or emotionally? Patients who lack supportive and trusting relationships may be isolated and vulnerable, and referral to community organisations or other services may be appropriate (Chapter 15).

Use of drugs and alcohol should be explored in a non-judgemental way. Substance abuse may be a form of self-medication for depression or may perpetuate denial and avoidant behaviours. Referral may be made to a treatment program or other specialist service. An accurate drug and alcohol assessment is essential prior to commencement of antiretroviral therapy due to the possibility of serious and life-threatening drug interactions.

For women with HIV infection, issues of family and children may be of particular concern. Fears about transmission or future care may influence a woman's desire for children, and full education and discussion is advised (Chapter 9). For a woman who already has children, there may be concerns that her children have HIV infection. Most infants with HIV develop signs of immune deficiency within the first year of life and antiretroviral therapies are available for children, although adherence to therapy can present difficulties. For women with HIV infection requiring support, referral to Positive Women's groups is recommended (Chapter 15).

In the era of combination antiretroviral therapy, patients may wish to address issues of returning to work, education or relationships in light of the improved prognosis. The demands of long-term adherence to therapy or the physical manifestations of drug toxicities may also give rise to other psychosocial concerns regarding body image, lifestyle and sexuality.

Psychological assessment⁶

Several Australian studies indicate a high prevalence of major depressive symptoms and dysthymia among people with HIV infection⁸⁻¹⁰ with particularly high rates among patients with fewer social supports and lower income. Depressive symptoms may impact on the person's ability to maintain safe sexual practice or lead to suicidal ideation.

Psychological assessment should be conducted to identify and treat major psychiatric illness. Recent acquisition of HIV may indicate that the patient has participated in some sort of self-destructive behaviour, which may be related to depression or suicidal ideation, drug and alcohol dependence, post-traumatic stress disorder or a range of other problems. Depression in people with HIV infection may be influenced by factors such as social rejection,

CASE STUDY 1

When is a viral load change significant?

Viral load changes and adherence

Alex has regular monitoring of his viral load and CD4 cell count every six months. When his viral load reaches 48,990 copies/mL (4.69 log) and his CD4 cell count is 300 cells/ μ L, he commences combination antiretroviral therapy.

He has a good virological response to treatment, recording a viral load of 570 copies/mL (2.76 log) three months later. Over the first 12 months of therapy his viral load is measured at 800 and 1,000 copies/mL (2.90 and 3.00 log). No action is taken by the clinician, as these results are not significantly different from the nadir of 570 copies/mL (i.e. not greater than a 0.3 log difference from 2.76 log).

However, 18 months later his viral load is 6,500 copies/mL (3.81 log). This is a significant rise in viral load (>0.5 log), which prompts a discussion of his adherence to therapy and whether he has taken any new medication that may have interacted with his antiretroviral drugs. Alex says that he finds it difficult to remember to take his pills and admits missing doses.

The clinician explores strategies to assist Alex in taking his pills, such as keeping pills in highly visible locations (e.g. next to his bed, toothbrush or keys) or using a beeper.

progression of HIV disease, lack of support networks or alcohol and drug use, and these factors should be identified and addressed.

Patients with significant immunosuppression may be at risk of developing organic brain disease and consideration should be given to the mental health implications of immune status. In addition, depressive, neuropsychological side-effects may be caused by antiretroviral agents, most commonly efavirenz.

Health promotion

Prevention

It is important that people with HIV infection have a clear understanding of HIV transmission so that they do not pass on the infection (Chapters 2 and 3, Appendix 1). A patient's knowledge of transmission, especially with regard to his or her own (possibly changing) behaviour, needs to be broached at regular intervals over the course of the therapeutic relationship. The risk of HIV transmission when the patient has undetectable or low viral load must also be addressed. Although viral load in the blood plasma often correlates with viral load in semen and vaginal fluids, this is not necessarily the case. Consequently, a person with undetectable virus in the blood may still be able to transmit HIV. The benefits of safe behaviours to the patient should be reiterated, such as prevention of sexually transmitted infections (STIs). Rates of STIs like syphilis, more

recently lymphogranuloma venereum (LGV) and possibly HCV remain high among people with HIV who have unprotected sex. Other STIs are also known to amplify the risk of HIV transmission to others. Unprotected sex between people with HIV

infection may carry the risk of re-infection with a drug-resistant or more aggressive virus, which may accelerate disease progression. Condoms remain the best prevention tool for the sexual transmission of HIV.

TABLE 10.4 Assessment and monitoring of the patient with HIV infection

Three-monthly reviews in all patients with HIV infection	Additional monitoring for patients taking antiretroviral therapy
<ul style="list-style-type: none"> Collection of history and symptom review 	<ul style="list-style-type: none"> Treatment-related monitoring is primarily conducted by the antiretroviral prescriber
<ul style="list-style-type: none"> General physical monitoring 	<ul style="list-style-type: none"> Frequent review during the first month of treatment
<ul style="list-style-type: none"> Weight, blood pressure, oral and dental checks 	<ul style="list-style-type: none"> Monitoring for severe side-effects (e.g. hypersensitivity, Stevens-Johnson syndrome, CNS toxicity)
<ul style="list-style-type: none"> Full blood count 	<ul style="list-style-type: none"> Management of treatable side-effects (e.g. nausea, diarrhoea)
<ul style="list-style-type: none"> Liver function tests and amylase 	<ul style="list-style-type: none"> Adherence monitoring and support. Tips to maximise adherence. Consideration of change of medication. Referral
<ul style="list-style-type: none"> CD4 cells and percentage 	<p>Three-monthly reviews</p>
<ul style="list-style-type: none"> Viral load 	<ul style="list-style-type: none"> Assessment of potentially adverse effects of treatment (e.g. peripheral neuropathy, lipoatrophy, lipodystrophy)
<ul style="list-style-type: none"> Psychosocial assessment and support 	<ul style="list-style-type: none"> Ongoing adherence monitoring and support
<ul style="list-style-type: none"> Patient education (transmission prevention and treatment updates) 	<p>Six-monthly reviews</p>
<ul style="list-style-type: none"> Health promotion (alcohol avoidance for patients with HCV co-infection, smoking cessation, dietary adjustment) 	<ul style="list-style-type: none"> Fasting cholesterol (including HDL and LDL), triglycerides, insulin and oral glucose tolerance
<p>Six-monthly reviews in all patients with HIV infection</p>	<ul style="list-style-type: none"> Monitoring of serum lactate, particularly in symptomatic patients, to detect lactic acidemia related to nucleoside analogue therapy (the utility of this monitoring in asymptomatic patients remains unclear)
<ul style="list-style-type: none"> Ophthalmological assessment if CD4 cell count is below 50 cells/mL (rule out asymptomatic CMV retinitis) 	<p>Annual reviews</p>
<ul style="list-style-type: none"> Cervical cytology by Papanicolaou smear in women with previous evidence of cervical dysplasia. Anal smears are performed by some GPs but predictive value of subsequent anal carcinoma is unproven 	<ul style="list-style-type: none"> Physical assessment for lipodystrophy, including DEXA scan for assessment of fat and bone mineral density
<ul style="list-style-type: none"> Syphilis serology (see guidelines²²) 	<ul style="list-style-type: none"> Assessment of cardiovascular risk factors (family history, smoking, hypertension, hyperlipidemia, insulin resistance)
<p>Annual reviews for all patients with HIV infection</p>	
<ul style="list-style-type: none"> Assessment of immunity to hepatitis B 	
<ul style="list-style-type: none"> Vaccinations 	
<ul style="list-style-type: none"> Cervical cytology by Papanicolaou smear in women 	
<ul style="list-style-type: none"> STI screening for all sexually active men who have sex with men (see guidelines²³) 	

Post-exposure prophylaxis – non-occupational

In cases of exposure (e.g. through condom breakage), non-occupational post-exposure prophylaxis (NPEP) may help patients prevent transmission of HIV to their partners. NPEP involves taking antiretroviral medication within 72 hours of a high-risk exposure to HIV (see Chapter 4). Knowledge of this intervention can help to increase the confidence of people with HIV infection to be sexually active, particularly those in serodiscordant relationships, but must not be promoted as a stand-alone prevention strategy. National guidelines on the use of NPEP for non-occupational exposure are available (see Chapter 4 for details).

Education

The clinician may need to provide the patient with information about HIV disease, monitoring and treatment to facilitate patient participation in health and treatment decisions. Appendix 1 provides a summary of basic information about HIV infection, which may assist the clinician in educating the patient. As concepts are introduced and reviewed, many patients will come to a sophisticated understanding of their infection and natural history.

The clinician has a central role in interpreting test results and providing the patient with an understanding of his or her prognosis. The patient should be aware that CD4 cell counts and viral load can vary from test to test and that trends are more important than absolute numbers. Graphing results over time may be a helpful way of demonstrating the patient's position. While population-based studies have provided an overview of average rates of disease progression, the patient should know that there is no way of predicting the course of HIV disease in individual people. Patient education involves conveying the uncertainties of HIV disease, such as time to disease progression and response to therapy.

Patient education also involves provision of general dietary and lifestyle advice. A healthy, balanced diet, low levels of stress and regular exercise are recommended. Potential drug-related harms and drug interactions with antiretroviral therapy should be discussed.

Resources for health care professionals and positive people

There is a wide range of resources available to support clinicians and patients. ASHM distributes regular bulletins to members and has a website, which is regularly updated, providing information for clinicians and patients. Treatment information for patients is also available from community organisations (Chapter 15). Australian commentary to the locally adopted US DHHS *Guidelines for the Use of Antiretroviral Agents in HIV-1 infected Adults and Adolescents* can be found on the ASHM website : <http://www.ashm.org.au/aust-guidelines>

HIV treatment issues

The aim of antiretroviral therapy is to reduce HIV viral load, prevent HIV disease progression and produce immunological reconstitution. The primary marker of successful therapy is suppression of HIV viral load to undetectable levels.

The effect of potent combination therapy on immune function, survival, AIDS progression and hospitalisation has been dramatic.¹¹ The relationship between viral load and treatment benefit from antiretroviral therapy has been analysed in over 5000 patients enrolled in 18 clinical trials. These studies have shown that:¹²

- Reduction in viral load is associated with improved outcome, with each 1 log (10-fold) reduction reducing the risk of clinical progression by 65%
- Reduction in risk of disease progression or death is independent of baseline plasma HIV-1 RNA and CD4 cell count
- Benefit is independent of the increase in CD4 cell counts secondary to treatment
- Rates of mortality, illness and hospitalisation have fallen significantly

The treatment-induced reduction in viral load is determined by several factors, including the potency of the regimen. Viral load reductions of greater than 2.0 log are expected with first-line combination antiretroviral therapy regimens.

Initiating antiretroviral therapy

The decision to commence antiretroviral therapy is made on the basis of the risk-benefit analysis and the patient's readiness to take treatment. Antiretroviral treatment guidelines, based on expert opinion and available scientific evidence, have been developed to guide decisions about commencing and switching treatment. Australia follows the United States guidelines with an Australian commentary where local issues are relevant. These guidelines are on the ASHM website (www.ashm.org.au/guidelines/).¹³⁻¹⁵

Recommendations prior to 2001 were based on the amount of virus present (>10,000 copies/mL) or an abnormal CD4 cell count (<500 cells/ μ L).¹⁵ However, the increased recognition of the risks of antiretroviral therapy in the form of long-term metabolic toxicities, combined with the realisation that eradication of HIV is unlikely to occur, has resulted in recommendations to delay the initiation of antiretroviral therapy until the CD4 cell count is around 350 cells/ μ L.

The following are indications to begin treatment with combination antiretroviral therapy:

- Symptomatic HIV infection
- Asymptomatic HIV infection with a CD4 cell count below 350 cells/ μ L

The question of when to commence antiretroviral therapy remains a topic of debate among expert physicians and GPs. Some may recommend therapy for a patient with a CD4 cell count greater than 350 cells/ μ L and a viral load greater than 100,000 copies/mL.

Table 10.5 Antiretroviral medications			
<i>*Drug information current at April 2007. See ASHM website (www.ashm.org.au) for updated information.</i>			
Nucleoside/nucleotide analogue reverse transcriptase inhibitors (NRTI)			
NRTI	Dose	Adverse effects	Comments
Abacavir (ABC)	300 mg bd or 600 mg qd	Hypersensitivity reaction	HLA B*5701 screening for abacavir hypersensitivity
Didanosine (ddI)	400 mg qd (>60 kg body weight) 250 mg qd (<60 kg)	Pancreatitis, peripheral neuropathy, nausea, diarrhoea	If used with tenofovir, reduce ddI dose to 250 mg/ 200mg qd
Emtricitabine (FTC)	200 mg qd	Skin discolouration, minimal adverse events	Renal excretion, adjust dose in renal failure
Lamivudine (3TC)	150 mg bd or 300 mg qd	Minimal adverse events, headache	Renal excretion, adjust dose in renal failure
Stavudine (d4T)	40 mg bd (>60 kg) 30 mg bd (<60 kg)	Peripheral neuropathy, pancreatitis, hepatic steatosis, lipodystrophy	
Tenofovir (TFV)	300 mg qd	Headache, nausea, vomiting, diarrhoea, renal insufficiency	
Zidovudine (AZT or ZDV)	250 mg bd	Headache, initial nausea, vomiting, malaise, anaemia, leukopenia, macrocytosis, lipodystrophy, hepatic steatosis, myopathy	
All nucleoside analogues have the potential to cause mitochondrial toxicity and a syndrome of chronic, low-grade lactic acidemia. In a small minority of individuals this may progress to life-threatening lactic acidosis.			
qd: every day; bd: twice a day; tds: three times a day			
Fixed-dose combination NRTI			
Trade name	Component NRTI and doses in each tablet	Daily dose	
Combivir	AZT 300 mg + 3TC 150 mg	1 bd	
Trizivir	AZT 300 mg + 3TC 150 mg + Abacavir 300 mg	1 bd	
Kivexa	Abacavir 300 mg + 3TC 300 mg	1 qd	
Truvada	Tenofovir 300 mg + emtricitabine 200 mg	1 qd	
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)			
NNRTI	Dose	Adverse effects	Comments
Delavirdine	400 mg tds	Rash, headache, abnormal liver function tests	Rarely used in Australia, because of high pill burden and tds dosing
Efavirenz	600 mg qd	Rash, insomnia, vivid dreams, other central nervous system effects, abnormal liver function tests	Contraindicated in pregnancy (potential teratogenicity)
Nevirapine	200 mg qd for first 14 days, then 200 mg bd	Rash (including Steven-Johnson syndrome), abnormal liver function tests to symptomatic hepatitis	Do not use as initial ARV therapy in men with CD4 cells >400 cells/ μ L and women with CD4 cells >250 cells/ μ L. Use with caution in those with cirrhosis

Table 10.5 continued Antiretroviral medications

Drug information current at April 2007. See ASHM website (www.ashm.org.au) for updated information.

Protease inhibitors (PIs)

PI	Dose	Ritonavir dose	Adverse effects	Comments
Atazanavir (ATZ)	300 mg qd	100 mg qd	Indirect hyperbilirubinemia, nausea, vomiting, diarrhoea	ATZ dose without ritonavir 400 mg qd (use only in naïve patients, or those not receiving tenofovir or efavirenz)
Darunavir (DRV)	600 mg bd	100 mg bd	Rash, diarrhoea, nausea, headache	
Fosamprenavir	1400 mg qd 700 mg bd	200 mg qd or 100 mg bd	Rash, nausea, vomiting, diarrhoea	qd dosing in PI naïve (fAPV) patients only
Indinavir (IDV)	800 mg bd	100 mg bd	Nephrolithiasis, nausea, vomiting, diarrhoea, hyperbilirubinemia	IDV can be dosed at 800 mg tds without ritonavir, but must have strict 2 hour windows around food consumption for each dose and must consume >2 litres water daily to prevent nephrolithiasis
Lopinavir/r (LPV)	2 x 200mg lopinavir/ 50 mg ritonavir tablets bd or 4 tablets qd	N/A co-formulated	Nausea, vomiting, diarrhoea, hyperlipidemia	If used in combination with efavirenz or nevirapine in ARV experienced patients – use 3 tablets bd
Nelfinavir (NFV)	1250 mg bd	Not used	Diarrhoea	
Saquinavir (SQV)	1000 mg bd	100 mg bd	Gastrointestinal intolerance, headache	
Tipranavir (TPV)	500 mg bd	200 mg bd	Hepatotoxicity, rash	

All protease inhibitors have the potential to cause hyperlipidemia, insulin resistance, lipodystrophy, abnormal liver function tests and hepatitis.

Entry inhibitors

Entry inhibitor	Dose	Adverse effects	Comments
Enfuvirtide	90 mg bd SCI of bacterial pneumonia,	Injection site reactions, possible increased rate for treatment experienced rare hypersensitivity reactions	Can only be given subcutaneously, indicated patients only

Deferral is generally recommended if a patient's CD4 cell count is greater than 350/μL and viral load is lower than 100,000 copies/mL.

The final decision rests with the patient and clinician in consultation. In making the decision to treat, consideration must be given to the patient's commitment to therapy, his or her awareness of the importance of strict adherence to the regimen, and the potential for adverse effects. Advice regarding the decision can be obtained from the antiretroviral prescriber and a number of sources listed in Chapter 15.

Treatment regimens

There are four classes of approved antiretroviral medications: nucleoside analogue reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and entry inhibitors.

These antiretroviral drugs inhibit one of two viral enzymes—reverse transcriptase or protease or prevent entry of HIV into the CD4 cell. Anti-HIV medications and their side effects are summarised in Table 10.5.

Patients commencing treatment should be started on a combination of either three or four drugs.

Generally, a combination includes drugs from at least two different drug classes. In general, patients initiate treatment either with two nucleoside analogues and an NNRTI, or two nucleoside analogues and a PI. Treatment regimens are developed at the individual level based on dosing requirements, toxicity profiles and co-morbidities.

Assessment of response to therapy

For a patient on treatment, a significant increase in HIV RNA or failure to achieve undetectable viral load requires consideration of the following factors:

- The patient may show poor adherence and changes to the treatment regimen may be required.
- Drug levels may be too low to suppress HIV replication due to drug interactions or poor absorption, requiring dose adjustments or a change in regimen.
- Resistance to the antiretroviral drugs may have developed and resistance assays may be conducted by the antiretroviral prescriber

These tests must be interpreted in the context of the patient's antiretroviral history.

Side-effects and interactions

Side effects of antiretroviral therapy may be early (e.g. headache), persistent (e.g. diarrhoea) or long term (e.g. lipodystrophy).¹⁶ Each antiretroviral drug has its own particular side effect profile with which the primary care clinician should be familiar (Table 10.5).

The patient should be supported through initial side effects, most of which are very common and usually short term (<http://www.medscape.com/resource/hivantiretrovirals>, or <http://aidsinfo.nih.gov/Guidelines/>). Some side effects are life-threatening and necessitate immediate cessation of the medication. These include acute hepatitis, severe rashes including the Stevens-Johnson syndrome (associated with the NNRTIs) and the abacavir-hypersensitivity reaction. This reaction occurs within six weeks of starting abacavir and symptoms include fever, nausea, vomiting, diarrhoea and malaise, with or without rash. Lactic acidosis is a rare adverse event associated with the nucleoside analogues, which may lead to organ failure and death. Usually the antiretroviral prescriber will be monitoring the patient very closely through this phase. If the patient presents to the primary care clinician with a problem, the antiretroviral prescriber should be directly consulted.

Protease inhibitors and nucleoside analogues have been associated with the lipodystrophy syndrome, which develops as a long-term toxicity of antiretroviral therapy. Lipodystrophy syndrome involves:

- Fat gain (particularly visceral abdominal fat)
- Peripheral subcutaneous fat loss in arms, legs, buttocks, face
- Increased serum lipids and insulin resistance

Chapter 6 includes a photograph of the clinical presentation of lipodystrophy (Figure 6.4).¹⁷

It is important to recognise the increased cardiovascular risk in patients with HIV infection, but also in those with insulin resistance and hyperlipidaemia. Appropriate management and attention to other risk factors, such as hypertension and smoking, is required. The Framingham risk evaluation should be carried out annually.

Drug interactions

The potential for drug interactions should also be considered. The PIs and the NNRTIs are metabolised by the hepatic cytochrome P450 3A4 enzymes. The PIs inhibit the P450 3A4 enzymes with varying potency and the NNRTIs can induce or inhibit the enzymes. It is no longer possible to remember all the drug interactions and there are several sources regularly updated that outline predicted interactions and known interactions. Useful websites include: www.hiv-druginteractions.org and <http://www.tthhivclinic.com/>

Always check one of the websites before introducing any new drugs. It is also known that some complementary medicines can cause reductions in PI concentrations (e.g. St John's Wort, garlic pills). The recreational drug ecstasy may also interact with PIs to produce very high levels of ecstasy in the blood and extreme caution should be advised regarding use of recreational drugs by people taking PIs.

Drugs contraindicated with concomitant use of PIs because of potential life-threatening reactions are:

- Terfenadine, astemizole – non-sedating anti-histamines (use loratidine as an alternative)
- Cisapride – prolongation of the Q-T interval, torsade de pointes arrhythmias
- Lovastatin – rhabdomyolysis
- Midazolam, triazolam – prolonged sedation

(It is important to inform anaesthetists about antiretroviral therapy because of the impact on procedures such as endoscopy or bronchoscopy. Propofol is recommended as an alternative.)

Additional contraindications and cautions apply in the case of the PI ritonavir.

Adherence issues

Medication must be taken properly to be effective in the long term. If the patient is regularly missing doses, not following dosing recommendations or has commenced a new medication or complementary medicine which affects the metabolism of the drugs, the reduced concentration of drug allows for the selection of drug-resistant HIV and 'failure' of the antiretroviral regimen.¹⁸ Unfortunately, there is often significant cross-resistance within the same class of antiretroviral drugs¹⁹ and resistance to one drug may undermine response to subsequent regimens. If the patient reports poor adherence, discussion with the HIV prescriber may be appropriate to consider simplification of the antiretroviral regimen to a once- or twice-daily regimen to make adherence easier. Management of side effects may also improve adherence.

In consultation with the patient's antiretroviral prescriber, consider referring the patient for adherence counselling. The AIDS Councils, specialist HIV units and domiciliary nursing organisations conduct adherence counselling.

Immune-based therapies

Immunomodulators are another form of therapy for HIV infection currently under investigation. Subcutaneous interleukin-2 is known to induce significant rises in CD4 cells, but treatment cycles are associated with often incapacitating, short-term side effects.²⁰ The current trials are investigating whether this rise in CD4 cells translates to a clinical benefit in terms of improved survival and reductions in disease progression to AIDS-defining illnesses. Other approaches to immunomodulation under investigation include therapeutic HIV vaccination.

Prophylaxis

When the CD4 cell count falls below 200 cells/ μ L, there is an increased risk of opportunistic infections and prophylaxis is recommended to prevent some common opportunistic infections. Table 10.6 contains the prophylactic regimen of choice and an alternative prophylactic regimen in the event of intolerance or drug allergy, and the CD4 cell count at which prophylaxis is recommended.²¹ For patients who have instituted prophylaxis and then experience immune reconstitution after combination antiretroviral therapy, prophylaxis may be discontinued safely if the CD4 cell count remains above 200 cells/ μ L for at least six months. However, prophylaxis should be recommenced if the CD4 cell count falls below that level again.

AIDS-related illness

Symptoms in the patient with HIV infection should be interpreted in the context of the patient's current and past immune function, current therapy and recent changes in medication or complementary therapy. In patients with normal CD4 cell levels, symptoms may represent community-acquired infections or medication side effects.

Patients who initiate therapy at low CD4 cell counts (less than 100–200 cells/ μ L) may present with 'immune reconstitution' illness. Fever, lymphadenitis, sweats and fatigue may be related to localisation of Mycobacterium organisms to the lymph nodes by a reconstituted immune system. Other common forms of 'immune reconstitution' illness are discussed in Chapter 6.

In immunocompromised patients (CD4 cell count less than 200–250 cells/ μ L), certain symptoms and signs should raise alarm bells and trigger investigation of an HIV-related infection or malignancy. Signs or symptoms which warrant further investigation include: persistent constitutional symptoms of unexplained weight loss, fatigue, malaise, fever, sweats, diarrhoea; skin conditions such as seborrheic dermatitis and eosinophilic folliculitis; respiratory complaints of dry cough and dyspnoea; neurological symptoms of headache, seizure, weakness, numbness, visual disturbances and psychiatric changes including the development of depression, sleep disturbances, memory problems and slowed reaction times or hypomania. If the patient develops unexplained symptoms or signs in the setting of immunodeficiency, it is important to contact an infectious diseases or HIV specialist for referral and guidance on investigation and management.

Summary

Given the long period of clinical latency typically seen in HIV disease, primary care management of HIV disease is often highly appropriate despite the increasing complexity of antiretroviral management. Monitoring of disease progression should focus on clinical, immunological or virological markers of disease progression. Referral to a specialist HIV antiretroviral prescriber (GP or physician) should be made when signs of disease progression occur. Psychosocial management, safe sex education and provision of information and referral are key features of HIV primary management.

TABLE 10.6 Recommended prophylaxis during HIV infection

Opportunistic infection	First-line prophylaxis	Alternative	CD4 cell count
Pneumocystis jiroveci pneumonia	cotrimoxazole 1 tablet qd	dapsone nebulised pentamidine	200 cells/ μ L
Toxoplasmosis	cotrimoxazole 1 tablet qd	dapsone/pyrimethamine	200 cells/ μ L
Mycobacterium avium complex	azithromycin 1200 mg weekly	rifabutin 300 mg qd	50 cells/ μ L
CMV retinitis	ophthalmological review 6 monthly		50 cells/ μ L
Pneumococcal pneumonia	Pneumococcal vaccine		500 cells/ μ L
influenza	influenza vaccine annually		any
tuberculosis (Mantoux positive)	isoniazid 300 mg/pyridoxine for 9 months		any

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