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Long term management of people with HIV

Background
Advances in the treatment of human immunodeficiency virus (HIV) have resulted in sustained improvements in the general health and longevity of people living with the virus. Primary care continues to be predominantly delivered by high caseload general practitioners and specialists, but GPs with limited HIV experience are increasingly likely to have contact with HIV positive patients through shared care arrangements.

Objective
The aim of this article is to review the management of stable patients with HIV and to provide an approach to important elements of their ongoing care.

Discussion
The long term care of people living with HIV is increasingly focused on chronic disease management and health promotion. Specific issues include mental health; drug and alcohol use; sexual and reproductive health; cardiovascular, renal, liver and bone disease; malignancies; and prevention, including immunisation. Treatment side effects such as lipodystrophy and peripheral neuropathy are less common with newer agents, but other toxicities are increasingly recognised. The majority of people living with HIV can be managed in the general practice setting, with specialist support where appropriate.

Management of human immunodeficiency virus (HIV) infection has greatly benefited from the development and introduction of a range of new medications and treatment strategies over the past decade. The use of combination antiretroviral therapy (cART) generally results in rapid and sustained control of HIV viraemia and sustained increase in CD4+ T-cell numbers. With improvements in efficacy of ART, the treatment goal has shifted to suppression of plasma HIV viral load to below the limit of detection of routine assays (<50 copies/mL) in all patients. In most patients virological suppression will be associated with an ongoing increase in peripheral CD4+ T-cell count into the normal range. These advances have greatly altered the prognosis of HIV infected patients, leading to decreased opportunistic infections such as *Pneumocystis* pneumonia and increased longevity.[1] The ongoing care of people living with HIV has increasingly focused on common elements of chronic disease management.

While patients with HIV should have at least intermittent contact with an experienced cART prescriber, many patients prefer to also maintain contact with their usual general practitioner.

Chronic disease management

Many of the challenges of long term management of HIV infection are common to other chronic conditions, and GPs will be familiar with strategies such as the use of recall and reminder systems and Medicare chronic disease item numbers. General practice management plans enable documentation of all relevant health issues, development of action and monitoring plans, clarification of multidisciplinary team care arrangements, and facilitate access to Medicare funded allied health professionals. Supporting long term treatment adherence is a central component of HIV care and is enhanced by good communication and effective collaboration between doctor and patient[2] and the use of multidisciplinary teams.[3,4]

Mental health, cognitive impairment and risk behaviour

Mental health conditions, particularly depression, are common in people living with HIV.[5] General practitioners are ideally placed to provide early detection and management of mental health problems, including development of mental health plans and referral to Medicare subsidised psychology or psychiatry services as required. It is also helpful for HIV care providers to become familiar with local HIV organisations, which provide a range of useful resources, including counselling and peer support groups.

Human immunodeficiency virus associated neurological disease is prevalent in outpatients, ranging from mild forms of cognitive impairment to HIV associated dementia.[6] General practitioners should have a high index of suspicion for cognitive impairment, and after consideration of a trial of antidepressant drug therapy, refer patients with suspected cognitive impairment for formal neuropsychological testing.

Harmful use of drugs and alcohol is common in people living with HIV and may adversely affect treatment adherence and outcomes.[7] Early and appropriate management is critical, and may include brief interventions, counselling or ongoing medical therapy, all of which may be carried out in the general practice setting.[8]

It is important to recognise that HIV infected patients have a lifelong, sexually transmissible infection, which has major impact on sexual relationships and reproduction.[9] The risk of HIV transmission is reduced while on effective cART, but may not be completely eliminated.[10] Patients therefore need to be supported in safer sex practices, especially condom use, and disclosure of HIV status to sexual partners. General practitioners should be aware that a range of assisted reproductive technologies are available for HIV infected patients, and referral should be considered for appropriate patients.

Cardiovascular and metabolic disease

Human immunodeficiency virus itself is strongly associated with an increased risk of cardiovascular events.[11] Several commonly used cART medications, particularly protease inhibitors and abacavir, have been associated with increased risk of cardiovascular events.[12,13]

Because of the increased risk associated with both HIV and its treatment, the management of modifiable risk factors such as hypertension, dyslipidaemia and obesity is critical. Assessment of absolute cardiovascular risk can be undertaken using modified National Heart Foundation of New Zealand cardiovascular risk charts (see *Resources*). As well as indicating the need for therapeutic interventions to reduce risk, these can be used as a motivating tool for demonstrating the risk reduction of various interventions to patients. Nonpharmacological interventions such as smoking cessation and management of diet and exercise should be pursued aggressively. Smoking is a particularly important modifiable risk factor in HIV patients due to higher prevalence in HIV positive populations when compared to the general population. Pharmacological interventions with statins, fibrates, fish oil, antihypertensives, are all used successfully in HIV positive patients, as are oral hypoglycaemics and insulin in patients with HIV and diabetes (*Table 1*). The use of these therapies is complicated, however, by potential interactions with cART medications. Drug-drug interactions should be checked for all new medications and online resources are available to assist (see *Resources*).

Renal disease

Human immunodeficiency virus associated nephropathy (HIVAN) is particularly common in individuals of African descent and usually improves with cART.[14] Renal dysfunction is also associated with the use of tenofovir, a nucleotide reverse transcriptase inhibitor. In some individuals, the use of tenofovir appears to result in defects in proximal tubule absorption, including the development of Fanconi syndrome. These effects are generally reversible with early cessation of therapy, but may result in long term impairment in renal function if treatment is continued. Patients receiving tenofovir should be monitored with creatinine and phosphate every 3–6 months[15] and all patients should have annual assessment of estimated glomerular filtration rate (eGFR) and urinary protein excretion.

Bone disease

Human immunodeficiency virus is associated with osteopenia, osteoporosis and avascular necrosis of the femoral head. With an aging HIV population, bone disease is likely to become more common. Monitoring guidelines have not been established, but annual measurement of calcium, phosphate and 25-OH vitamin D may be warranted. Human immunodeficiency virus is not currently an indication for Medicare subsidised assessment of bone mineral density, but this should be performed in individuals with low 25-OH vitamin D. Although not specifically validated for HIV infected patients, the FRAX fracture risk assessment tool may provide a useful assessment of fracture risk (see *Resources*). At present, dietary and exercise advice, and vitamin D and calcium supplementation are the main preventive strategies, while treatment of established bone disease is similar to that in the general population.

Liver disease

Co-infection with hepatitis B (HBV) and hepatitis C (HCV) occurs at increased prevalence in people with HIV due to shared routes of transmission. All HIV infected patients should therefore be screened at baseline for HBV and HCV. The clinical course of HBV is considerably altered by co-infection with HIV with higher HBV replication, more common progression to cirrhosis and increased liver related mortality.[16] Several antiretrovirals target HBV as well as HIV such as tenofovir, lamivudine and emtricitibine and it is recommended that these form part of the antiretroviral regimen in patients with both infections. Co-infection with HCV is present in up to 8% of HIV infected Australians, with likewise an accelerated progression to cirrhosis and less successful response rates compared to HIV negative patients.[17,18] Reduction of alcohol intake is recommended for patients with either co-infection, as is minimising exposure to medications with known hepatotoxicity.

Table 1. Targets for lipids and blood pressure in patients with HIV

	Clinical status	Target	Intervention	Comments
Fasting serum LDL cholesterol	No known CVD <2 risk factors*	<4.0 mmol/L	Dietary intervention for all patients Consider drug therapy if ≥4.9 mmol/L**	Where drug therapy is indicated, pravastatin or atorvastatin is usually the initial statin of choice due to decreased ARV interactions
	No known CVD ≥2 risk factors*	<3.4 mmol/L	Dietary intervention for all patients Consider drug therapy if ≥4.0 mmol/L**	
	Known CVD	<2.5 mmol/L	Consider drug therapy if ≥3.4 mmol/L	
Triglycerides	Absolute CVD risk of >15% in the next 5 years or 10–15% risk plus – first degree relative with CHD <60 years of age, or – metabolic syndrome	<1.5 mmol/L	Lifestyle +/- drug therapy to meet target	Fibrates or fish oil are the mainstays of therapy for hypertrigylceridaemia
	Lower absolute CVD risk		Consider drug therapy if ≥5.7 mmol/L	
Hypertension#	No known CVD, chronic kidney disease (CKD) or diabetes	<140/90	Lifestyle modification +/- drug therapy to meet target	
	Known CVD, CKD or diabetes	<130/80	Lifestyle modification +/- drug therapy to meet target	

* Risk factors are age (men ≥45 years, women ≥55 years), family history in first degree relative, current smoking, hypertension, low HDL cholesterol (<0.9 mmol/L)
** May not necessarily qualify for Pharmaceutical Benefit Scheme subsidy
# Hypertension guidelines derived from Australian Heart Foundation *Guide to management of hypertension*, 2008
Source: Dube MP, Stein JH, Aberg JA, Fichtenbaum CJ, Gerber JG, Tashima KT. Guidelines for t he evaluation and management of dyslipidemia in human immunodeficiency virus (HIV) – infected adults receiving antiretroviral therapy: Recommendations of the HIV medicine association of the Infectious Diseases Society of America and the Adult AIDS Clinical Trials Group. Clin Infect Dis 2003;37:613–27

Malignancies

As the life expectancy of patients with HIV has increased, the incidence of various cancers has also risen.[19] This is likely due to a combination of the aging of the HIV population and impairment of immune related detection and clearance of malignant cells, even in patients with high absolute CD4+ T-cell counts.[20] Annual Pap tests are recommended for all HIV positive women due to the increased risk of cervical cancer. Human papilloma virus is also implicated in the pathogenesis of anal cancer, but anal Pap smears have not been shown to be an effective anal cancer preventive strategy and are not currently recommended.[21]

Lipodystrophy

Lipodystrophy describes changes to body fat distribution resulting in one or more of central obesity, peripheral and facial lipoatrophy, visceral fat accumulation and 'buffalo hump' fat pads. This abnormal fat distribution is associated with metabolic disease and can be distressing for the patient. Lipodystrophy has been associated with the use of protease inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs), particularly stavudine and didanosine. More recently licensed NRTIs such as tenofovir and abacavir have a greatly reduced risk of lipodystrophy. Patients distressed by the presence of facial lipoatrophy may be referred to a specialist HIV centre for consideration of cosmetic injectable cheek implants.[22]

Peripheral neuropathy

Peripheral neuropathy (PN) is most strongly associated with the use of stavudine, a medication now uncommonly used in Australia. Peripheral neuropathy can develop within weeks of starting therapy and it is more likely to occur in older patients or those who have pre-existing neuropathy.[23,24] Neuropathy may continue to worsen following cessation of treatment and may persist long term.[25] More recently licensed NRTIs have not been associated with PN.

Vaccination

Annual influenza and 5 yearly pneumococcal vaccination reduce infection rates and are recommended for all HIV positive patients regardless of age.[26] Hepatitis B and hepatitis A (HAV) vaccination should be considered in patients without serological evidence of immunity, due to shared transmission routes and consequences of infection. Patients with HIV, especially those with lower CD4+ T-cell counts, are known to respond less well to HBV vaccination. Administration of a double dose of HBV vaccine at regular dosing intervals has been shown to improve response in HIV positive patients.[27]

Patients who do not have a history of chicken pox should be considered for varicella zoster vaccination, although it is not recommended for individuals with CD4+ counts less than 200 cells/μ/L. Live vaccines such oral polio, oral typhoid and yellow fever are not recommended in HIV patients due to the risk of potentiating disseminated active disease, however measles/mumps/rubella vaccine is recommended for patients with CD4 counts above 200 cells/μ/L.[28] Adult diphtheria and tetanus vaccine, inactivated polio, HiB, injectable typhoid and meningococcal vaccines are considered safe regardless of CD4 count.

A summary of recommended investigations and vaccines for people with HIV is shown in *Table 2*.

Table 2. Summary of recommended investigations/vaccines for people with HIV

Investigation	Frequency
CD4 count	3 monthly
HIV viral load	3 monthly
Full blood examination, urea and electrolytes, liver function tests	3 monthly
Fasting cholesterol, LDL, HDL, triglycerides	6 monthly
Fasting glucose	6 monthly
Pap test	Annually
Dipstick urinalysis (if on tenofovir)	Annually
Throat swab for gonorrhoea	3–6 monthly*
First pass urine for chlamydia	3–6 monthly*
Rectal swab for chlamydia/gonorrhoea	3–6 monthly*
Syphilis serology	3–6 monthly*
Vaccines**	
Influenza	Annually
Pneumococcal	5 yearly
Hepatitis B (double dose)	0, 1, 6 months
Hepatitis A	0, 6–12 month booster
Varicella (if CD4 >200)	Baseline

* If sexually active, otherwise annually

** Live vaccines such oral polio, oral typhoid and yellow fever are not recommended in HIV patients

Conclusion

Most HIV patients will have a primary care relationship with GPs and specialists with high HIV case loads, but other medical practitioners are increasingly likely to have some involvement in the care of these patients, for example as part of a shared care arrangement. The focus of HIV care has shifted in recent years toward chronic disease management and health promotion. Primary care settings are well placed to provide the preventive, monitoring and treatment interventions that form the basis for contemporary HIV care.

Resources

- Absolute Cardiovascular Risk Assessment and modified New Zealand Cardiovascular Risk Calculator published in the Heart Foundation Guide to management of hypertension 2008. Available at www.heartfoundation.org.au/Professional_Information/Clinical_Pratice/Hypertension/Pages/default.aspx
- The National Heart Foundation of New Zealand Cardiovascular Risk Chart. Available at www.nzgg.org.nz
- Drug interactions online resource. Available at www.hiv-druginteractions.org
- FRAX fracture risk assessment tool. Available at www.shef.ac.uk/FRAX/.

Conflict of interest: none declared.

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