

Initiation of antiretroviral therapy in the naïve patient

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The current gold standard of triple combination antiretroviral therapy (cART, previously referred to as highly active antiretroviral therapy or HAART) has evolved in the context of significant advances in the understanding of viral dynamics¹ and HIV drug resistance. Early trials of monotherapy with zidovudine demonstrated limited clinical benefit and virological and immunological failure, now known to be due in part to the development of drug resistance. Studies of dual nucleoside reverse transcriptase inhibitors (NRTIs) published in 1996-1997^{2,3} showed improved survival in asymptomatic individuals. Shortly after, the early studies of triple therapy with two NRTIs and a protease inhibitor (PI) demonstrated a reduction in morbidity and mortality in individuals with advanced HIV.⁴

Due to the existence of a latently infected pool of CD4 cells (established early in HIV infection),⁵ currently available antiretroviral therapy is unable to achieve eradication of HIV infection. The current goals of therapy are:

- attaining maximal and durable suppression of HIV replication (as measured by a viral load below the limit of detection)
- restoring and preserving immune function
- reducing HIV-related morbidity
- improving both quality of life and survival
- preventing vertical transmission.

As newer agents with simpler dosing schedules (including fixed-dose combinations) and more favourable toxicity profiles have become available, there has been a shift in emphasis towards early recognition and minimisation of treatment-related toxicities and early intervention with strategies to improve adherence, in order to achieve a durable treatment response.

Despite a plethora of clinical and other data, two critical questions face individuals living with HIV and their clinicians – when to start therapy and which regimen to choose. The discussion below outlines the current consensus approach in Australia which is based on a mix of available clinical trial data and expert opinion.⁶ The Australian commentary⁶ on the US Department of Health and Human Services (DHHS) antiretroviral guidelines⁷ are reviewed regularly in parallel with the review of the DHHS guidelines, and the most recent iteration may be found on the ASHM website (www.ashm.org.au/guidelines/).

7.1 When to start therapy in the individual with chronic HIV infection

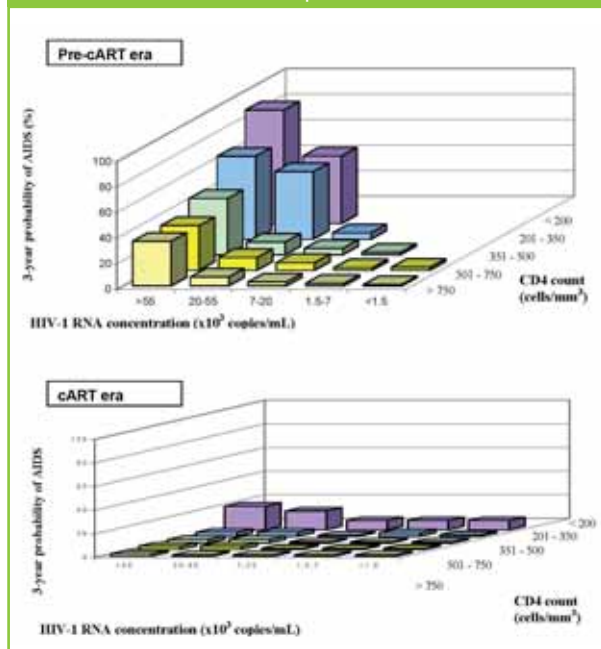
Cohort studies in the pre-cART era⁸ and cART era⁹ demonstrate the enormous benefit in terms of reduction in both mortality and progression to AIDS as a result of cART. These data, summarised in Figure 7.1, in addition to early randomised clinical trials^{10,11} have been pivotal in the development of the

current guidelines. The collaborative analysis by the ART Cohort Collaboration¹² of a number of cohorts followed prospectively has led to the development of online risk calculators which produce personalised estimates of progression to AIDS or death from one to five years after starting cART.¹³ These calculators, applicable to individuals with HIV-1 infection aged at least 16 years, and naïve to antiretroviral therapy, calculate risk of progression either at the time of starting cART or six months later. Current recommendations regarding the initiation of antiretroviral therapy, summarised in Table 7.1⁷ comprise a combination of clinical and laboratory indicators.

7.1.1 Patients with a history of AIDS defining illness or CD4 cell count <350 cells/ μ L

For individuals with a history of an AIDS-defining illness or a CD4 cell count of <200 cells/ μ L (who are at significant risk of opportunistic infections or AIDS-associated malignancies), there is strong evidence from randomised controlled trials¹⁰ and

Figure 7.1 Prognosis according to CD4 cell count and viral load in the pre-cART and cART eras



Note: Kaplan-Meier estimates of the probability of AIDS at three years are shown.

Source: Egger M, May M, Chene G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies *Lancet* 2002;360:119-29. Used with permission.

cART = combination antiretroviral therapy; RNA = ribonucleic acid.

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Table 7.1 Indications for initiation of antiretroviral therapy

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|--|
| All patients with a history of AIDS-defining illness (AI) |
| CD4 cell count <200 cells/ μ L (AI) |
| CD4 cell count 200–350 cells/ μ L (AII) |
| All patients in the following groups, regardless of CD4 cell count |
| (a) Pregnant women (AI) |
| (b) Patients with HIV-associated nephropathy (AI) |
| (c) Patients with HBV co-infection in whom hepatitis B virus treatment is indicated (BIII) |
| Note: CD4 cell count >350 cells/ μ L – the optimal time to start therapy in asymptomatic individuals remains ill-defined: patient characteristics and comorbidities should be taken into account. |
| Source: Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents DHSS, November 3, 2008, Table 5a, p23. |
| Strength of Recommendation A: Strong recommendation for the statement. B: Moderate recommendation for the statement. C: Optional recommendation. |
| Quality of Evidence for Recommendation I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints. II: One or more well designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes. III: Expert opinion. |

cohort studies^{9,14,15} for the initiation of cART, with the outcome of reduction in both mortality and clinical progression.

For individuals with a CD4 cell count between 200 and 350 cells/ μ L the question of the optimal timing of antiretroviral therapy has been more controversial, with recent data suggesting a move back to earlier initiation of antiretroviral therapy. This group, for which no prospective randomised clinical trial addressing the question of initiation versus deferral of cART exists, has previously been the subject of controversy and thus individual clinical practice has varied significantly. More recent clinical studies have provided indirect evidence leading to the current unequivocal recommendation to initiate therapy in this group. Studies by the ART Cohort Collaboration examining prognosis up to five years following initiation of cART demonstrated that the risk of AIDS or death is reduced in those initiating cART at a CD4 cell count between 200 and 350 cells/ μ L versus less than 200 cells/ μ L.¹⁶ At baseline, CD4 cell count, history of injecting drug use and AIDS were most predictive of progression, while after initiation of cART, both the six month CD4 cell count and viral load were prognostic and baseline CD4 cell count no longer had an impact. This would seem to indicate that both virological suppression and immune restoration are important long-term prognostic factors. More recently studies have examined the contribution of non-AIDS diseases to mortality. Analysis of 22 pooled seroconverter cohorts which included over 7500 patients from Europe, Canada and Australia (CASCADE Collaboration)¹⁷ demonstrated that for individuals with a CD4 cell count above 200 cells/ μ L, mortality from non-AIDS illnesses predominates with an inverse relationship with CD4 cell count. Data from the SMART study, a prospective multicentre study involving 5472 patients randomised to either continuous antiretroviral therapy or CD4 cell-guided episodic treatment (ceasing when the CD4 cell count reached 350 cells/ μ L and restarting at 250 cells/ μ L) have also favoured earlier commencement of cART.¹⁸ Analysis of a subgroup¹⁹ within the SMART cohort demonstrated that, for those with a baseline CD4 cell count of greater than 350 cells/ μ L, deferral

of cART (until CD4 cell count of 250 cells/ μ L) was associated with increased incidence of opportunistic diseases as well as non-AIDS clinical events. Together these data make a powerful case for the earlier initiation of antiretroviral therapy.

7.1.2 Patients with a CD4 cell count >350 cells/ μ L

Individuals with a CD4 cell count above 350 cells/ μ L have been shown in a number of studies to be at low risk of progression to AIDS or death,⁹ which provides the rationale for the current recommendation against early therapy. Some disadvantages of early therapy include the need for lifelong therapy, the risk of changes in adherence with consequent development of resistance and concern regarding long-term toxicities. Factors favouring the consideration of early therapy include the prognostic role of viral load,²⁰ theoretical public health benefits related to HIV transmission reduction and potential benefits at higher CD4 cell counts in terms of reduction of non-AIDS illness analogous to the findings of the SMART study.¹⁹

It should be noted that earlier versions of the guidelines have recommended cART for patients with non-AIDS symptomatic disease (such as non-AIDS infections, constitutional symptoms, immune thrombocytopenia). Although these latter groups are not specifically addressed by the current guidelines,^{6,7} where symptomatic illness is present and potentially attributable to HIV infection, cART should be considered even at CD4 cell counts higher than 350 cells/ μ L.

Initiation of cART in individuals with CD4 cell counts above 350 cells/ μ L should take into account the clinical scenario and a risk assessment (including baseline viral load, age, comorbidities and co-infections) of that individual. The clinician will be more likely to recommend cART in the context of a high plasma HIV RNA load (>100 000 copies/mL). It should be noted that gender influences the plasma HIV RNA level²¹ such that women with AIDS have three-fold lower levels of plasma HIV RNA than men. Despite this observation not being reflected in current antiretroviral guidelines, clinicians should be aware of potential gender differences.

Specific situations

(a) Pregnancy

Pregnant women with HIV infection not already on antiretroviral therapy should commence therapy, with the goal of maximising viral suppression and thereby reducing mother-to-child transmission. This is further discussed in Section 7.4.3.

(b) HIV-associated nephropathy

HIV-associated nephropathy, diagnosed by renal histology, most commonly occurs in individuals of African ethnicity and is seen rarely in Australia. Regardless of current CD4 cell count, initiation of cART is associated with improvements in both survival and renal function and should not be deferred.²² Doses of NRTIs other than abacavir need to be adjusted in the context of renal impairment while NNRTIs and PIs require no dose adjustment.⁷

(c) Hepatitis B virus co-infection

Of the currently available antiretroviral agents, emtricitabine, lamivudine and tenofovir all have activity against hepatitis B virus (HBV). Individuals with co-infection in whom therapy for either virus is indicated should commence a regimen

containing tenofovir with either emtricitabine or lamivudine, in order to minimise the risk of development of HBV resistance. The scenario is discussed in Section 7.4.

7.2 Which regimen to use in the individual with chronic HIV infection

There are many published studies of prospective clinical trials of antiretroviral regimens in drug-naïve persons with HIV infection comparing either various three-drug regimens or three-drug versus two-drug regimens. Many of these studies were limited by methodological variability including variable study design (e.g. randomised, controlled or open-labelled or observational), use of virological and immunological surrogate markers as opposed to clinical endpoints; many studies powered for equivalence; lack of stratification of CD4 cell count; and HIV RNA levels in analysis; and inclusion of up to 15% of antiretroviral-experienced individuals in some studies and are therefore not directly comparable.

Given the limitations of the available data, treatment guidelines are general and choice of regimen needs to be individualised, with an emphasis on efficacy, tolerability and durability. The general principles of antiretroviral therapy initiation include the following:

- Prior to initiation of cART – exclusion of active opportunistic infection and institution of prophylaxis as indicated (Table 6.1)
- Review of baseline genotype result – in Australia up to 12% of individuals, especially those recently diagnosed with the infection, may acquire HIV that is resistant to at least one class of antiretroviral agent
- Consideration of comorbidities (such as heart disease, liver disease, psychiatric illness) which may impact on choice due to drug interactions, potential toxicity and impact on adherence
- Consideration of co-infections (such as hepatitis B or C) which may require further evaluation and affect choice of antiretroviral agent
- Convenience of regimen in terms of dosing schedule and pill burden
- Adherence assessment prior to initiation
- Consideration of potential drug interactions (including recreational drugs) and toxicities
- Pregnancy potential or current pregnancy in women of child-bearing age
- Specific factors related to individual antiretroviral agents (such as abacavir – HLA B*5701, nevirapine – baseline CD4 cell count, gender and liver disease)
- Choice of a regimen that is known to be potent i.e. one which includes at least three drugs from at least two classes, generally two drugs from the nucleoside/nucleotide reverse transcriptase inhibitors (NRTI/NtRTI) class and a third from either the non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor (PI) class: in some instances there may be four drugs such as when low dose ritonavir is used to boost another PI
- Choice of a regimen that is currently recommended by the Australian Antiretroviral Guidelines Panel: alternatives to currently recommended therapy should generally only be used in the context of a clinical trial.

7.2.1 The choice of the third drug in a regimen: NNRTI vs PI

Clinical trials have demonstrated potency of both NNRTI- and PI-based regimens.²³⁻²⁵ The choice therefore rests upon consideration of the unique circumstances surrounding the individual to be treated, including the factors listed above. In general once-daily regimens of low pill burden are preferred. Toxicity issues, particularly lipodystrophy, remain a significant concern for many individuals. The majority of people with HIV in Australia have access to a range of information about HIV including choice of cART regimens. Consequently, discussions concerning choice of cART, including the benefits and risks, will be important.

7.2.2 Which NNRTI

While efavirenz and nevirapine are both effective agents,²⁵ other considerations may lead to one or other being the preferred agent. Efavirenz has a convenient, simple dosing schedule, however, in some individuals, neuropsychiatric side-effects prove treatment-limiting. In addition, efavirenz is potentially teratogenic, with cases of neural tube defects being reported in association with first trimester exposure.²⁶ Nevirapine is listed as an alternative rather than preferred agent by the US DHHS Antiretroviral Guidelines Panel due to its association with hepatotoxicity. These concerns are not mirrored in Australia where there is a large body of experience with this drug. The risk of severe hepatotoxicity is increased in women, individuals with liver disease and with higher CD4 cell counts (for women, >250 cells/μL and for men, >400 cells/μL) and can be minimised by attention to these parameters. It is important to initiate nevirapine at half dose (200 mg daily) for 14 days before increasing to full dose and to monitor liver function tests closely i.e. at baseline, two weeks, four weeks then monthly for three months.⁷ Currently recommended first-line regimens are outlined in Table 7.2. A number of antiretroviral agents and combinations should be avoided; these are summarised in Table 7.3.

Table 7.2 Antiretroviral regimens recommended as initial therapy.

| |
|---|
| <p>One of the following NRTI/NtRTI combinations:</p> <p>Preferred tenofovir/emtricitabine[#] (coformulated)</p> <p>Alternative abacavir/lamivudine[#] (coformulated) for patients who test negative for HLA B*5701 or zidovudine/lamivudine[#] (coformulated) or didanosine plus (emtricitabine or lamivudine)</p> |
| <p>Plus one of the following:</p> <p>Preferred NNRTI – efavirenz or nevirapine PI – atazanavir + ritonavir or fosamprenavir + ritonavir (bd) or lopinavir/ritonavir (bd)</p> <p>Alternative PI – atazanavir or fosamprenavir or fosamprenavir + ritonavir (qd) or lopinavir/ritonavir (qd) or saquinavir + ritonavir (qd)</p> |

Note: [#] Emtricitabine may be used instead of lamivudine and vice versa. Efavirenz is contraindicated in pregnancy and child bearing women with high pregnancy potential (teratogenic) and nevirapine is recommended only if CD4 cell count <400 cells/μL in men and <250 cells/μL in women (avoid hypersensitivity reactions).

HLA = human leukocyte antigens; NNRTI = non nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitors; NtRTI = nucleotide reverse transcriptase inhibitors.

| Drug or combination | Reason to avoid |
|-----------------------------------|--|
| Mono- or dual-therapy regimens | Inferior efficacy |
| Triple NRTI/NtRTI regimen | Inferior efficacy |
| stavudine, stavudine + didanosine | Significant mitochondrial toxicity |
| didanosine + tenofovir | Early virological failure Lower CD4 cell increment Rapid selection of resistance |
| emtricitabine and lamivudine | No additive effect Same resistance mechanism |
| stavudine and zidovudine | Antagonistic effect |
| efavirenz in pregnant women* | Potential teratogenicity |

* consider risks and benefits in women of child-bearing potential
Reference: Adapted from Tables 7 and 8, US Department of Health and Human Services Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Washington: US Department of Health and Human Services; November 3, 2008: 1-128. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. (cited February 2008).

NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor.

7.3 Antiretroviral treatment strategies

7.3.1 Acute HIV infection

Improved recognition of the clinical syndrome suggestive of acute HIV infection combined with use of newer diagnostic tests enables early identification of this group of individuals and thus consideration of antiretroviral therapy. At this juncture, it is unknown whether treatment of acute HIV infection results in long-term virological, immunological or clinical benefit.

Following the diagnosis of acute HIV infection, the physician's primary task is to assess the risk of progression to AIDS. Plasma HIV RNA level (viral set point) and CD4 cell count six months after seroconversion are independent predictors of disease progression⁸⁷ and current treatment recommendations (reviewed above) have their origins from these data. Plasma HIV RNA and CD4 cell count at the time of primary infection also provide prognostic information. Data from a Sydney cohort of 53 men with primary HIV infection²⁷ have demonstrated the following significant correlations:

- between the peak, nadir and median plasma HIV RNA levels in the first 30 days and at six to 12 months
- between the nadir and median CD4 cell counts in the first 30 days and at six to 12 months
- between the duration of symptoms during primary infection and CD4 cell count at six to 12 months

There was no association between plasma HIV RNA levels within the first 30 days and subsequent CD4 cell counts. The long-term clinical implications of these findings remain to be determined.

The potential benefits and risks of early antiretroviral therapy are summarised in Table 7.4. Although there is a scientific foundation to the potential benefits of treatment during primary infection, these benefits remain to be demonstrated in clinical studies.

Table 7.4 Summary of theoretical benefits and potential risks of antiretroviral therapy in acute HIV infection (within six months of known seroconversion)

| Benefits |
|--|
| <ul style="list-style-type: none"> • Reduction of the severity of symptoms of acute disease • Alteration of the virological set point thus potentially reducing the rate of disease progression • Preservation of immune function (specifically HIV-specific CD4 and CD8 cell responses) • Reduction of the risk of HIV transmission • Decrease in the rate of viral mutation by ongoing suppression of viral replication |
| Risks |
| <ul style="list-style-type: none"> • Effect on quality of life related to psychological issues associated with treatment and pill burden • Drug toxicity (short-term adverse events and long-term toxicity) • Limitation of future treatment options by development of drug resistance, especially if therapy fails to suppress viral replication • Need for lifelong therapy. |

Published clinical studies of treatment in this setting which evaluate clinical, virological and immunological endpoints largely include small cohorts and are neither randomised nor blinded hence it is difficult to reach definitive conclusions regarding the benefits of early therapy and the merits of particular antiretroviral regimens.

Important points to consider when initiating therapy for acute HIV infection:

- Paucity of evidence, so consider enrolment in a clinical trial
- Consider the possibility of transmitted drug resistance: obtain a genotype test prior to initiation. Should this be delayed or unavailable then consider use of a PI-based regimen on the basis that transmitted drug resistance to NNRTIs is more common
- Choice of agents and goals of therapy are similar to treatment of chronic HIV infection
- Optimal duration of therapy is unknown, but if one extrapolates from treatment interruption studies then lifelong therapy may be indicated.

7.3.2 Induction-maintenance strategies

Treatment simplification by use of lopinavir/ritonavir monotherapy following virological suppression has been examined in a number of studies, with the hypothesis that cheaper and less toxic maintenance therapy could be used without loss of efficacy. Lopinavir/ritonavir, with its high genetic barrier to resistance, is the agent favoured in these studies. While these studies generally show no loss of virological suppression with this strategy, patient numbers are small, study design variable and the follow-up no longer than 48 weeks.^{28, 29} In addition, low level viraemia is more common in the monotherapy arm. A study in Sweden, employing a similar study design but using atazanavir/ritonavir as maintenance monotherapy, was terminated early after five patients developed virological failure.³⁰ At present the data are insufficiently robust to recommend this strategy in routine clinical treatment.

An alternative strategy for induction-maintenance was chosen by investigators in the Forte trial,³¹ where the induction phase consisted of four drugs from three classes with subsequent reduction to a standard three-drug, two-class regimen (the comparator being standard triple therapy). This study demonstrated equivalence in terms of virological suppression at 24 weeks but superiority of the induction-maintenance arm at 32 weeks.

These studies need to be interpreted with caution as patient numbers were small, adherence was not assessed and importantly other contemporary studies have demonstrated greater efficacy.³²

In summary, induction-maintenance strategies – while desirable from the perspective of treatment simplicity and toxicity concerns – can not yet be recommended in routine practice

7.3.3 Treatment interruption

Interruption of antiretroviral therapy may be considered as:

- Short term – generally in the context of intercurrent illness, drug toxicity or lack of drug supply, or
- Long term – frequently patient choice.

Short-term interruptions

Clinical practice points are:

- During an episode of severe acute illness or suspected toxicity, cease all agents
- Planned short-term interruptions (e.g. surgery) – cease all drugs together if they have the same half-life; for an NNRTI-containing regimen (NNRTI have much longer half lives than NRTI or PI) the options are either to cease the NNRTI four to seven days before the NRTI component or alternatively substitute a protease inhibitor e.g. lopinavir/ritonavir for the NNRTI. (Note: in situations where nevirapine is being reinstated following a break, the standard dose escalation protocol should be followed with the two week lead-in at half dose).

Long-term interruptions

Treatment interruption has been suggested as a possible response to many different clinical scenarios, including virological suppression ('my therapy is working so I can have a break'), virological failure ('what's the point continuing?') and attainment of a high CD4 cell count ('I'm no longer at risk'). Based on the results of a number of studies with large cohorts of patients,^{18,33,34} all of which demonstrated increases in mortality, disease progression and non-AIDS illnesses, this strategy is not recommended in routine clinical practice (see also chapter 5).

Patient choice, however, will ultimately be the deciding factor. The following should be considered when counselling a patient who has decided on a break:

- Explanation of evidence against treatment interruption and potential consequences
- Exploration of the reasons behind the decision (there may be an alternative to a break)
- Reinforcement of the need for close clinical and laboratory monitoring as reversion to wild-type virus may be associated with rapid progression
- Confirmation that at the time of interruption the regimen is in fact suppressive (reinstitution of a non-suppressive regimen will be most likely associated with development of resistance).

Case Study 7.1 Should I have treatment for my hepatitis C?

John is a 30-year-old man diagnosed with HIV infection several years ago. He has a longstanding history of injecting drug use (heroin), chronic depression and is hepatitis C antibody positive. He is socially isolated with no contact with family. Although he has never had an AIDS-defining illness, he has required hospital admission on a couple of occasions, most recently with pneumococcal pneumonia in 2004. This episode of pneumonia was a wake-up call for John and he vowed to get his life on track. He attended a local community drug and alcohol treatment centre and was commenced on buprenorphine. Following recovery from the pneumonia his CD4 cell count had fallen from well above 350 cells/ μ L to about 280 cells/ μ L where it remained. At that time John was stable on buprenorphine and was no longer using. He was highly motivated to commence antiretroviral therapy; his doctor agreed and therapy with zidovudine/lamivudine and nevirapine was commenced. He tolerated this without incident and the following year re-enrolled at university. After a couple of years, John returned to the clinic asking whether he could access treatment for hepatitis C. At that point hepatitis C RNA was positive, liver function, blood counts and coagulation were normal. Hepatitis C genotype was 1a. John underwent further review with his physician and formal psychiatric assessment, as a workup for hepatitis C treatment. His viral load was undetectable, so he was switched from zidovudine/lamivudine to tenofovir/lamivudine. His treating physician explained the interaction between zidovudine and ribavirin and the risk of therapy-limiting bone marrow suppression. John was scheduled to commence hepatitis C therapy with ribavirin and pegylated interferon however in the interim he experienced a personal crisis during which time he recommenced using intravenous heroin. He attended a detoxification program and he and his doctor agreed to put the hepatitis C treatment on hold until things had stabilised.

Finally, another context in which treatment interruption is often considered is after pregnancy, in women where the only indication for therapy is prevention of mother to child transmission – this scenario is considered in 7.4 below.

7.4 Antiretroviral treatment in specific clinical scenarios

7.4.1 HIV and hepatitis C co-infection

HIV-hepatitis C virus (HCV) co-infection is increasingly prevalent in Australia, with clinical consequences for both diseases. The rate of progression of liver disease from hepatitis C (see Chapter 21.2) has long been known to be accelerated in the setting of co-infection and a recent meta-analysis demonstrated the risk of cirrhosis to be three-fold higher when compared with an HIV-negative control population.³⁵ Clinical trials of pegylated interferon plus ribavirin (standard of care therapy for individuals with HCV mono-infection) have shown sustained virological response rates of approximately 60-70% for genotype 2/3 and 25% for genotype 1,³⁶ which is the most common genotype in Australia. While these response rates are inferior to those obtained in the setting of HCV mono-infection, all individuals with HIV-HCV co-infection should have a thorough evaluation and be offered HCV therapy if indicated.

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Low-grade abnormalities of liver function tests are common in HCV and HIV infection, regardless of treatment status. A common practical problem facing the clinician following the initiation of antiretroviral therapy in the person with HIV-HCV co-infection is worsening liver function tests. All classes of antiretroviral drugs have been associated with hepatotoxicity.³⁷ Of the NNRTIs, nevirapine is associated with the greatest estimated hepatotoxicity, with two-thirds of the episodes of clinical hepatitis occurring within three months of starting nevirapine.³⁸ This risk however can be significantly reduced by following the guidelines regarding CD4 cell criteria discussed above. As a general rule nevirapine should be used with caution in individuals with co-infection with cirrhosis. In some instances following commencement of antiretroviral therapy, elevation of liver enzymes has been associated with a transient rise in HCV RNA,³⁹ attributed by some to immune restoration disease. At present the relative contributions of hepatitis C and antiretrovirals to hepatic toxicity remain uncertain. A practical approach to this problem includes avoidance of antiretroviral agents with a known association with significant hepatotoxicity and further evaluation of hepatitis C disease (Chapter 21.2). Mild abnormalities in liver function in the setting of HIV infection can be observed, but in cases of severe hepatotoxicity (elevation of enzymes greater than five times normal)³⁷ antiretroviral therapy should be withdrawn. Another potential cause of liver toxicity relates to mitochondrial damage due to NRTIs.⁴⁰ This has markedly reduced in the context of waning use of stavudine and didanosine.

Some specific considerations in antiretroviral therapy in the context of co-infection with hepatitis C include:

- Deciding which virus needs therapy first

- If the individual's HIV infection requires treatment, a regimen with minimal hepatotoxicity should be chosen and liver function monitored carefully
- Beware of specific drug interactions:
 - didanosine and ribavirin – contraindicated because of the risk of lactic acidosis and pancreatitis
 - zidovudine and ribavirin – anaemia
 - abacavir and ribavirin – reduction in ribavirin exposure

7.4.2 HIV and hepatitis B co-infection

Morbidity and mortality related to liver disease secondary to chronic hepatitis B infection in the context of HIV infection are increasing. The diagnosis of HIV-HBV co-infection has implications for the treatment of both infections (see Chapter 21.1). The two viruses, although classified in different families, have a number of similarities in replication pathways including a reverse transcription step (with the reverse transcriptase enzyme being virally encoded) and a number of analogous gene products. As a result, some reverse transcriptase inhibitors are active against both viruses. In addition, as is seen in HCV-HIV co-infection, progression of liver disease from chronic hepatitis B is accelerated with HIV co-infection.⁴¹

Treatment decisions in individuals with HIV-HBV co-infection are predicated upon whether neither, one or both viruses requires treatment. In addition to the usual HIV parameters used in guiding therapy, severity of liver disease, likelihood of response and risk of adverse events should be considered. Detailed treatment algorithms may be found in a recent review of the topic⁴² and also in Chapter 21.1. To date seven agents have been approved by the US Food and Drug Administration

Case Study 7.2 A man with a rash attends his local clinic

A 44-year-old man from Indonesia, previously known to have HIV infection, presented to his local medical officer with an unusual rash. He had no follow-up for HIV since diagnosis and was antiretroviral naïve. His CD4 cell count was 50 cells/ μ L and plasma HIV RNA is over 100 000 copies/mL. Investigation revealed elevated hepatic transaminase levels of twice normal. Hepatitis B surface antigen (HBsAg), hepatitis B envelope antibody (HBeAg) and anti-hepatitis B core antibody (anti-HBcAb) and hepatitis A IgG were detected. Delta antigen and antibody were not detected; HCV antibody was not detected and HCV polymerase chain reaction (PCR) was negative.

His doctor started prednisolone 50 mg daily for the rash, with rapid dose reduction, and two weeks later started Combivir, efavirenz and cotrimoxazole. Fourteen days later, the man developed pain in the right upper quadrant and jaundice. Examination revealed tender hepatomegaly, but no splenomegaly or signs of chronic liver disease. He had oropharyngeal candidiasis. Liver function tests revealed an alanine aminotransferase of 3900 U/L, gamma-GT of 390 U/L, alkaline phosphatase of 97 U/L and bilirubin of 297 μ mol/L. His albumin was 28 g/L and platelet count was 57×10^9 /L. Coagulation was abnormal. A diagnosis of acute exacerbation of chronic hepatitis B was made. The patient's hepatitis B virus (HBV) DNA was 266 pg/ml. His course was complicated by haematemesis and melaena from severe ulcerative oesophagitis, development of hepatic encephalopathy, persistent coagulopathy, and acute renal failure. He died six weeks after commencing antiretroviral therapy.

This man did not have an assessment of the severity of the chronic HBV before starting antiretroviral therapy (which included only a single agent with activity against hepatitis B: lamivudine). In addition, empirical use of prednisolone in this situation should be undertaken with great caution. The course in this man was complicated by the prednisolone withdrawal, which is known to cause a hepatitis flare in patients with HBV infection.

Consideration of antiretroviral therapy in patients with HIV and HBV co-infection should include:

- Assessment of other potential causes of liver disease including non-infectious causes, serology for HCV, hepatitis A virus and hepatitis D virus, and HCV PCR, and assessment of level of HBV replication by quantitative HBV DNA PCR assay
- Liver imaging and coagulation parameters and consideration of liver biopsy to determine degree of necroinflammatory and fibrotic changes present
- Counselling regarding alcohol intake and other hepatotoxic agents
- Advice regarding vaccination for hepatitis A if not immune, safer sexual behaviour and travel advice
- Choice of antiretroviral regimen directed against both HIV and hepatitis B, with avoidance of ritonavir and nevirapine;
- Advice about avoidance of treatment interruption: removal of anti-HBV agents may cause a severe flare in liver disease
- Regular monitoring of markers of liver disease in response to anti-HBV and antiretroviral therapy.

for the treatment of chronic hepatitis B,⁴² including interferon alpha-2b, pegylated interferon alpha-2a, lamivudine, adefovir, entecavir, telbivudine and emtricitabine. In Australia, pegylated interferon alpha-2a, lamivudine, adefovir, telbivudine and entecavir are available under S100 for treatment of hepatitis B.

In situations where therapy for hepatitis B alone is indicated, consideration may be given to treatment with pegylated interferon alpha-2a, which is more effective than standard interferon.⁴² Adefovir is generally avoided due to concerns regarding potential development of HIV resistance (this agent is closely related to tenofovir), nephrotoxicity and recent data showing its inferiority to tenofovir.⁴³ If lamivudine, emtricitabine or tenofovir is chosen it should only be administered in the context of a fully suppressive cART regimen which includes both tenofovir and either lamivudine or emtricitabine. Use of lamivudine alone is well-documented to be associated with the rapid development of resistance mutations to HIV while use of lamivudine in a cART regimen without another agent active against hepatitis B e.g. tenofovir will lead to HBV resistance mutations in 94% of individuals by four years.⁴⁴ While entecavir was initially believed not to have activity against HIV, a recent report showed that its use was associated with a 1 log drop in HIV viral load and selection of the M184V resistance mutation of HIV, thus conferring lamivudine resistance. In light of these data, entecavir should only be used in the context of a fully suppressive cART regimen.⁴⁵ There are at present insufficient data regarding the safety and efficacy of telbivudine in HIV-HBV co-infection.

In situations where therapy for both viruses or HIV alone is indicated, a fully suppressive cART regimen should be commenced, with the NRTI backbone including either lamivudine or emtricitabine and tenofovir.

All patients commencing therapy should be counselled regarding the risks of cessation of HBV active agents as a severe flare of liver disease may result. Liver function should be monitored carefully as immune reconstitution flares may occur. Development of abnormal liver function tests may indicate impending HBeAg seroconversion,⁴⁶ which is readily confirmed by checking HBeAg and eAb.

7.4.3 HIV infection in women

Following the advent of cART, studies of clinical outcome in large cohorts of individuals with advanced HIV infection demonstrated a reduction in mortality and morbidity (as defined by the development of *Pneumocystis jirovecii* pneumonia, *Mycobacterium avium* complex infection or cytomegalovirus retinitis), irrespective of gender.⁴ To date gender has not influenced treatment guidelines; the assumption that treatment is the same in men and women has been implicit. A study published in 2001,²¹ however, challenged this assumption. Sterling and colleagues demonstrated a similar progression to AIDS in men and women over ten years despite a three-fold lower initial median plasma HIV RNA level but similar CD4 cell counts in women compared with men. The precise implications of this study require clarification, as other cross-sectional studies have not shown differences in disease progression based on gender. In addition to the question of optimal timing of antiretroviral therapy in women, there are data to suggest that, despite attendance at health services, uptake of antiretroviral therapy and opportunistic infection prophylaxis is relatively low in women.⁴⁷ Further psychosocial, epidemiological and clinical

studies are needed to examine the potential differences in indications for, and access to, antiretroviral therapy in men and women.

7.4.4 Approach to pregnancy in women with HIV infection

Updated guidelines for antiretroviral therapy in the pregnant woman with HIV and strategies aimed at reducing transmission to the infant are contained in the US guidelines.⁴⁸ A number of cohort studies have ascertained that there is no increase in maternal mortality, progression to AIDS or plasma HIV RNA levels during pregnancy.⁴⁹ Pregnant women have lower CD4 cell counts than when non-pregnant, but the percentage of CD4 cells remains unchanged during pregnancy. Cohort and cross-sectional studies examining the effects of HIV on pregnancy outcome have found only a small increase in spontaneous abortion rates and a possible increase in the risk of intrauterine growth retardation and low birth weight. Outside the setting of advanced HIV disease, there is no increase in the rates of stillbirth, antenatal mortality, infant mortality, gestational diabetes and foetal malformations.⁵⁰

Reported rates of vertical transmission range from 13-40%, but may be reduced to less than 1% with optimal management of pregnancy and delivery. This figure suggests that prevention of vertical transmission may contribute significantly to controlling the HIV epidemic worldwide. Transmission may occur antepartum (transplacental transmission), peripartum (via contact with contaminated blood or body fluids during delivery) or postpartum (breast-feeding). Strategies aimed at reducing transmission need to take into account both the timing of infection (most infections in infants appear to be acquired late in pregnancy or at delivery) and risk factors for transmission. Risk factors include stage of maternal HIV infection (low CD4 cell count, high plasma HIV RNA), maternal cofactors (sexually transmissible infections, chorioamnionitis, poor nutritional state), prolonged rupture of membranes, and breast-feeding. The strongest risk factor for transmission from mother to child is maternal plasma HIV RNA level.⁵¹ In one cohort study, an HIV RNA >100 000 copies/mL was associated with a 41% risk of vertical transmission, 1-10 000 copies/mL was associated with a 17% risk, and less than 1000 copies/mL had a zero transmission rate.⁵² Although this study showed no cases of transmission at lower levels of virus, case reports suggest that there is no absolute level below which there is zero risk of mother-to-child transmission.⁵³

The seminal PACTG 076 study, published in 1994, revealed a 68% (95% CI, 41-82%) relative risk reduction of vertical transmission when zidovudine monotherapy was given to the mother in the antenatal period, intravenously during the intrapartum period and to the infant after delivery.⁵⁴ The pregnant women commenced oral zidovudine after week 20, the infant received six weeks of therapy postpartum, and no breast-feeding occurred. Since then, other studies using various antiretroviral strategies and completed in multiple sites, including developing countries, have been published. They are summarised in Table 1 of the US guidelines.⁴⁸ Strategies used commonly in developed countries such as Australia include cART during pregnancy, postexposure prophylaxis for the infant and avoidance of breast-feeding. As a result, mother to child transmission rates have fallen to under 1%.⁵⁵

7 Initiation of antiretroviral therapy in the naïve patient

The guidelines for the management of HIV infection in pregnancy in Australia recommend triple therapy antiretroviral treatment for the mother, aiming to achieve an undetectable viral load while using the safest combination possible. Preferably the triple regimen should include agents (e.g. zidovudine) which have been used in randomised clinical trials. Zidovudine administered intravenously is added to this regimen during labour, and the neonate receives oral zidovudine postpartum as prophylaxis. Single dose intrapartum nevirapine with or without infant nevirapine is generally avoided due to lack of evidence for additional efficacy and concerns regarding resistance. This strategy is in contrast to that in developing countries where lack of access to cART during pregnancy may mandate this approach.

Most information regarding the safety of antiretroviral agents in pregnancy is gleaned from animal toxicity data, supplemented by anecdote, drug-registry data and some clinical trial data. The majority of antiretroviral agents have not been studied comprehensively in pregnant women. The exception is zidovudine, for which there are considerable pharmacokinetic and safety data in pregnancy. Data indicating the safety of nevirapine, lamivudine, and more recently, abacavir and lopinavir/ritonavir, are also accumulating. In contrast, stavudine plus didanosine have been associated with reports of severe lactic acidosis and hepatic steatosis with or without pancreatitis, and this combination is generally not recommended in pregnancy. The neurological toxicity associated with exposure to efavirenz in animal models, along with case reports of infants born with neural tube defects,²⁶ means it should not be used in pregnancy. Atazanavir is not recommended because of potential kernicterus in the infant secondary to unconjugated hyperbilirubinaemia. Nelfinavir, previously regarded as safe in pregnancy, is now known to contain traces of a process-related chemical that is teratogenic and should be avoided (no longer available in Australia). In every instance, the benefits of antiretrovirals for the mother and the child are balanced against the potential risks to the child. Animal models have also shown bone abnormalities in the foetus from tenofovir exposure, hence tenofovir should be used with care and following expert advice. A detailed summary of antiretroviral drug use in pregnancy including pharmacokinetic and toxicity data may be found in Table 3 of the US guidelines.⁴⁸

Pregnant women with HIV are usually concerned about the effects of antiretroviral agents on the foetus and the neonate. Theoretical concerns about the nucleoside analogues exist because of the effect on mitochondrial DNA. Follow-up of infants treated with zidovudine has not revealed excess neurological or cardiac toxicity. There is also no evidence of growth, neurodevelopmental or immunological deficits. Follow-up to the age of six years has not revealed development of malnourishment.

The mode of delivery as a risk factor for HIV transmission remains unclear, with conflicting evidence regarding the benefits of Caesarean section. Randomised, controlled studies and a meta-analysis of non-breast-fed mother-baby pairs have shown elective lower section Caesarean section to be associated with a 50% reduced risk of vertical transmission. There is additional benefit of reduced risk in pregnant women with low HIV viral loads.⁵⁶ More recent studies have suggested that there may not be additional benefit from elective Caesarean section if

the mother's viral load at the time of delivery is less than 1000 copies/mL and she is receiving cART.⁵⁷

In developed countries where safe alternative formula food is available, breast-feeding is not recommended. No sterilisation method has been shown to be effective and without risk to the infant. The risk of breast-feeding is cumulative. There is no period without risk, and a recent study has shown that mixed feeding is potentially worse than exclusive breast-feeding.

A team approach with health care professionals experienced in the management of HIV and pregnancy should be embraced for the woman with HIV who is pregnant or is contemplating pregnancy. This should include an obstetrician, paediatrician, HIV-experienced clinician (with experience in managing HIV in pregnancy) and a counsellor. Key points in the management of the pregnant women with HIV include:

1. Antiretroviral therapy in the woman

Not on antiretroviral therapy:

- Counselling regarding antiretroviral therapy during pregnancy aimed at reducing maternal plasma HIV RNA and hence risk of transmission
- HIV genotype testing to inform choice of antiretroviral agents
- If there is a clinical indication for antiretroviral therapy in the woman, then it should be started immediately, otherwise antiretroviral therapy is generally commenced after the first trimester
- Some women, whose plasma HIV RNA levels and CD4 cell counts at the time of initiation would not normally indicate need for treatment, may opt to cease antiretroviral therapy after delivery. This question is not adequately addressed by treatment interruption studies, such as SMART, hence these women should be counselled appropriately and monitored closely.

On antiretroviral therapy:

- If pregnancy is diagnosed after the first trimester, continue antiretroviral therapy and ideally include zidovudine in the regimen
- Cease potentially teratogenic agents (e.g. efavirenz) and agents that may be associated with increased toxicity in pregnancy (e.g. stavudine)
- Monitor carefully for efficacy (ongoing virological suppression) and toxicity with frequent measurement of liver enzymes and electrolytes.

2. Mode of delivery

Caesarean section:

- Reduces transmission if no antiretroviral therapy or zidovudine prophylaxis and unknown plasma HIV RNA level
- Reduces transmission where maternal plasma HIV RNA is greater than 1000 copies/mL
- Insufficient data to determine role where maternal plasma HIV RNA is less than 1000 copies/mL, but unlikely to confer additional benefit in reducing transmission
- Decision may be individualised; in situations where maternal plasma HIV RNA is less than 1000 copies/mL women should be counselled regarding the uncertain benefit and known risks.

3. Prophylactic zidovudine therapy to reduce perinatal transmission

Pregnancy

Zidovudine: start between 14 and 34 weeks gestation, continue throughout pregnancy.

Dose

200 mg three times daily, or 300 mg twice daily in combination with other antiretrovirals considered safe in pregnant women.

Delivery

Intravenous infusion zidovudine at 2 mg/kg over one hour, then continuous infusion of 1 mg/kg/hour until delivery.

Post-partum

Oral zidovudine for the infant 2 mg/kg six hourly for six weeks, starting at 6–12 hours after delivery.

4. Post-delivery

Avoidance of breast-feeding

In particular, active support should be given to women from cultural backgrounds where alternatives to breast-feeding are regarded as highly abnormal and who therefore may be under considerable pressure to breast-feed (especially from relatives unaware of their HIV status).

HIV testing in the exposed infant

Maternal antibodies are detectable in infants for up to 12-18 months, hence this test is not used in the early diagnosis of HIV in infants born to mothers with HIV. In children over 18 months of age, HIV antibody testing may be used in diagnosis. The diagnosis of infants with HIV under 18 months of age is made by use of virological assays – either HIV DNA PCR or HIV RNA assays. At birth, nearly 40% of infants with HIV infection will have a positive HIV DNA PCR test while by two weeks postpartum, this proportion rises to 93%. The current paediatric treatment guidelines recommend testing at 14-21 days, 1-2 months and 4-6 months, with some experts also testing at birth.⁵⁸

Case Study 7.3 Maternal and child HIV infection

A 24-year-old woman is diagnosed with HIV infection at antenatal screening when 13 weeks pregnant with her second child. She recalls a prior sexual partner who died suddenly in New York five years ago. Neither her husband nor her three-year-old child has shown any signs of immune deficiency.

Important points in the management of this scenario:

- counselling, support and assessment of the woman, including assessment of her general health, staging of HIV infection (plasma HIV RNA and CD4 cell count), serology for HCV and HBV;
- HIV testing for the husband and three-year-old child – the husband is seronegative and should be re-tested at two to three months, and the three-year-old is HIV antibody positive;
- counselling regarding potential benefits of antiretroviral therapy for the mother and zidovudine prophylaxis for the infant;
- likelihood of transmission to the second child is less than 2% if maternal management is optimised and breast-feeding avoided;
- it is likely that the three-year-old will require opportunistic-infection prophylaxis and antiretroviral therapy dependent on her age-adjusted CD4 cell count and plasma HIV RNA – expert paediatric advice should be sought.

7.4.5 HIV infection in children

Most HIV-specialist clinicians in Australia will rarely, if ever, face the multiple challenges of managing an infant or young child with HIV infection. Ideally management should be directed by a clinician with experience in this area. The recognition of a number of differences in HIV infection between adults and children has led to some specific recommendations in paediatric practice. The US guidelines for the use of antiretroviral agents in paediatric HIV infection provide a comprehensive summary of management issues.⁵⁸ Specific considerations in the management of the child with HIV infection include:

- Perinatal transmission (i.e. known time of infection and immature immune system)
- *In utero*, intrapartum and postpartum exposure to zidovudine and other antiretroviral drugs
- Use of virological assays for diagnosis in infants aged under 18 months
- Differences in monitoring infection and threshold for therapy due to differences in CD4 cell counts, virological responses and clinical progression
- Changes in drug metabolism and clearance with age
- Issues of adherence to therapy, especially in adolescents.

Clinical progression in children

HIV infection in children is markedly more aggressive. One quarter of children who acquire HIV infection by vertical transmission progress to AIDS within the first year (rapid progressors), and the remainder progress to AIDS over five years (slow progressors). Typical early signs include candidiasis, lymphadenopathy, hepatomegaly, splenomegaly, and growth impairment. Common opportunistic infections include *Pneumocystis jirovecii* pneumonia, fungal infections, bacterial infections (particularly with encapsulated bacteria), mycobacterial infection and recurrent herpes zoster. The

Table 7.5 Indications for initiation of antiretroviral therapy in children

| Recommendation | Criteria |
|--------------------|--|
| Treat | <ul style="list-style-type: none"> • <12 months of age: all regardless of clinical, immune or virologic parameters • 1 to <5 years: AIDS or significant symptoms or CD4 cell count % <25 • ≥5 years: AIDS or significant symptoms or CD4 cell count <350 cells/μL |
| Consider treatment | <ul style="list-style-type: none"> • 1 to <5 years: asymptomatic/mild symptoms and CD4 cell count % ≥25 and VL ≥100 000 HIV RNA copies/mL • ≥5 years: asymptomatic/mild symptoms and CD4 cell count ≥350 cells/μL and viral load ≥100 000 HIV RNA copies/mL |
| Defer | <ul style="list-style-type: none"> • 1 to <5 years: asymptomatic/mild symptoms and CD4 cell count % ≥25 and viral load <100 000 HIV RNA copies/mL • ≥5 years: asymptomatic/mild symptoms and CD4 cell count ≥350 cells/μL and viral load <100 000 HIV RNA copies/mL |

Source: Guidelines for the use of Antiretroviral Agents in Pediatric HIV Infection (cited July 29 2008). Available at: <http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf>

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progression risk at given CD4 cell count levels in children over five years of age equates to that of adults. Due to the risk of rapid clinical progression, antiretroviral therapy is recommended for all infants with HIV infection aged under 12 months.

CD4 cell count in children

Children naturally have considerably higher and more variable CD4 cell counts than adults. As a result, the CD4 cell thresholds used to gauge the risk of opportunistic infection and progression have been adapted to the immunological development of infants and children with HIV infection. In addition, in children under the age of six years, CD4 cell percentage is more reliable than CD4 cell count.

Plasma HIV RNA in children

In infants who acquire HIV perinatally, the mean plasma HIV RNA level in the first year of life is 185 000 copies/mL, while rapid progression and death has been predicted by plasma HIV RNA >299 000 copies/mL. There may be overlap in levels between those who progress rapidly versus slowly. Regardless of plasma HIV RNA level, a CD4 cell count of less than 15% is highly predictive of disease progression and death.

Antiretroviral drug treatment recommendations in children

Specific recommendations regarding therapy initiation in children are summarised in Table 7.5. Regardless of the manufacturers recommendations, the current US guidelines state that all antiretroviral agents approved for use in adults may be considered in children. Currently recommended regimens for children include two NRTIs with either a PI (lopinavir/ritonavir (preferred) or ritonavir-boosted fosamprenavir (alternative, children under six years of age)) or NNRTI (efavirenz (preferred) or nevirapine (alternative under three years of age)).

7.4.6 HIV and dementia

In the cART era, new diagnoses of HIV-associated dementia are seen less frequently while prevalence has increased due to increased survival.⁵⁹ In addition the number of individuals presenting with minor cognitive deficits, with multiple predisposing factors including HIV-HCV co-infection, and drug and alcohol use, is increasing. Dementia in the context of HIV is reviewed in detail in Chapter 18.

Some key points to consider:

- dementia may be seen in individuals on cART as well as those who are treatment naïve or have ceased cART
- late commencement of cART and failure to recognise dementia are likely to be significant factors
- thorough evaluation (neuroimaging, neuropsychological testing and cerebrospinal fluid (CSF) examination) is indicated to exclude other causes and confirm the diagnosis
- cART improves the cognitive impairment due to HIV-associated dementia⁶⁰
- consideration should be given to the use of antiretroviral agents which penetrate the central nervous system (Table 7.6)⁶¹
- rarely, differential patterns of resistance mutations may be seen in plasma versus CSF⁶²
- individuals with HIV-associated dementia often have a very slow response to therapy over months rather than weeks
- during this time it may be necessary to institute directly observed therapy in a supported environment

- cognitive impairment is frequently associated with poor medication adherence

7.4.7 HIV and drugs of dependence

The prevalence of HIV infection in injection drug users in Australia, assuming no other risk factors for acquisition, is approximately 2%. Despite the relatively low numbers involved, the management of HIV infection in this group presents unique challenges.

Clinical implications

CD4 cell count and plasma HIV RNA provide prognostic information⁶³ and progression does not appear to be influenced by means of acquisition of HIV infection.⁶⁴ A range of infections occurs more commonly in injecting drug users with HIV infection,⁶⁵ including:

Table 7.6 Antiretroviral agents with significant central nervous system penetration

| |
|--|
| Nucleoside reverse transcriptase inhibitors |
| • zidovudine • stavudine • emtricitabine |
| • lamivudine • abacavir |
| Non nucleoside reverse transcriptase inhibitors |
| • nevirapine • delavirdine • efavirenz |
| Protease inhibitors |
| • indinavir • atazanavir/ritonavir |
| • fosamprenavir/ ritonavir • lopinavir/ritonavir |
| • atazanavir |

References:

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- Lanoy E. Improvement of survival after a neurological AIDS-defining event over time. Eleventh European AIDS Conference, 2007, Madrid, Abstract PS1/3.

Case Study 7.4 Patient with short-term memory loss

A 56-year-old man presents with short-term memory loss and a generalised epileptic fit. HIV is diagnosed and no opportunistic infection or other contributing factor is identified on brain-imaging studies. He lives alone, is dishevelled in appearance, and has lost weight recently.

Management of this man includes:

- baseline screening for dementia, and assessment of the severity of dementia, using formal neuropsychological testing
- assessment of cerebrospinal fluid HIV RNA, MRI and surrogate markers (CD4 cell count, plasma HIV RNA)
- choice of antiretroviral regimen including zidovudine (proven efficacy in HIV-associated dementia) as well as other agents with demonstrated penetration of central nervous system
- consideration of directly observed therapy with agents which may be dosed once-daily
- monitoring of clinical, radiological and cerebrospinal fluid response to therapy, including HIV RNA in both plasma and cerebrospinal fluid and consideration of compartmentalisation of resistant virus in the central nervous system if response is suboptimal.

Table 7.7 Antiretroviral-methadone interactions

| Antiretroviral | Interaction | Recommendations |
|--------------------------------------|--|--|
| efavirenz | Efavirenz decreases methadone C _{max} and AUC by mean 60% in PK study of patients on methadone maintenance. Symptoms of opiate withdrawal have been reported from 4 days to 4 weeks after the introduction of efavirenz. | Monitor for symptoms of opiate withdrawal and increase methadone dose as required PK study: increase methadone dose in increments of 10 mg until symptoms resolved (22% mean increase in methadone dose required) |
| nevirapine | Nevirapine decreases methadone AUC by mean 50% in PK study of patients on stable methadone dose. 30% of 45 patients in a prospective study of IV drug users on methadone maintenance required increase in methadone dose. | As for efavirenz (above). In PK study 16% mean increase in methadone dose required. Other case reports have required increase of 33% and 100% in methadone dose. |
| amprenavir | Preliminary data from PK study: decreases AUC methadone 12-24% | Combination appears safe based on preliminary data |
| atazanavir | Small PK study showed no effect and no symptoms of opiate withdrawal observed. | Can be used safely in combination without dose adjustment. |
| darunavir/ ritonavir [#] | No data however ritonavir known inducer of methadone metabolism. | Monitor closely and increase methadone as clinically indicated. |
| fosamprenavir/ ritonavir | PK study showed decrease AUC and C _{max} by 20% for active methadone and 40% for inactive methadone. No change in fosamprenavir or opiate withdrawal. | Combination appears safe without modification. |
| indinavir | No significant effect of indinavir on methadone AUC when compared with historical controls in PK study. No significant effect of methadone on indinavir AUC, but increase indinavir C _{min} 50-100% and decrease indinavir C _{max} 16-36%. (All historical controls) | Combination appears safe. |
| lopinavir/ ritonavir | Lopinavir/ritonavir decrease methadone AUC and C _{max} ~50% in PK study of healthy volunteers on methadone. | Monitor for symptoms of opiate withdrawal and increase dose if necessary. |
| ritonavir/ saquinavir | PK studies have demonstrated a clinically insignificant decrease in unbound methadone levels, and there was no evidence of opiate withdrawal. There has been one case report of opiate withdrawal requiring an increase in methadone dose. | Monitor for symptoms of opiate withdrawal and increase dose if necessary. |
| tipranavir/ ritonavir | PK study showed large (50%) decrease in methadone levels. | Dosage of methadone may need to be increase. |
| abacavir | No significant change in C _{max} , half-life or renal clearance of methadone despite slight increase in methadone clearance by abacavir. Slight delay in rate but not extent of abacavir absorption by methadone. | Combination appears safe. |
| didanosine, stavudine | PK study demonstrated d4T AUC decrease 23% and ddI AUC decrease 57%. Effect predominantly related to reduced bioavailability. | No data to guide dose adjustments. Monitor for virological failure. |
| zidovudine | Two PK studies have demonstrated zidovudine AUC increase 29-43%. | Monitor for zidovudine related toxicities. |
| etravirine | Small interaction study showed no significant effect. | No need for dose adjustment of either agent. |
| tenofovir | PK study showed no change in kinetics of methadone. | Combination appears safe. |
| maraviroc | No data, potentially safe in combination. | Monitor clinically. |

AUC = area under the curve; PK = pharmacokinetics; C_{max} = maximum concentration achieved; C_{min} = trough concentration.

References: Adapted from table of antiretroviral-methadone interactions, Tony Antoniou and Alice Tseng, 30 July 2007. Available at http://www.ahrn.net/library_upload/uploadfile/file1822.pdf (cited February 2009)

[#]Adapted from Table 22a Drug interactions among antiretrovirals and other drugs: PIs and maraviroc. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. Department of Health and Human Services. November 3, 2008 1-128. Available at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&Search=Off&GuidelineID=7&ClassID=1> (Cited February 2009).

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- bacterial infections (e.g. septicaemia, infectious endocarditis and pneumonia)
- sexually transmissible infections (especially in sex workers)
- tuberculosis
- co-infection with HBV or HCV

In addition, regular or intermittent use of illicit drugs may complicate assessment of psychiatric symptoms or confusional states.

Treatment implications

Social disadvantage, psychiatric co-morbidity, previous incarceration, and a history of sex work are common associations of HIV infection in injecting drug users. These circumstances impact on interactions with health care professionals, health care delivery and adherence to antiretroviral therapy. It is important to approach these individuals in a non-judgmental manner, in order to develop a relationship based on trust and mutual respect. Studies have demonstrated decreased uptake of antiretroviral therapy and higher use of non-cART regimens in injecting drug users. Initiation of cART has been associated with decreased use of injecting drugs and concurrent methadone.^{66,67}

Drug interactions in methadone- and buprenorphine-treated individuals receiving cART are an important consideration. (Tables 7.7 and 7.8) Concomitant use of zidovudine and methadone results in a 40% increase in zidovudine exposure, but does not affect methadone levels; thus, a dose reduction of zidovudine may be indicated.⁶⁸ Methadone is metabolised by the cytochrome p-450 system and would be expected to interact with PIs and NNRTIs.

While there are no clinical data on the interaction of methadone with the PIs, concomitant nevirapine and methadone administration has precipitated withdrawal symptoms. Stabilisation necessitates a substantial increase in methadone dosage.⁶⁹ Attention to potential drug interactions and education of the individual regarding the possible outcomes are required.

Harm minimisation strategies

Minimisation of risk to the individual and the community is the basis of the public health approach to HIV infection. Rates of transmission of HIV infection among injecting drug users can be reduced through needle-exchange programs, access to drug rehabilitation and education regarding sexual transmission.

Thus, optimal management of the injecting drug user with HIV infection includes a combination of specialist HIV care and expertise, and facilities for drug rehabilitation.

7.4.8 Interactions between recreational drugs and antiretroviral therapy

Information regarding current use of recreational drugs should be sought by the clinician at baseline and at regular intervals thereafter. It is important for patients to have an understanding of the (potentially dangerous) interactions between recreational drugs that are intermittently used and the antiretroviral drugs that are taken regularly. Table 7.9 summarises demonstrated and theoretical interactions between recreation drugs and antiretroviral agents. The recent increase in use of crystal methamphetamine in men who have sex with men in Australia is worth particular mention. Associated phenomena

Case Study 7.5 Man on methadone therapy

A 43-year-old man with a history of injecting drug use and heroin addiction currently maintained on methadone therapy presents for initiation of anti-HIV therapy. His HIV infection was diagnosed eight years previously. He has monitored his surrogate markers infrequently. In recent months he has noted increasing lethargy, weight loss and cough. He currently lives in a boarding house however he has been attacked on a number of occasions and has resolved to move out. His plasma HIV RNA is above 100 000 copies/mL and CD4 cell count 210 cells/ml (14%).

Considerations when initiating therapy include:

- assessment for occult infection (e.g. endocarditis, pneumonia, tuberculosis)
- status of hepatitis infections and vaccination
- address housing issue – referral to social worker or housing agency
- formal adherence assessment and plan to support adherence when commences therapy
- resistance testing if possible
- consideration of drug-drug interactions with methadone (e.g. nevirapine in the cART regimen will require an increase in methadone dose)
- assessment of social supports, and access to harm minimisation strategies.

Table 7.8 Interactions between buprenorphine and antiretroviral agents

| Mild-moderate enzyme inhibitors | Potent enzyme inhibitors | Enzyme inducers |
|---|---|---|
| atazanavir efavirenz fosamprenavir indinavir nelfinavir saquinavir | lopinavir/ritonavir ritonavir | efavirenz nevirapine tipranavir |
| Potential increase in narcotic concentration | Potential increase in narcotic concentration | Potential decrease in narcotic concentration |
| atazanavir: reports of opiate excess when used in combination, increase BUP levels, no significant change in ATV levels. Initiate BUP slowly and at reduced dose; if on BUP consider dose reduction when initiating ATV | lopinavir/ritonavir: addition not associated with significant change in AUC for BUP and clinical status unchanged | efavirenz: addition associated with 50% decrease in AUC of BUP, but no clinical evidence of opiate withdrawal. No effect on efavirenz |

Reference: Adapted from Drug interaction tables on the www.hiv-druginteractions.org website, University of Liverpool, http://www.hiv-druginteractions.org/frames.asp?drug/drg_main.asp (accessed March 2009)

BUP = buprenorphine; ATV = atazanavir; AUC = area under the curve.

Table 7.9 Interactions between antiretroviral and recreational drugs

| Drug | Interactions | Recommendations |
|---|--|--|
| Amphetamines | Possible increase levels with ritonavir | Avoid combination with RTV if possible. If not, start with 1/4 – 1/2 of initial amount of amphetamine taken |
| Codeine | Due to different pathways of metabolism may increase or decrease morphine levels | Monitor for signs of opiate toxicity or withdrawal |
| Gamma hydroxybutyrate (GHB) (Fantasy) | Possible increase levels/prolonged effect with antiretrovirals, especially RTV | Use cautiously with inhibitors of cytochrome P-450 (PIs, efavirenz). Users should be aware of signs/symptoms of GHB toxicity (e.g. seizures, respiratory depression) |
| Ketamine | Possible increase levels with antiretrovirals, especially RTV, NFV and EFV | Use cautiously with cytochrome P-450 inhibitors. Users should be aware of signs/symptoms of ketamine toxicity (e.g. hallucinations, respiratory depression) |
| Lysergic acid diethylamide (LSD) | Unknown | Use cautiously with cytochrome P-450 inhibitors. Users should be aware of signs/symptoms of LSD toxicity (e.g. hallucinations, psychosis, agitation) |
| Methylenedioxy-methamphetamine (MDMA) (Ecstasy) | Possible increase levels with RTV. Two deaths have been reported | Avoid combining with ritonavir if possible. If not, reduce MDMA dose by about 1/4 – 1/2 of usual amount used, and watch for signs of MDMA toxicity. Other precautions include staying well hydrated, avoiding alcohol and taking breaks from dancing |
| Oxycodone | Due to different pathways of metabolism may increase or decrease levels of active metabolite oxymorphone, resulting in possible opiate withdrawal or toxicity | Monitor for signs of opiate withdrawal or toxicity |
| Phencyclidine (PCP) | Possible increase levels with antiretrovirals | Use cautiously with cytochrome P-450 inhibitors. Ensure patient aware of signs/symptoms of phencyclidine toxicity (e.g. seizures, rhabdomyolysis, hypertension, hyperthermia) |
| Tetrahydro-cannabinol (THC), active moiety of marijuana, hashish and hash oil | Drugs which inhibit CYP3A4 or 2C9 (PIs) may increase THC concentrations. Drugs which induce CYP3A4 (EFV, NVP) may decrease THC concentrations. A randomised trial of the effects of cannabinoids on the pharmacokinetics of IDV and NFV: smoked THC decrease NFV AUC by 17%, and decrease IDV Cmax 21% | There have been no reports documenting adverse events secondary to the combination of THC and protease inhibitors despite the wide use of THC derivatives as antiemetics and appetite stimulants |

AUC = area under the curve; EFV = efavirenz; IDV = indinavir; NFV = nelfinavir; NVP = nevirapine; RTV = ritonavir.

Reference: Adapted from Antoniou T, Tseng A. Postulated and actual interactions between recreational drugs and antiretrovirals, 19 July 2002. Available at http://www.aidsctc.org/aidsctc?page=cm-314_rec_drugs. (cited February 2009)

and complications of use of this drug are well summarised elsewhere.⁷⁰ Although formal data regarding drug interactions are not available, methamphetamine is likely to be potentiated by ritonavir in a similar manner to methylenedioxymethamphetamine (MDMA). Patients should be advised to reduce the dose of crystal methamphetamine to one quarter to one half of normal. There is one report in the literature of an individual in Melbourne whose death was suspected to be due to the combination of methamphetamine use with concurrent antiretroviral therapy which included ritonavir.⁷¹

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