

Antiretroviral therapy

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5.1 Historical perspective

Since the introduction of zidovudine (AZT) in 1987, the approach to the management of HIV infection has undergone constant evolution. Zidovudine monotherapy was embraced enthusiastically, not only for patients with advanced disease,¹ but also for those who were asymptomatic with CD4 cell counts below 500 cells/ μ L.^{2,3} However, extended follow-up demonstrated that monotherapy failed to extend survival or improve outcomes in the long term.²

In 1995, the licensure of protease inhibitors (PIs) and the successful use of combination antiretroviral therapy (cART, previously known as highly active antiretroviral therapy or HAART) brought new hope. For the first time, therapy was able to achieve a reduction in viral load to below the limits of quantification of plasma viral load assays.^{4,5} This heralded the era of 'hit hard, hit early' as viral replication studies and mathematical modelling appeared to indicate that eradication of HIV might be possible.⁶⁻⁸

The hope of eradication of HIV was discarded with the recognition of latently infected T lymphocytes with an extremely long half-life (ranging from 6.4 to 44.2 months).⁹⁻¹¹ These cells are able to archive virus that can later re-emerge and propagate after the cessation of antiretroviral therapy. The existence of this cellular reservoir prevents the eradication of HIV with currently available antiretroviral therapy. As a result, cART must be continued indefinitely to maintain virological suppression.

Despite its inability to eradicate HIV, cART has revolutionised the treatment of HIV. Patients on cART have experienced reductions in viral load and increases in CD4 cell counts which translate into improved clinical outcomes and a dramatic reduction in patient mortality from AIDS-related illness.^{12,13} Not only are CD4 cell numbers increased, but there is also evidence of partial restoration of immune function, which allows the safe withdrawal of prophylactic therapy for several opportunistic infections (OI) including *Pneumocystis jirovecii* pneumonia, *Mycobacterium avium* complex infection and cytomegalovirus retinitis in patients who have significant CD4 cell count rises and remain on cART, even in those patients with prior history of these OI.¹⁴⁻¹⁶

Because of the success of cART, patients are remaining on antiretroviral therapy for longer periods and increasing numbers of patients are receiving at least three or more drugs for long periods of time. Between the late 1990s and 2007, the pendulum swung away from the 'hit hard, hit early' approach towards treating asymptomatic antiretroviral therapy-naïve patients at lower CD4 cell counts. This was because of increasing recognition of the morbidity – and in some cases mortality – associated with short, medium and long-term toxicities of

cART including the HIV lipodystrophy syndrome.¹⁷ It was felt that these toxicities, coupled with the inability to eradicate virus, had to be balanced against the gains secondary to cART when used at CD4 cell counts which were OI-protective. Up until 2007, the antiretroviral guidelines^{18,19} recommended that cART should be given to asymptomatic patients with CD4 cell counts <200 cells/ μ L and offered to asymptomatic patients with a CD4 cell count of 201-350 cells/ μ L; symptomatic patients should commence cART irrespective of their CD4 cell count. In December 2007, the recommendation to initiate therapy in asymptomatic individuals with CD4 cell counts <350 cells/ μ L came into force. The rationale for this recommendation in asymptomatic individuals arose from data gathered from large cohort studies. These data suggested that starting cART at 350 cells/ μ L would be associated with even better clinical outcomes, especially as fears over cART-related toxicities wane.

Over the past five years, cohort studies have shown a change in the pattern of morbidity and mortality in individuals with HIV infection. Although life expectancy has increased enormously as a consequence of cART use in the developed world, increasing morbidity and mortality from cardiovascular disease (CVD), liver cirrhosis and malignancy has been reported.²²⁻²⁵ As certain types of cART, particularly protease inhibitor containing regimens, were initially thought to be responsible for the increasing incidence of CVD disease, a number of structured treatment interruption studies were conducted which aimed to explore the equipoise between immune preservation, virological suppression and cART-related morbidity and mortality in patients on continuous cART versus those receiving intermittent use of cART i.e. with less overall exposure to cART. The most important of these studies was the SMART study, which enrolled 6000 patients with current CD4 cell counts above 350 cells/ μ L and randomised them to continuous cART or intermittent CD4 cell-guided cART.²⁶ The study was halted early due to the excess of OI, CVD, liver cirrhosis, end-stage renal disease, malignancy and mortality in the intermittent treatment arm.²⁶⁻²⁸ The SMART study investigators concluded that intermittent antiretroviral therapy guided by the CD4 cell count, as used in this study, significantly increased the risk of opportunistic disease or death from any cause, as compared with continuous antiretroviral therapy. This increased risk was thought to be related to CD4 cell decline and viral rebound. In addition, intermittent antiretroviral therapy did not reduce the risk of adverse events that have been associated with antiretroviral therapy.

The recently updated 2008 US Department of Health and Human Services (DHHS) guidelines with Australian commentary have been amended in light of these and other data, and now recommend that cART be started at CD4 cell counts of \leq 350 cells/ μ L in asymptomatic individuals.²⁹ These recommendations have not yet been embraced in the guidelines for resource

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poor settings although there is mounting data showing better outcomes with earlier therapy in that setting.³⁰ Moreover, once cART is started it should be continuous and life long. Starting cART at higher CD4 cell counts with a view to life long therapy does seem more achievable in 2008 as there are 24 licensed drugs in five classes of antiretroviral agents. Moreover, many of the new classes of agents appear, at least in the short term, to be free of many of the toxicities including metabolic disturbance associated with increased risk of CVD.²⁴ Many of the newer drugs are better tolerated than the earlier licensed compounds and have low pill burden because of coformulation.

However, the current DHHS guideline recommendations concerning when to start cART are not based upon data from randomised clinical trials, but are gathered from cohort studies with their inherent bias and confounded nature. The persistent uncertainties around when to start therapy, form the rationale for the commencement in 2008-9 of a large randomised study (START).³¹

5.2 Goals of therapy

Eradication of HIV is not achievable with currently available antiretroviral agents, and management must focus on attempting to control HIV replication with chronic suppressive therapy. Attempts to eradicate the latent reservoir by using antiretroviral agents in combination with anti-CD3 (OKT3 – a T lymphocyte-specific antibody) and interleukin-2 (a chemokine which stimulates T lymphocyte proliferation) have also been unsuccessful.³² However, there is interest in exploring the impact of using integrase inhibitors and chemokine receptor (CCR5) blockers in very early seroconversion in order to reduce the size of the viral reservoir, without any real expectation of complete eradication.³³

cART is able to reduce plasma HIV viral load to below the limits of quantification (LLQ) of licensed tests.^{4,5} The definition of below LLQ has moved as the tests become more sensitive, and the DHHS guidelines now recommend suppression to levels of <50 copies/μL.²⁹ This level of suppression in viral load is associated with statistically significant improvements in survival and clinical outcome. Recent data have shown that immune restoration continues for many years post cART commencement.³⁴ Predictors of poorer immune restoration include older age, longer duration of HIV-infection, lower baseline CD4 cell count, prior AIDS,³⁴ and persistent immune activation.³⁵ The increase in CD4 cell count is usually related to the amount of viral suppression, although sustained rises in CD4 cell counts have been observed in individuals with incomplete virus suppression, the so called discordant immune response. In contrast, up to one third of patients on cART fail to immune restore to the expected levels despite full virological suppression.^{34,36}

The goal of therapy, therefore, is maximal and durable suppression of viral load, and restoration and preservation of immunological function to improve quality of life and reduce HIV-related morbidity and mortality. Ideally, this goal would be achieved without any increase in morbidity or mortality from drug-related adverse events. Unfortunately, this is currently not always possible and much of the current management of patients with HIV disease involves managing therapy-associated toxicities. The latter is especially true of patients with multidrug resistance traditionally defined as triple class resistance i.e. to nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI), in whom viral suppression and

immune preservation are a far greater immediate priority than cART-associated toxicity.

Other factors to consider to achieve these goals, particularly in antiretroviral therapy (ART)-naïve patients starting therapy include maximising adherence to the antiretroviral regimen, rational sequential use of drugs to preserve future treatment options, and the use of resistance testing. Adherence to often more complex regimens with higher pill burden in patients with multidrug resistant virus has not been as well studied as it has been in the naïve population, and should be a focus of further research.

Clearly, ART is associated with side-effects. However, the risks of therapy need to be weighed up against the benefits when considering the commencement of therapy, and when selecting the component drugs in a patient's regimen. A patient's ability to adhere to a regimen is critical for successful treatment. Ninety to ninety-five percent adherence to therapy is required for unboosted PI regimens, (although this level of adherence is probably not required for NNRTI regimens, where greater than 70% is probably sufficient), as levels of adherence below this are associated with poor virological and immunological response, resulting in increased hospital admission days and increased risk of disease progression.^{37,38} Poor adherence leads to the development of drug resistance, further limiting the effectiveness of therapy. It is therefore important to consider factors such as toxicity, pill burden, dosing schedule (i.e. no more than twice a day), and dietary restrictions which may affect the ability of a patient to adhere to a given regimen. Other important factors include co-infection with hepatitis B and C, and illicit substance and alcohol use.^{39,40} The former is included because the toxicity of many antiretroviral agents is worse in the setting of viral hepatitis co-infection,⁴¹ and the latter because of greater risk of non-adherence and the potential for drug interactions. Directly observed therapy can improve virological outcomes in drug users with HIV infection.⁴²

5.3 Antiretroviral agents

Antiretroviral therapy has evolved considerably since the introduction of zidovudine in 1987. The subsequent development of four new drug classes and the accelerated licensing of many agents have resulted in the availability of at least 20 agents for use in combination regimens. New agents need to have greater antiretroviral potency with higher thresholds to the development of resistance, activity against resistant strains of HIV, more convenient dosing schedules (i.e. once-daily or twice-daily dosing), and fewer adverse effects.

The six classes of drugs currently licensed for use in Australia are:

- Nucleoside and nucleotide analogue reverse transcriptase inhibitors (NRTI)
- Non-nucleoside reverse transcriptase inhibitors (NNRTI)
- Protease inhibitors (PI)
- Entry inhibitors
- Fusion inhibitors
- Integrase inhibitors.

For treatment of previously untreated patients with HIV-1, there are now several combinations of drugs recommended as preferred or alternative treatment in the DHHS guidelines.²⁹ The guidelines recommend a two-drug NRTI backbone Truvada™ (fixed dose combination of tenofovir and emtricitabine); with either a NNRTI (preferred efavirenz) or a ritonavir-boosted PI (PI/r) – the latter preferred over unboosted PI. These

recommendations are made on the basis of at least 48-week data from randomised clinical trials.

In 2007, the new PIs, tipranavir and darunavir, and a new NNRTI, etravirine, became available. These drugs have the advantage of being useful in the setting of PI and NNRTI resistance respectively. Even more importantly, two new classes of drugs became available in 2007 for multidrug-resistant patients with HIV infection: raltegravir, the first-in-class integrase inhibitor and maraviroc, the first-in-class chemokine receptor-5 blocker. Raltegravir and maraviroc received accelerated approval by the Food and Drug Administration (FDA) in the USA,⁴³ and raltegravir and maraviroc have been approved by the Therapeutic Drugs Administration in Australia for patients with multidrug resistant virus. The availability of these new classes and new agents in existing classes, have positively influenced clinical outcomes for these patients. However there is still a need for more new agents in existing drug classes, new drugs classes and a better understanding of the efficacy and tolerability of novel combinations including NRTI-sparing combinations. The place of immunotherapy with recombinant interleukin-2 as an adjunct to cART is being explored in two studies ESPRIT³¹ and SILCAAT. These two clinical end-point studies will end in late 2008, with results expected in 2009. Other host-directed therapeutic approaches including RNA interference⁴⁴ hold promise, but are very early in their phase of development.

5.3.1 Antiretroviral classes

Nucleoside/nucleotide reverse transcriptase inhibitors

The NRTI/NtRTI interfere with HIV viral RNA-dependent DNA polymerase (reverse transcriptase) and inhibit viral replication causing premature DNA chain termination. All NRTIs require intracellular phosphorylation for activation, and inhibit the human mitochondrial DNA polymerase gamma to varying degrees. The nucleoside analogues are zidovudine (AZT), didanosine (ddI), stavudine (d4T), lamivudine (3TC), emtricitabine (FTC) and abacavir (ABC). Tenofovir disoproxil fumarate (tenofovir DF) is an orally bioavailable prodrug of tenofovir, an acyclic nucleotide analogue that is metabolised intracellularly into the active metabolite tenofovir diphosphate. Tenofovir also displays activity against the hepatitis B virus.

An important development within this class of drugs is the availability of fixed-dose combination tablets; initially, zidovudine plus lamivudine (CombivirTM), then zidovudine/lamivudine/abacavir (TrizivirTM) and now tenofovir/emtricitabine (TruvadaTM) and abacavir/lamivudine (KivexaTM). Moreover, tenofovir/emtricitabine has now been coformulated with efavirenz as AtriplaTM, and was licensed by the FDA in July 2006⁴³ but is not currently available in Australia.

Coformulation has meant that low pill burden combinations are available, greatly simplifying continuous pill taking for ART-naïve patients but also reducing pill burden for treatment-experienced patients with multidrug resistant (MDR) virus.

The most recent iteration of the DHHS guidelines has moved Combivir to an alternative NRTI backbone with didanosine/lamivudine or didanosine/emtricitabine. The use of stavudine plus lamivudine is not recommended for initial therapy. Abacavir/lamivudine is another alternative initial NRTI backbone for those patients who test negative for HLAB*5701, which accurately predicts the development of abacavir hypersensitivity,⁴⁵ a

reaction which occurs in 5-8% of individuals exposed to the drug and can be life threatening.

Stavudine, in particular, should be avoided because of the irreversible and sometimes serious toxicities of peripheral neuropathy, lipoatrophy, pancreatitis and serious and life threatening lactic acidosis with hepatic steatosis. The D drugs, stavudine (d4T) and didanosine (ddI), should never be used in combination because of unacceptable additive toxicity which has led to death, particularly in pregnant women. Zalcitabine (ddC) was withdrawn from use in 2007.

A guide to dosing of NRTI/NtRTI can be found in Table 5.1. Further details of the recommended cART for naïve patients can be found in Chapter 7.

Non-nucleoside reverse transcriptase inhibitors

The NNRTI class includes nevirapine (NVP), efavirenz (EFV) and delavirdine (DLV). A new second generation NNRTI, etravirine, is available through the Special Access Scheme (SAS) for use in patients with MDR virus. A guide to dosing of NNRTI can be found in Table 5.2.

Nevirapine binds directly to the reverse transcriptase enzyme and blocks the RNA-dependent and DNA-dependent polymerase activities by causing a disruption of the enzyme's catalytic site. This reduces enzyme activity and diminishes viral replication. The activity of nevirapine does not compete with template or nucleoside triphosphates. Nevirapine is not active against HIV-2 and does not inhibit human DNA polymerases. Women with a CD4 cell count of ≥ 250 cells/ μ L and men with a CD4 cell count of ≥ 400 cells/ μ L are at greater risk of nevirapine-related hepatotoxicity. Patients who fall into these categories should not be prescribed nevirapine if alternatives exist. Dosing with 200 mg once daily for the first two weeks followed by dose escalation to 200 mg twice daily (provided no adverse events have occurred) coupled with close monitoring is recommended for all patients commencing nevirapine.

Efavirenz is a non-competitive inhibitor of HIV reverse transcriptase. Like nevirapine, it does not inhibit HIV-2 reverse transcriptase or human DNA polymerases. Delavirdine is a selective non-nucleoside inhibitor of HIV reverse transcriptase that does not compete with the deoxynucleoside triphosphate substrate-binding site. Delavirdine is rarely used now in clinical practice because of the unacceptably high pill burden.

Guidance on the discontinuation of efavirenz and nevirapine is provided in the Antiretroviral Treatment Guidelines.²⁹ As the half-lives of these two agents are very long, cessation of all components in the regimen simultaneously effectively leaves the patient on functional monotherapy for a variable amount of time (1-3 weeks or more). As both drugs have a low genetic barrier to the development of resistance, the risk of selecting NNRTI resistance mutations is high. The best way of either staggering the stop of the regimen components or covering the tail of NNRTI decline is unclear. Many clinicians replace the NNRTI with a ritonavir-boosted PI and cease this and the NRTI backbone after one month or simply switch to a PI-based regimen. These data have very important implications for the use of nevirapine monotherapy in the prevention of mother-to-child transmission, and this approach should be avoided to prevent development of resistance.

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Table 5.1 Guide to nucleoside reverse transcriptase inhibitors dosing ²⁹

Drug (dose per tablet)	Dosing	Food requirement	Dose adjustment for renal impairment	Dose adjustment in hepatic impairment
abacavir (ABC) (300 mg)	300 mg bd or 600 mg qd	Take without regard to meals	No	No
didanosine (ddI) 250 mg or 400 mg	400 mg qd if >60 kg 250 mg qd if <60 kg	Take 30 minutes before food or 2 hours post meal	Yes **	No
emtricitabine (FTC) (200 mg)	200 mg qd	Take without regard to meals	Yes **	No
lamivudine (3TC) (300 mg/150 mg)	300 mg qd 150 mg bd	Take without regard to meals	Yes **	No
tenofovir (TDF) (300 mg)	300 mg qd	Take without regard to meals	Yes **	
zidovudine (AZT) (250 mg)	250 mg bd	Take without regard to meals	Yes (very severe impairment) **	No
Co-formulated preparations				
*Atripla™ (TDF 300 mg/ FTC 200 mg/ EFV 600 mg)	One tablet qd nocte	Take at night on empty stomach	Yes - cannot use coformulation for patients with creatinine clearance <50 mL/min	No
Combivir™ (AZT 300 mg / 3TC150 mg)	One tablet bd	Take without regard to meals	Yes - cannot use coformulation for patients with creatinine clearance <50 mL/min	No
Kivexa™ (ABC 600 mg/ 3TC 300 mg)	One tablet qd	Take without regard to meals	Yes - cannot use coformulation for patients with creatinine clearance <50 mL/min	No
Truvada™ (TDF 300 mg/ FTC 200 mg)	One tablet qd	Take without regard to meals	Yes, cannot use coformulation for patients with creatinine clearance <30 mL/min	No
*Not available in Australia; ** check product information for change in dosing according to creatinine clearance.				
qd = once daily; bd = twice daily; nocte = at night; EFV = efavirenz.				

Table 5.2 Guide to non-nucleoside reverse transcriptase inhibitors dosing ²⁹

Drug (dose per tablet)	Dosing	Food requirement	Dose adjustment for renal impairment	Dose adjustment in hepatic impairment
delavirdine (DLV) (100 mg)	400 mg tds	Take without regard to meals	No	Use with caution
efavirenz (EFV) (600 mg)	600 mg qd nocte	Take at night on empty stomach	No	Use with caution
etravirine (ETV) 100mg	200 mg bd	Yes	Use with caution	No Use with caution in Child - Pugh Class C
nevirapine (NVP) (200 mg)	200 mg bd (after 200 mg daily for 14 days)	Take without regard to meals	No	Avoid use in moderate to severe hepatic impairment
* Only available through the Special Access Scheme.				
qd = once daily; bd = twice daily; nocte = at night; tds = three times daily.				

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Etravirine, a second generation NNRTI, has efficacy even in the presence of the classic NNRTI mutation K103N. However, its virological impact diminishes in the presence of increasing numbers of etravirine-associated resistance mutations of which 13 (V90I, L100I, V106I, Y181C/I/V, A98G, K101E/P, V179D/F, G190A/S) have been identified. Overall, the mutations that have the biggest negative impact on response to etravirine are Y181V, G190S and V179F.⁴⁶ Etravirine is available through the SAS in Australia for patients with multidrug resistance.

Protease inhibitors

The PIs inhibit HIV-1 and HIV-2 proteases and prevent cleavage of the gag-pol polyprotein that occurs during maturation of the newly formed viral particle. This results in the production of immature, non-infectious virus. There are currently nine licensed PIs: atazanavir (ATV), fosamprenavir (FOS), indinavir (IDV), lopinavir/ritonavir (LPV/r), ritonavir (RTV), darunavir (DRV), tipranavir (TPV) and saquinavir (SQV). In 2006 nelfinavir was withdrawn from the market because of concern surrounding the appearance of carcinogenic impurities in the marketed product but by early 2008 nelfinavir was reassessed as being safe. Both the US FDA and the European Medicines Agency have lifted their safety warnings around contamination of nelfinavir. Ritonavir is now rarely used alone for its antiretroviral activity; rather, it is used as a pharmaco-enhancer by exploiting its inhibition of cytochrome p-450 (3A4) enzyme to boost levels of concomitantly administered protease inhibitors. The usual dose of ritonavir for this purpose is 100 mg once daily or 100-200 mg

twice daily (depending on the PI being boosted), and is referred to now as PI/r. Indinavir is also rarely used because of its toxicity profile, specifically nephrolithiasis and HIV-lipodystrophy; it still has a role in the treatment of HIV-related neurocognitive disease, as it is one of the few PIs with central nervous system penetration. LPV/r uses this combination strategy formulated in a single tablet (Table 5.3). The use of ritonavir boosting has simplified cART regimens enormously, as dosing can be once or at most twice daily. Moreover, the use of boosting with ritonavir has increased the inhibitory quotient⁴⁷ making the development of viral resistance much less likely to occur. Newer, recently licensed third generation PIs include tipranavir and darunavir; both must be given with ritonavir boosting and are licensed for use in patients with multidrug resistant virus on the basis of data from four pivotal studies, RESIST I and II⁴⁸ and POWER I and II.⁴⁹ It is possible that darunavir will receive licensure for use in antiretroviral-naïve patients based on the results of the ARTEMIS study.⁵⁰

Entry inhibitors

HIV entry is a complex, multistep process, and can be considered under the following basic steps which provide different targets for antiretroviral agents (Figure 5.1):

- Binding of HIV to CD4 receptor via the gp120 subunit of the envelope protein;
- Structural change in gp120, allowing it to bind to chemokine co-receptors CCR5 or CXCR4;
- Gp41-mediated fusion of the viral envelope with the cell membrane, completing viral entry.

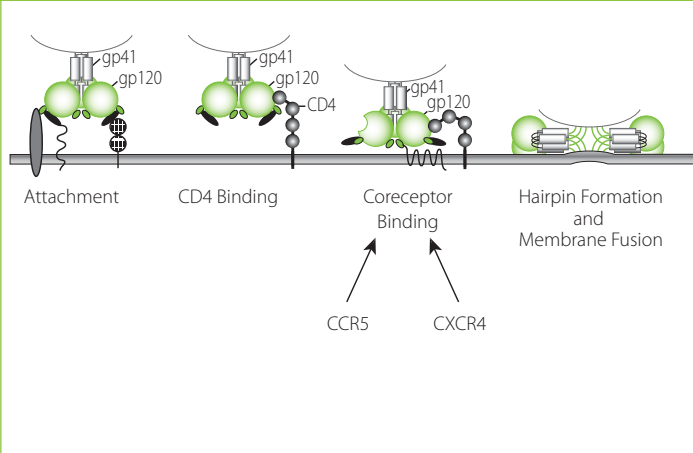
Table 5.3 Guide to protease inhibitor dosing²⁹

Drug	Dosing	Food requirement	Dose adjustment for renal impairment	Dose adjustment in hepatic impairment
atazanavir (ATV) (300 mg and 400 mg)	300 mg qd with ritonavir 100 mg qd Do not use unboosted with Truvada™	Yes, avoid antacids, Histamine 2 antagonists and proton pump inhibitors Seek expert advice if unsure	No	Yes. If Child-Pugh Class C - DO NOT USE. If Child-Pugh Class B use ATV (300 mg) qd (unboosted)
darunavir (DRV) (300 mg)	600 mg bd with ritonavir 100 mg bd	Yes	No	Use with caution
fosamprenavir (FOS) (700 mg)	1400 mg qd with ritonavir 200 mg qd for ART-naïve 700 mg bd with ritonavir 100 mg bd for treatment experienced. Guidelines allow for the use of unboosted FOS (alternate in ART-naïve). Not licensed in Australia at this dose	No food effect Can be taken on an empty stomach Food will increase tolerability of ritonavir	No	Child-Pugh Class A-B use FOS (700 mg) bd, avoid ritonavir boost Child-Pugh class C AVOID
lopinavir/ritonavir (LPV/r) (200 mg/50 mg)	400mg/100mg bd	No food effect	No	Use with caution
saquinavir (SQV) (500 mg)	1 g bd with ritonavir 100 mg bd	Yes, within 2 hours of food	No	Use with caution
tipranavir (TPV) (250 mg)	500 mg bd with ritonavir 200 mg bd	Yes	No	Caution in patients with hepatic impairment Avoid in patients with Child-Pugh Class B and C

Note: Ritonavir comes as 100mg capsules

qd = once daily; bd = twice daily

Figure 5.1 HIV entry into the cell



Source: Cooley LA, Lewin SR. HIV-1 cell entry and advances in viral entry inhibitor therapy. *J Clin Virol* 2003;26:121-32. Used with permission.

Each of these steps is targeted by a different subclass of entry inhibitor:

- Fusion inhibitors;
- Small molecule chemokine receptor-5 inhibitors and CCR5 receptor monoclonal antibodies (PRO140).⁵¹

Two types of entry inhibitor, fusion inhibitors and the small molecule CCR5-receptor antagonists, are currently licensed.

Fusion inhibitors

There is only one agent in this class, enfuvirtide (T-20). Enfuvirtide is a synthetic 36-amino acid peptide analogue. It binds to the first heptad repeat region of gp41, disrupting interactions with the second heptad repeat region of gp41, thereby interrupting the fusion reaction and preventing the virus from infecting the host cell. Enfuvirtide, an injectable agent, was licensed in 2003 on the basis of two pivotal studies in patients with multidrug resistant virus, TORO 1 and 2.^{52,53} Enfuvirtide is very well tolerated, its main disadvantage being the universal development of injection site reactions, which are unpleasant for the patient, and appear to be associated with skin sclerosis with long-term use. Other side-effects are listed in Table 5.4 and dosing in Table 5.5.

CCR5 antagonists

These drugs are the first host-directed therapies for HIV. Their development arose from the recognition that CCR5 is a key receptor for HIV,⁵⁴ at least early on in the disease, and that genetic

absence (delta 32 homozygosity) was associated with protection against HIV infection.⁵⁵ Moreover, people with reduced levels of CCR5 (delta 32 heterozygotes) have an attenuated disease course with lower HIV viral load.^{56,57}

These drugs are allosteric inhibitors that lock CCR5 into a conformation such that it is not able to bind HIV envelope protein. Maraviroc, the first drug in this class to be licensed⁵⁸⁻⁶⁰ is only effective in patients whose virus utilises CCR5 for cell entry (R5 tropic), and special tropism testing is mandated prior to the use of this drug. There is no virological efficacy in patients with CXCR4 (X4) or dual tropic HIV. A guide to dosing of licenced CCR5 inhibitors can be found in Table 5.6 and adverse effects in Table 5.7.

Integrase inhibitors

Raltegravir is the first integrase inhibitor to be licensed.^{43,61} It is an integrase strand transfer inhibitor preventing the integration of HIV DNA into the nucleus of the host cell. It is primarily eliminated by glucuronidation via the enzyme UDP-glucuronosyltransferases (UGT1A1). There is relatively little potential for drug-drug interactions in comparison to those drugs metabolised by CYP3A4, aside from when co-administered with potent UGT1A1 inducers such as rifampicin. A guide to dosing can be found in Table 5.8 and adverse effects in Table 5.9.

New agents in development

New antiretroviral agents in the existing classes are being developed with the aim of producing drugs that are active against drug-resistant virus, and with more favourable toxicity profiles. The only new class of agent in an advanced stage of development (phase II) is the maturation inhibitors. Maturation inhibitors block a late step in the gag processing cascade, causing defective core condensation and release of non-infectious virions from the cell.^{62,63}

5.3.2 Antiretroviral regimens

Combination therapy with at least three drugs is now standard treatment for patients with HIV starting cART for the first time. The DHHS guidelines recommend one NNRTI plus two NRTI or a single PI or ritonavir-boosted PI (PI/r) with two NRTI. The rationale for these recommendations is based upon randomised clinical trials and long-term safety data, which are summarised in the guidelines. Triple-NRTI combinations, such as abacavir, zidovudine and lamivudine (TrizivirTM) are not recommended because of inferior virological efficacy,²⁹ but there may be special circumstances in which the short-term use of TrizivirTM is acceptable i.e. during treatment of tuberculosis. Guidelines to dosing of antiretroviral agents are shown in Tables 5.1, 5.2, 5.3, 5.5, 5.6 and 5.8. Antiretroviral regimens or components that should not be offered at any time are shown in Table 5.10.

5.3.3 Adverse effects of antiretroviral agents

Adverse effects for fusion inhibitors, CCR5-antagonists, integrase, NRTI/NtRTI, NNRTI, and PI are found in Tables 5.4, 5.7, 5.9, 5.11, 5.12, and 5.13, respectively.

Table 5.4 Adverse effects of fusion inhibitors ²⁹		
Drug	Adverse effect	Potentially life-threatening adverse effects
enfuvirtide (T-20)	Local injection site reactions – almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis); Increased rate of bacterial pneumonia	Hypersensitivity reaction (<1%) - symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases - rechallenge not recommended

Table 5.5 Guide to fusion inhibitor dosing ²⁹

Drug (dose per injection)	Dosing	Food requirement	Dose adjustment for renal impairment	Dose adjustment in hepatic impairment
enfuvirtide (T-20)	90 mg subcutaneous injection bd	Take without regard to meals	No	No

Table 5.6 Guide to CCR5- antagonists dosing ²⁹

Drug (dose per tablet)	Dosing	Food requirement	Dose adjustment for renal impairment	Dose adjustment in hepatic impairment
maraviroc (150 mg and 300 mg)	<ul style="list-style-type: none"> 150 mg bd when given with all ritonavir (RTV) boosted protease inhibitors (PI) <u>EXCEPTION</u> tipranavir (TPV)/ritonavir (r) 300 mg bd when given with nucleoside reverse transcriptase inhibitors, enfuvirtide, nevirapine (NVP), tipranavir (TPV) 600 mg bd when given with efavirenz (EFV), or other CYP3A4 inducers e.g. rifampicin 	Take without regard to meals	No, but caution if CrCL <50 mL/min	Caution, concentration likely to be increased

qd = once daily; bd = twice daily; CrCL = creatinine clearance.

Table 5.7 Adverse effects of CCR5-antagonists²⁹

Drug	Adverse effect	Potentially life-threatening adverse effect
maraviroc	Abdominal pain; cough; dizziness; musculoskeletal symptoms; pyrexia; rash; upper respiratory tract infections; hepatotoxicity; orthostatic hypotension.	Not reported

Table 5.8 Guide to integrase inhibitor dosing ²⁹

Drug (dose per tablet)	Dosing	Food requirement	Dose adjustment for renal impairment	Dose adjustment in hepatic impairment
raltegravir (RAL) (400 mg)	RAL 400 mg twice daily	Take without regard to meals	No	No

Table 5.9 Adverse effects of integrase inhibitors²⁹

Drug	Adverse effect	Potentially life-threatening adverse effect
raltegravir (RAL)	Nausea, headache, diarrhoea, pyrexia, creatine phosphokinase elevation	Not reported

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Table 5.10 Antiretroviral regimens or components that should not be offered at any time,²⁹ for exceptions see the DHHS guidelines

Antiretroviral regimens not recommended	Rationale
Monotherapy with nucleoside reverse transcriptase inhibitors (NRTI) or non-nucleoside reverse transcriptase inhibitors (NNRTI)	Inferior virological activity plus rapid development of resistance
Dual-NRTI regimens	Inferior virological activity plus rapid development of resistance
Triple-NRTI regimens	Inferior virological activity plus rapid development of resistance. With didanosine (ddl), tenofovir, lamivudine (3TC) or Trizivir™; use of other triple NRTI combinations are being explored.
Antiretroviral components not recommended as part of an antiretroviral therapy regimen	Rationale
atazanavir (ATV) plus indinavir (IDV)	Higher risk of overlapping toxicity i.e. hyperbilirubinaemia
didanosine (ddl) and stavudine (d4T)	Higher incidence of overlapping toxicities including pancreatitis, peripheral neuropathy, lactic acidosis, lipodystrophy
efavirenz (EFV) in first trimester of pregnancy	Teratogenic in non-human primates
nevirapine (NVP) in antiretroviral therapy (ART)-naïve women and men with CD4 cell count ≥ 250 and 400 cells/ μL , respectively	Greater risk of severe, life-threatening hepatotoxicity
Unboosted saquinavir (SQV)	Virologically inferior
stavudine (d4T) with zidovudine (AZT)	Antagonistic effect on HIV-1
nevirapine (NVP) + efavirenz (EFV), or nevirapine (NVP) / efavirenz (EFV) + etravirine.	Higher incidence of toxicity

Table 5.11 Adverse effects of nucleoside/nucleotide analogue reverse transcriptase inhibitors²⁹

Drug	Adverse effect	Potentially life-threatening adverse effect
abacavir (ABC)	Usually minimal toxicity	Hypersensitivity reaction that can be fatal, symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, loss of appetite, respiratory symptoms such as sore throat, cough, shortness of breath (negative HLA*B5701 test prior to use)
didanosine (ddl)	Peripheral neuropathy; nausea	Pancreatitis Lactic acidosis with hepatic steatosis
emtricitabine (FTC)	Minimal toxicity Hyperpigmentation/skin discolouration	RARE: Lactic acidosis with hepatic steatosis
lamivudine (3TC)	Minimal toxicity	RARE: Lactic acidosis with hepatic steatosis
tenofovir (TDF)	Asthenia, headache, diarrhoea, nausea, vomiting and flatulence renal insufficiency	RARE: lactic acidosis with hepatic steatosis Fanconi syndrome
zidovudine (AZT)	Gastrointestinal intolerance, headache, insomnia, asthenia	Bone marrow suppression: macrocytic anaemia or neutropenia (can be severe) RARE: Lactic acidosis with hepatic steatosis; myopathy
Coformulated preparations - see above for individual components		
Atripla™ (TDF 300 mg/ FTC 200 mg/ EFV 600 mg)	See above and below (under EFV) for individual components	RARE: Lactic acidosis with hepatic steatosis
Combivir™ (AZT 300 mg / 3TC 150 mg)	Use of AZT and 3TC separately may increase tolerability as lower dose of AZT (i.e. 250 mg bd) can be used	RARE: Lactic acidosis with hepatic steatosis
Kivexa™ (ABC 600 mg/ 3TC 300 mg)	See above for individual components	RARE: Lactic acidosis with hepatic steatosis
Truvada™ (TDF 300 mg/ FTC 200 mg)	See above for individual components	RARE: Lactic acidosis with hepatic steatosis
bd = twice daily		

Table 5.12 Adverse effects of non-nucleoside reverse transcriptase inhibitors²⁹

Drug	Adverse effect	Potentially life-threatening adverse effect
efavirenz (EFV)	Rash (treat through unless progressing or associated with drug-induced hepatitis) Central nervous system symptoms Increased transaminase levels False-positive cannabinoid urine test Teratogenic in monkeys	<2% develop severe depression; Do not use in pregnancy BLACK BOX WARNING (see Table 5.14)
etravirine (ETV)	Rash, nausea	None reported to date
delavirdine (DLV)	Rash, nausea, diarrhoea, increased transaminase levels	
nevirapine (NVP)	Rash, fever, nausea, headache, increased transaminase levels, increased GGT levels	Rash including Stevens-Johnson Syndrome; Symptomatic hepatitis, including fatal hepatic necrosis

Table 5.13 Adverse effects of protease inhibitors²⁹

Drug	Adverse effect	Potentially life-threatening adverse effect
atazanavir (ATV)	Indirect hyperbilirubinaemia Hyperglycaemia Fat maldistribution	Prolonged PR interval - 1st degree symptomatic AV block in some patients; use with caution in patients with underlying conduction defects or on concomitant medications that can cause PR prolongation; possible increased bleeding episodes in patients with haemophilia
darunavir (DRV)*	Skin rash (7%) - (DRV has a sulfonamide moiety); diarrhoea, nausea; headache; hyperlipidaemia; transaminase elevation; hyperglycaemia; fat maldistribution	Possible increased bleeding episodes in patients with haemophilia, Stevens-Johnson syndrome and erythema multiforme have been reported (RARE)
fosamprenavir (FOS)	Skin rash (19%); diarrhoea, nausea, vomiting; headache; hyperlipidaemia; transaminase elevation; hyperglycaemia; fat maldistribution	Possible increased bleeding episodes in patients with haemophilia
Indinavir (IDV)	Nephrolithiasis; GI intolerance: nausea; indirect hyperbilirubinaemia; headache, asthenia, rash, alopecia, thrombocytopenia, and haemolytic anemia; hyperlipidaemia; hyperglycemia; fat maldistribution	Possible increased bleeding episodes in pts with hemophilia
lopinavir/ritonavir (LPV/r)	GI intolerance: nausea, vomiting, diarrhoea (higher incidence with once-daily than twice-daily dosing); asthenia; hyperlipidaemia especially hypertriglyceridaemia; hepatitis, asthenia; taste perversion; hyperglycaemia; fat maldistribution	Possible increased bleeding episodes in patients with haemophilia
ritonavir (RTV) (boosting)	Gastrointestinal (GI) intolerance, nausea, vomiting, diarrhoea; paresthesias – circumoral and extremities (rare with boosting doses of RTV); hyperlipidaemia especially hypertriglyceridaemia; hepatitis, asthenia; taste perversion; hyperglycaemia; fat maldistribution	Not reported with boosted doses of RTV <u>Caution</u> with drug-drug interaction for drugs with a narrow therapeutic index Possible increased bleeding episodes in patients with haemophilia
saquinavir (SQV)*	GI intolerance, nausea and diarrhoea; headache; elevated transaminase enzymes; hyperlipidaemia; hyperglycaemia; fat maldistribution	Possible increased bleeding episodes in patients with haemophilia
tipranavir (TPV)*	Hepatotoxicity; skin rash – TPV has a sulfonamide moiety, use with caution in patients with known a sulfonamide allergy; hyperlipidaemia (especially hypertriglyceridaemia); hyperglycaemia; fat maldistribution	Clinical hepatitis including hepatic decompensation has been reported, monitor closely, especially in patients with underlying liver diseases. Rare cases of fatal and nonfatal intracranial haemorrhages have been reported. Most patients had underlying comorbidity such as brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, alcoholism, or on medication with increased risk for bleeding; possible increased bleeding episodes in patients with haemophilia

*can only be administered with boosting doses of ritonavir.

HIV lipodystrophy syndrome

This syndrome deserves a special mention because the pathogenesis is still not fully understood and for many years PIs alone were blamed for its development. However, increasingly, the role of NRTI in the development of this syndrome has been recognised.⁶⁴ Moreover, in a recent study, efavirenz was found to be associated with more body fat changes than lopinavir/ritonavir.⁶⁵ The syndrome is described in greater detail in chapter 9. It consists of peripheral fat loss from the limbs, face and buttock coupled with truncal fat accumulation (breasts, neck, abdomen), insulin resistance that may progress to diabetes mellitus and dyslipidaemia.¹⁷ Aside from the stigmatising body habitus changes, the development of lipodystrophy is associated with an increased risk of cardiovascular disease especially in patients who have other risk factors for the development of cardiovascular disease including cigarette smoking.^{24,66} Avoidance of HIV lipodystrophy is critically important as there is only partial reversibility once it has developed. It remains one of the most important long-term adverse events of early cART combinations (which included stavudine) used in the late 1990s, and is still of great concern to patients and clinicians when making decisions about cART commencement i.e. when to start and what to use.

5.3.4 Drug interactions with antiretroviral agents

The metabolism of PIs, NNRTIs and the CCR5-receptor antagonist, maraviroc, is through the CYP3A4 pathway of oxidative metabolism in the liver. These agents may have inducing or inhibiting effects on this metabolic pathway, and therefore have the potential to affect and be affected by the metabolism of other drugs. This has a number of consequences, some advantageous and others potentially deleterious. In addition, there may be overlapping toxicities between agents, which can be deleterious.

Advantages of drug-drug interactions between antiretroviral agents

As already discussed, the potent inhibition of this metabolic pathway by low dose ritonavir is used to boost the levels of the second PI. This reduces the development of viral resistance and allows for twice daily, and in some cases once daily, dosing e.g. lopinavir/r, atazanavir/r, fosamprenavir/r.

Disadvantages of drug-drug interactions between antiretroviral agents

Disadvantages:

- Drug levels can be reduced and inadequate for viral suppression, allowing viral resistance to develop e.g. tipranavir and etravirine cannot be used together because etravirine levels are reduced by 75% in the presence of tipranavir⁶⁷
- Overlapping toxicities e.g. hepatotoxicity with tipranavir, maraviroc, nevirapine

Drug interactions between antiretroviral agents and other drugs can be potentially life threatening. This is especially true of drugs that have a narrow therapeutic margin. Examples include the co-administration of PI/r with the agents shown in Table 5.14, which must be avoided or used with extreme caution.

Other drugs with the potential for deleterious interactions either in a uni or bi-directional manner include many of the anti-arrhythmic agents, oral anticoagulants e.g. warfarin, anti-psychotic and anti-depressant medication, blood pressure lowering medication, opiates, hormonal contraceptives and anti-mycobacterial agents i.e. clarithromycin and rifabutin.

It is essential to check the potential for drug-drug interactions and the need for dose adjustment when patients on other concomitant medications are commenced on cART or patients on stable cART are commenced on other medications. Further details are available in the DHHS guidelines²⁹ and from the University of Liverpool drug interaction website (www.hivdruginteractions.org). Seek expert advice if in doubt.

US FDA Black Box warnings for antiretrovirals are listed in Table 5.15.

5.4 HIV vaccines

HIV infection has had devastating consequences worldwide and has been responsible for more than 40 million deaths and untold suffering since HIV was first recognised in 1981. Currently, there are about 33 million people living with HIV and in 2007 there were an estimated 2.1 million new infections.⁶⁸ Although industrialised countries have successfully embraced antiretroviral therapy, with subsequent reductions in HIV-related illness and death as well as a reduction of new infections, this has not been the case in resource-limited settings. The best

Table 5.14 Potentially life-threatening drug interactions between protease inhibitor boosted with ritonavir (PI/r) agents and other drugs

Drug or drug class	Adverse effect
Benzodiazepines e.g. midazolam or triazolam	Increased sedating effect
Carbamazepine, phenobarbitone, phenytoin	All potent enzyme inducers with the potential to reduce levels of co-administered PI/r; potential for bi-directional interaction with increased levels of carbamazepine and toxicity ensuing due to the narrow therapeutic window of this agent
Erectile dysfunction agents e.g. sildenafil	Potential of the effects can lead to priapism
Ergot alkaloids	Vasoconstrictive effects of ergot potentiated leading to myocardial infarction, stroke, peripheral vasoconstriction and gangrene
Rifampicin	Significant reduction in the levels of protease inhibitor/ritonavir (PI/r) resulting in ineffectual levels for antiviral effect
Statins e.g. simvastatin	Levels of statin greatly increased, resulting in higher risk of myopathy and rhabdomyolysis
Voriconazole	Potential for bi-directional interaction, with increased levels of voriconazole (leading to toxicity) and decreased levels of PI/r

Table 5.15 US Food and Drug Administration 'Black Box' warnings for antiretrovirals²⁹

Drug	Reaction
abacavir (ABC)	Hypersensitivity* reaction comprising two or more groups of the following signs and symptoms fever, rash, GI upset, constitutional upset, respiratory symptoms
didanosine (ddl)	<ul style="list-style-type: none"> Fatal and non-fatal pancreatitis Fatal and non-fatal lactic acidosis Fatal and non fatal lactic acidosis, hepatomegaly and hepatic steatosis
emtricitabine (FTC)	<ul style="list-style-type: none"> Lactic acidosis, hepatomegaly and hepatic steatosis Hepatitis B flare following discontinuation**
lamivudine (3TC)	<ul style="list-style-type: none"> Lactic acidosis, hepatomegaly and hepatic steatosis Hepatitis B flare following discontinuation
maraviroc	Hepatotoxicity which may be preceded by evidence of a systemic allergic reaction manifesting with pruritic rash, eosinophilia or raised immunoglobulin E (IgE)
nevirapine (NVP)	<ul style="list-style-type: none"> Severe life threatening hepatotoxicity, including fulminant hepatitis, necrosis and hepatic failure Severe life threatening skin reactions include Stevens-Johnson Syndrome <p>Women with a CD4 cell count of ≥ 250 cells/uL and pregnant women are at a greater risk of hepatotoxicity.</p>
ritonavir (RTV)	Co-administration with certain non-sedating anti-histamines, sedative hypnotics, antiarrhythmics, ergot alkaloids may results in serious or life-threatening adverse events
saquinavir (SQV)	Only co-administer with ritonavir boost in order to achieve therapeutic levels
stavudine (d4T)	<ul style="list-style-type: none"> Fatal and non-fatal pancreatitis Fatal and non-fatal lactic acidosis especially in pregnant women Fatal and non fatal lactic acidosis, hepatomegaly and hepatic steatosis
tenofovir (TDF)	<ul style="list-style-type: none"> Hepatitis B flare following discontinuation** Fatal and non fatal lactic acidosis, hepatomegaly and hepatic steatosis
tipranavir	<ul style="list-style-type: none"> Fatal and non-fatal intra-cranial haemorrhage Clinical hepatitis and hepatic decompensation. Extra vigilance recommended for patients with HIV and hepatitis C or B co-infection
zidovudine (AZT)	<ul style="list-style-type: none"> Haematological toxicity including severe anaemia and granulocytopenia, especially amongst patients with advanced HIV Symptomatic myopathy with prolonged use Fatal and non fatal lactic acidosis, hepatomegaly and hepatic steatosis

*largely avoidable now with pre-use HLA*B5701 testing
** tenofovir (TDF) and emtricitabine are not currently licensed for use in the treatment of hepatitis B, although both drugs are active against hepatitis B

hope of controlling the HIV epidemic is vaccination to prevent new infections. The development of a vaccine has proved to be an enormous scientific challenge. Efforts over the last decade have been focused on T cell vaccines aimed at improving host immunological control of HIV in the event of infection. The focus on T cell vaccines is a consequence of positive data from this approach on a background of poor performance of vaccines aimed at raising anti-HIV neutralising antibodies. However, the recent early cessation of the STEP study, has probably put a halt to the further development of T-cell vaccines in HIV, effectively leaving the field devoid of any really promising candidate vaccines.

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