ARTICLE

Prescribing for patients taking antiretroviral therapy

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SUMMARY

Current first-line antiretroviral therapy comprises a combination of drugs that are generally well tolerated. Adverse effects include hypersensitivity reactions, renal and liver toxicity, rhabdomyolysis, hyperlipidaemia, weight gain and neuropsychiatric disorders.

Most drug–drug interactions related to antiretroviral therapy involve drug absorption, metabolism or elimination. Some interactions may increase toxicity or reduce the effectiveness of antiretroviral therapy potentially resulting in treatment failure.

Routinely checking for adverse drug effects and potential drug–drug interactions is an important part of the care of people taking antiretroviral therapy. This includes asking about the patient's use of over-the-counter and complementary medicines.

Introduction

Antiretroviral therapy is recommended for everyone living with human immunodeficiency virus (HIV) starting from the time of diagnosis. The aim is to suppress the viral load and maintain immune function. A suppressed viral load also prevents HIV transmission.

In Australia, antiretroviral therapy is prescribed by accredited S100 prescribers. GPs may see patients taking antiretroviral therapy and should be aware of the implications for prescribing. These include encouraging adherence to therapy and being alert for adverse effects and drug interactions.

Antiretroviral therapy

The six main classes of antiretroviral drugs (Table) target various steps in the HIV replication cycle (Fig.) If drugs are used individually, resistance rapidly develops, so antiretroviral therapy is given as a combination of drugs. Most commonly the combination includes a 'backbone' of two nucleoside/nucleotide reverse transcriptase inhibitors plus an integrase strand inhibitor (the preferred initial third drug for most people with HIV), a protease inhibitor, or a non-nucleoside reverse transcriptase inhibitor. Entry inhibitors and fusion inhibitors are reserved for when standard treatments have failed.

Two-drug regimens (e.g. dolutegravir/lamivudine or rilpivirine/dolutegravir) are increasingly being used when certain criteria are met. The first long-acting injectable antiretroviral therapy (cabotegravir/rilpivirine) is now available on the Pharmaceutical Benefits Scheme.

Antiretroviral drugs are also used to prevent HIV infection. A regimen for pre-exposure prophylaxis (PrEP) is tenofovir disoproxil fumarate/emtricitabine. For post-exposure prophylaxis tenofovir disoproxil fumarate/emtricitabine can be used with the addition of dolutegravir, raltegravir or rilpivirine for higher risk exposures.

Booster drugs

Some antiretroviral drug combinations include ritonavir or cobicistat to inhibit the cytochrome P450 (CYP) liver enzymes that metabolise protease inhibitors and elvitegravir. This inhibition boosts the plasma concentrations of these antiretroviral drugs, allowing lower doses to be used. As many drugs are metabolised by the CYP system, the pharmacokinetic boosters are particularly prone to cause drug–drug interactions. Before prescribing a new drug for a patient taking antiretroviral therapy, drug interactions should be checked via the University of Liverpool's HIV Drug Interactions website. If there is any doubt, it is best to contact the prescribing doctor or a specialist in HIV medicine as certain drug interactions may lead to a failure of antiretroviral therapy.

Adverse effects of antiretroviral drugs

The current regimens are generally well tolerated. This is important because adherence to treatment is essential. Some patients may have an increased risk of adverse effects because of comorbidities such as reduced renal function.

Nucleoside and nucleotide reverse transcriptase inhibitors

Nucleoside and nucleotide reverse transcriptase inhibitors are the backbone of today's antiretroviral therapy. They inhibit the reverse transcription of viral RNA to double-stranded DNA (Fig.). The usual

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Table **Classes of antiretroviral therapy**

Antiretroviral class	Comments
Entry inhibitors	
Maraviroc (CCR5 antagonist)	• Not routinely used. • Only indicated for CCR5-tropic strains of HIV.
Fusion inhibitors	
Enfuviritide	• Not routinely used. • Twice daily subcutaneous injections, high rate of injection-site reactions.
Nucleoside and nucleotide reverse transcriptase inhibitors	
Abacavir	• Hypersensitivity reaction, check for HLA-B*5701 allele before prescribing. • Potential increased cardiovascular risk, avoid if cardiovascular risk factors.
Lamivudine Emtricitabine	• Also used to treat hepatitis B in combination with tenofovir to avoid the development of hepatitis B virus resistance. • Generally well tolerated.
Tenofovir alafenamide	• Can cause renal toxicity – avoid if eGFR <30 mL/min. • Potential weight gain and raised lipids. • Drug interactions with rifampicin, rifabutin, phenytoin and phenobarbital (may reduce exposure to tenofovir). • Used with another drug to treat hepatitis B co-infection.
Tenofovir disoproxil fumarate	• Reduced renal function – avoid if eGFR <60 mL/min. Associated with renal tubulopathy and urine phosphate wasting. Monitor renal function. • Avoid nephrotoxic drugs e.g. NSAIDs. • Associated with decreases in bone mineral density and osteomalacia. Avoid in osteoporosis. • Used with another drug to treat hepatitis B co-infection.
Zidovudine	• Rarely used now. • Can cause anaemia.
Non-nucleoside reverse transcriptase inhibitors	
Rilpivirine	• Take with a meal for optimal absorption. • Contraindicated with proton pump inhibitors (cause virological failure), H_2-receptor antagonists and antacids. Should be dosed separately to rilpivirine. • Adverse effects include raised serum creatinine concentration without an effect on renal function, skin rash, QT prolongation on the ECG, exacerbation of psychiatric symptoms. • Drug interactions with carbamazepine, rifampicin, dexamethasone and St John's wort. Avoid with other drugs that can increase risk of torsades de pointes.
Efavirenz	• Rarely used now. • Neuropsychiatric adverse effects are common, e.g. vivid dreams. Avoid if the patient has a history of psychiatric illness. Take on an empty stomach to reduce adverse effects. • Causes raised lipids. • Drug interactions with oral contraception, direct-acting oral anticoagulants (apixiban and rivaroxaban), rendering them ineffective. Avoid with other drugs that can increase risk of torsades de pointes. Reduces methadone concentrations, so may lead to withdrawal symptoms.
Nevirapine Etravirine	• Rarely used now. • Nevirapine causes serious and potentially fatal toxicity (hepatotoxicity, Stevens-Johnson syndrome, toxic epidermal necrolysis). Reduces plasma concentrations of direct-acting oral anticoagulants (apixiban and rivaroxaban), rendering them ineffective.

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Table **Classes of antiretroviral therapy *(continued)***

Antiretroviral class	Comments
Integrase strand inhibitors	
Bictegravir	• Raised serum creatinine concentration, nil effect on renal function. • Raised creatine kinase. • Concentration decreased by products containing polyvalent cations.* • CYP3A4 and UGT1A1 substrate, potential for drug–drug interactions e.g. with rifampicin.
Dolutegravir	• Raised serum creatinine concentration, nil effect on renal function. Hepatotoxicity, raised creatine kinase. • Neuropsychiatric adverse effects. • Concentration decreased by products containing polyvalent cations.* • Interaction with metformin – do not exceed metformin 1 g daily. • Interactions with phenytoin, phenobarbital, rifampicin, St John's wort, carbamazepine.
Elvitegravir/cobicistat	• Take with food. • Lots of potential drug interactions due to cobicistat. • Raised lipids. • Raised serum creatine kinase concentration, monitor for myopathy and rhabdomyolysis.
Raltegravir	• Depression, suicidal ideation (rare – usually if pre-existing psychiatric conditions). Concentration decreased by products containing polyvalent cations.* • Statins – increased risk of rhabdomyolysis. • Rare cases of severe hypersensitivity reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis).
Protease inhibitors†	
Darunavir	• Absorption is improved with food. • Skin rash, raised serum transaminases, raised lipids, potential cardiovascular risk.
Atazanavir	• Absorption depends on food and a low gastric pH. Absorption reduced with proton pump inhibitors which should be avoided. H_2-receptor antagonists and antacids should be avoided or dosed apart. Adverse effects include jaundice, indirect hyperbilirubinaemia, cholethiasis, nephrolithiasis and prolongation of the PR interval on the ECG.
Indinavir	• Raised lipids.
Lopinovir	• Raised lipids.

* Polyvalent cations include aluminium, calcium, iron, magnesium and zinc.

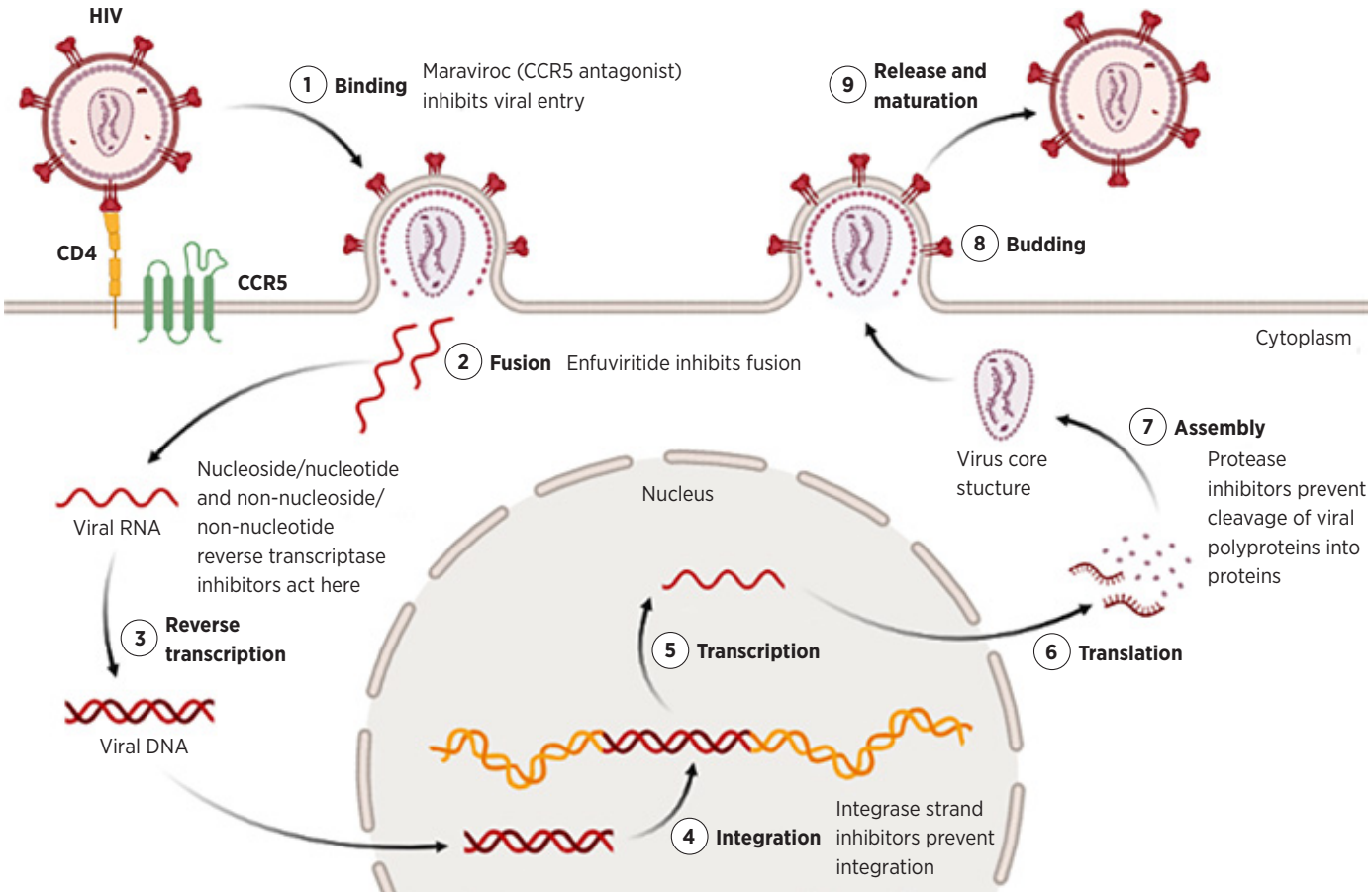
† All protease inhibitors are 'boosted' with either cobicistat or ritonavir which are inhibitors of CYP3A, increasing the concentrations of drugs metabolised through the same pathway. This interaction is seen with statins, phosphodiesterase 5 inhibitors, direct-acting oral anticoagulants, calcium channel blockers, beta blockers and some antiarrhythmic drugs (amiodarone and flecainide). Cushing's syndrome has been reported in patients taking cobicistat or ritonavir with fluticasone, budesonide or mometasone, which are predominantly metabolised by CYP3A enzymes (inhaled, intranasal, intra-articular, topical, and intraocular corticosteroids). Beclomethasone is not metabolised by CYP3A4 and so is suitable to use.

eGFR estimated glomerular filtration rate

NSAIDs non-steroidal anti-inflammatory drugs

CYP cytochrome P450

Fig. **Viral replication cycle and sites of antiretroviral therapy action**



HIV primarily infects host immune cells, mainly CD4 T-cell lymphocytes. After successful binding and fusion with the CD4 cell (1,2), the virion's single-stranded RNA is transported to the cell's interior. Here it is reverse transcribed (3) by the viral reverse transcriptase enzyme into double-stranded DNA. This is integrated into the host DNA by viral integrase (4), and then transcribed into RNA (5), which is then translated into viral polyproteins (6) which are cleaved by viral protease. The viral proteins (reverse transcriptase, integrase and protease) are combined with viral genomic RNA and assembled into viral packages (7) which bud from the host cell (8), forming new virions which are released (9) and which then infect other host CD4 cells.

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Adapted from 'HIV Replication Cycle', by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates/t-5f32d8b236677100ac51c32e-hiv-replication-cycle

combinations are abacavir/lamivudine, tenofovir alafenamide/emtricitabine or tenofovir disoproxil fumarate/emtricitabine. Emtricitabine and lamivudine have had fewer reported adverse effects than other nucleotide reverse transcriptase inhibitors.[1-3]

Abacavir

Abacavir can cause a potentially lethal, multisystem hypersensitivity reaction within six weeks of starting treatment.[4] Patients who have the HLA-B*5701 genotype are especially susceptible, so genotypic screening is needed before prescribing abacavir.

Abacavir has been associated with an increased risk of ischaemic cardiovascular events in some cohort studies.[5-8] However, other studies and meta-analyses concluded that abacavir does not confer a higher risk of cardiovascular events compared to regimens without abacavir.[9] While the data remain conflicting and no plausible biological mechanism explains the increased risk, most experts and international guidelines recommend avoiding abacavir in patients with cardiovascular risk factors.[10-12]

Tenofovir formulations

Tenofovir disoproxil fumarate is primarily eliminated by the kidneys. It has been associated with renal toxicity, including Fanconi syndrome manifesting as type 2 renal tubular acidosis and phosphate wasting.[13-15] The drug is not recommended for patients with an estimated glomerular filtration rate (eGFR) below 60 mL/minute. Monitoring of renal function is essential and includes the eGFR, urinalysis for glucose

and protein, and the protein:creatinine ratio. Renal monitoring (six-monthly eGFR) is also recommended in PrEP users, although the risk of toxicity in this group is much lower than in people living with HIV.[16-18] Reduced bone mineral density has been reported so tenofovir disoproxil fumarate should be avoided in patients with osteoporosis.[19-20]

Renal and bone effects occur to a lesser extent with tenofovir alafenamide as serum drug concentrations are lower, however this formulation should be avoided in patients with an eGFR below 30 mL/minute. Tenofovir alafenamide has previously been reported to cause greater weight gain, especially when combined with dolutegravir, compared to tenofovir disoproxil fumarate. Whether this is an effect of weight gain with tenofovir alafenamide, weight loss with tenofovir disoproxil, or simply represents better gastrointestinal tolerability and improved health is uncertain.[21-22]

Tenofovir disoproxil fumarate and tenofovir alafenamide are first-line drugs for hepatitis B management. In patients co-infected with HIV and hepatitis B, dual therapy with tenofovir disoproxil fumarate or tenofovir alafenamide in combination with either lamivudine or emtricitabine is used to avoid the development of hepatitis B virus drug resistance. These patients also require a third drug with activity against HIV, for example bictegravir/tenofovir alafenamide/emtricitabine. Patients with hepatitis B should be advised on the importance of adherence as stopping their hepatitis B antiviral therapy can result in a flare of hepatitis.

Integrase strand inhibitors

Integrase strand inhibitors are highly effective with few adverse effects and are recommended for most patients in combination with nucleotide reverse transcriptase inhibitors. Possible adverse effects include headache, nausea and diarrhoea. Several studies have concluded that integrase strand inhibitors, particularly dolutegravir, lead to greater weight gain than other classes of antiretroviral therapy, but the mechanism and clinical significance are unclear.[23-26]

Bictegravir, dolutegravir and raltegravir can increase serum creatine kinase and there are case reports of rhabdomyolysis with raltegravir.[27-29] Serum creatine kinase should be checked in those presenting with myalgia and specialist advice sought as the patient may require switching to a different regimen.

Bictegravir, dolutegravir and certain other drugs (e.g. rilpivirine, cobicistat) inhibit creatinine excretion in the proximal renal tubule. This causes a physiological, but clinically unimportant 10–20% increase in serum creatinine within the first eight weeks of treatment. Aside from measuring serum creatinine to establish a new baseline when starting therapy, no further action is required.

Integrase inhibitors have rarely been associated with central nervous system effects, such as insomnia and headache. A meta-analysis reported no significant effect of dolutegravir on the risk of suicide-related adverse events.[30]

Non-nucleoside and non-nucleotide reverse transcriptase inhibitors

The most prescribed drug in this class is rilpivirine which is generally well tolerated, however it needs to be taken with a meal to facilitate its absorption. An important adverse effect is prolongation of the QT interval on the ECG which also has implications for drug–drug interactions. Rilpivirine may also exacerbate existing psychiatric conditions, but has fewer neuropsychiatric adverse effects than efavirenz.

Efavirenz, although rarely used nowadays, can cause dizziness and vivid dreams. Taking it at bedtime on an empty stomach reduces insomnia and dizziness. It can also cause or worsen depression and increase the risk of suicidal ideation.[31]

Protease inhibitors

Gastrointestinal adverse effects may occur with any antiretroviral therapy, but are most common with protease inhibitors, especially when in combination with a booster drug (cobicistat or ritonavir). Troublesome diarrhoea may be managed with loperamide after exclusion of other causes.

Hyperlipidaemia is a common adverse effect of protease inhibitors, especially ritonavir-boosted regimens. This may require drug treatment in addition to optimising diet and exercise.[32] Simvastatin is contraindicated with boosted regimens as there is an increased risk of rhabdomyolysis. Atorvastatin, rosuvastatin and pravastatin should be started at low doses with careful dose titration to the lowest effective dose with measurement of creatine kinase if indicated. The maximum dose of these statins is reduced when they are taken with boosted regimens.

Common and serious drug–drug interactions

It is crucial to regularly review treatments, including over-the-counter or complementary medicines, in patients taking antiretroviral therapy and to check for potential interactions using the University of Liverpool HIV Drug Interactions website. Drug interactions may not be specific within antiviral classes and may not be easily recognised. If there is any doubt, seek specialist advice as drug interactions can result in antiretroviral therapy failing to suppress

viral replication or can lead to serious and potentially fatal toxicity.

There are specific drug interactions that need to be highlighted to minimise the risk of toxicity or failure of antiretroviral treatment.

Nephrotoxic drugs and tenofovir

The concentrations of renally eliminated drugs such as aciclovir, valaciclovir, aminoglycosides and non-steroidal anti-inflammatory drugs (NSAIDs) may be increased when taken with tenofovir disoproxil fumarate. Acute renal failure after starting high-dose NSAIDs has occurred in patients taking tenofovir disoproxil fumarate.[33] Patients taking tenofovir-based regimens, including PrEP, should be advised not to take NSAIDs and to check with a pharmacist before using over-the-counter medicines.

Metformin and integrase inhibitors

The organic cation transporter 2 is involved in the renal excretion of drugs including metformin. Dolutegravir inhibits this transporter so co-administration doubles the concentration of metformin.[34] The US prescribing information advises that the daily dose of metformin should not exceed 1 g when starting metformin or dolutegravir.

Antacids, multivitamins and integrase inhibitors

The absorption of integrase strand inhibitors is impaired by co-administration of antacids and mineral supplements containing polyvalent cations such as aluminium, magnesium, calcium and iron. These bind and chelate integrase strand inhibitors, impairing their ability to bind to the active site of the HIV integrase enzyme.[35,36] To avoid this interaction, antacids and supplements containing polyvalent cations should be taken separately from the integrase strand inhibitor. For example, dolutegravir should be taken two hours before or six hours after products containing polyvalent cations.[37]

Acid-suppressing drugs and rilpivirine and atazanavir

The absorption of rilpivirine and atazanavir requires an acidic pH so drugs such as proton pump inhibitors and H_2-receptor antagonists reduce absorption.[38] Proton pump inhibitors are contraindicated with rilpivirine as they can cause a failure of therapy. If a patient is taking a proton pump inhibitor with rilpivirine, seek immediate specialist advice. H_2-receptor antagonists should only be taken 12 hours before or at least four hours after rilpivirine.

Steroids and regimens containing ritonavir or cobicistat (boosted protease inhibitors or elvitegravir)

Ritonavir and cobicistat are potent CYP3A inhibitors so they increase the concentration of drugs metabolised through the same pathway including some steroids. Iatrogenic Cushing's syndrome and adrenal suppression can occur in patients taking ritonavir or cobicistat with steroids such as fluticasone, budesonide or mometasone.[39] This interaction has been observed with inhaled, intranasal, intra-articular, topical, and intraocular corticosteroids.[40-42] Seek expert advice if this drug interaction is suspected. As beclomethasone is not metabolised by CYP3A4, it is suitable to use with ritonavir or cobicistat-boosted regimens.

Phosphodiesterase 5 inhibitors and regimens containing ritonavir or cobicistat

The concentrations of phosphodiesterase 5 inhibitors such as sildenafil are increased by boosters (ritonavir and cobicistat), increasing the risk of adverse effects such as priapism and hypotension. A reduced dose (e.g. sildenafil 25 mg) and no repeat dosing within 48 hours is advised.

Vaccination

HIV primarily affects CD4 T-cell numbers and function but also impacts other parts of the immune system, increasing the risk of some infections, many of which are vaccine-preventable. However, patients older than five years with CD4 T-cell counts below 200/microlitre should not be given live attenuated vaccines, such as measles, mumps and rubella vaccine.[43] In addition, responses to certain vaccinations, for example hepatitis B vaccine, may be reduced and so increased doses are recommended. The Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine provides excellent guidance on vaccination.

Vaccination against COVID-19 is advised for people living with HIV. No safety or efficacy data have emerged to cause concern that they are at any greater risk of adverse effects from COVID-19 vaccination.[44] There are no interactions between COVID-19 vaccines and antiretroviral drugs.[45] The Australian Technical Advisory Group recommends that a third primary dose of COVID-19 vaccine should be offered to those with advanced HIV (CD4 counts <250/microlitre) or those with a higher CD4 count unable to be established on effective antiretroviral therapy.[46]

Conclusion

Most current first-line antiretroviral drugs are well tolerated by patients. However, there are important drug interactions and adverse effects that prescribers should be aware of. The safest approach is to check for drug interactions each time using the University of Liverpool HIV Drug Interactions website.

People living with HIV have an increased risk of poorer outcomes from some vaccine-preventable conditions. Immunisation is recommended when possible. ≺

Conflicts of interest: Louise Tomlins has received speaker fees for Gilead Sciences. She is a member of advisory boards for Gilead Sciences and Viiv Healthcare.

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