Antiretroviral pharmacology

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Abstract

There are now >30 antiretroviral medications available for the treatment of HIV. These drugs have distinct sites of action in the HIV life cycle, and unique pharmacological properties that dictate how they can be used safely in the treatment of HIV. Drug–drug interactions (DDIs) can occur because of alterations to several pharmacodynamic processes, including absorption and drug transport, but hepatic metabolism is clinically the most important. Co-administration of antiretrovirals with other, more commonly used drugs is becoming commonplace, and clinicians must be aware of potentially serious interactions that can lead to treatment failure and toxicity.

Keywords Antiretrovirals; drug–drug interactions; HIV; MRCP; pharmacology

Key points

- Antiretrovirals can have unpredictable interactions with many commonly used medications, leading to dangerous toxicities and treatment failure. All interactions should be checked at www.hiv-druginteractions.org, and advice should be sought from a specialist HIV pharmacist
- Switching or stopping therapy can involve complex pharmacokinetic considerations; it is recommended that this is only done under the guidance of an HIV specialist in order to minimize the window period for the development of resistant virus

Introduction

In the era of highly active antiretroviral therapy, human immunodeficiency virus (HIV) can now be managed as a chronic medical condition that requires the continuous use of combination antiretroviral therapy to maintain viral suppression for the individual's lifetime. If this is achieved, the life expectancy of a newly diagnosed person on treatment can approach that of the general population.

A person taking antiretrovirals (ARVs) continuously for an indefinite period poses clinicians and allied healthcare professionals some challenges. This is not least because the ARV agents currently used are not without adverse effects and are prone to drug–drug interactions (DDIs).

Furthermore, as patients are likely to be taking these medications for decades, the likelihood of them requiring co-medications associated with advancing age increases with time. It therefore becomes important that physicians from all disciplines are aware of the broad range of potential interactions that exist between ARVs and medications used in the treatment of other conditions. These interactions can lead to decreased effectiveness of either the ARV or concomitant medication, as well as cause significant toxicity of either drug, although most cases can be safely managed. An understanding of the inherent pharmacological properties of these agents can prolong treatment success, minimize toxicity and avoid dangerous or life-threatening DDIs.

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Antiretroviral medications and their mechanisms of action

There are now >30 ARV drugs available as either single agents or combination tablets. These come from five classes of ARV, each acting at distinct sites in the HIV life cycle (Figure 1). Entry inhibitors prevent attachment of HIV to the target cell surface (CD4+ lymphocytes, various other cells). Non-nucleoside and nucleos(t)ide reverse transcriptase inhibitors (NNRTIs and NRTIs, respectively) prevent production of the double-stranded DNA from the virus RNA. Integrase inhibitors block the transfer and incorporation of the viral DNA strand into the host cell genome. Protease inhibitors prevent assembly of new HIV particles.

Table 1 lists the currently licensed drugs and co-formulations. The aim of therapy is to construct a regimen that enables maximum and durable suppression of HIV replication; the principles of this are discussed elsewhere in this chapter, but it normally consists of at least three drugs to which the virus is susceptible.[1]

Pharmacokinetic considerations

Pharmacokinetic variability

ARVs are subject to substantial intra- and interpatient variability, much like the commonly used anticoagulant warfarin. The numerous factors that cause pharmacokinetic variability include food effects, hepatic and renal impairment, age, sex, pregnancy, endogenous transport proteins, genomics and DDIs (see below).

What is vital in the treatment of HIV is that the amount of drug available to act on the virus is sufficient to fully suppress viral replication; otherwise, there is a risk that drug resistance will develop. Crucial to this is the concept of 'forgiveness', that is, the flexibility to miss doses without risk of virological failure. Both pharmacological and virological forgiveness depend on the presence of viral replication in the presence of drug.[2]

Pharmacological forgiveness and half-lives

Pharmacological forgiveness depends on how long drug concentrations remain above the level shown to be the minimum

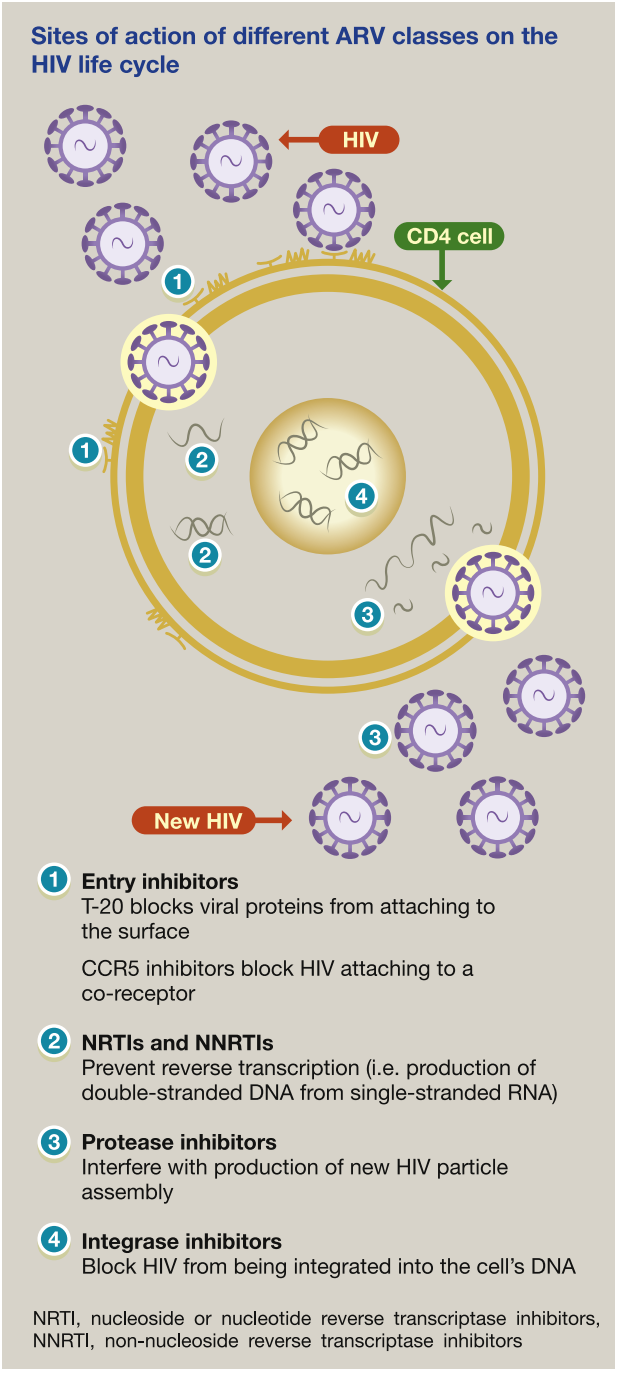

Figure 1 Source: Adapted, from Collins S. Introduction to combination therapy. HIV i-Base Publications, also available at http://i-base.info/guides/wp-content/uploads/2016/09/Intro-to-ART-Sep2016e.pdf (accessed 5 Nov 2017).

required to suppress viral replication (i.e. minimum effective concentration). This is in turn highly dependent on the half-life of the drug (i.e. the time taken for the drug concentration to fall to half its maximum concentration). The half-lives of the various ARVs are extremely diverse and can range from a few hours to >100 hours. Once the drug concentration of any drug in the combination falls below the minimum effective concentration, there is a risk that viral replication may not remained suppressed. This will be partly dependent on the potency of the remaining agents and partly on the amount of time they remain in the therapeutic range.

The presence of drug in the presence of viral replication can and often will result in the selection of drug-resistant variants that may then render one or more components of the regimen ineffective. This is why such attention has been given to the importance of strict timing of taking medication, to avoid development of drug resistance.

Generally speaking, it is very important that patients should not be allowed to run out of medication or have their ARV medication withheld or delayed so as not to compromise their future treatment options. Having an understanding of the relative half-lives of agents in a combination can provide some insight into the likely forgiveness of any particular regimen with regard to the amount of time the drugs are still likely to be active after missing a dose.

An understanding of the half-lives of agents in a regimen can also provide some insight into predicting whether or not resistance to any of the agents may have developed if the patient stopped their medication, either intentionally or unintentionally. Stopping a patient's ARVs is usually not to be recommended unless in an emergency. In practice, there are few indications for discontinuing antiretroviral therapy; if this has to be done (e.g. for toxicity), it should be in consultation with HIV specialist advice.

Virological forgiveness

There is also an interplay between the pharmacological properties of an ARV and its ability to select for resistance if the virus is not fully suppressed. Virological forgiveness generally refers to the number of genetic mutations that are required on the viral genome before the drug loses susceptibility. A drug with a low genetic barrier to resistance is generally one for which a single mutation can cause a significant loss of susceptibility; conversely, a drug with a high genetic barrier to resistance can require the accumulation of multiple mutations before susceptibility is lost.

Generally before considered, the ritonavir and cobicistat-boosted protease inhibitors are considered to have a 'high genetic barrier to resistance'. Conversely, some NNRTIs and NRTIs and first-generation integrase inhibitors (raltegravir and elvitegravir) can develop significant resistance after the development of a single mutation. For these compounds, it is critical to ensure full viral suppression to prevent the virus selecting out drug-resistant variants, leading to regimen failure. Table 2 illustrates ways in which HIV drug failure can be reduced.

Drug–drug interactions

DDIs between ARV agents and other medications are very common. It can be expected that, more often than not, there will be a drug interaction both between ARV agents in a regimen and between ARV drugs and co-medications.

The interactions can occur at many levels from simple absorption onwards. Most interactions result from the induction or

Currently licensed ARVs

Nucleoside or nucleotide reverse transcriptase inhibitors	
Single drugs (abbreviation)	*Co-formulated NRTIs (constituents)*
Lamivudine (3TC)	Truvada (TDF + FTC)
Abacavir (ABC)	Kivexa (ABC + 3TC)
Emtricitabine (FTC)	Combivir (AZT + 3TC)
Tenofovir DF (TDF)	Descovy (TAF + FTC)
Zidovudine (AZT, ZDV)	
Non-nucleoside reverse transcriptase inhibitors	
Single drugs	*Single-tablet regimens (constituents)*
Efavirenz (EFV)	Atripla (TDF + FTC + efavirenz)
Nevirapine (NVP)	Eviplera (TDF + FTC + rilpivirine)
Etravirine (ETR)	Odefsey (TAF + FTC + rilpiverine)
Rilpiverine (RPV)	Triumeq (ABC + 3TC + dolutegravir)
	Stribild (TDF + FTC + elvitegravir + cobicistat)
	Genvoya (TAF + FTC + elvitegravir + cobicistat)
	Symtuza (TAF + FTC + darunavir + cobicistat)
	Integrase inhibitor
	Raltegravir (RAL)
	Dolutegravir (DTG)
	Elvitegravir + cobicistat (ELV/c)
Protease inhibitors[a]	
Atazanavir (ATV)	**Entry inhibitors**
Darunavir (DRV)	Enfurvirtide (T-20)
Lopinavir (LPV)	Maraviroc (MVC) (CCR5 inhibitor)
	Co-formulated protease inhibitor
	Kaletra (lopinavir + ritonavir)
	Evotaz (atazanavir + cobicistat)
	Rezolsta (darunavir + cobicistat)
Ritonavir (RTV)	

TAF, tenofovir alafenamide.
[a] Typically prescribed with a small dose of ritonavir or cobicistat to pharmacoenhance ('boost') levels of the protease inhibitor.

Table 1

Pharmacology of antiretroviral (ARV) therapy key points

Maintenance of therapeutic drug levels is essential to maintain viral suppression and prevent development of drug resistance

- ARV therapy should not be stopped without discussion with an HIV physician, except in emergency situations
- Patients should be allowed to carry their own supply of ARV medication so administration is not delayed
- Accurate and regular timing between doses is important to maintain optimal drug concentrations
- Co-administration with food can significantly alter drug concentrations
- Proton pump inhibitors and antacids can significantly reduce the drug concentrations of several ARVs

Drug interactions are common with HIV ARVs

- Assume that the drug you are going to prescribe for the patient will have a drug interaction with the patient's ARVs
- Most major drug interactions are mediated through the CYP450 enzyme system or drug transporter systems
- HIV drugs can be inhibitors, inducers and substrates of the CYP450 and drug transporter systems
- Take early advice from pharmacists before administering new compounds *or*
- Take advice from web-based resources such as www.hiv-druginteractions.org
- Take special care when prescribing drugs with a narrow therapeutic index that are prone to drug—drug interactions themselves

Table 2

inhibition of cytochrome P450 (CYP450) enzyme systems, with a lesser amount through induction or inhibition of glucuronidation or drug transporter systems; renal interactions tend to be limited to the nucleoside/nucleotide analogue class.

Absorption

ARV absorption can be altered by a number of factors. The presence or absence of food in the stomach is important; some drugs (e.g. the NNRTI rilpivirine) should be taken with food to achieve therapeutic levels. Drugs that change gastric pH can have a significant effect on the availability of some protease inhibitors, notably atazanavir, and also rilpivirine.[3] (see also Edurant in Further reading). Drugs that act to hasten or delay gastric emptying, and those that enhance (e.g. St John's wort) or inhibit metabolism or drug transporters in the gut wall, can also produce changes in drug bioavailability.

Hepatic metabolism

Most ARVs are substrates for liver enzyme metabolism either via the CYP450 system (most ARVs) or by glucuronidation via UDP glucuronosyltransferase family 1 member A1 (UGT1A1) (raltegravir). Induction or inhibition of CYP450 enzymes produces many important DDIs, and a drug can be an inhibitor and inducer at the same time, while being metabolized by a different pathway altogether (e.g. the NNRTI etravirine). CYP3A4 has relatively the most importance of the CYP450 isoenzymes, but each must be considered independently when assessing for interactions.

A comprehensive list of drugs and their interactions with ARVs is beyond the remit of this article; however, examples worth noting include the antimycobacterial agent rifampicin, which is a potent inducer of several CYP450 enzymes, making the treatment of tuberculosis in HIV challenging. In addition, interaction between the pharmacokinetic boosters ritonavir or cobicistat (a CYP450 inhibitor and inducer) and corticosteroids in any form can lead to massively increased corticosteroid concentrations and subsequent cortisol deficiency[4] (see also Corbett in Further reading).

A list of drugs that can give rise to clinically important interactions with ARVs is given in Table 3 (see PEPSE in Further reading). Some interactions can be less predictable than the examples given above; therefore the website www.hiv-druginteractions.org, maintained by the University of Liverpool, is strongly recommended for accessing comprehensive

Drugs that can have clinically important interactions with antiretroviral drugs

Drug class	Examples	Caution	Possible alternative
Metal cations	Aluminium/magnesium hydroxide and calcium carbonate, ferrous sulphate/fumerate	Co-administration of integrase inhibitors with some antacids, iron or multivitamins with polyvalent cations can result in reduced integrase plasma levels	Stop antacids and prescribe a PPI or H_2 antagonist as an alternative if required Avoid oral iron or multivitamins if possible, or space away from integrase dose
Lipid-lowering agents	Simvastatin	May occur when co-administered with ritonavir or cobicistat-boosted PIs; potential for serious reactions such as myopathy and rhabdomyolysis	Atorvastatin is less affected by PI inhibition effect. Use the lowest possible dose and titrate up
Acid-reducing agents	Omeprazole, lansoprazole	Significant decreases in atazanavir and rilpivirine plasma concentrations can occur	H_2 blockers with temporal separation can be used; seek pharmacy advice
Contraceptive hormones	Combined oral contraceptive, subdermal implant	Levels of contraceptive hormone can be decreased by nevirapine, efavirenz and ritonavir	Intrauterine device or depot recommended as main method (plus condom use)
Anticonvulsants	Phenytoin, phenobarbital	Decreased levels of PIs, etravirine, rilpiverine, tenofovir, alafenamide ± anticonvulsant	Levetiracetam
Antidepressants	Fluoxetine Sertraline	Levels of SSRIs may be increased by ritonavir-boosted PIs	Start with the lowest possible dose and titrate up
Benzodiazepines	Midazolam	Levels significantly increased by ritonavir orcobicistat-boosted PIs	Use lowest possible dose and expect prolonged effect
Antimicrobials	Erythromycin, clarithromycin, fluconazole, ketoconazole	Dose adjustments can be required: decreased ketoconazole levels may occur when administered with nevirapine	Penicillins, doxycycline, ofloxacin, trimethoprim and fluconazole suffer the fewest drug interactions
Antimycobacterials	Rifampicin	Rifampicin is a strong CYP3A inducer and can cause profound decreases in concentrations of other PIs and tenofovir alafenamide by P-gp induction. Co-administration is contraindicated	Use modified dose rifabutin if a ritonavir, cobicistat-boosted PI must be used, or double-dose raltegravir, dolutegravir; otherwise efavirenz is preferred as a third agent Seek expert advice
Antihypertensives/ antiarrhythmics	Calcium channel blockers, amiodarone	Calcium channel blocker concentrations can be altered when co-administered with PIs/NNRTIs, caution is advised; co-administration of amiodarone with ritonavir/cobicistat-boosted PIs is likely to increase amiodarone concentrations with potential to produce life-threatening cardiac arrhythmias	Suggest use of β-adrenoceptor blockers or ACE inhibitors as first-line
Immunosuppressants	Tacrolimus	Tacrolimus can be elevated to dangerously high levels when administered with ritonavir/cobicistat-boosted PIs	Stop tacrolimus and reintroduce at lower doses according to tacrolimus levels. Change to an alternative third ARV; seek expert advice
Corticosteroids via any route	Fluticasone, prednisolone, triamcinolone	Co-administration with ritonavir/cobicistat-boosted PIs increases corticosteroids concentrations, potentially leading to Cushing's syndrome and cortisol deficiency	Beclometasone is the main alternative inhaled steroid (not metabolized by the CYP450 route). Consider use of an alternative ARV if more than short-course corticosteroids are required
Erectile dysfunction agents	Sildenafil	Co-administration with ritonavir/cobicistat-boosted PIs substantially increases sildenafil concentrations and can increase adverse events	Use lowest dose and follow maximum frequency guidance
Opioids	Methadone	Co-administration of methadone and ritonavir-boosted PIs and NNRTIs can decrease methadone levels	Dose increases should be considered based on the patient's clinical response to methadone therapy

Table 3 (*continued*)

Drug class	Examples	Caution	Possible alternative
Recreational drugs	Ecstasy (MDMA)	When taken with ritonavir/cobicistat-boosted PIs, MDMA levels can increase	
Over-the-counter medications	St John's wort	Substantially decreases levels of PIs/ NNRTIs/TAF. Contraindicated	

This table should be used as guidance only to raise awareness of potential drug—drug interactions with ARVs. Decisions on prescribing remains the responsibility of the prescribing physician and should be based on the most up-to-date information available.
ACE, angiotensin-converting enzyme; PI, protease inhibitor; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 3

information about potential interactions between commonly prescribed drugs and ARVs. A traffic light system is used to advise about the effects of using combinations of drugs, although caution should be exercised in interpreting 'yellow'/'orange' interactions as there can be a wide range of reasons for this symbol (including a lack of data).

As many as a third of HIV patients may be at risk of clinically important DDIs, so the importance of a thorough medication history cannot be overstated[5] (see also Marzolini et al. in Further reading). This should include enquiry about recreational and over-the-counter medications, as well as creams, herbal remedies, eye drops and inhalers. A specialist HIV/infectious diseases pharmacist should be consulted for advice in interpreting complex DDIs. Further information can also be found in the Electronic Medicines Compendium (www.medicines.org.uk/emc) and from the medical information departments of pharmaceutical companies.

P-glycoprotein (P-gp) and other drug transporters

P-gp 1, also known as multidrug resistance protein 1, is one of many important transmembrane drug transporter systems that are widely distributed around the body. Their role is to actively efflux many foreign substances, including drugs, out of cells. Therefore, drugs that are substrates for transporter-mediated elimination can also be susceptible to DDIs.

The newer NRTI tenofovir alafenamide (TAF) is a substrate of the P-gp transporter. Consequently, drug concentrations can be significantly affected by products that induce P-gp activity (e.g. rifampicin, rifabutin, carbamazepine, phenobarbital); these reduce TAF concentrations in the target cell. Conversely, TAF concentrations can be increased in the target cell for products that inhibit P-gp (cobicistat, ritonavir, ciclosporin) (see Descovy in Further reading). Other ARVs can inhibit or induce drug transporters themselves, and thus elevate or decrease concentrations of concomitant drugs.

Switching therapy

Consideration must be given to many of the previously discussed pharmacokinetic issues when switching ARV therapy because of toxicities or other problems. It is necessary to address the potential induction or inhibition effects of the drugs being stopped and started, and the possibility of persistence of drug long beyond the time of stopping and, essentially, to know whether the viral load is suppressed at the time of switching (and perhaps how long for). Switching ARV therapy is a complex management issue informed by few data and should be done only in consultation with a clinician with the relevant HIV expertise. ◆

KEY REFERENCES

1 BHIVA Treatment Guidelines Writing Group. British HIV Association guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). Available at: http://www.bhiva.org/documents/Guidelines/Treatment/2016/treatment-guidelines-2016-interim-update.pdf (accessed 4 Nov 2017).

2 Bangsberg DR, Kroetz DL, Deeks SG. Adherence-resistance relationships to combination HIV antiretroviral therapy. *Curr HIV/AIDS Rep* 2007; **4:** 65—72.

3 Stöhr W, Back D, Dunn D, et al. Factors influencing lopinavir and atazanavir plasma concentration. *J Antimicrob Chemother* 2010; **65:** 129—37.

4 Foisy MM, Yakiwchuk EM, Chiu I, et al. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. *HIV Med* 2008; **9:** 389—96.

5 Miller CD, El-Kholi R, Faragon JJ, et al. Prevalence and risk factors for clinically significant drug interactions and antiretroviral therapy. *Pharmacotherapy* 2007; **27:** 1379—86.

FURTHER READING

Corbett AH, Sheffield CI. Key pharmacologic principles and drug-drug interactions in HIV patient care. inPractice® HIV. Available at: http://www.clinicaloptions.com/inPractice/Index/HIV.aspx. [Accessed 29 December 2012].

Descovy summary of product characteristics. Gilead Sciences, October 2017.

Edurant summary of product characteristics. Janssen-Cilag, November 2012.

Marzolini C, Elzi L, Gibbons S, et al. Prevalence of co-medications and impact of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antivir Ther* 2010; **15:** 413—23.

PEPSE Guideline Writing Group. UK guideline for the use of post-exposure prophylaxis for HIV following sexual exposure (PEPSE). 2015. Available at: https://www.bashh.org/documents/PEPSE%202015%20guideline%20final_NICE.pdf. [Accessed 4 November 2017].