Antiretroviral pharmacology and drug–drug interactions

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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 commonplace, and clinicians must be aware of potential serious interactions that can lead to treatment failure and/or drug 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 (ARV) therapy, human immunodeficiency virus (HIV) can now be managed as a chronic medical condition, requiring the continuous administration of combination ARV therapy to maintain viral suppression for the individual's lifetime. If this is achieved, the life expectancy of a newly diagnosed person on treatment is comparable to that of the general population.

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

Furthermore, as people living with HIV are likely to be taking these medications for decades, the prospect of them requiring co-medications associated with advancing age will increase over time. For these reasons, it is 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.

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/attachment 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 virus.

Table 1a and b list 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 usually consists of at least three drugs or in certain combinations two drugs, to which the virus is susceptible.[1]

Pharmacokinetic considerations

Pharmacokinetic variability

ARVs are subject to substantial intra- and interpatient variability, much like the 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.

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

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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 required to suppress viral replication (i.e. minimum effective concentration). This is in turn highly dependent on the half-life of the drug (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 will resume, resulting in detectable levels of virus in the blood. This will depend partly on the potency of the remaining agents and partly on the amount of time they remain in the therapeutic range.

Suboptimal drug concentrations in the presence of viral replication can and often do result in the selection of drug-resistant variants that can 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 prevent the development of HIV drug resistance.

Generally speaking, it is very important that patients should not have their ARV treatment interrupted in order to avoid compromising 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 could have developed if the individual has stopped their medication, either intentionally or unintentionally. Stopping a patient's ARVs is usually not recommended unless in an emergency. In practice, there are few indications for discontinuing ARV therapy; if this has to be done (e.g. for toxicity), HIV specialist advice should be sought beforehand.

Virological forgiveness

There is a connection between the pharmacological properties of an ARV and its ability to select for resistance if the virus is not fully suppressed. Virological forgiveness 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.

As a generalization protease inhibitors with a pharmacokinetic enhancer (e.g. cobicistat, ritonavir) are considered to have a 'high genetic barrier to resistance', as are the second-generation integrase inhibitors (e.g. dolutegravir, bictegravir). Conversely, some NNRTIs and NRTIs and first-generation integrase inhibitors (raltegravir, 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

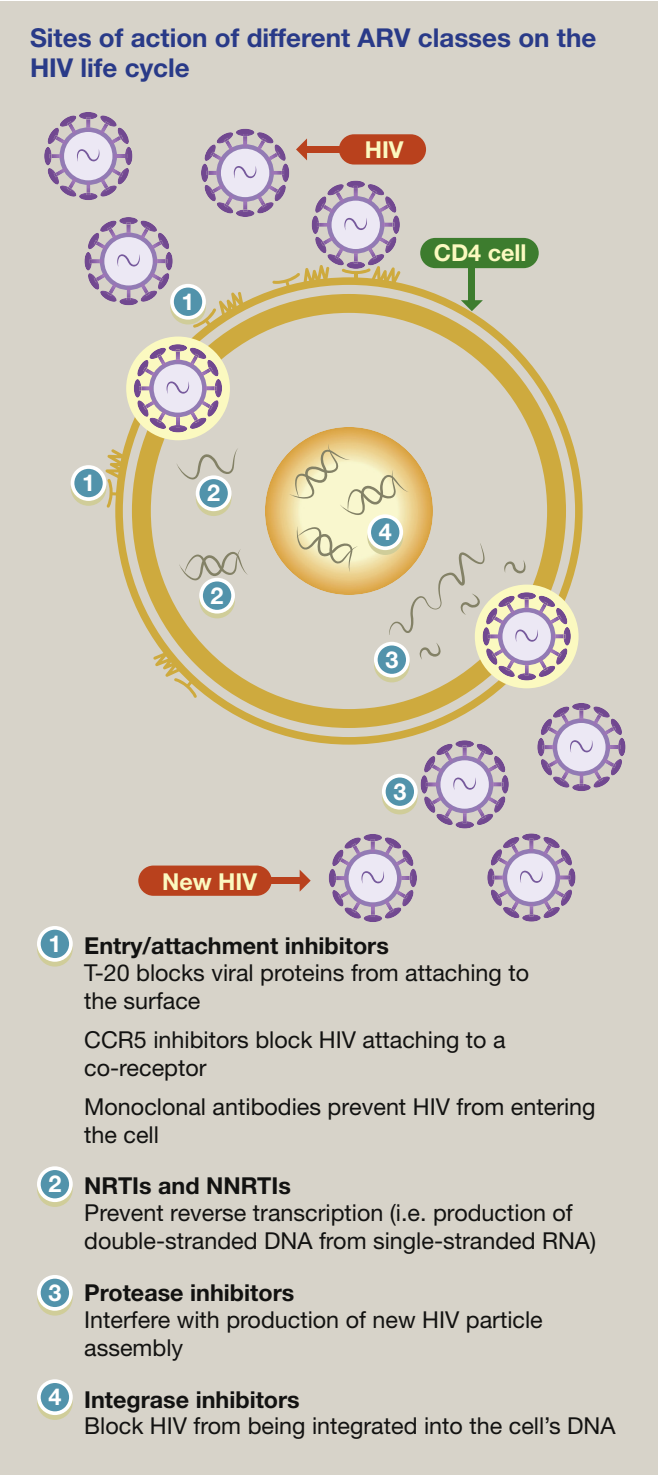

Figure 1 Adapted from Collins S. Introduction to ARV October 2019. https://i-base.info/guides/wp-content/uploads/2019/09/Intro-to-ART-Oct-2019.pdf (accessed 4 January 2022).

Currently licenced ARVs and those in Phase III clinical trials — generic name, (abbreviation) and trade name

Currently licensed ARVs

NRTIs	*Protease inhibitors*	*NNRTIs*	*Fusion inhibitors*	*Entry inhibitors*	*Integrase inhibitors*	*Attachment inhibitors*	*Pharmacological boosters*
Abacavir (ABC) Ziagen	Atazanavir (ATV) Reyataz	Delavirdine[a] (DLVD)	Enfuvertide[a] T20 Fuzeon	Ibalizumab — antibody (IBAL) Trogarzo	Bictegravir (BTG) None	Fostemsavir — capsid inhibitor (FTV) Rukobia	Cobicistat (Cobi/c)
Didanosine[a] (ddI) Videx	Darunavir (DRV) Prezista	Doravirine (DOR) Pifeltro		Maraviroc (MVC) Celsentry	Cabotegravir (CAB LA) Vocabria		Ritonavir (RTV/r) Norvir
Emcitritabine (FTC) Emtriva	Fosamprenavir (fAPV) Telzir	Efavirenz (EFV) Sustiva			Dolutegravir (DTG) Tivicay		
Lamivudine (3 TC) Epivir	Indinavir[a] (IDV) Crixivan	Etravirine (ETR) Intelence			Elvitegravir (EVG) Vitekta		
Stavudine[a] (d4T) Zerit	Lopinavir/ritonavir (LPV/r) Kaletra	Nevirapine (NVP) Viramune			Raltegravir (RTG) Isentress		
Tenofovir AF (TAF) Vemlidy	Nelfinavir[a] (NFV) Viracept	Rilpivirine (RPV)					
Tenofovir DF (TDF) Viread	Saquinavir[a] (SQV) Fortovase						
Zidovudine[a] (ZDV) Retrovir	Tipranavir[a] (TPV) Aptivus						

Agents in Phase III trials

NRTIs	*PIs*	*NNRTIs*	*Fusion inhibitors*	*Entry inhibitors*	*Integrase inhibitors*	*Nucleoside reverse transcriptase translocation inhibitor*	*Capsid inhibitor*
Azvudine				PRO-140 — monoclonal antibody Leronlimab		Islatravir	Lenacapavir

AF, alafenamide; DF, disoproxil fumarate.
[a] These agents are no longer in common usage in the developed world.

Table 1a

Currently approved co-formulated ARV agents

Agent	Type	Trade name
• Abacavir/lamivudine	Dual NRTI	Kivexa
• Emtricitabine/tenofovir AF	Dual NRTI	Descovy
• Emtricitabine/tenofovir DF	Dual NRTI	Truvada
• Lamivudine/zidovudine[a]	Dual NRTI	Combivir
• Lopinavir/ritonavir	Boosted PI	Kaletra
• Darunavir/cobicistat	Boosted PI	Rezolsta
• Atazanavir/cobicistat	Boosted PI	Evotaz
• Dolutegravir/lamivudine (complete regimen)	NRTI + INSTI	Dovato
• Cobicistat/elvitegravir/emtricitabine/tenofovir AF	Dual NRTI + INSTI + booster	Genvoya
• Cobicistat/elvitegravir/emtricitabine/tenofovir DF	Dual NRTI + INSTI + booster	Stribild
• Abacavir/dolutegravir/lamivudine	Dual NRTI + INSTI	Triumeq
• Efavirenz/emtricitabine/tenofovir DF	NNRTI + dual NRTI	Atripla
• Emtricitabine/rilpivirine/tenofovir AF	NNRTI + dual NRTI	Odefsey
• Emtricitabine/rilpivirine/tenofovir DF	NNRTI + dual NRTI	Eviplera
• Dolutegravir/rilpivirine (complete regimen)	INSTI + NNRTI	Juluca
• Cabotegravir/rilpivirine (intramuscular injections — complete regimen)	INSTI + NNRTI	Vocabria
• Bictegravir/emtricitabine/tenofovir AF	Dual NRTI + INSTI	Bictarvy
• Cobicistat/darunavir/emtricitabine/tenofovir AF	Dual NRTI + boosted PI	Symtuza
• Doravirine/lamivudine/tenofovir DF	NNRTI + dual NRTI	Delstrigo

AF, alafenamide; DF, disoproxil fumarate; INSTI, integrase inhibitor; PI, protease inhibitor.
[a] These agents are no longer in common usage in the developed world.

Table 1b

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 the 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 concentrations. Drugs that change the gastric pH can have a significant effect on the availability of some protease inhibitors, notably atazanavir, and also rilpivirine.[3] 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. It is recognized that polyvalent metal cations (e.g. calcium, magnesium, iron and zinc, often found in antacids and multivitamins) can, when co-administered with integrase inhibitors, result in reduced integrase plasma drug concentrations.

Pharmacology of ARV therapy key points

Maintenance of therapeutic drug concentrations 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 any 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 DDIs themselves

Table 2

Drugs that can have clinically important interactions with ARV drugs

Drug class	Examples	Caution	Possible alternative
Metal cations	Aluminium/magnesium hydroxide and calcium carbonate, ferrous sulphate/fumarate	Co-administration of integrase inhibitors with some antacids, iron or multivitamins with polyvalent cations can result in reduced integrase plasma concentrations	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 the integrase dose
Lipid-lowering agents	Simvastatin	Can 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 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	Concentrations 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 concentrations of PIs, etravirine, rilpivirine, tenofovir alafenamide ± anticonvulsant	Levetiracetam
Antidepressants	Fluoxetine Sertraline	Concentrations of SSRIs may be increased by ritonavir-boosted PIs	Start with the lowest possible dose and titrate up
Benzodiazepines	Midazolam	Concentrations significantly increased by ritonavir- or cobicistat-boosted PIs	Use the lowest possible dose and expect prolonged effect
Antimicrobials	Erythromycin, clarithromycin, fluconazole, ketoconazole	Dose adjustments can be required: decreased ketoconazole concentrations can occur when administered with nevirapine	Penicillins, doxycycline, ofloxacin, trimethoprim and fluconazole suffer 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 a reduced dose of rifabutin if a ritonavir or cobicistat-boosted PI must be used. If using raltegravir or dolutegravir, a double-dose must be given. Otherwise, Efavirenz would be the preferred third agent. Seek expert advice
Antihypertensives/ anti-arrhythmics	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 the 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 concentrations when administered with ritonavir/cobicistat-boosted PIs	Stop tacrolimus and reintroduce at lower doses according to tacrolimus concentrations. 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 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

Table 3 (*continued*)

Drug class	Examples	Caution	Possible alternative
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
Biguanides	Metformin	Dolutegravir increases metformin concentrations. Metformin is eliminated renally so it is important to monitor renal function with co-administration. This combination can also increase risk of lactic acidosis in individuals with moderate renal impairment	Metformin, when co-administered with dolutegravir, should not exceed a dose of more than 1 g in a 24-hour period. Monitor renal function
DOACs	Apixaban	Co-administration of apixaban with ritonavir/cobicistat boosted PIs substantially increases apixaban concentrations because of CYP3A4 and P-gp inhibition. This can increase bleeding risk and it is not recommended to be co-administered	Consider the alternative DOAC edoxaban or betrixaban (P-gp) at reduced doses. Alternatively, consider changing ARVs to one of the drugs from the integrase inhibitor class
Opioids	Methadone	Co-administration of methadone and ritonavir-boosted PIs and NNRTIs can decrease methadone concentrations	Dose increases should be considered based on patient's clinical response to methadone therapy
Recreational drugs	Ecstasy (MDMA)	When taken with ritonavir/cobicistat-boosted PIs, MDMA concentrations can increase	
Over-the-counter medications	St John's wort	Substantially decreases concentrations of PIs/NNRTIs/tenofovir alafenamide Contraindicated	

This table should be used only as guidance to raise awareness of potential DDIs 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; DOAC, direct oral anticoagulants PI, protease inhibitor; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 3

Hepatic metabolism

Most ARVs are substrates for liver enzyme metabolism either via the CYP450 system (most ARVs) or by glucuronidation via UGT1A1 (UDP glucuronosyltransferase family 1 member A1; 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. CYP3A4 has, in relative terms, the greatest 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. It is important to recognize that a drug can act as either a perpetrator or a victim of a drug interaction, and sometimes both. 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 potent pharmacokinetic boosters ritonavir and cobicistat (via CYP450 inhibition) and corticosteroids in any form can lead to massively increased corticosteroid concentrations and the potential development of Cushing syndrome. This can even occur with potent inhaled steroids such as fluticasone and injected steroids such as triamcinolone.

A list of drugs that can give rise to clinically important interactions with ARVs is given in Table 3. Some interactions can be less predictable than the examples given above; therefore consulting the website www.hiv-druginteractions.org, maintained by the University of Liverpool, is strongly recommended for accessing comprehensive 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 one-third of HIV patients may be at risk of clinically important DDIs, so the importance of a thorough medication history cannot be overstated. 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 [MDR1] and ATP-binding cassette sub-family B member 1 [ABCB1]), 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 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 tenofovir alafenamide concentrations in the target cell. Conversely, tenofovir alafenamide concentrations can be increased in the target cell for products that inhibit P-gp (cobicistat, ritonavir, ciclosporin). 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 the drug long beyond the time of stopping, in addition to, essentially, knowing 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. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 50-year-old man was found to be HIV positive and was ready to start antiretroviral therapy. He had a history of osteoarthritis after suffering a motorcycle injury several years previously. He was due to be given intra-articular injections of triamcinolone from his pain management team. He had no other medical conditions and was not taking any other medications. He had a fully susceptible HIV virus, with an HIV viral load of 56,000 copies/ml, and a CD4 count of 450 cells/mm^3.

What is the most appropriate regimen?

A. Tenofovir DF + emtricitabine with ritonavir-boosted darunavir
B. Tenofovir AF + emtricitabine + darunavir + cobicistat (Symtuza)
C. Tenofovir DF + emtricitabine + elvitegravir + cobicistat (Stribild)
D. Lamivudine + dolutegravir (Dovato)
E. Dolutegravir + rilpivirine (Juluca)

Question 2

A 24-year-old man with HIV was reviewed because his recent viral load was detectable at 700 copies/ml. It had previously been undetectable. He was shocked as he had been fully adherent to his regimen and had really started looking after his health. He was attending the gym, and taking health supplements such as multivitamins and omega-3. A pill count verified that he had been adherent, and he was not on any other medication besides his antiretrovirals. He was taking Genvoya (tenofovir AF + emtricitabine + elvitegravir + cobicistat).

What is the most likely reason for his increase in HIV viral load?

A. Creatine powder from his gym supplements
B. Omega-3
C. Multivitamins
D. Protein powder
E. High caffeine pre-workout powder

Question 3

A 65-year-old woman presented with a stroke from a cerebral infarct. Treatment with rivaroxaban was being considered. She was HIV positive with an undetectable HIV viral load. Her antiretroviral drug adherence had been excellent. She was taking tenofovir DF + emtricitabine with ritonavir-boosted darunavir. She had remained on a protease inhibitor because she had had historic non-nucleoside and reverse transcriptase inhibitor (NNRTI) drug resistance.

What is the most appropriate advice about rivaroxaban?

A. Give the medication with the dose unadjusted
B. Switch from ritonavir-boosted darunavir to an NNRTI
C. Switch from ritonavir-boosted darunavir to an unboosted integrase inhibitor
D. Switch to Genvoya (tenofovir AF + emtricitabine + elvitegravir + cobicistat)
E. Increase the dose of rivaroxaban