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

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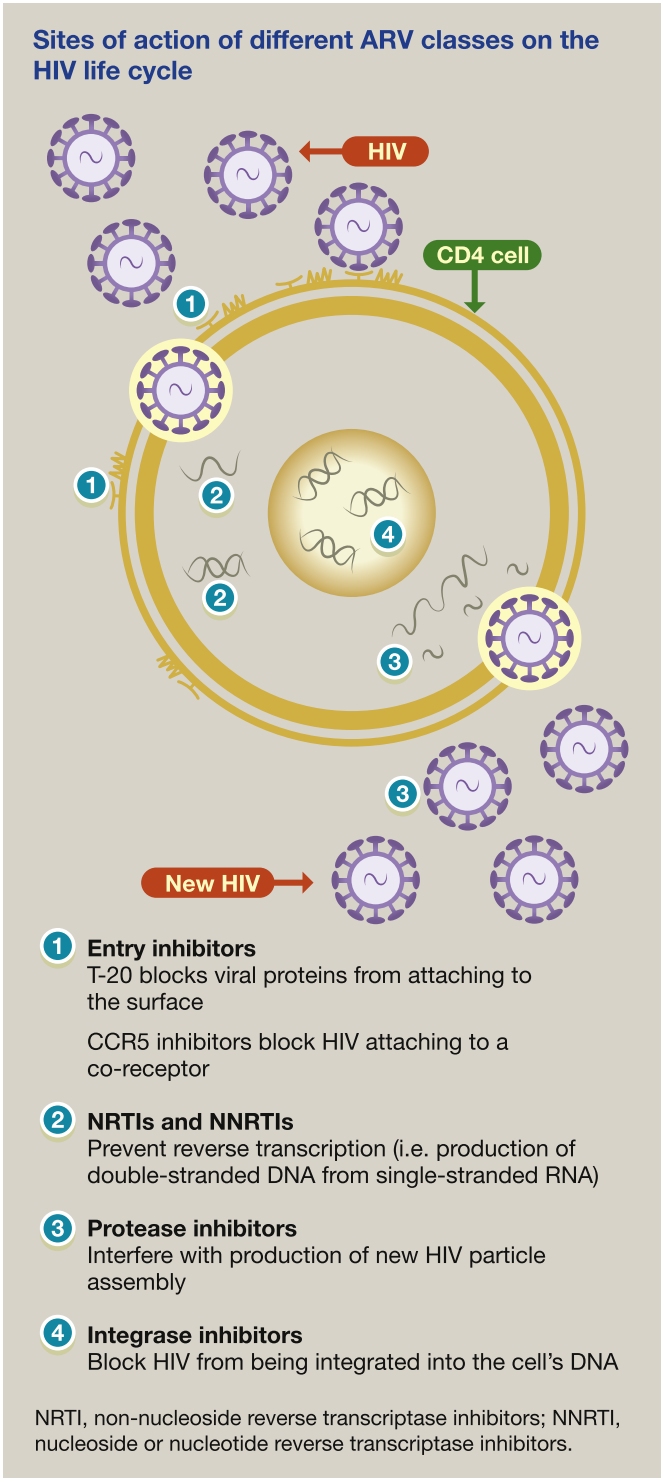

Figure 1 Source: Adapted, from Collins S. Introduction to combination therapy. HIV i-Base Publications, also available at http://i-base.info/guides/wp-content/uploads/2016/09/Intro-to-ART-Sep2016e.pdf (accessed 5 Nov 2017).

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

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