Antiretroviral drug interactions: often unrecognized, frequently unavoidable, sometimes unmanageable

Kay Seden1*, David Back2 and Saye Khoo2

1NIHR Biomedical Research Centre, Royal Liverpool & Broadgreen University Hospitals Trust, Liverpool, UK; 2Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, UK

Patients with HIV who are receiving antiretroviral (ARV) therapy are at high risk for drug–drug interactions (DDIs), which can significantly impact patient care and represent a substantial opportunity cost for healthcare systems. DDIs are prevalent in the developed world and in resource-poor settings, with the cost being potentially greater in the latter. Although practically unavoidable in HIV care, many DDIs can be better managed, reducing the risks to patients and the burden on resources. The scope for DDI management is likely to be greater in the developed world, due to the availability of new agents and second-line drugs, which allow greater flexibility of ARV regimens and co-administered drug choice. The advent of electronic prescribing and patient medication records represents an opportunity to aid the identification and management of DDIs. Searchable electronic databases of HIV drug interactions are available, which are a useful tool for HIV healthcare professionals and non-specialists for managing DDIs involving ARVs. Although general active systems that alert prescribers to DDIs currently exist, there is an indication for the development of specialist active databases to be incorporated into electronic prescribing or dispensing systems, with the aim of improving the quality of prescribing and the safe dispensing of the therapeutically risky drugs and complicated regimens used in HIV management.

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Introduction

Drug–drug interactions (DDIs) are an important, widely under-recognized source of medication errors, which represent a significant opportunity cost for healthcare systems. The co-administration of contraindicated drugs has been found to account for 5.2% of 209 hospital admissions in patients receiving antiretrovirals (ARVs). Although studies are limited, clinically significant DDIs involving ARVs are common, affecting at least 14% of 342 patients in the USA and 23%–26% of 220 HIV-infected outpatients in the Netherlands. A substantial proportion of these could have had an adverse impact on ARV exposure. Data from developing countries are sparse, though it is likely that clinically significant DDIs are prevalent.

Lowering of ARV or concomitant drug levels to below therapeutic ranges can lead to treatment failure and also drug resistance, reducing the number of effective regimens available to treat the patient. Conversely, DDIs may result in increased exposure to ARVs or co-administered drugs, precipitating drug toxicity or greater severity and incidence of adverse reactions.

Polypharmacy is largely unavoidable for patients receiving ARVs in both the developed world and resource-poor settings, with life-long treatment and changes of drug combinations along the way almost a certainty. Highly active antiretroviral therapy (HAART) involves a regimen of at least three agents. One study in general medical patients found that the risk of DDIs rose from 13% in patients taking two drugs to 82% in patients taking seven or more.

DDIs may arise due to the pharmacokinetics or pharmacodynamics of administered compounds. ARVs are among the most therapeutically risky drugs for DDIs, due to potent inhibition or induction of liver enzymes, such as the cytochrome P450 isoenzymes (CYP450), which metabolize a broad array of other medications. DDIs involving protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are more likely to be attributable to hepatic metabolic pathways than DDIs involving nucleoside or nucleotide reverse transcriptase inhibitors, which in some cases can be due to competition for renal tubular secretion. Studies undertaken during drug development, in Phase IV and retrospectively from patient...
Risk factors for HIV DDIs

New drugs

The introduction of new ARV agents increases the number of effective regimens available, but also the complexity of treatment. Assessment of the potential for DDIs during the clinical phase of drug development, although comprehensively undertaken, is at best incomplete. Screening of a new molecular entity for potential as a substrate, inducer or inhibitor of Phase I and Phase II metabolic enzymes and influx/efflux drug transporters is limited by a lack of validated expression systems and standardized protocols, particularly for drug transporters.

It cannot be assumed that drugs from the same class have broadly similar potential for interaction. One example is the novel class of HIV drugs, the integrase inhibitors, of which raltegravir is the first licensed. Raltegravir is predominantly metabolized by UGT1A1-mediated glucuronidation, with little potential to interact with CYP450 enzymes; whereas elvitegravir, an integrase inhibitor currently in Phase III trials, though conjugated by UGT1A1 and 1A3, is largely metabolized by CYP3A4, and therefore DDIs are possible with the many drugs that also interact with this pathway. These effects may be complex in the presence of ritonavir boosting, since the overall dominant effect may vary according to the interacting medication.

In addition, there will always be surprises from unanticipated DDIs that emerge after licensing, and may lead to increased risk of toxicity or diminished therapeutic effect. These shed new light on mechanisms of drug metabolism and disposition. One example is the interaction observed with lopinavir and rosuvastatin: since the latter is not extensively metabolized by CYP450 enzymes, a significant interaction was not anticipated. However, interaction studies revealed a 4.7-fold increase in rosuvastatin plasma levels, coupled with a diminished lipid-lowering effect.

One possible explanation for this is inhibition of the hepatic influx transporter OATP1B1, leading to a greater plasma exposure with associated risk of statin-induced myopathies, but a blunted lipid-lowering effect, since rosuvastatin exerts its effect in the liver. This highlights the need for standard protocols for interaction screening of new drugs, as well as clinical vigilance as experience in their use develops.

Co-infection

In many developing countries, HIV/AIDS epidemiology may overlap with other infections such as tuberculosis (TB). In some African countries, up to 70% of new TB cases are detected in HIV-infected individuals; however, TB infection risk is considerably higher in HIV-infected patients, irrespective of the setting. TB therapy, like HIV treatment, is complicated by drug resistance and requires multiple agents, which have varying potential to interact with ARVs. Difficulties in treating TB in HIV patients may arise due to interactions with rifampicin, a potent inducer of liver enzymes. Many ARVs contraindicate the use of rifampicin, while others may require dose modification. Not all dose adjustments are straightforward however; for example, when co-administered with rifampicin, there are wide inter-individual variations in plasma efavirenz concentrations.

Associations between efavirenz plasma concentrations and factors such as weight and ethnicity have been noted; dose adjustments may be required in some patients and specialist advice is essential.

The problems facing developing countries may be greater due to inflexibility of treatment regimens and lack of access to safer alternatives when there is a risk of DDIs. The resources to monitor patients for signs or symptoms of adverse reactions may be limited, and the access to therapeutic drug monitoring may not be available to determine the pharmacokinetic implications of co-administered drugs. ARV coverage in middle- and low-income countries has increased 45% between 2006 and December 2007. As ARV coverage increases, it is likely that access to other medications will also improve, e.g. various integrated programmes for ‘neglected’ tropical diseases, which aim to combine mass drug administration for conditions such as helminth infection. This inevitably increases the scope for DDIs.

Infection with hepatitis C virus (HCV) is a common cause of morbidity in HIV patients. Therapy for chronic HCV infection, which conventionally involves ribavirin and interferon, is set to dramatically change with the proliferation of new drugs directed against HCV polymerase, protease and other targets. Emerging HCV therapies join ARVs in being among the most therapeutically risky drugs for DDIs, due to inhibition or induction of liver enzymes. Preliminary data for two HCV PIs in advanced development, telaprevir and boceprevir, suggest that DDIs are likely to be major issues in this class of drugs, in a manner analogous to HIV PIs. Interactions may also exist with HCV polymerase inhibitors and ribavirin. It therefore follows that treatment of co-infection will become increasingly complex.

There are a number of well-recognized opportunistic infections associated with HIV infection, for which patients may require treatment or prophylaxis. Although HIV specialists may be experienced in the treatment of such conditions, the agents used often have complex interactions with ARVs. For example, the exposure of manyazole antifungals is increased by PIs and decreased by NNRTIs, but some azoles such as fluconazole may also increase exposure of nevirapine and other ARVs.

Polypharmacy and an ageing population

The introduction of HAART in the mid-1990s has led to increased life expectancy for HIV patients. Due to the increasing ability to significantly alter the natural history of HIV infection, patients are more likely to be exposed to a broader range of concomitant medication. As one would expect, the likelihood of being prescribed contraindicated medication alongside ARV regimens has been found to increase significantly in older patients. There is an increasing number of patients over 50 years of age living with HIV, hence, HIV can be viewed as a chronic condition, which will eventually need to be managed alongside chronic conditions associated with ageing.

As a result of disease state and metabolic side effects of ARV regimens, HIV patients often are at high risk for cardiovascular disease. The choice of lipid-lowering agents, antihypertensives and smoking cessation therapy need to be carefully considered in these patients, and the most appropriate agents may not always be those used first line in hospital formularies.

Over the counter products cannot be disregarded; 19% of 632 patients taking ARV in Canada and 61% of 293 HIV patients
surveyed in the UK have used herbal remedies or supplements.\textsuperscript{18} In the UK study, 20\% could have potentially compromised their HIV management as a result. It is likely that in practice the use of herbal remedies and supplements that have potential to be problematic in HIV care, such as St John’s wort, garlic and echi-nacea,\textsuperscript{19} are often under reported by patients or the information not routinely requested by healthcare professionals.

Another factor that may be significant is the impact of recreational or illicit drug use on HIV management. Interaction studies are few and patients may not give accurate information about their use.

**Decentralized care**

In the UK, the care model for HIV has very much been within tertiary care. However, aspects of HIV treatment are likely to progressively decentralize to primary or secondary care settings over the next few years, meaning that HIV-infected patients are likely to receive various medications from multidisciplinary teams. Patients may already receive medication for other conditions from other hospital departments, general practitioners or community pharmacies. A lack of comprehensive medication history available to those involved in patient care may increase the risk of DDIs.

Similarly in the developing world, HIV management is likely to decentralize from tertiary centres to district level, where HIV patients may be managed by practitioners with less expertise in HIV management as a result. It is likely that in practice the use of herbal remedies and supplements that have potential to be problematic in HIV care, such as St John’s wort, garlic and echinacea,\textsuperscript{19} are often under reported by patients or the information not routinely requested by healthcare professionals.

What can be done to minimize harm from DDIs?

While most DDIs involving HIV drugs are essentially unavoidable, many can be better managed. For example, dose adjustments to manage efavirenz-based interactions have been associated with significant reductions in HIV viral load.\textsuperscript{19} Therefore, the identification of clinically significant DDIs is fundamental to improving the quality of prescribing in HIV management. Studies have shown that physician awareness of DDIs is poor: less than half of clinically significant DDIs were recognized by physicians in a survey of 159 consecutive patients receiving ARVs.\textsuperscript{20}

In resource-poor settings, inflexibility of regimens may make management of DDIs more of a challenge. On a public health level, the scale-up and coverage of ARVs, antimalarials and anti-TB drugs may take precedence over the quality of prescribing in the first instance. However, as coverage increases, a programmatic approach could be taken on national or regional levels to improve vigilance for and recognition of important DDIs.\textsuperscript{21} In areas where disease epidemiology overlaps, protocols for treatment of co-infection could be incorporated into existing ARV programmes, taking into account local drug availability.

To identify DDIs effectively, all prescribers must have access to a complete list of medication currently taken by the patient. In a study where a complete list of currently used drugs was supplied to the prescriber prior to HIV outpatient clinics, the reduction in DDI incidence as a result of the intervention was found to be significant.\textsuperscript{3} Included in the list was a report from the patients’ regular community pharmacist, detailing medicines issued in primary care. Such an intervention may, however, rely on the patient consenting to disclose their HIV status to practitioners in primary care. The UK Department of Health is extending a programme to create an electronic summary of medical details, accessible to authorized healthcare professionals.\textsuperscript{22} This will include details of the patient’s current medication and will eventually become a national database, as no doubt will become common practice worldwide. Electronic records may help to ensure continuity between sets of hospital notes and community records, and access may aid safer, better-informed prescribing by general practitioners. Likewise, if community pharmacists have access to a patient’s electronic healthcare records, they are better equipped to advise patients on the most appropriate therapies for minor ailments and the use of vitamins, dietary supplements and herbal remedies.

Computer programs containing databases of interacting drugs represent a practical and effective method for detecting potential DDIs. However, there are limitations. Searchable databases, which are essentially passive, rely on the motivation of the prescriber or pharmacist to seek further information on a particular combination. Concordance may also differ between databases.\textsuperscript{23} Active systems may be integrated into electronic prescribing systems, and also at the point of dispensing. They are designed to alert the prescriber or pharmacist to potential interactions at each prescribing or dispensing activity, taking into account the recorded drug history for that patient. However, there is often the option to suppress interaction alerts, so that they are not flagged on subsequent prescribing or dispensing of a particular combination. ‘Alert fatigue’ may occur, if relatively minor interactions are overcalled, or if new or non-formulary drugs have a default warning.\textsuperscript{23} A study that identified ARV medication errors in hospitalized patients found that warnings concerning contraindicated drugs had frequently been ignored.\textsuperscript{3} Although DDIs may effectively be identified, the impact of the intervention is reliant upon the individual to assess the clinical relevance of DDIs and act accordingly. Twenty-two per cent of surveyed general practitioners admitted that they had overridden electronic DDI alerts without first checking for clinical relevance.\textsuperscript{24}

The importance of currency of information found in databases is clear, particularly when new ARVs and ARV classes are introduced to practice, and new data concerning their use are updated as clinical experience develops. The performance in terms of sensitivity and specificity of electronic systems to identify DDIs involving ARVs have not been formally assessed, and variation between databases is likely. It is possible that general, non-specialist databases could flag major interactions between drugs that are commonly co-prescribed in HIV care, such as dose-adjusted rifabutin with atazanavir or ritonavir.\textsuperscript{25} Hence, there is an indication for the development of specialist databases to be incorporated into electronic prescribing or dispensing systems, with the aim of improving the quality of prescribing and the safe dispensing of the complicated regimens seen with HIV management.

**Conclusions**

DDIs are largely unavoidable in HIV management, and the problem is likely to worsen. They can significantly impact patient care and lead to morbidity if not appropriately managed. Tools that are currently available to minimize harm arising from DDIs include HIV drug databases such as the UK’s national medicines database, computer programs containing databases of interacting drugs and electronic prescribing systems. However, there are limitations. Searchable databases, which are essentially passive, rely on the motivation of the prescriber or pharmacist to seek further information on a particular combination. Concordance may also differ between databases. Active systems may be integrated into electronic prescribing systems, and also at the point of dispensing. They are designed to alert the prescriber or pharmacist to potential interactions at each prescribing or dispensing activity, taking into account the recorded drug history for that patient. However, there is often the option to suppress interaction alerts, so that they are not flagged on subsequent prescribing or dispensing of a particular combination. ‘Alert fatigue’ may occur, if relatively minor interactions are overcalled, or if new or non-formulary drugs have a default warning. A study that identified ARV medication errors in hospitalized patients found that warnings concerning contraindicated drugs had frequently been ignored. Although DDIs may effectively be identified, the impact of the intervention is reliant upon the individual to assess the clinical relevance of DDIs and act accordingly. Twenty-two per cent of surveyed general practitioners admitted that they had overridden electronic DDI alerts without first checking for clinical relevance.

The ability to incorporate such tools into electronic prescribing in order to actively manage DDIs through ‘interaction alerts’ would represent a major advance. We also propose that audits of the frequency and severity of potential DDIs are routinely incorporated into metrics for quality of prescribing, both in the developing and developed world.

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