J Antimicrob Chemother 2013; **68**: 1–3
doi:10.1093/jac/dks346 Advance Access publication 22 August 2012

Journal of Antimicrobial Chemotherapy

Global patient safety and antiretroviral drug–drug interactions in the resource-limited setting

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Scale-up of HIV treatment services may have contributed to an increase in functional health facilities available in resource-limited settings and an increase in patient use of facilities and retention in care. As more patients are reached with medicines, monitoring patient safety is increasingly important. Limited data from resource-limited settings suggest that medication error and antiretroviral drug–drug interactions may pose a significant risk to patient safety. Commonly cited causes of medication error in the developed world include the speed and complexity of the medication use cycle combined with inadequate systems and processes. In resource-limited settings, specific factors may contribute, such as inadequate human resources and high disease burden. Management of drug–drug interactions may be complicated by limited access to alternative medicines or laboratory monitoring. Improving patient safety by addressing the issue of antiretroviral drug–drug interactions has the potential not just to improve healthcare for individuals, but also to strengthen health systems and improve vital communication among healthcare providers and with regulatory agencies.

Keywords: medication errors, HIV, drug interactions

In Epidemics 400 BC, the ancient Greek physician Hippocrates advises '*Primum non nocere*'—first do no harm. While there is debate as to whether this is actually part of the Hippocratic Oath, many medical schools incorporate the dictum into their graduation ceremonies. Though intentional maleficence is rare, concerns about patient safety (defined as the absence of preventable harm to a patient during the process of healthcare) have prompted the formation of a WHO patient safety programme in response to a World Health Assembly in 2002. The vision of the WHO patient safety programme is that 'every patient receives safe health care, every time, everywhere'.

According to an Institute of Medicine Report, medication errors (broadly described as any error in the prescribing, dispensing or administration of a drug) are among the most common type of preventable medical errors.[1] Commonly cited preventable causes of medication error include the speed and complexity of the medication use cycle combined with inadequate systems and processes.[2] In the USA, medication errors have been estimated to occur at a rate of 2%–14% of patients admitted to hospital and account for 1 in 20 hospital admissions per year and result in 7000 deaths per year.[3,4] Data on medication errors in the resource-limited setting are restricted to a number of small studies. A recent study in Egypt noted errors in 4.18% of prescriptions in an obstetrics emergency ward and were largely attributable to either administration or medication omission errors, especially at night.[5] The prevalence of prescribing errors in an intensive care unit of a specialist hospital in Ethiopia was 52.5%, with 32.5% related to antibiotic usage.[6] A non-randomized interventional study in an ophthalmology clinic in Thailand reported a medication prescribing error rate of 32.9%.[7] The first cross-sectional exploratory study evaluating prescription errors in Sudan found that only 0.1% of prescriptions were considered ideal and error free.[8]

Unrecognized drug–drug interactions (DDIs) are one of the most common causes of medication errors. DDIs may be pharmacokinetic or pharmacodynamic in nature and can result in raising or lowering the concentration of co-prescribed drugs. Depending on the magnitude of the interaction, elevated drug concentrations may be associated with drug toxicity and lower concentrations may be associated with therapeutic failure. Subtherapeutic drug concentrations are of particular concern in the discipline of infectious diseases due to the possible emergence of drug-resistant strains that can compromise the utility of anti-infectives on an individual patient or population basis.

Antiretroviral (ARV) drugs are among the therapeutic agents with the highest potential for DDIs. Both the protease inhibitors

and the non-nucleoside reverse transcriptase inhibitors are substrates for and modulators of the cytochrome P450 isoenzyme system. Additionally, drug interactions with ARV drugs can occur through other mechanisms, including drug transporters, glucuronidation, nuclear receptor activation and pH-dependent drug absorption. Overlapping toxicities also require consideration when administering drugs alongside ARV regimens, e.g. myelosuppression with zidovudine, or cardiac QT interval prolongation with some protease inhibitors. Consensus international and national guidelines for the management of HIV-infected patients recommend initiating therapy with either a protease inhibitor- or non-nucleoside-based regimen and then switching to a non-nucleoside- or protease inhibitor-based regimen, respectively, in cases of therapeutic failure. This represents an unprecedented risk for DDIs, as it often results in discontinuation of a potent inhibitor or inducer and switching to a potent inducer or inhibitor, respectively. Detection of subtherapeutic ARV levels is complex in the absence of therapeutic drug monitoring, as there is often a delay between the index prescribing event and the emergence of clinical or virological failure. Furthermore, the wide inter-individual variability in drug levels characteristic of drugs metabolized by cytochrome P450 3A4 makes generalizability problematic.

Data from the developed world suggest that DDIs occur at rates of 14%–41% in the Netherlands, the USA, Switzerland and the UK.[9–12] In a detailed study in Liverpool, UK, 27% of HIV-infected patients were noted to have clinically significant drug interactions, defined as those for which the manufacturer's Summary of Product Characteristics advised that the combination was (i) contraindicated, (ii) not recommended, (iii) should be avoided, (iv) requires dose modification or (v) clinical or laboratory monitoring for serious toxicity is recommended. Furthermore, 15% of the DDIs had the potential for lowering the concentration of ARV drugs with the attendant risks of generating resistance. Only 36% of clinically significant drug interactions were recognized by physicians. We reported that clinically significant drug interactions in HIV care are common and unavoidable and that recognition is necessary for safe and effective prescribing.[12]

The Swiss HIV cohort reports that 40% of patients had a potential DDI and 4% had the potential to lower ARV drug concentrations. The authors suggest that the results were possibly biased by the fact that data were drawn from expert care clinics with specialized doctors, nurses, pharmacists, clinical pharmacologists and access to web-based drug interaction databases.[11] The rates of potential DDIs despite expert care supports the conclusion of the Liverpool group that such interactions are largely unavoidable, although they are often manageable if recognized.

There are limited data on clinically significant DDIs in the resource-limited setting. Resource-limited settings are at high risk for ARV DDIs because of the large number of individuals on treatment, limited laboratory monitoring, limited training of some healthcare workers and limited ability to manage DDIs by altering dosing due to the use of fixed-dose combinations. Medication recording may be poor, particularly between hospitals and the community, and within hospitals where 'vertical' programmes for HIV, tuberculosis and malaria exist. Moreover, the high rate of background illness resulting in fever, hepatic dysfunction or gastrointestinal or neurological symptoms may mask patient harms due to DDIs.

The identification and management of DDIs requires accurate documentation of the medication history at all patient care service points. For patients accessing HIV care in the UK, concordance of medication recording between hospital departments has been found to be poor:[13] 22% of DDIs observed in a UK cohort occurred between ARVs and medication that was not recorded in the HIV clinic notes, e.g. medication prescribed in primary care.[14]

The wide availability and accessibility to over-the-counter medication and herbal remedies make polypharmacy common in resource-limited settings. Polypharmacy increases the risk for DDIs as well as adverse drug reactions. Inadequate human resources in the health sector in a setting with a high disease burden poses significant challenges for adequate risk–benefit evaluation and comprehensive documentation by the prescribing physicians. Many hospitals in resource-limited settings often have poorly defined systems and policies for inpatient prescribing, and inpatient prescriptions may exclude patients' ongoing ARV drugs. It is not uncommon for patients or their relatives to continue administering ARV drugs in addition to inpatient medicines, with or without the knowledge of healthcare workers. Often the physician is restricted to a limited choice of drugs to prescribe depending on availability in the public health facility. Availability of the less expensive fixed-dose combinations and scarcity of separate pills makes the alteration of drug combinations difficult even when the physician has knowledge of potential DDIs. Computerized records and access to online prescribing resources are usually limited to centres of excellence. Specific considerations for ARV DDIs in the resource-limited setting include the high rates of comorbidities with tuberculosis and malaria. The cornerstones of treatment for both tuberculosis and malaria involve drugs that are known to interact with ARV drugs.[15,16] Additionally, healthcare provision in many resource-limited settings involves independent silos of healthcare delivery, which again complicates the communication process and increases the risks for unrecognized DDIs. Task shifting as endorsed by the WHO as a response to the lack of healthcare providers has been adopted in many resource-limited settings. Task shifting refers to the training of mid-level practitioners to perform tasks traditionally assigned to doctors, thereby enabling non-professional personnel to perform less technical tasks in order to expand the total output from both the formal and informal health systems. The management of HIV-infected patients in many resource-limited settings may be carried out by nurses or clinical officers. While task shifting may be seen as a risk factor for ARV DDIs, it could also be viewed as an opportunity, as task shifting usually involves adherence to standard operating procedures and referral for cases that fall outside of that framework. Therefore, including specific instructions for managing commonly encountered drug interactions in the standard operating procedures may be beneficial. Herbal medicines have the potential to interact significantly with ARVs, and estimates in Uganda suggest that ~30% of HIV-infected patients use traditional medicines concurrently with ARVs.[17]

In the developed world, the management of DDIs may involve substitution of a medication or adjustment of doses. Clinical vigilance and laboratory monitoring are routinely utilized in such situations, but these afford little protection to patients in resource-limited settings.

Detection of the consequences of DDIs is problematic in the resource-limited setting due to the high patient threshold for

seeking healthcare and the confounding effect of syndromic management of fever, which may be a common presenting feature of drug toxicity. Furthermore, pharmacovigilance and post-marketing surveillance, which are essential components of the patient safety chain, are very poorly developed and grossly underutilized in the very settings that most need them.

To our knowledge there is only one study on clinically significant drug interactions with ARVs in a resource-limited setting. A study of 996 consecutive Kenyan patients found that 33.5% were at risk of clinically significant DDIs, with 12% of the interactions potentially lowering ARV drug concentrations. The DDIs most commonly involved rifampicin, azoles, steroids and antimalarial drugs. Multivariate analysis identified patients with lower CD4 cell counts, lower body weights and more advanced disease as being at highest risk of clinically significant DDIs.[18] Although the commonly co-administered medication differs, these data are reassuringly comparable to drug interaction data from the developed world. However, this may not be representative of other resource-limited settings, as the study was conducted in a tertiary university teaching hospital within a well-funded donor programme. We await further similar studies in diverse settings to assess the generalizability of these data.

Any efforts to improve patient safety in the developing world must involve existing ARV treatment programmes, in view of the recent mass deployment of ARV therapy, which is a recognized high-risk therapeutic area. However, the very existence of wide-scale access to ARV therapy provides us with a positive proof of principle of just what is possible in the developing world. Additionally, this is an unprecedented time in history, with opportunities to innovate using solar power, mobile technology including mobile applications, Internet access even in remote locations and the acceptability of task shifting in many settings. Studies that seek to not only record the prevalence of errors and drug interactions, but also to record the impact in terms of actual patient harms are needed. Improving patient safety by addressing the issue of ARV DDIs has the potential not only to improve healthcare for individuals, but also to strengthen health systems and improve communication among healthcare providers and regulatory agencies.

Acknowledgements

We thank the National Institute of Health Research (NIHR Department of Health) and the Northwest Development Agency (NWDA) for infrastructural and project support.

Transparency declarations

S. H. K. has received research funding for web site development from Merck, Bristol-Myers Squibb, Gilead, ViiV, Tibotec and Abbott, and honoraria and travel support for conference attendance from Roche, Tibotec and ViiV in the past 3 years. All other authors: none to declare.

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