**Drug interactions and the role of pharmacokinetic trials in guiding choices in first-line HIV therapy**

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**Abstract**

***Purpose of review:*** Low and middle income countries (LMICs) face specific challenges in the treatment of patients living with HIV. Drug-drug interactions (DDIs) involving antiretrovirals (ARVs) are prevalent in all settings and have considerable potential to cause clinical harm to patients via toxicity, or reduced efficacy of treatment. Differing co-morbidities, endemic infections and traditional medicines may complicate ARV therapy in LMICs, which is often protocol-driven in these settings, with fewer alternative regimens available.

This review discusses the issues surrounding pharmacokinetic DDI studies and their application to ARV treatment in LMICs, with particular reference to first line ARV regimens.

***Recent findings:***

Pharmacokinetic studies with clinical endpoints are the gold standard for informing management of DDIs, however data relevant to LMICs are sparse, and of low quality. There is significant potential for clinically relevant DDIs between ARVs and antimalarials, antimycobacterials and drugs used in the treatment of neglected tropical diseases.

***Summary:***

Many PK studies are difficult to interpret in LMICs, due to differences in patient factors including weight, disease state and genetic polymorphisms. DDI studies relevant to LMICs may also be lacking, due to the neglected nature of relevant comorbidities. The ARVs currently available as first-line therapy in LMICs are among those with highest propensity for DDIs.

**Key words:** Drug-drug interactions, pharmacokinetics, HIV/AIDS

**Introduction**

Drug interactions have considerable potential to cause clinical harm to patients via toxicity, or reduced efficacy of treatment and/or drug resistance. The prevalence of drug-drug interactions (DDIs) involving antiretrovirals (ARVs) in low and middle income countries (LMICs) is high, reported at 18.7% and 33.5% in Ugandan and Kenyan adult outpatients respectively,[1, 2], 51% of Argentinian adolescents,[3] and 34% of Thai patients.[4]

Well-designed pharmacokinetic studies which include clinical outcomes are the benchmark for high quality evidence to inform treatment recommendations in the presence of DDIs.[5] Such studies accurately characterise how one drug may affect the exposure of another and if clinical endpoints are included, describe the prevalence of toxicity or treatment failure which results, putting the clinical significance in context. However, for reasons of cost, practicality, and sometimes ethics, such studies are rare. Most PK studies are powered to show a change in a key PK parameter rather than clinical outcomes, and include a small number of volunteers who are not affected by the disease in question, which is permissible for drug licensing. The relevance of interactions is therefore often difficult to interpret in the context of clinical care, particularly for special populations (liver/renal impairment, pregnancy, children). Considered alongside, or in the absence of PK DDI studies, observational cohort studies or case reports may characterise clinical harm from potential DDIs, and in real patient cohorts, but they may be subject to various confounders.

When seeking to make recommendations on the management of DDIs, the quality of the evidence which informs the recommendation should be taken into account. As for guideline development, or systematic review, the quality of evidence rating and strength of recommendation are affected by several factors.[6] In the case of PK data, study design (single vs multiple dose), sampling methods (sparse or rich), sample size, disease status of participants and magnitude of PK effect are important, however, formal methods for taking these factors into account have only recently been published.[5]

This paper explores the issues surrounding DDIs in LMICs, the role and challenges of using PK studies to inform treatment, and the DDIs of importance in these settings. Tuberculosis will be discussed elsewhere in this issue.

**Challenges in low & middle income countries**

When PK data are available to inform a particular DDI, studies may have sampled populations which differ significantly to those relevant in LMICs. For example, Thai patients may be of lower body weight to many study samples, which may affect exposure to some ARVs, such as tenofovir and raltegravir.[7, 8] African patients are more likely than Caucasians to carry polymorphisms of the metabolic enzyme CYP2B6, which lead to higher exposure to efavirenz, which has been linked to central nervous system (CNS) side effects.[9, 10] The antimalarial proguanil is predominantly metabolised by CYP2C19, and the frequency of poor metabolisers differs between Africans (3%), South East Asians (20%) and Caucasians.[11]

However, DDI studies rarely take ethnicity, genotype or even weight into consideration, and such data are not usually required for licensing of drugs.

There are some conditions with epidemiology specific to LMICs, such as neglected tropical diseases (NTDs). The lack of data in this area may in part result from the lack of politic voice of the affected populations, and also the use of medicines which were licensed decades ago. Post-licensing generics offer affordable options, however their manufacturers are unlikely to perform PK safety studies which were absent with previous licensing, for example to inform dosing in special populations, or in case of DDIs with co-administered medicines.

In many cases, poor availability of alternative drugs or regimens may confound attempts to tailor therapy to individuals in LMICs, even when relevant, well carried out PK studies exist, and clinicians are able to make a risk vs benefit assessment. Protocol-based ARV treatment in sub-Saharan Africa (SSA), introduced in order to rapidly scale up ARV treatment, may reduce the ability of guideline developers and individual clinicians to adapt therapy adequately. Likewise, monitoring for a particular adverse event (eg. Reduced renal function), is often unavailable. Moreover, the mainstay of first line therapy in SSA, for example, is the NNRTIs efavirenz and nevirapine. These drugs have considerable potential for PK DDIs, as both perpetrator and victim drugs, via metabolism by, and induction of CYP450 enzymes 3A4 and 2B6. The nucleos(t)ide reverse transcriptase inhibitor backbone commonly comprises zidovudine/lamivudine or tenofovir disoproxil fumarate (TDF)/lamivudine. TDF is associated with a risk of renal impairment, whereas the newer prodrug of TDF, tenofovir alafenamide fumarate (TAF) carries less renal risk. Zidovudine leads to anaemia in a relatively high proportion of patients, and has been associated with body fat changes. It is less often used in higher income countries.

To aid the scale up of ARV services to meet the growing HIV epidemic, many SSA countries adopted a strategy of task shifting, whereby lower cadres of healthcare workers are trained to perform tasks traditionally carried out by physicians, nurses or pharmacists. Such health workers may be less aware and less vigilant about DDIs, although they may prescribe medicines or advise patients. Particularly in remote locations, unpaid community health workers may have the most contact with patients. In order to manage DDIs, recognition and detection is vital. When detected, via a medicine information, or DDI checker, such as [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org), the information must be interpreted, and a course of action decided upon. DDI training for all cadres of health workers with patient contact, is fundamental for appropriate management. Important drugs and comorbidities of relevance in LMICs are discussed below.

**Neglected Tropical Diseases**

A project to update the online drug interaction resource [www.hiv-druginteractions.org](http://www.hiv-druginteractions.com) to include all of the WHO Model List of Essential Medicines in 2013, revealed potential for complex DDIs involving treatments for NTDs, but clinical evidence to inform recommendations are sparse.[12]

NTDs remain neglected since they do not individually rank highly in terms of mortality data, yet leishmaniasis, trypanosomiasis, leprosy, onchocerciasis, cause severe physical, emotional and mental morbidity and have a profound effect on cycles of poverty. NTDs are particularly neglected from the perspective of clinical pharmacology as only two studies were identified evaluating drug interactions between antiretroviral drugs and drugs for the treatment of NTDs, and these were conducted in healthy volunteers rather than in the relevant patient population.[12]

There is little financial incentive to develop new, less toxic treatments for leishmaniasis, for example; and little incentive to study the clinical pharmacology of existing treatments, when few alternative options are available for treatment of either the NTD or HIV.

**Malaria**

In the case of malaria, where endemic areas often overlap with areas with high HIV prevalence, a systematic review has shown that the quality of evidence for antiretroviral-antimalarial DDIs is generally low, with the evidence for 6 of 400 interactions were rated as ‘high’ quality, and 20 rated as ‘moderate’, showing the area is neglected.[5] Few of the drug interaction recommendations were made based on optimally designed pharmacokinetic clinical studies. The interactions of greatest concern were between amodiaquine and efavirenz, where a healthy volunteer study was prematurely discontinued due to drug-induced liver injury.[13] There was a marked reduction in artemether (and lumefantrine) concentrations with efavirenz.[14, 15] Artemesinins are common to all first line combinations, and are metabolised by CYP3A4 and 2B6, and efavirenz predominantly by CYP2B6. It is unclear whether or how polymorphisms in CYP2B6 (which are relatively frequent in many African populations) impact on this interaction. While population pharmacokinetic modelling[16] and *in vitro-in vivo* extrapolation[17] can predict rational dose adjustments, clinical studies are required to determine efficacy and acceptability. Difficulties were experienced in interpreting data in healthy volunteers, due to differences in drug PK in patients with/without malaria. For example, the protein binding and plasma half-life of quinine increases with severity of malaria,[18] lumefantrine absorption is decreased during acute malaria[19] and the pharmacokinetics of mefloquine alters with disease.[20]

**Contraception**

Progesterone contraceptive implants are widely used in SSA, in patients taking ARVs.

Within 1 year of combined use, levonorgestrel exposure was markedly reduced in Ugandan women who received efavirenz-based ART, accompanied by contraceptive failures. In contrast, nevirapine-based ART did not adversely affect levonorgestrel exposure or efficacy.[21]

 Cases of pregnancy in women taking EFV-containing regimens and using etonogestrel implants have been reported, which are thought to be related to EFV enzyme induction.[22] A pharmacokinetic study in HIV positive Brazilian patients observed a decrease in etonogestrel exposure (AUC) of 63.4% in patients taking EFV-based ARVs, compared to patients taking no ARVs. In patients taking LPV/r-based ARVs, exposure increased by 52%, suggesting that enzyme induction and inhibition by the ARVs is the mechanism.[23] In a study of Thai patients given oral ethinylestradiol/desorgestrel, NVP did not significantly alter the exposure to the active metabolite, etonogestrel.[24] There are no data, however concerning the effect of NVP on etonogestrel implant exposure or contraceptive efficacy.

While data suggest that NVP may be a safe option in combination with progesterone implants, many prescribers, guidelines and medicines information sources consider this combination a risk. DDIs with the first line agent EFV significantly reduce contraceptive options, thus medroxyprogesterone depo injection is preferred, which is unaffected by EFV/NVP.[25] Of concern, is the fact that many patients in LMICs may access contraceptives from district clinics, and not disclose their HIV status. There is therefore a risk that serious DDIs may remain undetected.

**Non-infectious chronic diseases**

As patients with HIV in LMICs are living longer, they are at increasing risk of morbidity and mortality from non-communicable diseases such as hypertension. As for ARV therapy, options for treating non-communicable chronic conditions are often limited in LMICs. For example, the mainstay of treatment for hypertension in many LMICs is calcium channel blockers, many of which are metabolised via CYP3A4. The exposure to antihypertensives such as amlodipine and nifedipine may therefore be reduced by ARV regimens containing EFV or NVP, potentially reducing antihypertensive efficacy. With no pharmacokinetic studies to confirm the magnitude of the potential interaction, or to deduce rational dose adjustments, uncontrolled hypertension may persist in HIV positive patients in LMICs, where use of alternatives such as ACE inhibitors or angiotensin receptor inhibitors, is prohibitive due to cost or availability.

**Traditional medicines**

In Uganda, over 103 herbal components used in HIV patients were identified by traditional healers.[26] In western Uganda, 46.4% of patients had used herbal medicines alongside ARVs, 39.8% reported using herbal medicines daily. Almost none of these patients had reported their use of herbal medicines to their ARV prescriber. The most frequently used were Aloe vera (25%) and Vernonia amygdalina (21%).[27] Aloe vera has been found to inhibit CYP3A4 *in vitro*,[28] and increase indinavir exposure in rats.[29] An in vitro study examined the effect of several herbal medicines on CYP2B6, an enzyme responsible in part for EFV and NVP metabolism. The most potent inhibitor of CYP2B6 was Hyptis suaveolens (pignut) extract, followed by Myrothamnus flabellifolius (resurrection plant) extract, Launaea taraxacifolia (African lettuce) extract, and Boerhavia diffusa (spreading hogweed) extract.[30] If clinically relevant *in vivo*, such interactions may cause toxicity in patients taking EFV or NVP, and in the case of CYP3A4 inhibition, also protease inhibitors and some integrase inhibitors. Case studies also suggest potential interactions, for example two patients in Argentina who were taking EFV-based ARVs, had detectable viral load, and on investigation had initiated Equisitum arvense (horsetail) supplements. On stopping the supplements, viral load re-suppressed in both patients.[31]

Although *in vitro* studies and case reports suggest potentially significant interactions, PK DDI studies in patients or healthy subjects taking herbal medicines at realistic doses, alongside ARVs are rare.[32] In the absence of such data, clinicians lack evidence with which to caution patients on safe herbal use, or alternatively issue patients with a blanket ban on using herbals alongside their ARVs, which may potentially lead to patients not discussing their medicines use with ARV prescribers. Another potential issue may arise from patients buying unlabelled (and unregulated) herbal remedies from hawkers or markets, without knowing what they contain. Some herbal products have been found to be adulterated with prescription drugs.[33, 34]

**Food interactions**

Lipid-based nutritional supplements decreased exposure to NVP, but not EFV, in Ethiopian patients, although the clinical relevance is unclear.[35] Compared to historic controls from higher income countries, food-insecure children in Uganda had higher exposure to EFV and LPV/r, but lower exposure to NVP. Virological failure rates were comparable in patients taking EFV, LPV/r or NVP.[36] Ugandan patients had a higher TDF (19%) and EFV (47%) exposure in a fed state, compared to a fasted state. The study concluded that the fixed dose combination of TDF/emtricitabine/EFV may be taken with or without food in this population, but patients with EFV-related CNS side effects should take doses without food.[37]

Ugandan and US studies report poorer adherence to ARVs that should be taken with food, and a higher risk of detectable viral load, in patients with food insecurity.[38, 39]

Food effects may considerably affect patient adherence to ARVs and the prevalence of adverse events. Patients should be counselled appropriately when initiating ARVs, or switching regimen, and any side effects or adherence issues should be considered. Patients should particularly be counselled to take ARV doses at the usual time, even if food is not available.

**Conclusion**

Currently available antiretrovirals for first and second line regimens in LMICs comprise drugs which are the most susceptible to DDIs, and with the highest propensity to cause laboratory anomalies, of all the globally available ARVs. Unfortunately, LMICs are the least able to consistently monitor patients, switch regimens due to toxicity, or tailor treatment to individuals. More recent regimens and agents which are currently recommended first line in higher income countries, such as dolutegravir, reduced dose EFV (400mg), or TAF would be better suited to the protocol driven, and reduced ARV option treatment programs in SSA. While the introduction of such regimens is delayed due to cost and availability, efforts to conduct PK DDI studies which are relevant to these settings, and inform national and international guidelines, are important in reducing morbidity as well as mortality from HIV in LMICs. Ongoing education of prescribers in evidence-based medicine and interpretation of PK data, is necessary to sensitise prescribers and institutions to change, as HIV treatment programs in LMICs evolve, to adopt patient-centred care, after successful ARV scale up.

**Key Points**

* Drug-drug interaction studies involving antiretrovirals and antimalarials/drugs used for neglected tropical diseases are sparse, and often of low quality
* Pharmacokinetic studies are often difficult to interpret in low & middle income countries, due to differing patient factors such as body weight, genetic polymorphisms, and disease states
* First-line antiretroviral regimens in Low & middle income countries have high propensity for pharmacokinetic drug interactions

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