Drug–drug interactions between antiretrovirals and drugs used in the management of neglected tropical diseases: important considerations in the WHO 2020 Roadmap and London Declaration on Neglected Tropical Diseases

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The group of infections known as the neglected tropical diseases (NTDs) collectively affect one billion people worldwide, equivalent to one-sixth of the world's population. The NTDs cause severe physical and emotional morbidity, and have a profound effect on cycles of poverty; it is estimated that NTDs account for 534 000 deaths per year. NTDs such as soil-transmitted helminth infections and the vector-borne protozoal infections leishmaniasis and trypanosomiasis occur predominantly in the most economically disadvantaged and marginalized communities. It is estimated that all low-income countries harbour at least five of the NTDs simultaneously. NTDs are neglected because they do not individually rank highly in terms of mortality data, and because they affect populations with little political voice. There is considerable geographic overlap between areas with high prevalence of NTDs and HIV, raising the possibility of complex polypharmacy and drug–drug interactions. Antiretrovirals pose a particularly high risk for potential drug–drug interactions, which may be pharmacokinetic or pharmacodynamic in nature and can result in raising or lowering plasma or tissue concentrations of co-prescribed drugs. Elevated drug concentrations may be associated with drug toxicity and lower drug concentrations may be associated with therapeutic failure. The aim of this paper is to review the currently available data on interactions between antiretrovirals and drugs used in the management of NTDs. It is intended to serve as a resource for policy makers and clinicians caring for these patients, and to support the recent WHO 2020 Roadmap and the 2012 London Declaration on NTDs.

AIDS 2013, **27**:675–686

Keywords: drug interactions, HIV/AIDS, neglected tropical diseases, pharmacokinetics

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Received: 12 October 2012; revised: 6 November 2012; accepted: 15 November 2012.

DOI:10.1097/QAD.0b013e32835ca9b4

Introduction

The WHO 2020 Roadmap on neglected tropical diseases (NTDs) and the 2012 London Declaration on NTDs aim to 'enable more than a billion people suffering from neglected tropical diseases to lead healthier and more productive lives' and 'chart a new course towards health and sustainability'. Two out of the five strategies for the prevention, control, elimination and eradication of NTDs set out in the WHO 2020 Roadmap involve sustaining and expanding existing drug donation programs to meet demand through to 2020. To this end, the governments of the US, UK and United Arab Emirates, the World Bank and the Bill and Melinda Gates Foundation along with 13 pharmaceutical companies, have announced the largest collaborative effort to date to combat NTDs.

The NTDs (Table 1) cause severe physical, emotional and mental morbidity and have a profound effect on cycles of poverty. They are neglected because they do not individually rank highly in terms of mortality data, and because they affect populations with little political voice and do not travel well to the western world. The NTDs collectively affect one billion people; equivalent to one-sixth of the world's population. Though often described as causing morbidity rather than mortality, it is estimated that NTDs account for 534 000 deaths per year [1]. NTDs occur predominantly in the most economically disadvantaged, marginalized and vulnerable communities and it is estimated that all the low-income countries harbour at least five of the NTDs simultaneously [2].

There is considerable geographic overlap between areas with high prevalence of NTDs and HIV, raising the possibility of complex polypharmacy and drug–drug interactions. Antiretroviral drugs pose a particularly high risk for potential drug–drug interactions. These may be pharmacokinetic or pharmacodynamic in nature and can result in raising or lowering the plasma or tissue concentrations of co-prescribed drugs. Depending on the magnitude of the interaction, elevated drug concentrations may be associated with drug toxicity and lower drug concentrations may be associated with therapeutic failure. Sub-therapeutic concentrations are of particular concern in the discipline of infectious diseases due to the possible emergence of drug-resistant strains, which can compromise the utility of anti-infective agents on an individual patient or a population basis. The bi-directional nature of drug–drug interactions raises the possibility of alteration of drug levels of either the prescribed antiretroviral drugs or the drugs used to treat the NTD. Sub-therapeutic levels may go unnoticed, as there is often a delay between the use of treatment and the emergence of clinical failure or resistance. Furthermore, when available, therapeutic drug monitoring for either antiretrovirals or NTD medicines is complex and expensive.

Consensus international and national guidelines for the treatment of HIV-infected patients recommend initiating therapy with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor-based regimen. These two commonly prescribed classes of antiretroviral drugs are both substrates for and modulators of the cytochrome P450 isoenzyme system. Additionally drug interactions with antiretroviral drugs can occur through mechanisms including drug influx and efflux transporters, glucuronidation, nuclear receptor activation and pH-dependent absorption. Also, overlapping toxicities of antiretrovirals and co-administered drugs must be taken into consideration, as severe toxicities may be exacerbated with some drug combinations.

The aim of this paper is to review the currently available data on interactions between antiretroviral drugs and drugs used in the management of NTDs. It is intended to serve as a resource for policy makers and clinicians caring for these patients to support the WHO 2020 Roadmap and the 2012 London Declaration on NTDs. Additionally it is envisaged that it can inform the research agenda in this area. The Liverpool HIV drug interactions website (www.hiv-druginteractions.org) has recently been updated to include drugs from the WHO Model List of Essential Medicines, including those used in the treatment of NTDs as discussed in this review. As such, this will serve as an ongoing resource in this neglected and important area of clinical care.

Table 1 summarizes current WHO Treatment Guidelines and the prevalence and distribution of NTDs. The metabolism and elimination profiles of the drugs are summarized, and the potential for pharmacokinetic interaction with antiretrovirals. Since there is overlap in the drugs used in the management of NTDs we have discussed the available data by drug rather than disease. Table 2 summarizes potential drug–drug interactions between drugs for NTDs and antiretrovirals. Rifampicin, azithromycin, streptomycin and steroids were not included in the discussion as these are well described in the literature due to their therapeutic importance outside of the scope of NTDs.

Potential interactions with antiretrovirals

Albendazole and mebendazole

Albendazole and mebendazole are structurally related and may both be used to treat infection with soil-transmitted helminths, including *Ascaris* and *Tricuris* species, and hookworm. Albendazole may also be used in lymphatic filariasis (Table 2). Additionally, albendazole is effective in cestode infections such as cysticercosis and echinococcosis (hydatid disease) and tissue nematode infections. Albendazole rapidly undergoes extensive first-pass metabolism in the liver and is generally not detected in the plasma. Albendazole sulfoxide is the primary

Table 1. Current WHO-recommended treatments for neglected tropical diseases.

Disease	Distribution and prevalence [3]	Recommended drug therapy	Metabolism/elimination	Potential for pharmacokinetic interaction with antiretrovirals
Buruli ulcer	30 countries in Africa, the Americas, Asia, Western Pacific, e.g. Côte d'Ivoire ~24 000 cases 1978 -2006; Ghana ~11 000 cases since 1993. Increasing reports from Australia, Congo, Cameroon, Gabon, Sudan, Togo, Uganda	Rifampicin	The principle pathways of metabolism are by hydrolysis and desacetylation. Rapidly eliminated in bile and undergoes enterophepatic circulation. The desacetyl metabolite retains antibacterial activity. Intestinal reabsorption is reduced by deacetylation and elimination facilitated. ~30% of a dose is excreted in the urine, ~50% as unchanged drug. Rifampicin is a potent inducer of certain cytochrome P-450 enzymes and glucuronidation [4].	Contraindicated with all PIs due to significant reductions in PI exposure. Rifampicin is not recommended with NVP or RIL due to significant reduction in exposure of the NNRTIs, however EFV may be used with rifampicin with expert advice. Rifampicin reduces exposure to ZDV, MVC, RAL, and potentially ABC [5].
		Streptomycin	Rapidly excreted unchanged by glomerular filtration, with ~30–90% of a dose usually excreted within 24 h [20].	Based on the metabolism/ elimination data, there is little potential for pharmacokinetic interaction with ARVs
Chagas disease	Estimated 10 million people infected with *Trypanosoma cruzi* (parasite that causes Chagas disease) worldwide, mostly in Latin America.	Benznidazole	Extensively metabolized, with minimal renal elimination of unchanged drug [21]. Thought to undergo NADPH dependent nitroreductive metabolic biotransformation, however mechanisms are not well understood [22–25].	Little potential for pharmacokinetic interaction with ARVs, however due to the lack of available data, caution is required when co-administering
		Nifurtimox	Extensively metabolized, with minimal renal elimination of unchanged drug [20]. Thought to undergo NADPH-dependent nitroreductive metabolic biotransformation, however mechanisms are not well understood [22–25].	Little potential for pharmacokinetic interaction with ARVs; however, due to the lack of available data, caution is required when co-administering
Dengue	Incidence increased 30-fold over past 50 years. 50–100 million infections estimated annually in >100 endemic countries in Asia and Latin America, with almost half of the world population at risk.	No specific drugs	There are new antiretrovirals for dengue at early stages of the preclinical development pipeline. Targets include viral NS4B viral protein, E-glycoprotein and NS2B-NS3 protease [6–9].	The potential for interaction between antiretrovirals and the various new chemical entities in development for dengue treatment is unknown. Clinical pharmacokinetic studies are warranted.
Dracunculiasis (Guinea worm)	In 2011, Ethiopia, Ghana, Mali, Sudan were endemic. Reported cases dropped to 143 January-April 2012. Total of 1058 cases reported in 2011.	No drug treatment	-	-
Lymphatic filariasis	An estimated 120 million people in tropical and subtropical areas of the world are infected with lymphatic filariasis. ~66% of those at risk of infection live in the WHO South-East Asia Region and 33% in the African Region.	Albendazole	Extensive first-pass stereoselective hepatic metabolism to albendazole sulfoxide (active metabolite). CYP3A4 is involved in formation of (-)albendazole sulfoxide, and flavine-containing monooxygenase in forming (+)albendazole sulfoxide. Also involvement of CYP1A2 (major) and CYP2C9 [13,14]	Levels of the active metabolite may be altered by inhibitors or inducers of CYP3A4 such as HIV PIs, and NNRTIs.

Table 1 (*continued*)

Disease	Distribution and prevalence [3]	Recommended drug therapy	Metabolism/elimination	Potential for pharmacokinetic interaction with antiretrovirals
		Ivermectin	Metabolized primarily by CYP3A (*in vitro*). The parent drug and metabolites are excreted almost exclusively in the faeces.	Levels of ivermectin may be altered by inhibitors or inducers of CYP3A4 such as HIV PIs, and NNRTIs.
		Diethylcarbamazine	Mainly excreted in the urine unchanged and as the *N*-oxide metabolite. Urinary excretion and plasma half-life is dependent on urinary pH. ~5% of a dose is eliminated in the faeces.	Little potential for pharmacokinetic interaction with ARVs; however, few data are available
Leishmaniasis	Endemic in 88 countries, predominantly: India, Bangladesh, Brazil, Sudan, Nepal, Bolivia, Peru, Afghanistan, Iran, Saudi Arabia, Syria. Estimated 2 million new cases annually, with ~12 million infected.	Paramomycin	Not metabolized *in vivo*, excreted unchanged in the urine via glomerular filtration [45].	Based on the metabolism/ elimination data, there is little potential for pharmacokinetic interaction with ARVs
		Meglumine antimoniate	Predominantly excreted unchanged via renal glomerular filtration [33,34]	Based on the metabolism/ elimination data, there is little potential for pharmacokinetic interaction with ARVs
		Sodium stiboglutonate	Predominantly excreted unchanged via renal glomerular filtration [50,51]	Based on the metabolism/ elimination data, there is little potential for pharmacokinetic interaction with ARVs
Leprosy	Global prevalence in early 2011 was 192 246 cases, with 228 474 new cases detected in 2010. Areas of high endemicity remain in Angola, Brazil, Central African Republic, Democratic Republic of Congo, India, Madagascar, Tanzania Mozambique, Nepal	Rifampicin	As above	As above
		Dapsone	Metabolism of dapsone is mainly by N-acetylation with a component of N-hydroxylation, and is via multiple CYP P450 enzymes including CYP3A4, CYP2C9, CYP2D6, 2C8 and 2C19 [14].	Clinically significant interactions via modulation of CYP450 enzymes by ARVs such as PIs and NNRTIs are unlikely due to the multiple enzymes involved, but cannot be excluded
		Clofazimine	Clofazimine accumulates and is largely excreted unchanged in the faeces, as unabsorbed drug and via biliary excretion. ~1% of the dose is excreted in the urine as unchanged clofazimine and metabolites. Three metabolites, two glucuronides, have been identified [26].	Based on the metabolism/ elimination data, there is little potential for pharmacokinetic interaction with ARVs
Oncocerciasis	Prevalent in West/Central Africa, Yemen and six countries in Latin America. Estimated half a million people blind due to infection.	Ivermectin	As above	As above

Soil-based helminthes (ascaris/trichrius/ hookworm)	Recent estimates suggest *A. lumbricoides* infects >1 billion, *T. trichiura* 795 million, and hookworms (*A. duodenale* and *N. americanus*) 740 million. Most infections occur in sub-Saharan Africa, the Americas, China, east Asia.	Albendazole	As above	As above
		Mebendazole	Extensive first pass hepatic metabolism. Parent drug and amino/hydroxlated amino metabolites undergo enterohepatic circulation. Extensive metabolism and poor solubility means bioavailablity is 1–2%. Data with cimetidine and ritonavir suggest a role for CYP450 enzymes in mebendazole metabolism [10,17]	Enzyme inducers (e.g. some NNRTIs) may decrease levels of mebendazole. Ritonavir significantly decreased mebendazole exposure, likely due to ritonavir-mediated induction of CYP2C9, CYP1A2, UGT or transporters
		Pyrantel	Metabolized by CYP2D6 *in vitro* [14]. Only a small proportion of a dose of is absorbed from the gastrointestinal tract. ~7% is excreted as unchanged drug and metabolites in the urine, >50% is excreted unchanged in the faeces [20].	Based on metabolism/ elimination data, there is little potential for pharmacokinetic interaction with ARVs
Shistosomiasis	Affects ~240 million worldwide; >700 million live in endemic areas. Estimated >200 000 deaths annually are due to schistosomiasis in sub-Saharan Africa.	Praziquantel	Metabolized by CYP3A4, CYP1A2 and CYP2C19 [14] Data with rifampicin, carbamazepine, phenytoin [47,48] and ketoconazole [49] show that levels of praziquantel are significantly affected by CYP450 enzyme inducers and inhibitors.	Some NNRTIs may reduce praziquantel levels via enzyme induction, protease inhibitors may increase exposure to praziquantel via enzyme inhibition.
Trachoma	Affects ~21.4 million people (~2.2 million visually impaired, 1.2 million blind.) Endemic in remote rural areas of Africa, Asia, Central/South America, Australia, Middle East.	Azithromycin	~12% of an intravenous dose is excreted unchanged in urine within three days. High concentrations of unchanged azithromycin have been found in human bile; 10 metabolites were also detected, which were formed through N- and O-demethylation, hydroxylation of desosamine- and aglycone rings and degradation of cladinose conjugate. Azithromycin does not interact significantly with the hepatic cytochrome P450 system [11].	No clinically significant drug interactions have been observed or are expected between Azithromycin and ARVs [5]
African Trypanosomiasis	Affects mostly poor populations in remote rural areas of Africa. The estimated number of actual cases is currently 30 000; in 2010, 7139 cases were reported.	Pentamidine	Pentamidine is predominantly metabolized via CYP1A1 [14], with minimal renal elimination of unchanged drug.	Based on metabolism/ elimination data, there is little potential for pharmacokinetic interaction with ARVs
		Eflornithine	~80% of oral/i.v. doses are excreted unchanged via the kidneys [28]. There are no available data determining whether excretion is via active tubular secretion or glomerular filtration	Some potential for competition with ARVs eliminated via active renal transport mechanisms, such as tenofovir, which may lead to increased levels of either drug

Table 1 (*continued*)

Disease	Distribution and prevalence [3]	Recommended drug therapy	Metabolism/elimination	Potential for pharmacokinetic interaction with antiretrovirals
		Suramin	Suramin is predominantly eliminated unchanged by the kidneys [58]. There are no available data determining whether excretion is via active tubular secretion or glomerular filtration	Some potential for competition with ARVs eliminated via active renal transport mechanisms, such as tenofovir, which may lead to increased levels of either drug
		Melarsoprol	Melarsoprol is a prodrug and is rapidly metabolized to the active form, melarsen oxide [30]. Plasma half-life is 30 min and excretion is via the faeces and urine. *In vitro* studies suggest that melarsen oxide may be formed by hydrolysis, and not only in liver microsomal reactions [31].	Based on limited metabolism/elimination data, there is little potential for interaction with ARVs, although due to lack of data, vigilance is warranted

ABC, abacavir; ARVs, antiretrovirals; EFV, efavirenz; MVC, maraviroc; NNRTIs, non-nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PIs, protease inhibitors; RAL, raltegravir; RIL, rilpivirine; ZDV, zidovudine.

metabolite which is thought to be the active moiety in effectiveness against systemic infections. Formation of albendazole sulfoxide is stereoselective with CYP3A4 involved in the formation of (-)- albendazole sulfoxide, whereas formation of (+)-albendazole sulfoxide is mediated by the flavine-containing monooxygenase system. CYP2C9 and CYP1A2 are also involved in albendazole and albendazole sulfoxide metabolism [13,14]. Albendazole sulfoxide appears to be principally eliminated in the bile with only a small proportion appearing in the urine.

Mebendazole also undergoes extensive first pass metabolism in the liver and both the parent drug and its amino and hydroxlated amino metabolites undergo enterohepatic circulation. This extensive liver metabolism and the poor solubility mean that bioavailablity is only 1–2% [15].

The interaction potential of both mebendazole and albendazole with emtricitabine, lamivudine, tenofovir, abacavir, didanosine, stavudine, maraviroc, raltegravir and rilpivirine is thought to be low although no formal pharmacokinetic studies exist.

Albendazole, and less frequently mebendazole have been shown to cause bone marrow suppression and may increase the risk of haematological toxicity associated with zidovudine. This is of particular concern in patients with liver disease including echinococcosis who are already at higher risk of pancytopaenia, agranulocytosis and leukopenia. There is a single case report of an HIV-infected patient with alveolar echinococcosis who developed pancytopaenia with haemoglobin of 5.8 mg/dl, thrombocytopenia and neutropenia when albendazole at a dose of 400 mg twice daily was added to his regimen of zidovudine, lamivudine and nelfinavir. The patient's regimen was changed to stavudine, abacavir and lopinavir boosted with ritonavir for HIV, and mebendazole for echinococcosis. Therapeutic drug monitoring of mebendazole then showed that therapeutic concentrations of mebendazole were achieved with one-tenth of the normal dose of mebendazole [16]. Hence caution is advised when administering mebendazole and by inference albendazole to patients receiving CYP3A4-inhibiting drugs such as the HIV protease inhibitors.

Ritonavir has the potential to reduce plasma concentrations of the active metabolite of albendazole [17]. In two sequential studies, healthy male volunteers were administered either a single oral dose of 400 mg of albendazole or 1000 mg of mebendazole. After short-term (2 weeks) and long-term (8 days) treatment with ritonavir 200 mg twice daily, pharmacokinetic parameters of albendazole and its metabolite were not changed by short-term administration of ritonavir. Long-term administration resulted in significant decrease in albendazole and albendazole sulfoxide area under curve (AUC) (73 and 59%, respectively) and C_{max} (74 and 48%,

Table 2. Potential drug–drug interactions between antiretrovirals and drugs used to treat neglected tropical diseases.

			Drugs used in Neglected Tropical Diseases																	
			Albendazole	Mebendazole	Clofazimine	Benznidazole	Dapsone	Diethylcarbamazine	Eflornithine	Ivermectin	Meglumine antimonate	Melarsoprol	Nifurtimox	Paromomycin	Pentamidine	Praziquantel	Pyrantel	Triclabendazole	Sodium stibogluconate	Suramin
Antiretrovirals	PIs	ATV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	3	4	4	4	4
		DRV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	3	4	4	4	4
		FPV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	3	4	4	4	4
		IDV	4	4	4	4	4	4	4	4	4	4	4	4	4	3	4	4	4	4
		LPV/r	4	4	4	4	4	4	4	4	4	4	4	4	4	3	4	4	4	4
		NFV	4	4	4	4	4	4	4	4	4	4	4	4	4	3	4	4	4	4
		RTV	3	3	4	4	4	4	4	4	4	4	4	4	4	3	4	4	4	4
		SQV/r	4	4	4	4	4	4	4	4	●	4	4	4	●	3	4	4	●	4
		TPV/r	3	3	4	4	4	4	4	4	4	4	4	4	4	3	4	4	4	4
	NNRTIs	EFV	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		ETV	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		NVP	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		Ril	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	NRTIs	ABC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		ddI	4	4	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		d4T	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		FTC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		3TC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		TDF	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
		ZDV	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Entry-I	MVC	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
	Int-I	RAL	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4

3TC, lamivudine; ABC, abacavir; ATV/r, atazanavir/ritonavir; d4T, stavudine; ddI, didanosine; DRV/r, darunavir/ritonavir; EFV, efavirenz; Entry-I, entry inhibitor; ETV, etravirine; FPV/r, fosamprenavir/ritonavir; FTC, emtricitabine; IDV, indinavir; Int-I, integrase inhibitor; LPV/r, lopinavir/ritonavir; MVC, maraviroc; NFV, nelfinavir; NNRTIs, nonnucleoside reverse transcriptase inhibitors; NRTIs, nucleoside reverse transcriptase inhibitors; NVP, nevirapine; PIs, protease inhibitors; RAL, raltegravir; Ril, rilpivirine; RTV, ritonavir; SQV/r, saquinavir/ritonavir; TDF, tenofovir; TPV/r, tipranavir/ritonavir; ZDV, zidovudine. ◆ No clinically significant interaction expected. ■ Potential interaction – may require close monitoring, alteration of drug dosage or timing of administration. ● These drugs should not be coadministered. Quality of Evidence [12]. 1. High. 2. Moderate. 3. Low. 4. Very Low.

respectively). A trend towards an increase in mebendazole exposure after short-term intake of ritonavir was seen but long-term administration resulted in a significant decrease in mebendazole AUC (57%) and C_{max} (59%). These reductions for both albendazole and mebenazole are most likely due to ritonavir mediated induction of metabolizing enzymes (CYP2C9, CYP1A2, UGT) or transporters although changes in absorption are possible [17]. The clinical significance of this is unknown but may result in decreased efficacy especially in the treatment of systemic helminthiasis. Further studies are needed especially with commonly prescribed protease inhibitor regimens such as ritonavir boosted lopinavir.

Phenytoin, carbamazepine and phenobarbitone appear to induce the oxidative metabolism of albendazole [18]. Whereas there are no data on the interaction between albendazole or mebendazole and efavirenz, etravirine, nevirapine, an interaction cannot be excluded in view of their CYP3A-inducing properties and should be formally evaluated.

Triclabendazole

Triclabendazole is used to treat fluke infections such as fascioliasis, where praziquantel is ineffective, and paragonimiasis. There are no data on interactions between antiretroviral drugs and triclabendazole. *In vivo,*

triclabendazole is rapidly oxidized to its sole oxide metabolite [19] and there is low potential for interactions with nucleoside reverse transcriptase inhibitors or raltegravir. Coadministration of triclabendazole and protease inhibitors, NNRTIs and maraviroc may result in increased levels of the antiretroviral drugs, as triclabendazole has been found to inhibit metabolism mediated by CYP3A4. There is potential for protease inhibitors to increase levels of triclabendazole via enzyme inhibition, but due to the short-term dosing of triclabendazole, this is unlikely to be clinically relevant. NNRTIs may reduce exposure to triclabendazole and therefore potentially reduce its efficacy.

Benznidazole and nifurtimox

Benznidazole and nifurtimox are used in the treatment of *Trypanosoma cruzi* infection (Chagas' disease). Oral benznidazole and nifurtimox are well absorbed and are rapidly and extensively metabolized, with minimal renal elimination of unchanged drug [20,21]. Both benznidazole and nifurtimox are thought to undergo NADPH-dependent nitroreductive metabolic biotransformation; however, the mechanisms are not well understood [22–25]. Data are lacking to predict whether pharmacokinetic interactions will occur between benznidazole or nifurtimox and antiretrovirals. Clinicians should therefore use such combinations with caution.

The most severe adverse effects of benznidazole are bone marrow depression, thrombocytopenic purpura and agranulocytosis [20]. Caution should therefore be exercised when administering benznidazole with zidovudine.

Clofazimine

Clofazimine is used in multidrug regimens for the treatment of multibacillary leprosy. Information on the metabolism of this drug is limited. Three metabolites have been identified in urine and unchanged clofazimine is excreted via the bile [26]. Available data suggest limited potential for interactions between clofazimine and any of the antiretroviral drugs with the exception of the buffered formulation of didanosine. A healthy volunteer cross-over study demonstrated that an aluminium magnesium antacid decreased clofazimine bioavailability by 22% [27]. No interaction is expected with the more commonly used enteric-coated capsule didanosine formulation.

Dapsone

Dapsone is used as part of multidrug regimens in the treatment of all forms of leprosy, and also for prophylaxis of pneumocystis pneumonia in patients with HIV. Due to minimal excretion of unchanged drug via the kidneys, there is negligible potential for interactions between dapsone and renally excreted nucleoside reverse transcriptase inhibitors (NRTIs) via competition for renal elimination pathways. Dapsone is metabolized mainly by N-acetylation with a component of N-hydroxylation, and via multiple CYP P450 enzymes including CYP3A4, CYP2C9, CYP2D6, 2C8 and 2C19 [14]. Clinically significant interactions via modulation of CYP450 enzymes by antiretrovirals are therefore unlikely, but cannot be excluded. Although specific studies have not been performed, the manufacturer of saquinavir advises that co-administration of saquinavir/ritonavir with dapsone may result in elevated dapsone plasma concentrations, and that this combination should be given with caution. It is recommended that regular blood counts are performed during treatment with dapsone, and that it is used with caution in anaemia. Care should therefore be taken when co-administering with zidovudine, due to its myelosuppressive potential.

Diethylcarbamazine

Diethylcarbamazine is used to treat lymphatic filariasis, and can also be used in loiasis and toxocariasis. It is readily absorbed through the gastrointestinal tract, skin and conjunctiva and is excreted unchanged and as the N-oxide in the urine [20]. There is limited potential for drug interactions based on available data on the metabolism of this drug, although no formal trials with antiretroviral drugs have been conducted.

Eflornithine

Eflornithine is used intravenously to treat African trypanosomiasis due to *Trypanosoma brucei gambiense* (sleeping sickness). Approximately 80% of an oral or intravenous dose of eflornithine is excreted unchanged via the kidneys [28]. As there are no data available to determine whether excretion is via active tubular secretion or glomerular filtration, there is potential for competition with tenofovir, lamivudine, emtricitabine or stavudine for active renal transport mechanisms, which may lead to increased levels of either drug. Rilpivirine can inhibit the active renal tubular secretion of creatinine, and may increase exposure to drugs eliminated via this pathway, vigilance is therefore warranted if administering with eflornithine.

Intravenous or oral eflornithine treatment commonly causes myelosuppression that may lead to anaemia, leucopenia and thrombocytopenia. Anaemia, neutropenia and leucopenia can be expected to occur in patients receiving zidovudine, so if concomitant treatment is necessary, then monitoring of haematological parameters is advised.

Ivermectin

Ivermectin is used to treat lymphatic filariasis and also onchocerciasis ('river blindness'). It is metabolized in the liver and the parent drug and metabolites are excreted almost exclusively in the faeces. In-vitro data show that ivermectin is primarily metabolized by CYP3A [29] suggesting the theoretical possibility of interactions with protease inhibitors, which may increase ivermectin levels, and NNRTIs, which may potentially decrease ivermectin

levels, although the clinical significance of this is unknown.

Melarsoprol

Melarsoprol is effective in the treatment of all stages of African trypanosomiasis due to *T.b. gambiense* or *T. brucei rhodesiense*, but is usually reserved for stages of disease with central nervous system (CNS) involvement, due to its toxicity. The pharmacokinetics of melarsoprol have not been fully evaluated, and administration of melarsoprol with antiretrovirals has not been investigated. Melarsoprol is a prodrug and is rapidly metabolized to the active form, melarsen oxide [30]. Melarsoprol has a plasma half-life of 30 min and is excreted in the faeces and urine. In-vitro studies suggest that melarsen oxide may be formed by hydrolysis, and not only in liver microsomal reactions [31]. A clinical study investigating urinary arsenic clearance and toxicity found that urinary pharmacokinetic parameters are not predictive of toxicity or therapeutic efficacy [32]. Based on limited data concerning metabolism, elimination and toxicity, there is little potential for interaction with antiretrovirals.

Meglumine antimoniate

The pentavalent antimonials meglumine antimoniate and sodium stibogluconate are used in the treatment of leishmaniasis including cutaneous, visceral and mucocutaneous forms. The pentavalent antimony compounds are poorly absorbed orally but are rapidly distributed by the parenteral route. Elimination occurs in two phases: a rapid elimination phase in which the majority is excreted via the kidneys and a slower phase possibly reflecting reduction to the trivalent antimony. There is little potential for competition for renal clearance of meglumine when coadministered with emtricitabine, lamivudine or tenofovir, as elimination occurs via glomerular filtration with no significant active transport [33,34]. However, renal impairment and sometimes fatal renal failure have been described with meglumine antimoniate treatment, and monitoring of renal function is warranted [35–37]. Cardiotoxicity including QTc interval prolongation and torsades de pointes have been observed during meglumine administration [38–42]. Coadministration with other drugs known to increase the risk of cardiotoxicity should be performed under caution. The manufacturer of saquinavir states that co-administration of ritonavir-boosted saquinavir and other medication which may prolong the QT interval is contraindicated.

Ritonavir is also associated with PR interval prolongation in healthy volunteers and heart block has occurred in patients with underlying structural heart disease who were receiving medicinal agents known to prolong the PR interval [43,44]. For patients taking protease inhibitors, it may be advisable to switch to another third agent for the duration of meglumine treatment, for example raltegravir. Rilpivirine has been associated with QTc prolongation at supra-therapeutic doses of 75 to 300 mg daily. Cardiotoxicity has not been observed at the recommended doses of rilpivirine of 25 mg daily and hence can be used with caution with medicinal products known to cause torsades de pointes.

Pancreatitis is a relatively common serious adverse effect of pentavalent antimonials [35,36] and since it is also described with didanosine, ritonavir-boosted lopinavir and stavudine; meglumine should only be used with extreme caution in these patients.

Pentamidine

Parenteral pentamidine is used in the treatment of early African trypanosomiasis due to *T.b. gambiense*, but is not effective in cases with CNS involvement. It may also be used in visceral leishmaniasis, and mucocutaneous leishmaniasis due to *Leishmania braziliensis* or *L. aethiopica* that has not responded to antimonials. Pentamidine is predominantly metabolized via CYP1A1 [14], with minimal renal elimination of unchanged drug. Pentamidine is well known for its allergic reactions but also has toxic effects. It is both hepatotoxic and nephrotoxic and anecdotal evidence suggests that it should be used with extreme caution in combination with other nephrotoxic drugs such as aminoglycoside antibiotics. This caution extends to many antiretrovirals such as tenofovir, which can also affect renal function, and the renally excreted NRTIs. It has frequently been used as an inhaled formulation in HIV patients in the developed world for treatment of pneumocystic carinii pneumonia associated with HIV, however adverse effects are frequent and sometimes severe when it is given parenterally and toxicity is more common in patients with AIDS [20]. Pentamidine can also cause thrombocytopenia and leucopenia and as such should be used cautiously in combination with zidovudine. Fatalities due to pancreatitis have been reported with pentamidine use; therefore caution must be exercised if co-administering stavudine or didanosine, as risk of pancreatitis may be increased. Likewise, hepatotoxicity has been reported, and the manufacturers advise liver function monitoring every 3–5 days in patients taking other potentially hepatotoxic drugs; this may be warranted in patients taking stavudine, didanosine or nevirapine.

In addition, pentamidine may cause arrhythmias and as such should be used cautiously with ritonavir, some protease inhibitors such as lopinavir/ritonavir and rilpivirine.

Paromomycin

Paromomycin is used parenterally in visceral leishmaniasis, and can also be used for intestinal protozoal infections such as giardiasis. Paromomycin is not metabolized *in vivo* and is excreted unchanged in the urine [45]. There is little potential for interaction via competition for active renal elimination pathways; however, aminoglycosides as a class have an inherent

potential for causing nephrotoxicity [45]. Concurrent or sequential use of other potentially nephrotoxic drugs should be avoided because of the possibility of additive toxicity. Since paromomycin may also result in pancreatitis [46]; extreme care is advised when coadministering paromomycin with drugs associated with pancreatitis such as stavudine or didanosine-containing regimens. Paromomycin is also used in the treatment of intestinal protozoal infections, including amoebiasis, cryptosporidiosis and giardiasis. It should be noted that in patients with chronic gastrointestinal infection, absorption of antiretroviral drugs may be significantly impaired.

Praziquantel

Praziquantel is used to treat schistosomiasis, and is also effective in treatment of fluke infections and tapeworm infection, including neurocysticercosis. Praziquantel is metabolized by CYP3A4, CYP1A2 and CYP2C19 [14] and as such there is limited potential for interaction with the nucleoside reverse transcriptase inhibitors, maraviroc, raltegravir or rilpivirine. Available data show that known enzyme inducers carbamazepine, phenytoin and rifampicin reduce plasma praziquantel levels [47,48]. In the absence of interaction data with NNRTIs, metabolism and elimination data suggest the possibility of an interaction between praziquantel and NNRTIs, which may reduce concentrations of praziquantel. Single doses of praziquantel in patients on NNRTIs may have reduced efficacy, and clinical vigilance for treatment failure is advised. Data from a crossover healthy volunteer study with ketoconazole showed that praziquantel exposure doubled in the presence of ketoconazole [49]. Therefore interactions are possible between praziquantel and the boosted protease inhibitors via enzyme inhibition, which may increase levels of praziquantel; however, no clinical data are available.

Pyrantel

Pyrantel may be used to treat soil-transmitted helminth infection, including mixed or single infections with intestinal nematodes including roundworms (*Ascaris lumbricoides*), threadworms or pinworms (*Enterobius vermicularis*), and *Trichostrongylus spp.*, the tissue nematode *Trichinella spiralis*, and hookworms. Pyrantel is metabolized by CYP2D6 *in vitro* [14], however only a very small proportion of pyrantel embonate is absorbed from the gastrointestinal tract [20] and therefore there is limited potential for interactions.

Sodium stibogluconate

Sodium stibogluconate is excreted rapidly via the kidneys. Renal elimination of this drug is similar to the rate of glomerular filtration [50,51], therefore there is limited potential for interaction with emtricitabine, lamivudine or tenofovir via competition for active renal transport. Pancreatitis has been described as a relatively common serious adverse effect of sodium stibogluconate [52–54] and it should therefore be used with extreme caution in patients taking stavudine, didanosine and ritonavir-containing regimens. Similar to meglumine antimonate, sodium stibogluconate is associated with QTc prolongation and torsades de pointes [55–57]. Hence ritonavir-boosted saquinavir is contraindicated and caution is advised in patients on other ritonavir-boosted regimens or rilpivirine. Sodium stibogluconate has been reported to cause haematological suppression in 44% of patients [52,53]: hence caution is advised in patients taking zidovudine.

Suramin

Suramin is used in the treatment of African trypanosomiasis and also may be used as an anthelmintic in the treatment of onchocerciasis. Suramin is predominantly eliminated unchanged by the kidneys [58] which limits its potential interaction with the protease inhibitors and NNRTIs. However, there is a possibility of competition for renal elimination with emtricitabine, lamivudine or tenofovir. Suramin is associated with myelosuppresssion and may increase the risks of adverse reactions with zidovudine.

Conclusion

Neglected tropical diseases are neglected by virtue of their geographic distribution in the poorest communities rather than any lack of importance in terms of burden of disease and human suffering. As such they are an uncomfortable testament to contemporary inequity in global health which has prompted the WHO 2020 Roadmap and 2012 London Declaration on NTDs. From this review it is clear that these diseases are additionally 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. In the absence of formal drug interaction studies, we utilized what knowledge was available on the clinical and preclinical pharmacology of these drugs to make recommendations in this article and we acknowledge the limitation of this approach. Pharmacokinetics may differ considerably between healthy volunteers, HIV-positive patients and people suffering from NTDs who may have different diet, absorption and nutritional status. Protein levels and alpha1 acid glycoprotein levels may differ, in addition to differences in key drug disposition genes from their healthy volunteer counterparts. Additionally these patients may be suffering from more than one NTD in addition to HIV. Due to the extensive geographic overlap and co-endemicity of these diseases, efforts to expand global access to drugs will likely aim to integrate treatment programs via harmonization and coordination of the partnerships involved in control or elimination of the most prevalent NTDs and linking

them with national health ministries and the WHO [1]. Therefore, there is potential for complex interactions between multiple drugs which are difficult to predict in the absence of data from specific pharmacokinetic studies.

Clinical pharmacology research in the area of NTDs is clearly needed and should ideally address treatment regimens for both mass treatment programmes and management of acute infections which may differ in terms of dosing or duration of drugs. In the interim strengthening pharmacovigilance may yield helpful data and is extremely important in view of the possibility of serious adverse events with pancreatitis and cardiac toxicity. Case reports are also valuable and formed a significant part of the evidence base for this review.

Unfortunately it is more difficult to capture therapeutic failure due to drug–drug interactions as this treatment failure does not fall under the purview of traditional pharmacovigilance and sadly is often accepted in the communities affected by these diseases as the inevitable consequences of the infections themselves.

We recognize the clear humanitarian imperative to make drugs widely available to those populations who need them most, yet can afford these agents least. However, alongside this must also run an ethical imperative, to ensure that treatment is both safe, effective and management of drug–drug interaction with antiretrovirals is evidence-based. A series of well designed relatively inexpensive pharmacokinetic studies in the affected populations could bring excellence in prescribing and quality assurance to the populations who most need it, and thereby ensure that the good intentions of the donors and policy makers translate into 'healthier and more productive lives'.

Acknowledgements

K.S. undertook the literature search, C.M. and K.S. wrote the manuscript, S.K., D.B., M.L., P.B.-K., N.P. and J.M. made significant contribution to the content and writing of the manuscript.

Conflicts of interest

We acknowledge support from a Wellcome Trust Programme Grant award: PK-PD modelling to optimize treatment for HIV, TB and malaria. (ref 083851/Z/07/Z).

M.L. and P.B. are supported by European and Developing Countries Clinical Trials Partnership grants (TA.09.40200.020 and TA.11.40200.047).

Transparency Declaration: D.J.B. and S.H.K. have received research funding for development of the web site www.hiv-druginteractions.org from Viiv, BMS, Gilead, Janssen, Merck, Boehringer-Ingelheim. DJB has received honoria for lectures or Advisory Boards from Viiv, BMS, Gilead, Janssen, Merck.

M.L. has received grants from Janssen and is supported by the Sewankambo scholarship at IDI which is funded by Gilead Foundation.

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