


# Prevalence and management of drug–drug interactions with antiretroviral treatment in 2069 people living with HIV in rural Tanzania: a prospective cohort study\*

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## Objectives

Widespread access to antiretroviral therapy (ART) has substantially increased life expectancy in sub-Saharan African countries. As a result, the rates of comorbidities and use of co-medications among people living with HIV are increasing, necessitating a sound understanding of drug–drug interactions (DDIs). We aimed to assess the prevalence and management of DDIs with ART in a rural Tanzanian setting.

## Methods

We included consenting HIV-positive adults initiating ART in the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) between January 2013 and December 2016. DDIs were classified using [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org) as red (contra-indicated), amber (potential clinical relevance requiring dosage adjustment/monitoring), yellow (weak clinical significance unlikely to require further management) or green (no interaction). We assessed management of amber DDIs by evaluating monitoring of laboratory or clinical parameters, or changes in drug dosages.

## Results

Of 2069 participants, 1945 (94%) were prescribed at least one co-medication during a median follow-up of 1.8 years. Of these, 645 (33%) had at least one potentially clinically relevant DDI, with the highest grade being red in nine (< 1%) and amber in 636 (33%) participants. Of the 23 283 prescriptions, 19 (< 1%) and 1745 (7%) were classified as red and amber DDIs, respectively. Overall, 351 (2%) prescriptions were red DDIs or not appropriately managed amber DDIs.

## Conclusions

Co-medication use was common in this rural sub-Saharan cohort. A third of participants had DDIs requiring further management. Of the 9% of participants with not appropriately managed DDIs, most were with cardiovascular and analgesic drugs. This highlights the importance of physicians' awareness of DDIs for their recognition and management.

**Keywords:** drug–drug interaction management, drug–drug interaction, HIV infection, sub-Saharan Africa

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## Introduction

The increasing availability of antiretroviral therapy (ART) has led to a dramatic reduction in AIDS-related deaths worldwide and prolonged life expectancy in people living with HIV (PLWH) [1,2]. The number of PLWH accessing ART is increasing with implementation of the current 'test and treat' strategy to start ART regardless of CD4 cell count [3]. Antiretroviral drugs have a high potential for drug–drug interactions (DDIs) as a consequence of the induction and inhibition of cytochrome P450 isoenzymes and overlapping toxicities [4]. Therefore, the management of DDIs remains a key priority in the daily routine care of PLWH. Unrecognized, DDIs can lead to toxicities or underdosing with a decrease in drug efficacy [5,6]. When it is not possible to avoid DDIs, appropriate management such as close monitoring or dose adjustment of clinically relevant DDIs is important [4].

In resource-limited settings, management of DDIs can be complicated by the inflexibility of treatment regimens, which often consist of fixed-dose combinations, or by the challenges in treatment monitoring [7]. For example, until 2015, routine viral load testing, allowing for monitoring of treatment failure attributable to DDIs, was not recommended in most sub-Saharan African hospitals [8]. Furthermore, long distances to the clinic are associated with costs for patients and higher rates of loss to follow-up [9] and might complicate adherence to additional visits. The presence of coinfections such as tuberculosis is common [10] and necessitates the use of co-medication with a high potential for DDIs, such as rifampicin. Rifampicin is a strong inducer of drug metabolism and therefore can reduce the exposure of antiretroviral drugs, resulting in a lack of efficacy.

Previous studies in Uganda [11] and Kenya [12] found that the prevalences of potential DDIs – identified in 19% and 34% of patients, respectively – were comparable between sub-Saharan Africa and high-income countries, which report a prevalence ranging from 27% to 41% [13,14]. However, the co-medications involved in DDIs differ by setting, as a result of differences in the comorbidity profiles of the patient populations, and, consequently, the co-medications prescribed [11,13]. Most studies were retrospective in character. Therefore, they only reported potential DDIs without an indication of whether or not potential DDIs were managed correctly (i.e. in terms of dosage adjustment and clinical monitoring). As a consequence of this important limitation, the prevalence of clinically relevant DDIs might have been overestimated.

The aim of our study was to assess the prevalence and particularly the management of clinically relevant DDIs with ART in a prospective cohort in rural Tanzania in

order to give a more accurate picture of the prevalence of DDIs that are not appropriately managed.

## Methods

### Study setting and population

The study was conducted using data from the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) study, an ongoing cohort study of patients attending the Chronic Diseases Clinic Ifakara (CDCI). CDCI is the care and treatment centre for PLWH of the St Francis Referral Hospital, located in a rural area in south central Tanzania. Started in 2005, KIULARCO has enrolled more than 10 000 patients to date with approximately 4000 currently under active HIV care. Details of the cohort have been published elsewhere [15,16]. In brief, information on demographics, clinical parameters, comorbidities, prescription of ART and co-medications including drug dosages, adherence and laboratory monitoring is prospectively registered within an electronic patient database during all patient visits, thus enabling systematic analysis of whether monitoring or dosage changes had been made in the recommended interval. Routine clinic visits and laboratory monitoring are scheduled twice a year. While all drug prescriptions are recorded, dispensing is done and recorded only for antiretroviral drugs and not co-medications, which patients need to buy separately. Actual drug consumption is not captured except for pill count of ART and questions regarding adherence to ART medication.

### Study design

We included all consenting adults ( $\geq 15$  years of age) who initiated ART in 2013–2016 with follow-up until September 2017. We classified co-medications according to their Anatomical Therapeutic Chemical classification/daily defined dosages (ATC/DDD 2017) [17]. Polypharmacy was defined as being on five or more non-HIV drugs.

All DDIs were classified according the Liverpool Drug Interaction Database ([www.hiv-druginteractions.org](http://www.hiv-druginteractions.org), accessed on 20 December 2017). In the Liverpool database, drug pairs are classified as having (1) 'contra-indicated drug interactions' (red), if they may lead to serious side effects or lack of therapeutic effect, (2) 'potentially clinically significant drug interactions' (amber), if they can be managed by modification of the dosage or close monitoring, (3) 'interactions of weak clinical significance' (yellow), if they do not require any further management, or (4) 'no interaction expected' (green) [18]. For this study, we assessed only interactions between ART and co-medications. Concomitant use of prophylactic co-

trimoxazole and antiretrovirals was classified as green, while in the Liverpool database the interaction between co-trimoxazole and zidovudine is amber. The basis for this adaptation was the lack of influence of oral co-trimoxazole on zidovudine levels [19]. DDIs were classified on a patient and on a prescription level. On the prescription level, we counted each combination of co-medication and an antiretroviral drug once, as long as the patient received the same medication.

For amber DDIs, we additionally assessed the clinical management of the interaction to determine its clinical significance. Specifically, we defined in advance the appropriate management of the most commonly available drug combinations from a clinical perspective (CS and MW), which was reviewed by a pharmacologist (CM), and according to the available diagnostics in a rural African setting. This included dosage adjustment if an interaction would lead to a decrease or increase in drug levels, additional clinical monitoring, or additional diagnostic measures for suspected toxicities such as creatinine measurement, blood pressure measurements or electrocardiogram monitoring. Amber DDIs that were not handled according to these pre-specified criteria were considered not appropriately managed.

To assess the outcome of not appropriately managed DDIs, we screened the patient's clinical or laboratory data up to 6 months after the prescription to determine the occurrence of negative clinical outcomes (e.g. renal impairment or uncontrolled blood pressure). If measurements were not available within these 6 months, the outcome was considered as not known. For DDIs leading to a risk of interval on electrocardiogram (QT) prolongation, we defined sudden cardiac death and loss to follow-up as a negative outcome, as death occurring outside the clinic is registered in the database.

#### Definition of clinical and laboratory parameters

Baseline characteristics of patients such as weight, body mass index (BMI), CD4 cell count and HIV World Health Organization (WHO) stage were captured within 24 weeks before and up to 4 weeks after ART initiation. Information on comorbidities was obtained within 12 weeks before until up to 4 weeks after ART initiation. For this study, tuberculosis was defined as sputum-positive smear microscopy, a positive Xpert (Cepheid, Banksmeadow, Australia) assay in sputum or an extrapulmonary sample, or a chest radiography with changes suggestive of tuberculosis plus at least one symptom compatible with tuberculosis, by physician diagnosis International Statistical Classification of Diseases and Related Health Problems 10th Revision ICD-10 code (International Statistical

Classification of Diseases and Related Health Problems 10th Revision), and anti-tuberculosis treatment. Comorbidities, recorded with the ICD-10 code, were categorized as: opportunistic infections [including cryptococcosis, *Pneumocystis jirovecii* pneumonia (PCP), toxoplasmosis, candida oesophagitis and Kaposi's sarcoma], nonopportunistic infections (pneumonia, gastroenteritis, pelvic inflammatory disease and fungal skin infection) and noncommunicable diseases (arterial hypertension, kidney disease and diabetes). Arterial hypertension was defined as systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg on two consecutive measurements. Reduced kidney function was diagnosed if the estimated glomerular filtration rate calculated with the Chronic Kidney Disease Epidemiology Formula (CK-EPI) from a creatinine measurement was  $\leq 60$  mL/min/1.73 m<sup>2</sup>. As routine blood glucose screening is not implemented, blood glucose was measured upon clinical suspicion for diagnosis of diabetes.

#### Statistical analysis

Baseline data such as sociodemographic, clinical and treatment information were summarized using descriptive statistics according to prescription of co-medications and management of DDIs. As the reasons for lack of appropriate management of DDIs were mainly structural, for example that only fixed-dose combinations were available or no electrocardiogram (ECG) monitoring was available, we did not perform formal statistical modelling to assess factors associated with having DDIs and/or appropriate management.

#### Ethical considerations

The Ifakara Health Institute Institutional Review Board and the National Health Research Ethics Review Committee of the National Institute for Medical Research of Tanzania provided ethical approval for KIULARCO. Written informed consent is sought from all participants at registration at the CDCI. Those who refused consent were excluded from our analyses. All data analysed were captured under routine care at the CDCI, including the tracing procedures. Data are stored on a secure server and were de-identified before analysis.

## Results

#### Patient characteristics and treatments

Of 2069 participants, 1368 (66%) were female and the median age was 39 years [interquartile range (IQR) 32–

47 years], with 19% aged  $\geq 50$  years (Table 1). At the start of ART, the majority of the 1945 participants ever prescribed a co-medication had a CD4 count  $< 350$  cells/ $\mu\text{L}$  and about half had an advanced HIV WHO disease stage. Tuberculosis was the most frequent comorbidity, followed by nonopportunistic infections. Most individuals were started on a tenofovir disoproxil fumarate (TDF)-based therapy, mainly TDF/lamivudine (3TC)/efavirenz (EFV), which at the time of the study was the recommended first-line regimen in Tanzania [20]. Of the 1945 (94%) patients receiving at least one co-medication while treated with ART (Fig. 1), the prevalence of polypharmacy (five or more drugs) was 24%. Anti-infectives were the most commonly prescribed non-HIV co-medications.

### DDIs on a patient level

Among the 1945 patients receiving at least one co-medication and considering the worst (highest) level of DDI, 955 (49%) patients had green, 345 (18%) yellow, 636 (33%) amber and nine ( $< 1\%$ ) red DDIs (Fig. 1). When

looking at DDIs requiring management, 181 (9%) patients had at least one DDI that was not appropriately managed. Those patients tended to be older, and have more advanced HIV disease with lower CD4 counts compared to the group with appropriate DDI management (Table 1). Furthermore, not appropriately managed DDIs tended to be more frequent in patients with tuberculosis and non-communicable comorbidities. In these patients, polypharmacy consisting mostly of analgesics and cardiovascular comedications was more common than in the group with appropriate DDI management.

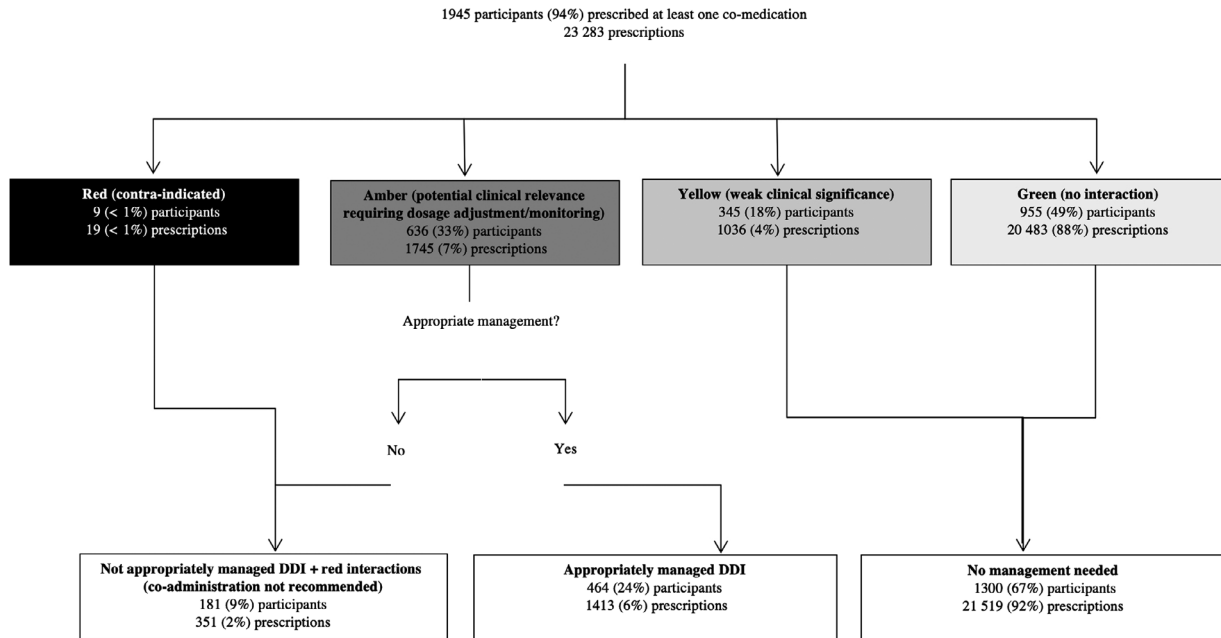
### DDIs on a prescription level

Of the 23 283 prescribed co-medications, the majority were antibiotics, with 15 848 prescriptions (68%; Fig. 2). Cardiovascular drugs and vitamins/supplements were also prescribed frequently, accounting for 2717 (12%) and 1848 (8%) prescriptions, respectively. Overall, 20 483 (88%) prescriptions of co-medications were classified as green, 1036 (4%) as yellow, 1745 (7%) as amber and 19 ( $< 1\%$ ) as red DDIs (Fig. 1).

**Table 1** Participant characteristics at antiretroviral therapy (ART) initiation according to co-medication status

Characteristic at ART initiation	Ever prescribed a co-medication ( $n = 1945$ ; 94%)		Never prescribed a co-medication ( $n = 124$ ; 6%)
	Appropriately managed DDI ( $n = 1764$ ; 91%)	Not appropriately managed DDI ( $n = 181$ ; 9%)	
Female	1164 (66)	117 (65)	87 (70)
Age			
15–29 years	341 (19)	14 (8)	21 (17)
30–49 years	1109 (63)	105 (58)	81 (65)
$\geq 50$ years	314 (18)	62 (34)	22 (18)
Body mass index			
Underweight ( $< 18.5$ kg/ $\text{m}^2$ )	333 (19)	31 (18)	6 (7)
Normal weight (18.5–25 kg/ $\text{m}^2$ )	1064 (62)	105 (61)	63 (69)
Overweight or obese ( $\geq 25$ kg/ $\text{m}^2$ )	321 (19)	37 (21)	22 (24)
CD4 count $< 350$ cells/ $\mu\text{L}$	1165 (75)	124 (81)	20 (35)
WHO stage			
1	661 (39)	49 (28)	34 (65)
2	249 (15)	26 (15)	8 (15)
3	499 (30)	71 (41)	5 (10)
4	274 (16)	27 (16)	5 (10)
First ART regimen			
TDF-based	1574 (89)	149 (82)	88 (71)
Non-TDF-based	186 (11)	32 (18)	36 (29)
PI-containing	17 (1)	0 (0)	3 (3)
Comorbidities			
Tuberculosis	352 (20)	57 (31)	2 (2)
Opportunistic infections	105 (6)	17 (9)	4 (3)
Nonopportunistic infections	303 (17)	36 (20)	5 (4)
Noncommunicable comorbidities	203 (12)	38 (21)	6 (5)
Alcohol use	282 (17)	36 (21)	18 (23)
Number of co-medications			
0	169 (10)	13 (7)	124 (100)
1–4	1205 (68)	95 (52)	0 (0)
$\geq 5$	390 (22)	73 (40)	0 (0)

Values are  $n$  (%).DDI, drug–drug interaction; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.



**Fig. 1** Prevalence of drug–drug interactions (DDIs) at a patient and prescription level in 2069 patients. Percentages refer to the total number of patients with co-medications and prescriptions, respectively. Numbers are per patient and per prescription whereby one prescription equals the same drug given at several visits.

All red DDIs involved the co-administration of rifampicin and a protease inhibitor (lopinavir/ritonavir or atazanavir/ritonavir) or nevirapine (Table 2). Of interest, DDIs with rifampicin were mostly managed correctly by doubling the dose of lopinavir/ritonavir (i.e. 800/200 twice daily) in the presence of rifampicin as per recommendation, if no alternative treatment is available [21]. The DDI between efavirenz and ketoconazole shampoo was not considered relevant as ketoconazole reaches low systemic levels with topic administration [22]. Thus, only four red DDIs were considered to be problematic and not addressed properly.

The 1745 amber DDIs (prescription level) were mainly interactions of rifampicin with efavirenz (1011; 58%) followed by nonsteroidal anti-inflammatory drugs (NSAIDs) interacting with tenofovir or efavirenz (199; 11%), and nifedipine interacting with nonnucleoside reverse transcriptase inhibitors (NNRTIs) (162; 9%; Table 3). These co-medications also belonged to the most commonly prescribed drug classes (Fig. 2).

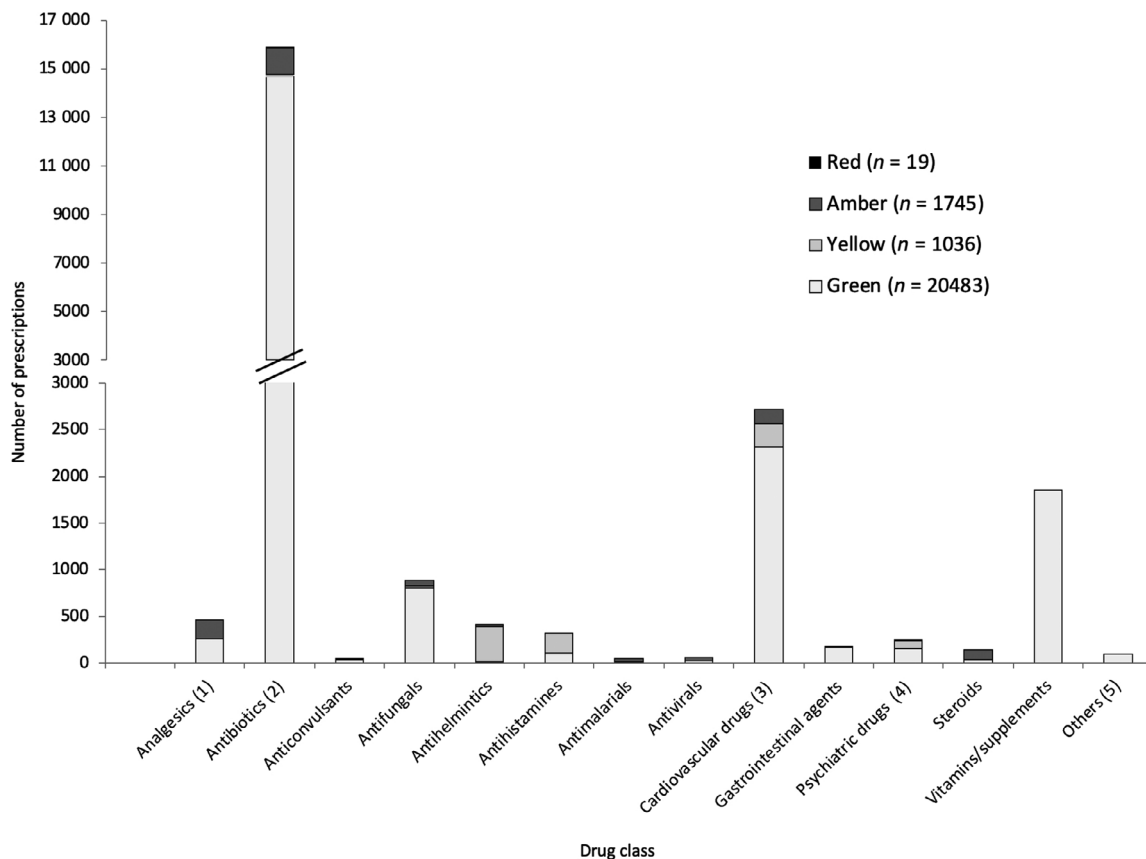
### Management of DDIs

Overall, appropriate clinical monitoring and dose adjustments were performed in 1413 of 1745 (81%) amber DDIs and included predominantly the management of DDIs of rifampicin with efavirenz (1007 prescriptions; 71%). In

our setting, the fixed-dose antiretroviral combination contains 600 mg of efavirenz and the fixed-dose anti-tuberculosis combination contains 10 mg/kg of rifampicin, which was considered as being correctly managed according to the current guideline recommendations [23]. Nineteen out of 1745 (1%) amber DDIs were considered to be not clinically relevant and did not require further monitoring or dosage adjustment as a consequence of the short treatment duration of < 7 days (e.g. albendazole and zidovudine).

Other management requirements were laboratory monitoring, for example creatinine or haemoglobin measurements (269 prescriptions; 16%), and clinical monitoring, including blood pressure monitoring (180 prescriptions; 10%). In prescriptions requiring laboratory monitoring, a high proportion of appropriate monitoring was found, notably for creatinine. However, clinical monitoring was only appropriately managed in a third of the prescriptions, partly as a consequence of the lack of ECG monitoring facilities in the clinics.

Overall at a prescription level, 351 (2%) DDIs were considered not appropriately managed – these were 20% of the amber and red interactions. Nifedipine + efavirenz, ibuprofen + tenofovir and rifampicin + zidovudine were the co-medications most frequently involved in DDIs that were not appropriately managed. We attempted to assess the outcomes of DDIs that were not appropriately



**Fig. 2** Prescribed co-mediations and prevalence of drug–drug interactions (DDIs) within each therapeutic class. The figure displays prescribed co-mediations classified by therapeutic class. The distribution of DDI categories is represented within each therapeutic class. (1) Prescriptions of analgesics included 272 prescriptions of nonsteroidal anti-inflammatory drugs (NSAIDs), 176 of paracetamol and 14 of opioid analgesics. (2) Prescriptions of antibiotics included 10 013 prescriptions of cotrimoxazole, 2362 of antituberculosis drugs, 2294 of isoniazid preventive therapy, 1125 of other antibiotics and eight of antibiotics/anti-helminthics (tinidazole). (3) Prescriptions of cardiovascular drugs included 85 prescriptions of acetylsalicylic acid 100 mg, 136 of  $\beta$ -blockers, 574 of calcium channel blockers, 1320 of diuretics and 586 of Angiotensin converting enzyme (ACE)/angiotensin II inhibitors. (4) Prescriptions of psychiatric drugs included 176 prescriptions of antidepressants, 13 of sedatives/anti-anxiety and 90 of neuroleptics. (5) Other prescriptions included 25 prescriptions of benzyl benzoate, 14 of salbutamol, 13 of trihexyphenidyl, 12 of oral rehydration salt, four of aminobenzoic acid, three of metformin, three of silver nitrate, three of zinc oxide, two of aminophylline, one of boric acid, one of chlorhexidine, one of hydroxypropylmethylcellulose, one of norethisterone, one of pancreas lipase, one of sildenafil and one of tetanus vaccine/antitoxin.

**Table 2** Red drug–drug interactions in co-medication prescriptions ( $n = 19$ )

Co-medication	ARV	Prescriptions ( $n = 19$ )	Description of the interaction	Recommended management	Co-administration not recommended ( $n = 19$ )
Rifampicin	ATV/r	1	Reduction in PI concentration	Avoid	18 <sup>†</sup>
	LPV/r	17 <sup>‡</sup>			
	NVP	1 <sup>‡</sup>	Reduction in NVP concentration	Avoid	1

ATV/r, atazanavir/ritonavir; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NVP, nevirapine; PI, protease inhibitor.

<sup>†</sup>Including six prescriptions for both a PI and zidovudine.

<sup>‡</sup>15 prescriptions of LPV/r + rifampicin correctly adapted with a double dose of lopinavir/ritonavir (i.e. 800/200 mg twice daily).

<sup>‡</sup>Including one prescription for both NVP and zidovudine.

managed by analysing regular monitoring intervals after the occurrence of a DDI. However, because of limited follow-up data, only 126 (36%) of the prescriptions could be

followed up. In most prescriptions, the required outcome parameter (e.g. viral load for DDIs decreasing the plasma level of the antiretroviral drug) was not available, or the



Table 3 Amber drug-drug interactions (*n* = 1745)

Co-medication	ARV	Prescriptions ( <i>n</i> = 1745)	Description of the interaction	Recommended management	Not appropriately managed ( <i>n</i> = 332)
Rifampicin	EFV	1011*	Decrease in EFV concentration	Dose adjustment: EFV dose $\geq$ 600 mg daily	4*
	ZDV	31	Potential decrease in ZDV exposure	Avoid	31
NSAID	EFV	186†	Increase in NSAID exposure	Dose adjustment: use lowest NSAID dose possible in patients with cardiovascular risk factors	30‡
	TDF	13	Risk of nephrotoxicity	Laboratory monitoring: creatinine monitoring every 30 days if prescription > 1 week	47
Ibuprofen	ZDV	4§	Haematotoxicity	Laboratory monitoring: haematology monitoring	0
Nifedipine	NNRTI	162	Decrease in nifedipine exposure	Clinical monitoring: blood pressure monitoring every 30 days	112
Steroids	NNRTI	104	Decrease in steroid exposure	Dose adjustment: oral dose > 10 mg daily (aside from tapering), topical use no management necessary	5
Aciclovir/valaciclovir	ZDV/r	5	Increase in steroid exposure	Dose adjustment: prednisolone dose max. 40 mg daily	3
	TDF	42	Potential risk of nephrotoxicity	Laboratory monitoring: creatinine monitoring every 30 days if prescription > 7 days	9
Artemether	NNRTI	35	Decrease of antimalarial efficiency	Dose adjustment: would necessitate increase in artemether dosage, but only fixed dose available; no management possible	35
Griseofulvin	NNRTI	33	Decrease in NNRTI exposure	Dose adjustment: EFV $\geq$ 600 mg daily, increase NVP with therapeutic drug monitoring (not available)	1
Doxycycline	NNRTI	28	Decrease in doxycycline exposure	Dose adjustment: doxycycline dose at least 200 mg daily	2
Carbamazepine	NNRTI	18	Decrease in NNRTI and carbamazepine exposure	Use alternative anticonvulsant (gabapentin)	18
Fluconazole	ZDV/NVP	23	Increase in ZDV/NVP concentrations	Laboratory monitoring: monitor for side effects (haematology and liver enzymes) every 30 days if prescription > 1 week	16
Albendazole	ZDV	12	Haematotoxicity	Short treatment, no management	0
Haloperidol	PI	14	Risk of QT prolongation	Clinical monitoring: ECG monitoring, but no ECG available	14
Gentamicin	TDF	5	Risk of nephrotoxicity	Laboratory monitoring: creatinine monitoring every 30 days if prescription > 1 week	0
Mebendazole	LPV/r/ ZDV	3	Decrease in mebendazole exposure/haematotoxicity	Short treatment, no management	0
Metronidazole	LPV/r	3	Side effect attributable to alcohol content in LPV/r solution	Avoid oral solution in children; no management needed in adult population	0
Praziquantel	NNRTI/PI	4	Decrease/increase in praziquantel exposure	Dose adjustment: increase praziquantel dose to 60 mg/kg (NNRTI). Short treatment, no management (PI)	2
Clarithromycin	EFV/TDF	2	Decrease in clarithromycin exposure/increase in TDF exposure	Short treatment, no management	0
Morphine	EFV	2	May lead to increased morphine concentration	Clinical monitoring: monitor daily for sign of opiate toxicity while on treatment	1
Azithromycin	ZDV/r	1	Risk of QT prolongation	Clinical monitoring: ECG monitoring, but no ECG available within KIULARCO	1
Isoniazid	d4T	1	Increased risk of sensory neuropathy	Clinical monitoring: clinical follow-up of polyneuropathy 1 month after initiation	1
Loperamide	ZDV/r	1	Increase in loperamide exposure	No particular management (probably only used as antidiarrhoeal)	0
Nitrofurantoin	ZDV	1	Both drugs can cause myelosuppression	Short treatment, no management	0
Quinine	EFV	1	Decreased exposure of quinine	Dose adjustment: increase quinine dose	0

ARV, antiretroviral; ZDV, zidovudine; d4T, stavudine; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NNRTI, nonnucleoside reverse transcriptase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; NVP, nevirapine; PI, protease inhibitor; QT, interval prolongation on electrocardiogram; TDF, tenofovir disoproxil fumarate.

\*Including three prescriptions for both EFV and ZDV.

†Including 182 prescriptions for both EFV and TDF.

‡Including nine not appropriately managed prescriptions for both EFV and TDF.

§Including one prescription for both ZDV and EFV.

outcome measurements could obviously be influenced by parameters other than the DDI (e.g. haematotoxicity in DDI involving zidovudine).

## Discussion

In this study investigating prospectively 2069 PLWH on ART in a rural Tanzanian setting, we found that (1) the use of co-medications was high (94% of participants), (2) potentially clinically relevant DDIs between ART and co-medications were present in 33% of participants with co-medications and in 7% of prescriptions, (3) management of DDI was appropriate in 81% of red and amber prescriptions, and (4) reasons for inadequate management in the remaining 19% were mostly related to the inability of patients to come for additional visits.

Our patient-level prevalence of potentially clinically relevant DDIs of 33% among patients on co-medications is in line with previous studies reporting a prevalence ranging from 19% to 49% both in developed and in resource-limited settings [11,13,24,25]. Similarly to our observations, the prevalence of red DDIs in these studies was low [11,13,24,25]. The interacting co-medications differ among studies as a consequence of different patterns of comorbidities and thereby use of co-medications across different settings. While we observed red DDIs exclusively for rifampicin in combination with protease inhibitors, Seden *et al.* [11] reported red DDIs mostly for nevirapine in combination with ketoconazole in their cohort in Uganda. Other studies in Switzerland and Spain reported mainly on red interactions between protease inhibitors/NNRTIs and central nervous system drugs or proton-pump inhibitors [13,26]. These drug categories were rarely prescribed in our cohort. In our study, amber DDIs included mostly anti-infectives, notably rifampicin, consistent with other studies in sub-Saharan African settings [11,12]. Interestingly, the second most prevalent amber DDIs were with cardiovascular drugs, which is explained by the aging of the population of PLWH. Despite a high proportion of women of childbearing age in our cohort, we had only a few reports of hormonal contraception; however, as the analysis was based on prescriptions from our clinic only, women might have been prescribed contraceptives at another health facility. Previous studies concluded that there is a need to detect and avoid drug combinations resulting in amber DDIs, or to appropriately monitor and/or adjust dosages if possible [24]. In our study, only 2% of prescriptions resulted in DDIs that were not appropriately managed. While clinicians are well aware of and familiar with managing DDIs with anti-tuberculosis drugs in a setting where tuberculosis is highly prevalent, the management of other DDIs

was less straightforward, thus highlighting the importance of clinicians having the knowledge and tools to screen for DDIs.

While in our cohort laboratory monitoring is performed routinely, additional visits for monitoring of laboratory parameters were mostly not scheduled because of additional transport time and costs for patients, who refused to come back outside regular antiretroviral dispensing visits. Also, costs of reagents and costs related to staff needed to ensure the smooth running of clinical and laboratory consultations are a challenge, as they are not covered by regular programmes [27]. Furthermore, ECG to screen and monitor for QT prolongation was mostly not available. In addition, for specific laboratory tests or investigations such as ECG, patients might need referral to another health facility. Taken together, these economic and infrastructure limitations explain the limited number of amber DDIs managed appropriately from a clinical monitoring standpoint. Regarding amber DDIs requiring a dosage adjustment, the most prevalent DDI was for the combination of efavirenz and rifampicin (58%). The product label for efavirenz recommends an increase in efavirenz dose from 600 to 800 mg in the presence of rifampicin, particularly for patients weighing > 50 kg. However, current American and British HIV treatment guidelines recommend using the standard dose of efavirenz irrespective of body weight. This recommendation is supported by a recent meta-analysis including studies mostly from African populations, which found that efavirenz concentrations remain within the therapeutic range when dosed at 600 mg in the presence of rifampicin [28]. In our cohort, only one adolescent patient received inadvertently a daily dose of 400 mg as part of a paediatric formulation instead of the adult dosage of 600 mg contained in the fixed-dose combination. Recently, Cerrone *et al.* [29] demonstrated that, even during a co-medication of 400 mg of efavirenz with rifampicin, HIV viral load remained suppressed. Thus, no clinical consequence from this interaction is expected. As a matter of fact, the rifampicin-efavirenz combination has recently been changed to yellow in the Liverpool Drug Interaction Database.

During the study period, the first-line ART consisted of TDF/3TC/EFV, but since January 2019 this therapy has been replaced by an integrase-inhibitor-based regimen in Tanzania. Unboosted integrase inhibitors, such as dolutegravir, have a lower potential to cause DDIs [30,31]. However, current studies are limited to high-income countries and the implication of this switch for DDIs in resource-limited settings will need further evaluation. In settings with a high prevalence of tuberculosis, the



interaction of dolutegravir with rifampicin is clinically relevant and double dosing of dolutegravir is required [32].

While fixed-dose combinations may offer huge benefits in terms of correct drug prescription and adherence [33], the unavailability of single drugs is a major drawback for specific situations necessitating drug adjustment of single substances. In our cohort, this was particularly relevant for artemether/NNRTI, with 35 out of 47 (74%) prescriptions being not appropriately managed as a consequence of use of the artemether/lumefantrine fixed-dose combination and the same dose recommendation for all patients. It is very likely that the low number of artemether prescriptions captured in this cohort is an underestimation, as most patients seek antimalarial treatment directly at a local pharmacy or dispensary rather than in the HIV clinic and therefore would not be recorded in our database. In pharmacokinetic models, the combination of EFV and fixed-dose artemether/lumefantrine has been shown to significantly decrease lumefantrine exposure [34], which might affect the outcome of malaria. One study showed that HIV-infected patients on EFV treated with artemether/lumefantrine had a higher risk of recurrent parasitaemia [35], underlining the importance of reaching effective antimalarial levels in these patients.

The strengths of this study are its prospective nature, the large cohort and the systematic approach used in assessing the monitoring of DDIs through recordings of all visits and prescriptions in the database. Three important limitations need to be pointed out. First, the analysis was based on the reported prescribed drugs in the database and not on actual consumption of co-medications. Patients must buy non-ART drugs on their own in a pharmacy and might not correctly take the medications as prescribed or may simply not buy them for economic or other reasons. Secondly, only drugs prescribed by a physician of the HIV clinic were analysed. Thus, we could have missed co-medications sold over the counter, herbal drugs from a traditional practitioner, or drugs prescribed in other clinics; in women, most importantly, contraceptives. As management was defined taking into account diagnostic availabilities in this setting, our results might not be applicable to other settings with different access to monitoring. Finally, we only analysed DDIs between ART and co-medications, and not between non-HIV co-medications, nor between anti-tuberculosis drugs and co-medications in 409 patients receiving anti-tuberculosis treatment, which is an important other source of DDIs.

In conclusion, the management of DDIs remains a key aspect of the care of PLWH. Our results indicate a high awareness of DDIs involving rifampicin; however, management of DDIs with other co-medications remains

suboptimal. It is therefore essential to continuously train prescribing physicians regarding DDIs. New approaches using mobile technologies have been successfully evaluated [36] and could be considered for this rural setting to improve DDI awareness. Patient counselling about the risk of DDIs, especially in the context of self-administered co-medication or herbal drugs, should be emphasized.

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## References

- 1 World Health Organisation (WHO). WHO | Global AIDS Update [Internet], 2016. Available at <http://www.who.int/hiv/>

- pub/arv/global-aids-update-2016-pub/en/ (accessed 01 May 2019).
- 2 UNAIDS. Global Report 2013 [Internet], 2013. Available at <http://www.unaids.org/en/resources/campaigns/globalreport2013/globalreport> (accessed 01 May 2019).
  - 3 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. [Internet], 2016. Available at <http://www.ncbi.nlm.nih.gov/books/NBK374294/> (accessed 1 April 2017).
  - 4 Seden K, Back D, Khoo S. Antiretroviral drug interactions: often unrecognized, frequently unavoidable, sometimes unmanageable. *J Antimicrob Chemother* 2009; **64**: 5–8.
  - 5 Seden K, Khoo SH, Back D *et al.* Global patient safety and antiretroviral drug-drug interactions in the resource-limited setting. *J Antimicrob Chemother* 2013; **68**: 1–3.
  - 6 Agu KA, Oqua D, Adeyanju Z *et al.* The incidence and types of medication errors in patients receiving antiretroviral therapy in resource-constrained settings. *PLoS One* 2014; **9**: e87338.
  - 7 Dooley KE, Flexner C, Andrade AS. Drug interactions involving combination antiretroviral therapy and other anti-infective agents: repercussions for resource-limited countries. *J Infect Dis* 2008; **198**: 948–961.
  - 8 The United Republic of Tanzania. National Guidelines for the Management of HIV and AIDS. Fifth Edition, May 2015. Available at [https://aidsfree.usaid.gov/sites/default/files/04\\_11\\_2016.tanzania\\_national\\_guideline\\_for\\_management\\_hiv\\_and\\_aids\\_may\\_2015\\_tagged.pdf](https://aidsfree.usaid.gov/sites/default/files/04_11_2016.tanzania_national_guideline_for_management_hiv_and_aids_may_2015_tagged.pdf) (accessed 01 May 2019).
  - 9 Bekolo CE, Webster J, Batenganya M, Sume GE, Kollo B. Trends in mortality and loss to follow-up in HIV care at the Nkongsamba Regional hospital, Cameroon. *BMC Res Notes* 2013; **6**: 512.
  - 10 World Health Organization (WHO). Global TB Report 2015. Geneva; 2015.
  - 11 Seden K, Merry C, Hewson R *et al.* Prevalence and type of drug-drug interactions involving ART in patients attending a specialist HIV outpatient clinic in Kampala, Uganda. *J Antimicrob Chemother* 2015; **70**: 3317–3322.
  - 12 Kigen G, Kimaiyo S, Nyandiko W *et al.* Prevalence of potential drug-drug interactions involving antiretroviral drugs in a large Kenyan cohort. *PLoS One* 2011; **6**: e16800.
  - 13 Marzolini C, Elzi L, Gibbons S *et al.* Prevalence of comedication and effect of potential drug-drug interactions in the Swiss HIV Cohort Study. *Antivir Ther* 2010; **15**: 413–423.
  - 14 Evans-Jones JG, Cottle LE, Back DJ *et al.* Recognition of risk for clinically significant drug interactions among HIV-infected patients receiving antiretroviral therapy. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2010; **50**: 1419–1421.
  - 15 Vanobberghen F, Letang E, Gamell A *et al.* A decade of HIV care in rural Tanzania: trends in clinical outcomes and impact of clinic optimisation in an open, prospective cohort. *PLoS One* 2017; **12**: e0180983.
  - 16 Letang E, Kalinjuma AV, Glass TR *et al.* Cohort profile: the Kilombero and Ulanga Antiretroviral Cohort (KIULARCO) – a prospective HIV cohort in rural Tanzania. *Swiss Med Wkly* 2017; **147**: w14485.
  - 17 WHOCC – ATC/DDD Index [Internet]. Available at [https://www.whocc.no/atc\\_ddd\\_index/](https://www.whocc.no/atc_ddd_index/) (accessed 31 May 2018).
  - 18 Liverpool HIV Drug Interaction Checker [Internet]. Available at [https://hiv-druginteractions.org/site\\_updates/288](https://hiv-druginteractions.org/site_updates/288) (accessed 2 December 2017).
  - 19 Cañas E, Pachon J, Garcia-Pesquera F *et al.* Absence of effect of trimethoprim-sulfamethoxazole on pharmacokinetics of zidovudine in patients infected with human immunodeficiency virus. *Antimicrob Agents Chemother* 1996; **40**: 230–233.
  - 20 The United Republic of Tanzania. National Guidelines for the Management of HIV and AIDS. Available at [www.nacp.go.tz/site/download/NATIONAL\\_DECEMBER\\_2017.pdf](http://www.nacp.go.tz/site/download/NATIONAL_DECEMBER_2017.pdf) (accessed 01 May 2019).
  - 21 Kaletra EPAR Product Information. December 2018.
  - 22 Wang K, Wu Y, Chi Z *et al.* A highly sensitive LC-MS/MS method for determination of ketoconazole in human plasma: application to a clinical study of the exposure to ketoconazole in patients after topical administration. *J Pharm Biomed Anal* 2016; **128**: 504–509.
  - 23 British HIV Association guidelines for the management of tuberculosis in adults living with HIV 2018 (2019 interim update). Available at <https://www.bhiva.org/TB-guidelines> (accessed 01 May 2019).
  - 24 Miller CD, El-Kholi R, Faragon JJ, Lodise TP. Prevalence and risk factors for clinically significant drug interactions with antiretroviral therapy. *Pharmacotherapy* 2007; **27**: 1379–1386.
  - 25 Córdova E, Porteiro N, Loiza E, Mingrone H. Prevalence of potential drug-drug interactions involving antiretroviral drugs in Buenos Aires, Argentina. *Rev Chilena Infectol* 2016; **33** (Suppl 1): 54–59.
  - 26 Molas E, Luque S, Retamero A *et al.* Frequency and severity of potential drug interactions in a cohort of HIV-infected patients Identified through a Multidisciplinary team. *HIV Clin Trials* 2018; **19**: 1–7.
  - 27 Kimaro GD, Mfinanga S, Simms V *et al.* The costs of providing antiretroviral therapy services to HIV-infected individuals presenting with advanced HIV disease at public health centres in Dar es Salaam, Tanzania: findings from a randomised trial evaluating different health care strategies. *PLoS One* 2017; **12**: e0171917.
  - 28 Atwine D, Bonnet M, Taburet A-M. Pharmacokinetics of efavirenz in patients on antituberculosis treatment in high human immunodeficiency virus and tuberculosis burden countries: a systematic review. *Br J Clin Pharmacol* 2018; **84**: 1641–1658.

- 29 Cerrone M, Wang X, Neary M *et al.* Pharmacokinetics of Efavirenz 400 mg once daily coadministered with isoniazid and rifampicin in human immunodeficiency virus-infected individuals. *Clin Infect Dis Off Publ Infect Dis Soc Am* 2018; **68**: 446–452. <https://doi.org/10.1093/cid/ciy491>
- 30 Demessine L, Peyro-Saint-Paul L, Gardner EM, Ghosn J, Parienti J-J. Risk and cost associated with drug-drug interactions among aging HIV patients receiving combined antiretroviral therapy in France. *Open Forum Infect Dis* 2019; **6**: ofz051.
- 31 Baecke C, Gyssens IC, Decoutere L, van der Hilst JCH, Messiaen P. Prevalence of drug-drug interactions in the era of HIV integrase inhibitors: a retrospective clinical study. *Neth J Med* 2017; **75**: 235–240.
- 32 Dooley KE, Sayre P, Borland J *et al.* Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. *J Acquir Immune Defic Syndr* 2013; **62**: 21–27.
- 33 Clay PG, Nag S, Graham CM, Narayanan S. Meta-analysis of studies comparing single and multi-tablet fixed dose combination HIV treatment regimens. *Medicine (Baltimore)* 2015; **94**: e1677.
- 34 Maganda BA, Ngaimisi E, Kamuhabwa AAR, Aklillu E, Minzi OMS. The influence of nevirapine and efavirenz-based anti-retroviral therapy on the pharmacokinetics of lumefantrine and anti-malarial dose recommendation in HIV-malaria co-treatment. *Malar J* 2015; **14**: 179.
- 35 Maganda BA, Minzi OMS, Kamuhabwa AAR, Ngasala B, Sasi PG. Outcome of artemether-lumefantrine treatment for uncomplicated malaria in HIV-infected adult patients on anti-retroviral therapy. *Malar J* 2014; **13**: 205.
- 36 Seden K, Kiiza D, Laker E *et al.* Task shifting and mobile technology for HIV drug-drug interaction screening in Uganda (THPEE766). Presented at: 22nd International AIDS Conference, 2018, Amsterdam.