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 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 (≥ 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, 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 pharmacist (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 esophagitis 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 ≥ 140 mmHg and/or diastolic blood pressure ≥ 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 ≤ 60 mL/min/1.73 m². 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 ≥ 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/μL 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
comedication while treated with ART (Fig. 1), the
prevalence of polypharmacy (five or more drugs) was
24%. Anti-infectives were the most commonly pre-
scribed 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, polyphar-
armacy 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)                                     | 67 (37)                                       |
| Age                            | 341 (19)                                      | 14 (8)                                        |
| 15–29 years                    | 1109 (63)                                     | 105 (58)                                      |
| 30–49 years                    | 314 (18)                                      | 62 (34)                                       |
| ≥ 50 years                     | 333 (19)                                      | 31 (18)                                       |
| Body mass index                | 1064 (62)                                     | 105 (61)                                      |
| Underweight (< 18.5 kg/m²)     | 321 (19)                                      | 37 (21)                                       |
| Normal weight (18.5–25 kg/m²)  | 1165 (75)                                     | 124 (81)                                      |
| Overweight or obese (≥ 25 kg/m²)| 63 (39)                                       | 49 (28)                                       |
| CD4 count < 350 cells/μL       | 26 (13)                                       | 17 (10)                                       |
| WHO stage                      |                                               |                                               |
| 1                              | 661 (39)                                      | 49 (28)                                       |
| 2                              | 249 (15)                                      | 26 (15)                                       |
| 3                              | 499 (30)                                      | 71 (41)                                       |
| 4                              | 274 (16)                                      | 27 (16)                                       |
| First ART regimen              |                                               |                                               |
| TDF-based                      | 1574 (89)                                     | 149 (82)                                      |
| Non-TDF-based                  | 186 (11)                                      | 32 (18)                                       |
| PI-containing                  | 17 (1)                                        | 0 (0)                                         |
| Comorbidities                  |                                               |                                               |
| Tuberculosis                   | 352 (20)                                      | 57 (31)                                       |
| Opportunistic infections       | 105 (6)                                       | 17 (9)                                        |
| Nonopportunistic infections    | 303 (17)                                      | 36 (20)                                       |
| Noncommunicable comorbidities  | 203 (12)                                      | 38 (21)                                       |
| Alcohol use                    | 282 (17)                                      | 36 (21)                                       |
| Number of co-medications       |                                               |                                               |
| 0                              | 169 (10)                                      | 13 (7)                                        |
| 1–4                            | 1205 (68)                                     | 95 (52)                                       |
| ≥ 5                            | 390 (22)                                      | 73 (40)                                       |

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

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**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.
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

Fig. 2 Prescribed co-medications and prevalence of drug–drug interactions (DDIs) within each therapeutic class. The figure displays prescribed co-medications 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-helmintics (tinidazole). (3) Prescriptions of cardiovascular drugs included 85 prescriptions of acetylsalicylic acid 100 mg, 136 of β-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 benzocaine, 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-medications | 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†                                       |
|                | LPV/r| 17                     |                                 |                        |                                           |
|                | NVP  | 1                      | Reduction in NVP concentration  | Avoid                  | 1                                         |

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

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| Co-medication     | ARV       | Prescriptions (n = 1745) | Description of the interaction                                                                 | Recommended management                                                                                     | Not appropriately managed (n = 332) |
|-------------------|-----------|--------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-------------------------------------|
| Rifampicin        | EFV       | 1011*                    | Decrease in EFV concentration/Increase in ZDV exposure                                              | Dose adjustment: EFV dose ≥ 600 mg daily/ Avoid                                                                 | 4^                                   |
|                   | ZDV       | 31                       |                                                                                                |                                                                                                              | 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                                   |
|                   | ZDV/r     | 5                        | Increase in steroid exposure                                                                       | Dose adjustment: prednisolone dose max. 40 mg daily/ Laboratory monitoring: creatinine monitoring every 30 days if prescription > 7 days | 3                                   |
| Aciclovir/Valaciclovir | TDF     | 42                       | Potential risk of nephrotoxicity                                                                    | Laboratory monitoring: creatinine monitoring every 30 days if prescription > 1 week                          | 9                                   |
| Artemether        | NNRTI     | 35                       | Decrease of antimalarial efficiency                                                                | Dose adjustment: would necessitate increase in artemether dosage; no management possible                      | 35                                  |
| Griseofulvin      | NNRTI     | 33                       | Decrease in NNRTI exposure                                                                           | Dose adjustment: EFV ≥ 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     | 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                        | Decrease 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 electrocardiogramm; 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-ART 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 counseling 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/
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 antiretroviral 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 artesether-lumefantrine treatment for uncomplicated malaria in HIV-infected adult patients on antiretroviral 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 (THPPE766). Presented at: 22nd International AIDS Conference, 2018, Amsterdam.