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CLINICALLY SIGNIFICANT DRUG-DRUG INTERACTION IN A LARGE ANTIRETROVIRAL TREATMENT CENTRE IN LAGOS, NIGERIA

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ABSTRACT

Background
An important cause of treatment failure to antiretroviral therapy (ART) is the potential interaction between the antiretroviral (ARV) drugs and concomitant drugs (CD) used for the treatment of opportunistic infections and comorbid ailments in HIV-infected patients.

Objectives
The study evaluated potential Clinically Significant Drug Interactions (CSDIs) occurring between recommended ART regimens and their CD.

Method
This study was carried out in a large HIV treatment centre supported by AIDS Preventive initiative in Nigeria (APIN) clinic in a teaching hospital in Lagos, Nigeria, caring for over 20,000 registered patients. Electronic Medical Records (EMRs) of 500 patients, who received treatment between 2005 and 2015, were selected using systematic random sampling, reviewed retrospectively, and evaluated for potential CSDIs using Liverpool HIV Pharmacology Database and other databases for drug-drug interaction check.

Results
Majority of patients, 421 (84%) prescribed CDs were at risk of CSDIs, of which 410 (82%) were moderate and frequently involved co-trimoxazole + combinations of Nucleoside Reverse Transcriptase Inhibitors (NRTIs) such as zidovudine (or stavudine) /lamivudine 386 (77.2%) and Non-nucleoside Reverse Transcriptase

Inhibitors (NNRTIs) or Protease Inhibitors (PIs) + artemisinin-based combination therapies (ACTs) 296 (59.2%). Age (p=0.13), sex (p=0.32) and baseline CD4+ cell counts (p=0.20) were not significantly associated with CSDIs. The interactions, however, were significantly associated with the development of antiretroviral treatment failure (p <0.001) which occurred in nearly a third 139 (27.8%) of the patients.

Conclusion

There is a high prevalence of CSDIs between ART and CDs, most of which were categorized as moderate. Further studies are required to evaluate the pharmacokinetic and clinical relevance of these interactions.

Keywords: potential drug interaction, antiretroviral therapy, co-prescribed non-antiretroviral

The introduction of highly active antiretroviral therapy (HAART) into the pharmacotherapy of HIV/AIDS infection has dramatically decreased the mortality and morbidity of patients living with HIV.[1] HAART is a combination of different classes of antiretroviral drugs that act on different targets of HIV during replication in the host, but, the type prescribed is based on factors such as, the patient's viral load, the particular strain of the virus, the CD4+ cell count, comorbid illness, concomitant drugs, age and other considerations such as the disease symptoms.[2]

In spite of the success stories of HAART, drug resistance, adverse toxicity, non-adherence to therapy, and treatment failure to different regimen including the first-line, second-line and salvage-therapy have been reported as major challenges facing HIV/AIDS treatment.[3–5] Another important cause of treatment failure to these regimens is the potential interaction between ARV and non-ARV drugs (CDs) when both are used concomitantly. The risk for potential interaction is high due to the use of CDs in ART to treat co-existing opportunistic infections and comorbid illnesses such as malaria, typhoid, mycoses, tuberculosis, hypertension, diabetes, and psychoses etc.[6]

Theoretically, drug-drug interaction is defined as a phenomenon of 2 or more medicines interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered.[6] An interaction is deemed clinically significant if it requires dosage modification of the object drugs, therapy monitoring or consists of a drug combination that is contraindicated due to its high potential for clinical adverse effects.[7]

Interactions during drug absorption, distribution, hepatic metabolism, or renal excretion, resulting in an increased or a decreased plasma concentration and consequently altering the pharmacological effects, are termed pharmacokinetic interactions; while synergistic or antagonistic effects of 2 or more co-administered drugs, occurring at their sites of action, are termed pharmacodynamic interactions.[7]

An interaction that reduces the potency of antiretroviral drugs is of grave concern as it has the undesirable potential to cause viral rebound and the associated likelihood of causing treatment failure and development of resistance. This is exemplified in the inadequate plasma concentration of protease inhibitors resulting in treatment failure when co-administered with rifampicin due to enzyme induction and upregulation of P-glycoprotein caused by the latter.[8] If the interaction, however, leads to an increase in the plasma concentration of antiretroviral drugs, the consequence may be severe toxicity such as the increased risk of peripheral neuropathy caused by concomitant use of stavudine or didanosine co-administered with isoniazid.[9]

Most pharmacokinetic drug interactions with ARV drugs affect mainly the Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) and the protease inhibitors (PIs) because they are largely eliminated via the hepatic cytochrome P450 (CYP 450) enzyme system, principally by the CYP3A4 isoenzyme.[7] The NNRTIs, particularly nevirapine and efavirenz are enzyme inducers of CYP 3A4[10,11] while delavirdine and PIs in general are inhibitors of the same enzyme.[11,12] Thus, when the antiretroviral drugs are co-administered with CDs, their serum concentrations may be significantly reduced or increased thereby causing treatment failure or toxicity, respectively. Therefore, preventing and managing drug-drug interactions is very important in the optimization of HIV therapy.

Previous studies have shown that anti-tuberculous, antifungal, antibacterial and antimalarial drugs are major

classes of non-ARV drugs that are often co-prescribed with ARVs[13] and some of them have been associated with potential clinically significant drug interactions (CSDIs).[14] For example, the anti-tuberculous drug, rifampicin interacts with all classes of ARVs save the Nucleoside Reverse Transcriptase Inhibitors (NRTIs), except zidovudine and the HIV fusion inhibitor (enfuvirtide).[15] This is because rifampicin upregulates drug transporters and induces multiple metabolizing enzymes including cytochrome P450 enzymes.[16] The azoles are the most common class of antifungal drugs that are often co-prescribed with ARVs. Unlike ketoconazole and itraconazole which are extensively metabolized by CYP 3A4, fluconazole is less associated with CSDIs when co-administered with ARV drugs because it is excreted largely unchanged.[17]

Reports from developed countries indicated that prevalence of 20–41% for CSDIs have been reported for ARV drugs.[18,19] However, data from developing countries, including Nigeria, are sparse. A Kenyan study reported a prevalence of 33.5% for potential CSDIs in adult HIV-infected patients.[20] We have previously reported a prevalence of 67% CSDIs amongst HIV-infected children in Nigeria.[14]

This study aimed to add to the body of evidence of drug interaction studies in the adult population of people living with HIV/AIDS in Nigeria by identifying, as well as rating the severity of the potential CSDIs that may occur between ARV and co-prescribed drugs.

SUBJECTS AND METHODS

Study Design

This is a 10-year cohort study involving a retrospective review and analysis of prescriptions for 500 adult patients who were prescribed ARV and, at least, one non-ARV drugs (CDs). These patients were among those registered and followed up between 2005 and 2015 at the HIV treatment centre of the Lagos University Teaching Hospital (LUTH) known as AIDS Prevention Initiative in Nigeria (APIN) clinic. A total number of 20782 patients living with HIV had registered at the clinic as of December, 2015.

Data were extracted from 8 units of the APIN clinic including medical, pharmacy, nursing, counselling, hematology, medical records, administrative and data units. The clinic is one of the United States of America Presidential Emergency Plan for HIV AIDS Relief (PEPFAR) funded centres for HIV/AIDS relief program in Nigeria. It is a large HIV treatment centre which presently provides ARV drugs free of charge to over 15,000 registered HIV-infected patients coming from different parts of Southwestern Nigeria with an average of 350 old and new adults, children and pregnant women attended to daily.

The Electronic Medical Records (EMRs) for the 500 subjects were randomly selected. The inclusion criteria were as follows: being adult male or female of age ≥18yrs, confirmation of HIV infection with western blot test, enrolment on ART at the APIN clinic of LUTH in the year 2005. Exclusion criteria included discontinuation of program within one year of enrolment for any reason apart from death.

Sample Size Determination

A total of 18802 patients registered at the clinic from January 2005 to January 2015 constitute the population size. Using Raosoft[23]online sample size calculator at 5% error margin, 95% confidence level and 50% response distribution, a sample size of 377 was determined to be adequate for the study. However, it was increased to 500 for ease of data analysis.

Data Abstraction

Each of the 500 randomly selected patients was assigned an identification number and with the assistance of a data officer at the clinic and one of the co-authors, a standard form purposely designed for the study was used to extract their data on sex, age, mode of contracting HIV, comorbid illnesses, ARV drugs, co-prescribed non-ARV drugs, laboratory test results at baseline and at follow up throughout the 10-year study period (2005–2015). Data extracted were double checked and reviewed.

Identification of Potential CSDIs between ARV and Co-prescribed Non-ARV Drugs

All co-prescribed non-ARV and ARV drug pairs were screened for potential interactions using drug interaction checker database of the Liverpool HIV Pharmacology Group (LHPG) website. (www.hiv-druginteractions.org).[21] This website comprises a comprehensive database of over 5,000 drug-interaction pairs and uses a "traffic light" system to flag potential interactions. CSDIs were defined as those with co-usage

considered to be contraindicated/not recommended (Red indicating major interaction), or those requiring a dose adjustment (Orange colour indicating moderate interaction) to avoid side effects. Those with little or no CSDIs which can be safely used together are flagged with green colour (indicating minor or no interaction). Interactions information not found in LHPG were checked in other drug interaction checker databases.[22,23]

Classification of Potential CSDIs between Concomitant Non-ARVs and ARV Drugs

The severity of interactions (CSDIs and non-CSDIs) was rated from A to X (Table 1), according to a method of Armahizer et al.[24] The following symbols were used to rate the interaction: "X" for severe interactions in which the co-administration of the drugs is contraindicated; "C" for moderate interactions in which the drugs could be co-administered but with dosage/dosing interval adjustment and monitoring of patients for adverse effects and "A" for unknown or minor interactions in which the drugs could be safely co-administered.

Data Analysis

All data from the Electronic Medical Records were coded and results presented as frequency and percentage of patients in relation to dependent variables. Evaluation of age, sex, adherence, baseline CD4 counts and class of ARV drugs as risk factors for the development of CSDIs was made with multivariate logistic regression using Statistical Package for Social Science (SPSS) (IBM SPSS Statistics Version 21).

Ethical Considerations

The study protocol was approved by the Health Research Ethics committee of LUTH. At the point of enrollment on ART, written consent was given by the patients or their next of kin for their information to be stored in the hospital database and used for research. However, the confidentiality of their information was assured.

RESULTS

Demographics of adult HIV-infected patients

The case files of 500 HIV-infected adult patients were reviewed. Majority of the patients were female 310 (68%) and, married 305 (61%). Nearly half of the patients were illiterate 264 (53%). The median age of the patients was 46 years (range 18–83 years). Less than a 1 in 10 31 (6.2%) of the patients died within 10 years of commencement of HAART. More than half of the patients had baseline CD4+ cell count of >201 cells/mm^3. Majority were infected with HIV-1 478 (96%) while the type of HIV-infection was undocumented for the remaining patients 22 (4.4%). HIV infection was contracted mainly from heterosexual contact 454 (91%), followed by blood transfusion 45, (9%) and mother to child transmission 1 (0.2%) (see Table 1). ***Prescribed ART Regimen***

A total of 35582 prescriptions were reviewed involving 47 different ART regimens prescribed for the patients over the 10-year study period. They comprised 14 first-line regimens with 31546 (89%) prescriptions, 31 second-line regimen with 4034 (11%) prescriptions and 2 third-line regimens with only 2 (0.02%) prescriptions.

HAART regimen of zidovudine + lamivudine + nevirapine (AZT+3TC+NVP) 13500 (38%) was the most frequently prescribed, followed by stavudine + lamivudine + nevirapine (D4T +3TC+NVP) 11327 (32%). A total of 139 (28%) patients were switched to second line ART regimen due to therapeutic failure which occurred at a median time of 29 months. HAART switched to other first-line regimen was mainly due to adverse drug reactions 7 (1.4%), suspected major interactions with anti-tuberculous drugs 27 (5.4%), and inadequate supply of some ARV drugs including stavudine 8 (1.6%). There were no dosage adjust-ments in relation to potential CSDIs. All the ART were prescribed at recommended dosages based on the National treatment guideline in Nigeria.

Co-medication with ARV Drugs for HIV-Infected Adults

A total of 46 different non-ARV drugs were prescribed to the patients while on ART. The non-ARV drugs were prescribed for comorbid ailments, prevention or treatment of opportunistic infections and also to boost the immune system. Antibiotics (4156; 36%) especially co-trimoxazole 3242 (28%), were most commonly prescribed followed by haematinics 3039 (27%), anti-tuberculous drugs 1541 (13%), analgesics 1139 (10%), antimalarial drugs 781 (6.8%), and antifungals 202 (1.8%). Most of the

TABLE 1 Demography of HIV-Infected Patients attending APIN Clinic

Demographic Data		Frequency	Percentage (%)
Sex	Male	190	32
	Female	310	68
Marital status	Divorced	25	5
	Married	305	61
	Single	111	22
	Widow/widower	59	11
Education level	Primary	44	8.8
	Secondary	101	20
	Tertiary	91	18
	Illiterate	264	53
Age (Years)	18–30	19	3.8
	31–40	97	19
	41–50	224	45
	51–60	112	22
	>60	48	9.6
Mode of Transmission	Heterosexual	454	91
	Blood transfusion	45	9
	Mother to child	1	0.2

patients were prescribed multivitamins 452 (90%) for immune boosting, followed by ACTs 361 (72%) for malaria, paracetamol 305 (61%) for fever and pain, co-trimoxazole 241 (48%) for the prevention and treatment of opportunistic infections of *Pneumocystis carinii* infection, antihistamines 229 (46%) for allergy, anti-tuberculous drugs 168 (34%) for the treatment of tuberculosis and antifungals 130 (26%) for tinea, oral, and vaginal candidiasis

Identification of Potential Interactions between Concomitant non-ARVand ARV Drugs

The prevalence and nature of potential interactions between individual ARV drugs and co-prescribed non-ARV drugs are presented in Table 2. The majority of the interactions were rated "C" to (moderate potential CSDIs), while only 4 different types of interactions were rated "X" (major potential CSDIs).

A total of 4771 prescription-based potential CSDIs were identified in 421 (84 %) patients including pharmacokinetic interactions and those that were predicated on overlapping toxicities. Although the majority of the interactions were moderate 4700 (99%), there were few major ones 71 (1.5%), that were contraindicated, which frequently involved rifampicin and lopinavir/ritonavir (n= 5), rifampicin and saquinavir/ritonavir 62; 1.3%), erythromycin and saquinavir/ritonavir (n= 1), nevirapine and rifampicin (n= 1) and efavirenz and amodiaquine (n= 2). ART first-line regimen of AZT+3TC+NVP 1665 (35%) was the most commonly involved in potential CSDIs with co prescribed drugs followed by AZT+TDF+3TC+LPVr (919; 19%), d4T+3TC+NVP 492 (10%) and AZT+TDF+FTC+LPVr 337 (7.1 %).

However, interaction between individual ARV and co-prescribed drugs most frequently involved co-trimoxazole + zidovudine/lamivudine 2219 (47%), followed by co-trimoxazole + stavudine/lamivudine 359; (7.5%), efavirenz + rifampicin 299 (6.3%) and nevirapine + artemether/lumefantrine 256 (5.37%). Although the frequency of prescription was low 616 (13 %), artemisinin-based combination therapy was prescribed for majority 295 (59%) of the subjects (Table 2)

Potential CSDIs of 787 (17 %) which might have led to decrease in plasma concentration of ARV drugs

TABLE 2 Prevalence and Nature of the Potential Clinically Significant Drug Interactions between Individual ARV and Co-prescribed Drugs in HIV-Infected Adults on Antiretroviral (ARV) Therapy

SN	Antiretroviral Drugs	Potential Interacting non-ARV Drugs	CSDIs Rating	Total Number of Patient (n)	Prescriptions
	MODERATE POTENTIAL INTERACTION				
1	Zidovudine/ lamivudine	Co-trimoxazole (2219), Sulfadoxine/pyrimethamine (24), Erythromycin (7)	C	275	2250 (47)
2	Stavudine	CT (359), Isoniazid (114), Sulfadoxine/pyrimethamine (10)	C	145	483 (10)
3	Nevirapine	Artemether with lumefantrine (256), Artesunate with amodiaquine (109), Erythromycin (16), Dihydroartemisinin/piperaquine (11), Artesunate (8), Artesunate with sulfadoxine/ pyrimethamine (3), Dihydroartemisinin with amodiaquine (2), Fluconazole (2), Ketoconazole (1), Dihydroartemisinin only (1), Artesunate with mefloquine (1)	C	213	410 (8.6)
4	Lopinavir/ ritonavir	Artemether with lumefantrine (123), Ciprofloxacin (65), Loratadine (64), Loperamide (40), Artesunate/amodiaquine (36), Metronidazole (31), Erythromycin (20), Dihydroartemisin/piperaquine (9), Chlorpheniramine maleate (7), Fluconazole (3), Artesunate (3), Artesunate with sulfadoxine/ pyrimethamine (2), Artesunate with mefloquine (1), Amitriptyline (1) , Amodiaquine (1)	C	201	406 (8.5)
5	Efavirenz	Rifampicin (299), AL (20), Isoniazid (7), DHAP (3), IBU (2), AS/SP (1), ERY (1), FLU (1)	C	43	334 (7.0)

TABLE 2 Prevalence and Nature of the Potential Clinically Significant Drug Interactions between Individual ARV and Co-prescribed Drugs in HIV-Infected Adults on Antiretroviral (ARV) Therapy *(Continued)*

SN	Antiretroviral Drugs	Potential Interacting non-ARV Drugs	CSDIs Rating	Total Number of Patient (n)	Prescriptions
6	Zidovudine/ emtricitabine	CT (238), SP (3)	C	19	241 (5.1)
7	Emtricitabine	CT (237)	C	30	237 (5.0)
8	Lamivudine	CT (162)	C	23	162 (3.4)
9	Zidovudine	FLU (114), CT (14), SP (1)	C	44	129 (2.7)
10	Saquinavir/ ritonavir	AL (12), CPX (5), LRTD (4) MDZ (2), DHAP (1),	C	10	24 (0.5)
11	Atazanavir/ ritonavir	Artemether with lumefantrine (4), Amitryptiline (3), LOR (3), RFB (3) AS/AQ (2), CPM (2), DHAP (2), CPX (1),	C	14	20 (0.4)
12	Darunavir/ ritonavir	AS/AQ (1), CPX (1)	C	2	2 (0.04)
13	Tenofovir	Acyclovir (2)	C	2	2 (0.04)
	MAJOR POTENTIAL INTERACTION				
14	Saquinavir/ ritonavir	Rifampicin (62), Erythromycin (1)	X	2	63 (1.2)
15	Lopinavir/ ritonavir	Rifampicin (5)	X	2	5 (0.10)
16	Efavirenz	AS/AQ (2)	X	2	2 (0.04)
17	Nevirapine	Rifampicin (1)	X	1	1 (0.02)
Total					4771 (100)

Note: A refers to little or no interaction, C: refers to a moderate potential interaction, X refers to a major potential interaction (contraindicated).

ABC = abacavir, ACY = acyclovir, AL = artemether/lumefantrine, AM = artemether, AMT = amitriptyline, AS/AQ = artesunate/amodiaquine, AQ = amodiaquine, AS = artesunate, ATVr = ritonavir boosted atazanavir, AZT = zidovudine, CPM = chlorpheniramine maleate, CPX = ciprofloxacin, CXT = co-trimoxazole, DHAP = dihydroartemisinin/piperaquine, d4T-stavudine, DRVr-ritonavir boosted darunavir, EFV = efavirenz, ERY = erythromycin, FLU = fluconazole, FTC = emtricitabine, IBU = ibuprofen, INH = isoniazid, KTZ = ketoconazole, LPD = loperamide, LPVr = ritonavir boosted lopinavir, LRT = loratadine, MQ = mefloquine, MDZ = metronidazole, NVP = nevirapine, RFB = rifabutin, RFP = rifampicin, RTV = ritonavir, SQVr = ritonavir boosted saquinavir, SP = sulphadoxine/pyrimethamine, 3TC = lamivudine, TDF = tenofovir, TMP = trimethoprim.

were identified in more than half of the subjects 252 (50 %). Such interactions might have occurred between rifampicin and ARVs such as saquinavir/ritonavir 62 (1.3%), efavirenz 299 (6.3%), lopinavir/ritonavir 5 (0.10 %), nevirapine 1 (0.02%) and atazanavir/ritonavir 3 (0.06 %). Similarly, there is a potential interaction between ACTs and ARV drugs includ-ing nevirapine 378 (7.9%), efavirenz 23 (0.48%), saquinavir/ritonavir 12 (0.25%), atazanavir/ritonavir (n= 3), and lopinavir/ritonavir (n= 1). Conversely, a higher number of potential CSDIs 3552 (74%) that might have led to increase in the plasma concentrations of ARV drugs were also identified. They included potential interactions between co-trimoxazole and ARV drugs such as zidovudine/lamivudine 2395 (50.20%), zidovudine/emtricitabine 475 (10%), and stavudine/lamivudine 359 (7.5%); erythromycin versus efavirenz n= 1) and saquinavir/ritonavir (n= 1) loperamide versus lopinavir/ritonavir 40 (0.84%); acyclovir versus tenofovir (n= 2); fluconazole versus zidovudine 114 (2.4%) and lopinavir/ritonavir n= 3); sulphadoxine/pyrimethamine versus zidovudine/lamivudine 31 (0.65%) and stavudine/lamivudine 10 (0.21%); loratadine versus atazanavir/ritonavir (n=3), saquinavir/ritonavir (n=4)and lopinavir/ritonavir 64 (1.3%); ketoconazole versus nevirapine (n=1) and metronidazole versus saquinavir/ritonavir (n=2)and lopinavir/ritonavir 31 (0.65%)

Table 3 summarizes the consequences of all the potential CSDIs identified and possible ways of managing them.

Multivariate logistic regression revealed that the risk of CSDI was not significantly associated with sex (Odds ratio [OR] 0.78 [0.48 – 1.27], p = 0.32), age (OR 1.02 [0.99 – 1.04], p=0.13); and baseline CD4 counts below 350 cells/mm^3 (p>0.05), but was significantly associated with therapeutic failure (OR 5.6 [2.4 - 13], p<0.001 (Table 4).

DISCUSSION

Prevalence of Potential CSDIs in People Living with HIV in LUTH (PLWHL)

This study is an audit of the APIN clinic prescribing pattern and serves as an important feedback to improving ART prescribing in line with treatment guidelines. The study found CSDIs occurring in adult population of PLWHA at a higher (84%) prevalence than that of a similar study among Nigerian pediatric population,[49] which found CSDIs occurring at a prevalence of 67%. This difference may be explained by the higher number of concurrent infections in adults than in children. These high burden of concurrent infections in adults require additional co-prescribed non-ARV drugs. Similarly, the current result is higher than those reported in other African countries,[20] America[18,19] and Europe.[59,60] Unlike Europe and America, Nigeria is a malaria endemic nation, necessitating the frequent use of antimalarial drugs, which account for a large percentage of the interaction and this may be responsible for the higher prevalence of CSDIs obtained in our study compared to the European and American studies. Methodological differences used in assessing CSDIs in our study and previous studies further account for the variations in the prevalence. Another reason could be due to the discrepancies between different interaction checker databases as previously reported.[61]

Risk Factors for Potential CSDIs in PLWHL

Our study showed that age, sex and baseline CD4 count were not significantly associated with the risk of CSDIs. However, CSDIs were a significant risk for treatment failure. This finding is in agreement with that of a previous study highlighting therapeutic failure as a major consequence of CSDIs.[62] Thus, resolving drug-drug interactions would go a long way in preventing therapeutic failure; a major concern in ART.[63]

Potential CSDIs Between ARVs and Antimicrobial Drugs

Most of the potential CSDIs involved co-trimoxazole (68%) whose trimethoprim component compete with the NRTIs such as zidovudine, lamivudine, stavudine and emtricitabine for tubular secretion thereby inhibiting their renal excretion and increasing their plasma concentration with little or no effect on the pharmacokinetics of trimethoprim and sulphamethoxazole.[21,22] Except for lamivudine,[63] pharmacokinetic interactions between co-trimoxazole and other NRTIs (stavudine, zidovudine and emtricitabine) in humans have not been studied. However, in animal models, plasma exposure of zidovudine was increased when co-administered with co-trimoxazole.[64] Increased zidovudine exposure may increase the toxicity of

TABLE 3 Nature and Frequency of Potential Interaction between ARV and Concomitant Drugs in People Living With HIV and Remarks/ Recommendations for Management

ART Regimen	Concomitant Drugs	Suspected Interacting Drugs	Result of Interactions	Mechanism of Interaction	R	n	f	Remarks/ Recommendations
ABC+AZT+3TC AZT+3TC+NVP	CXT	AZT vs CXT	TMP↑AZT level[25], anaemia	CXT↓renal tubular clearance of AZT[25]	C	258	2219	Reduce dosage of AZT in renal impairments[22]
	FLU	AZT vs FLU	FLU ↑ AZT level [26, 27], potential anaemia	FLU↓renal tubular clearance of AZT[26,273]	C	40	114	Monitor adverse effects of AZT. Reduce dose of AZT[21, 22]
ABC+3TC+NVP AZT/3TC/NVP d4T/3TC/NVP TDF+3TC+NVP TDF+FTC+NVP	AL	NVP vs AL	NVP↓AM level[28], NVP↑ LM[28], AL↓NVP[28], potential ART failure	NVP↑CYP3A4[29], AM↑ CYP3A4[30],	C	112	256	Monitor patients for reduced antimalarial and antiretroviral effects[21]
	CXT	3TC vs TMP	TMP↑3TC[31]	TMP↓renal tubular clearance of 3TC[31]	C	23	162	Monitor for adverse effects of lamivudine in renal impairment[23].
	INH	d4T + INH	*Increased risk of peripheral neuropathy[9].	Additive toxicity[9]	C	3	126	Monitor adverse effects and adjust dosage timng if necessary.[21]
	AS/AQ	NVP vs AS/AQ	NVP↑AS level[32], NVP↓AQ level[33], potential hepatotocity	Unknown[32, 33]	C	67	109	Monitor patients for decreased antimalarial effects[21]
	AS/SP	NVP vs AS	NVP↑AS[32]	Unknown[33]	C	5	5	Dosage adjustment of AS may be necessary
	CXT	AZT/3TC vs SP	*potential haemotoxicity and nephrotoxicity.[21]	*SP/AZT potential additive haemotoxicity/ nephrotoxicity.	C	17	25	Monitor renal function and hematological parameters and consider dose reduction if required.[21]

TABLE 3 Nature and Frequency of Potential Interaction between ARV and Concomitant Drugs in People Living With HIV and Remarks/ Recommendations for Management *(Continued)*

ART Regimen	Concomitant Drugs	Suspected Interacting Drugs	Result of Interactions	Mechanism of Interaction	R	n	f	Remarks/ Recommendations
	DHA/AQ	NVP vs DHA/AQ	NVP↓AQ[33], NVP↓DHA level[33] Potential Malarial treatment failure	Unknown[33]	C	4	4	Monitor for therapeutic efficacy of DHA/AQ[24]
	ERY	ERY vs NVP	*ERY↑NVP level, *NPV↓ERY level Potential hepatotoxicity	ERY↓CYP3A4[34] NVP↑CYP3A4[29]	C	10	16	Monitor side effects and reduce dosages as necessary.[22]
	RFP	NVP vs RFP	RFP↓NVP level[35], Potential ART failure and hepatotoxicity	RFP↑CYP3A4[16]	X	1	1	Avoid co-administration, use RFB in place of RFP[21] or increased dose of NVP[36].
TDF+FTC+EFV TDF+3TC+EFV d4T/3TC/EFV	AL	EFV vs AL	EFV↓AL level[37], AM↓EFV level[37], potential ART & malarial treatment failure	EFV↑CYP3A4[10], AM↑CYP3A4[30]	C	9	20	Monitor AL therapeutic effects
	AS/AQ	EFV vs AQ	EFV↑AQ level[38], hepatoxicity[38]	EFV↓CYP2C8[39]	X	2	2	Avoid co-administration
	IBU	EFV vs IBU	*EFV↑IBU	EFV↓CYP2C9[39]	C	2	2	Reduce IBU dose in elderly and patients with risk factors for cardioavascular and GIT complications, and in renal, or hepatic impairment.
	DHAP	EFV vs DHAP	*EFV↓DHA level *EFV↓PQ level	EFV↑CYP3A4[10]	C	3	3	Monitor for adverse effects of DHAP

TABLE 3 Nature and Frequency of Potential Interaction between ARV and Concomitant Drugs in People Living With HIV and Remarks/ Recommendations for Management *(Continued)*

ART Regimen	Concomitant Drugs	Suspected Interacting Drugs	Result of Interactions	Mechanism of Interaction	R	n	f	Remarks/ Recommendations
	INH	EFV vs INH	*Hepatotoxicty	EFV/INH additive hepatotoxicity[40,41]	C	1	7	Monitor for hepatotoxicity
	RFP	EFV vs RFP	RFP↓EFV level[36], potential ART failure, drug resistance	RFP↑CYP3A4[16]	C	25	299	Increase dose of EFV from 600 to 800mg[21]
ABC+TDF+3TC+LPVr ABC+TDF+FTC+LPVr AZT+3TC+LPVr	CXT	FTC vs CXT	*TMP↑FTC level	*TMP↓tubular secretion of FTC	C	30	237	Monitor for adverse effects of FTC[21]
	AL	LPVr vs AL	LPVr↑LM level[42], LPVr↓AM level[42], Malarial treatme nt failure, lumefan trine toxicity	LPVr↓CYP3A4[43] LPVr↑CYPs 2C9, 2C19, & 2B6[43]	C	45	123	Monitor for malarial treatment failure and lumefantrine toxicity
	LRT	LPVr vs LRT	LPVr↑LRT	LPVr↓CYP3A4[43]	C	36	64	Monitor for adverse effects of loratadine
	ACY	TDF vs ACY	*ACY↑TDF, renal toxicity	ACY↓tubular secretion[44]	C	2	2	Monitor renal toxicity and reduce dose in patients with renal disease.[21]
	AMT	LPVr vs AMT	*LPVr↑AMT, potential cardiotoxicity	LPVr↓CYP 2D6[45], 2C19	C	2	2	Monitor for adverse effects of amitripyline
	AS/AQ	LPVr vs AS/AQ	*LPVr↑AQ *LPVr↓AS	LPVr↓CYP2C8[46] LPVr↓CYP3A4[43]	C	20	40	Use with caution in patients with liver impairment
	AS/MQ	LPVr vs AS/MQ	MQ↓RTV level[47] *Cardiotoxicity	Unknown. Additive QTc-interval prolongation[48]	C	1	1	Monitor for cardiotoxicity
	CPM	LPVr vs CPM	*LPVr↑CPM	LPVr↓CYP2D6[45]	C	4	7	Monitor for adverse effects of CPM
	CPX	LPVr vs CPX	*Cardiotoxicity	Potential Additive ↑QTc interval[49,]	C	34	65	Monitor cardiac toxic effects

TABLE 3 Nature and Frequency of Potential Interaction between ARV and Concomitant Drugs in People Living With HIV and Remarks/ Recommendations for Management *(Continued)*

ART Regimen	Concomitant Drugs	Suspected Interacting Drugs	Result of Interactions	Mechanism of Interaction	R	n	f	Remarks/ Recommendations
	DHAP	LPVr vs DHAP	*LPVr↓DHAP, Malarial treatment failure	LPVr↑CYP2B6[50], 2C9/2C19[43]	C	2	9	Monitor malarial treatment failure
	ERY	LPVr vs ERY	*ERY↑ LPVr level, Potential cardiotoxicity	ERY↓CYP3A4[34,] Additive QTc-interv al prolongation[51]	X	4	20	Monitor for adverse effects of CPX
	FLU	LPVr vs FLU	Potential cardiotoxicity	Additive↑QTc-interval[51]	C	3	3	Monitor cardiac toxic effects
	LPD	LPVr vs LPD	LPVr↑LPD level	LPVr↓CYP3A4[43]	C	15	29	Reduce dosage of LPD
	LRT	LPVr vs LRT	*LPVr↑LRT level	LPVr↓CYP3A4[43], 2D6[45]	C	36	64	Monitor for adverse effects of LRT
	MDZ	LPVr vs MDZ	*MDZ↑LPVr level, potential cardiotoxicity	MDZ↓CYP3A4, Additive QTc-interval prolongati on[51, 52]	C	31	31	Monitor closely for adverse effects
	RFP	LPVr vs RFP	RFP↓LPVr level[53], potential ART failure	RFP↑CYP3A4[16]	X	1	2	Substitute rifampicin with rifabutin or give 9 months INH therapy.
AZT+TDF+3TC+ATVr AZT+TDF+FTC+ATVr AZT+3TC+ATVr AZT+TDF+3TC+ATV TDF+3TC+ATVr	AMT	ATVr + AMT	*ATVr↑AMT level, potential cardiotoxicity	RTV↓CYP2D6[54], additive QTc-interv al prolongation[55]	C	2	3	Monitor for adverse effects
	AS/AQ	ATVr + AS/AQ	*ATVr↑AQ, *ATVr↓AS/ DHA	RTV↓CYP2C8, RTV↓CYP3A4[43]	C	2	2	Monitor for adverse effects
	AL	ATVr + AL	*ATVr↓AM/ DHA, *ATVr↑LM	RTV↓CYP2C9[43] ATVr↓CYP3A4[56]	C	1	1	Monitor for adverse effects
	CPX	ATVr + CPX	*Cardiotoxicty	Additive↑QTc-interval prolongat ion[49, 51]	C	3	5	Monitor for adverse effects
	DHAP	ATVr + DHAP	ATVr↓DHAP, Malarial treatment failure	ATVr↑CYP2B6, 2C9, 2C19	C	1	1	Monitor malarial treatment efficacy

TABLE 3 Nature and Frequency of Potential Interaction between ARV and Concomitant Drugs in People Living With HIV and Remarks/ Recommendations for Management *(Continued)*

ART Regimen	Concomitant Drugs	Suspected Interacting Drugs	Result of Interactions	Mechanism of Interaction	R	n	f	Remarks/ Recommendations
	CPM	ATVr + CPM	*ATVr↑CPM	RTV↓CYP2D6[54]	C	2	2	Monitor for adverse effects of CPM
	LRT	ATVr + LRT	*ATVr↑LRT	ATVr↓CYP3A4, 2D6[43,54,56]	C	1	3	Monitor for adverse effects of LRT
	RFB	ATVr + RFB	ATVr↑RFB	ATVr↓CYP3A4[43,56]	C	1	3	Reduce dose of RFB
AZT+ SQVr AZT+TDF+3TC+SQV TDF+SQVr TDF+FTC+SQV**r**	AL	SQVr + AL	SQVr↑AL, SQVr↓DHA	SQVr↓CYP3A4	C	3	5	Monitor for adverse effects of AL
	RFP	SQVr + RFP	RFP↓SQV, hepatotoxicity	RFP↑CYP3A4[16]	X	6	62	Avoid co-administration.
	CPX	SQVr + CPX	Cardiotoxicty	Additive↑QTc-interval prolongation	C	3	5	Monitor for adverse effects
	MDZ	SQVr + MDZ	*MDZ↑SQV level, *cardiotoxicity	MDZ↓CYP3A4, Additive QTc-interv al prolongation[51,52]	C	1	2	Monitor for adverse effects of SQV & MDZ
	LRT	SQVr + LRT	*SQVr↑LRT	SQVr↓CYP3A4[57]	C	1	3	Monitor for adverse effects of LRT
	ERY	SQVr + ERY	*ERY↑SQV level, cardiotoxicity	ERY↓CYP3A4[34], Additive QTc-interval prolongati on[51, 97]	C	1	1	Monitor for adverse effects of SQV & ERY
	DHAP	SQVr + DHAP	*SQVr↓DHAP level	SQVr↓CYP3A4[57]	C	1	1	Monitor for adverse effects
		SQVr + AL	*SQVr↑LM level,	SQVr↓CYP3A4[57]	C	2	12	Monitor for adverse effects[24]
TDF+FTC+DRVr	AS/AQ	DRVr + AS/AQ	*DRVr↑AQ level, potential hepatotoxicity	RTV↑CYP2C8[58]	C	2	2	Monitor adverse effects of AQ[24]

**co-administration has not been studied.*

n = number of patients, f = frequency of prescriptions, R = CSDIs rating, ↑ = Increased/Induced, ↓ = decreased/inhibited, ABC = abacavir, ACY = acyclovir, AL = artemether/lumefantrine, AM = artemether, AMT = amitriptyline, AS/AQ = artesunate/amodiaquine, AQ = amodiaquine, AS = artesunate, ATVr = ritonavir boosted atazanavir, AZT = zidovudine, CPM = chlorpheniramine maleate, CPX = ciprofloxacin, CXT = co-trimoxazole, DHAP = dihydroartemisinin/piperaquine, d4T-stavudine, DRVr-ritonavir boosted darunavir, EFV = efavirenz, ERY = erythromycin, FLU = fluconazole, FTC = emtricitabine, IBU = ibuprofen, INH = isoniazid, KTZ = ketoconazole, LPD = loperamide, LPVr = ritonavir boosted lopinavir, LRT = loratadine, MQ = mefloquine, MDZ = metronidazole, NVP = nevirapine, RFB = rifabutin, RFP = rifampicin, RTV = ritonavir, SQVr = ritonavir boosted saquinavir, SP = sulphadoxine/pyrimethamine, 3TC = lamivudine, TDF = tenofovir, TMP = trimethoprim. A = refers to little or no interaction, C = refers to a moderate potential interaction, X = refers to a major potential interaction (contraindicated). CYP = Cytochrome P enzyme

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TABLE 4 Multivariate Logistic Regression of Risk for Clinically Significant Drug Interactions

Variables	Frequency n (%)	Clinically Significant Drug Interactions		Odds Ratio (95% CI)	*p-value*
		Yes	No		
Sample size	500 (100)	421 (84.2)	79		
Sex					
Male	190 (38)	156 (82.1)	34 (45)	0.78 (0.48 – 1.3)	0.32
Female	310 (62)	265 (85.5)	(14.5)		
Age in years (mean SD)	47.36 (10.39)	48 (10.2)	46 (10.9)	1.019 (0.99 – 1.04)	0.13
Baseline CD4 counts (cells/mm^3)					
< 50	53 (11)	40 (75.5)	13 (24.5)	0.60 (0.28-1.30)	0.20
51 – 100	56 (11)	47 (83.9)	9 (16.1)	1.03 (0.44-2.4)	0.95
101 – 200	136 (27)	116 (85.3)	20 (14.7)	1.14 (0.59-2.20)	0.708
201 – 350	121 (24)	106 (87.6)	15 (12.4)	1.388 (0.68-2.82)	0.364
> 350	134 (27)	112 (83.6)	22 (16.4)		
Treatment status					
Failure	139 (27.8)	133 (95.7)	6 (4.3)	5.62 (2.38-13.24)	0.000
No failure	361 (72.2)	288 (79.8)	73 (20.2)		
Total	**500 (100)**				

sulphamethoxazole by pharmacodynamic synergism. A human study has reported exacerbation of anemic and neutropenic toxicity when zidovudine and co-trimoxazole were co-administered.[54–65] Although the increased exposure of the NRTIs by co-trimoxazole may not be significant as found in the lamivudine study.[63] However, caution should be exercised when both NRTIs are co-administered with co-trimoxazole. Adverse effects such as lactic acidosis should be monitored when patients are on NRTIs therapy.[66] The interaction with stavudine is no longer relevant because its usage has been discontinued since 2010[2] due to its long term adverse effects including lipoatrophy,[67] lactic acidosis[66] and peripheral neuropathy.[68]

The finding that co-trimoxazole was the most commonly co-prescribed non-ARV drug could account for its high prevalence of CSDIs. This finding, as reported in previous studies[69]is due to the WHO recommendation[70] of dispensing co-trimoxazole to patients with CD4-cells count below 350 cells/mm^3 for prophylaxis against pneumocystosis and toxoplasmosis.[69]

A major potential CSDI was identified between erythromycin and saquinavir/ritonavir. Concomitant administration of both drugs is contraindicated[21–23] because of additive cardiotoxicity including life threatening cardiac arrhythmia.[21,22] Co-administration of saquinavir/ritonavir with erythromycin has not been studied in human[21] but the antibiotic administered (250 mg 4 times daily) concurrently with unboosted saquinavir (1200 mg 3 times daily) increased saquinavir AUC and Cmax by 99% and 106%, respectively.[71]

The ACTs accounted for a small but significant (13%) proportion of the potential interactions. This value is low compared to 40% obtained in a similar

study[14] in pediatric patients. Unlike children, adult patients may be taking antimalarial drugs on their own and only those that were prescribed at the clinic were documented. Another reason is that about half of the adult patients were on co-trimoxazole prophylaxis which has been found to protect against malaria.[72] Potential interactions were identified in all the anti-malarial drugs co-prescribed with ARV drugs. While sulphadoxine, pyrimethamine and proguanil had potential to interact and increase the concentration of the NRTIs,[21,22] especially zidovudine, lamivudine and emtricitabine requiring toxicity monitoring. The ACTs including artemether, artesunate, dihydroar-temisinin, piperaquine, lumefantrine, amodiaquine, and mefloquine had potential to interact and decrease the concentration of the NNRTIs and the PIs.[21–23] Conversely, the NRTIs may not significantly affect the exposure and C_{max} of the ACTs, the NNRTIs and the PIs may decrease and increase, respectively, the exposure of the antimalarials[21,22] due to their re-spective induction and inhibition effects on CYP450 enzymes. Some of the above potential interactions have been confirmed in pharmacokinetic studies in-volving ARV drugs and ACTs.[73–76] Clinical studies are required to determine the impact of these interactions on parasitaemia, efficacy and toxicity of antimalarial therapy in adult population of HIV-infected patients with malaria co-morbidity.

Overall, CSDIs involving antimalarial drugs were classified as moderate, except those occurring between efavirenz and amodiaquine, which was classified as major or contraindicated due to liver toxicity.[74] Among the anti-tuberculous drugs, 68 major CSDIs were identified. Pharmacokinetic study[35] has shown that rifampicin significantly reduced the exposure of nevirapine which may render the antiretroviral drug ineffective. The single prescription involved is an indication that the prescriber may have realized the consequence of the interaction and discontinued the co-prescription of both drugs. On the other hand, co-administration of saquinavir, ritonavir or lopinavir and rifampicin is contraindicated because it can result in severe hepatotoxicity and significant reduction in exposure of the PIs,[30,55,77] which may lead to thera-peutic failure. The drugs may have been co-prescribed despite the contraindication after considering that the benefits outweighed the risk. It is also possible that the clinicians were not aware of the major interaction as of the time they were prescribing the drugs. Other interactions[26,60] with the anti-tuberculous drugs were rated moderate (C) and frequently involved EFV vs rifampicin and atazanavir/ritonavir versus rifabutin. Pharmacokinetic study[70] have confirmed the reduction, by rifampicin of the plasma concentration of EFV below therapeutic level and another study[78] had reported in-creased toxicity when both drugs are co-administered. Some of the CSDIs of the anti-tuberculous drugs are pharmacodynamic rather than pharmacokinetic, including increased risk of peripheral neuropathy with co-administration of isoniazid with didanosine or stavudine.[9]

The high prevalence of potential moderate CSDIs may in reality be mild CSDIs in the context of patient care data. Previous studies comparing drug-drug interactions in patients on cardiovascular drugs have reported that proprietary drug-drug interaction databases rated drug interaction higher in severity than did pharmacists and clinicians involved in the management of the patients[24].

Study Limitations

Limitations of this study included lack of correlation of CSDIs with adverse therapeutic outcomes arising from the interactions, lack of information about self-medicated drugs such as antimalarials, home remedies, and traditional herbal medicines. Accurate determination of the true prevalence of CSDIs would, therefore, require a detailed medication history of the patients. Genetic testing to rule out potential genetic polymorphism[79] was not done.

Further studies, including therapeutic drug monitoring and correlation of the CSDIs with the actual outcome of therapy in the patients, using laboratory and clinical data such as adverse drug reactions monitoring, liver and other vital organ function tests, CD4-cells count, viral load, blood chemistry and hematological test results are required.

CONCLUSION

The prevalence of CSDIs in the study population is relatively high. Apart from the haematinics, all classes of non-ARVs showed potential to cause CSDIs

with ARV drugs and this put the population of adult patients receiving ART in APIN clinic of LUTH at risk of treatment failure or drug toxicity. Specifically, artesunate/amodiaquine regimen with EFV-based ART regimen and rifampin with NVP or protease inhibitor-based ART regimen showed potential to cause major CSDIs and should not be co-prescribed

Further studies including correlation of the drug interaction findings with actual clinical outcomes and results of laboratory investigations are needed to ascertain the validity of our findings.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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