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Potential drug–drug interactions in HIV-infected children on antiretroviral therapy in Lagos, Nigeria

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Background: Multi-therapy is common in HIV-infected children, and the risk for clinically significant drug interactions (CSDIs) is high. We investigated the prevalence of CSDIs between antiretroviral (ARV) and co-prescribed drugs for children attending a large HIV clinic in Lagos, Nigeria.

Methods: The case files of pediatric patients receiving treatment at the HIV clinic of the Lagos University Teaching Hospital (LUTH), Idi-Araba, between January 2005 and December 2010 were reviewed. The ARV and co-prescribed drug pairs were evaluated for potential interactions using the Liverpool HIV Pharmacology Group website. The potential interactions were rated as A (no known interaction), B (minor/no action needed), C (moderate/monitor therapy), D (major/therapy modification), and X (contraindicated/avoid combination).

Results: Of the 310 cases reviewed, 208 (67.1%) patients were at risk of CSDIs. Artemisinin-based combination therapy was prescribed for over one-half of the patients, accounting for 40% of the CSDIs. Excluding this drug class, the prevalence of CSDIs reduced from 67.1% to 18.7% in 58 patients. Most of the CSDIs (579; 97.2%) were moderately significant and frequently involved nevirapine and fluconazole (58; 9.7%), zidovudine and fluconazole (55; 9.2%), zidovudine and rifampicin (35; 5.9%), and nevirapine and prednisolone (31; 5.2%). Age (P=0.392), sex (P=0.783), and moderate (P=0.632) or severe (P=0.755) malnutrition were not associated with risk for CSDIs.

Conclusion: There is a tendency for CSDIs between ARV and co-prescribed drugs among the group of children evaluated in this study. Measures are necessary to prevent important drug interactions and to manage those that are unavoidable.

Keywords: infection, antiretroviral drug, co-prescribed drug, prevalence, therapy monitoring, therapy modification, contraindication

Introduction

Highly active antiretroviral (ARV) therapy (ART), defined as the combination of three or more ARV agents taken concurrently to suppress HIV replication, represents the current standard of care of ART for children infected with HIV.[1] This strategy evolved from the recognition that treatment of chronic HIV infection with only one or two ARV agents typically results in rapid treatment failure and the development of ARV resistance, compromising future therapeutic options.[1,2] In addition to the ART regimens, other medicines are typically required to manage numerous concurrent infections and systemic consequences of HIV/AIDS. Therefore, the likelihood of drug–drug interactions is increased in HIV-infected children on ART.

Theoretically, drug–drug interaction is defined as a phenomenon of two or more medicines interacting in such a manner that the effectiveness or toxicity of one or more drugs is altered.[3] An interaction is said to be clinically significant

if it requires a dosage adjustment of the culprit drugs or therapy monitoring or consists of a drug combination that is contraindicated due to its high potential for clinical adverse effects.[4] Most of the previous studies that evaluated clinically significant drug interactions (CSDIs) were based on the use of electronic resources, databases, and/or reference books to assess the interactions and to determine if they were significant or not;[4–8] however, in practice, only few cases of clinically significant interactions between coadministered medicines and ARV drugs have been reported.[9–12] This suggests that CSDIs may be less common than non-CSDIs in practice.

Case reports of CSDIs between ARV and coadministered drugs are lacking in children; however, such reports in adults have been documented in the literature. Bruce and Altice[9] reported three cases of clinically significant pharmacokinetic interaction between opioid partial agonist (buprenorphine) and protease inhibitors ([PIs] atazanavir or atazanavir/ritonavir) that resulted in cognitive dysfunction of the patients. Atazanavir, alone or in combination with ritonavir, is known to be associated with substantial increase in buprenorphine exposure and delayed clearance.[10] Similarly, clinical pharmacokinetic interactions between nevirapine (NVP) and methadone that resulted in opiate withdrawal syndrome have been reported.[11] Efavirenz (EFV) is a potent inhibitor of CYP2C8 enzyme in vitro and may, therefore, potentially increase the plasma levels of amodiaquine when coadministered;[12] however, the interaction is not expected to affect the therapeutic efficacy of the antimalarial, as both amodiaquine and its metabolite, N-desethylamodiaquine, are active antimalarials, but it may have implications for toxicity. German et al[12] reported a case of 1.5–3-fold increase in the area under the plasma concentration curve for amodiaquine when coadministered with EFV and artesunate to two HIV-infected patients. The interaction between the drugs also resulted in asymptomatic but significant elevations in hepatic transaminases. Uriel and Lewthwaite[13] also reported a case of an HIV-infected patient on abacavir (ABC), lamivudine (3TC), and NVP who also had *Plasmodium falciparum* malaria. The patient failed to respond to quinine treatment, which led the authors to suspect an interaction between NVP and quinine. Following a switch from quinine to atovaquone/proguanil (Malarone®), the patient responded to the new antimalarial therapy and was subsequently discharged home after 48 hours.

Treatment may be compromised in children infected with both HIV and tuberculosis due to a significant interaction between lopinavir/ritonavir (LPV/r) or NVP and rifampicin; however, these interactions are documented only in theory,[14,15] suggesting that they may be rare in clinical practice.

A good understanding of the mechanisms of drug interactions is essential to minimize or prevent adverse events and to prevent inadequate treatment. Interactions during drug absorption, distribution, hepatic metabolism, or renal excretion, resulting in an increased or a decreased plasma concentration and consequent altering of the pharmacological effects, are termed "pharmacokinetic interactions."[1] The synergistic or antagonistic effects of two or more coadministered drugs, occurring at their sites of action, are termed "pharmacodynamic interactions."[6]

All the PIs and non-nucleoside reverse transcriptase inhibitors (non-NRTIs) recommended by the World Health Organization (WHO) for HIV treatment in sub-Saharan African countries are metabolized in the cytochrome P450 system, principally by the CYP3A4 isoenzyme. The tendency for these groups of drugs to induce or inhibit CYP3A4 enzyme may lead to a decrease or increase in the serum levels of CYP3A4 substrates.[16] Therefore, preventing and managing drug–drug interactions become major challenges in the optimization of HIV therapy.[17,18]

CSDIs are common, and a prevalence of 20%–41% has been reported in developed countries;[4,8,18–21] however, there is a paucity of data from developing countries. A recent study by Kigen et al[8] reported a risk of 33.5% for a potential CSDI with a tendency to lower ARV drug concentrations in 12% of adult HIV patients. HIV-infected African children often present late with acute opportunistic infections and other AIDS-associated conditions.[22] These often require multiple therapies involving other medications that may increase the potential of the ARV drugs for CSDIs.

To our knowledge, there are no studies concerning drug–drug interactions in HIV-infected children on ARV drugs; such data would be of particular importance for African populations. We therefore investigated the frequency of potential drug–drug interactions in the prescriptions for HIV-infected children enrolled in ART at a teaching hospital in Lagos, Southwest Nigeria.

Materials and methods

Study design

We retrospectively analyzed the clinical records of HIV-infected children who were receiving treatment at the AIDS Prevention Initiative in Nigeria (APIN) clinic, Lagos University Teaching Hospital (LUTH) in Nigeria, between January 2005 and December 2010. The APIN clinic is one of the United States Presidential Emergency Plan for AIDS Relief-funded centers

for HIV relief program. The clinic is run every Monday to Friday, between 8 am and 4 pm.

On average, about 350 old and new patients (adults and children) are attended to daily at the APIN clinic. A total of 18 doctors, comprising four consultants, eight residents, and an average of six house officers, attend to the HIV-infected children during their visits to the APIN clinic. ARV drugs prescribed to the patients on ART enrollment are dispensed at the pharmacy free of charge. Patients were seen usually at the outpatient clinic every 4 weeks after commencing ART, and those on concomitant treatment for malaria, opportunistic infections, and comorbid conditions or manifesting adverse drug effects were initially followed up weekly, then biweekly, and, later, every 4 weeks.

All the HIV-infected children, including those who had progressed to full-blown AIDS, according to WHO criteria,[1] and those who met the inclusion criteria, were included in the study. The inclusion criteria included children less than 16 years old who had been initiated on ART. Patients must have used ARV drugs at least once after enrollment and have had complete data documented in their records.

Data abstraction

Eligible cases were identified through the main register, obtained from the medical record of the APIN clinic. A co-researcher (SL) reviewed each case file and, using a standard form purposely designed for the study, extracted data on sex; weight; height; mode of contracting HIV; comorbid diseases and concomitant infections at presentation and follow-up; co-prescribed drugs; and the ARV drug regimen prescribed for each patient. Data extracted were double-checked by the lead researcher (KAO), a pediatric clinical pharmacologist, and another senior researcher (IAO).

The nutritional status of each patient was determined from the WHO child growth standards based on length or height, weight, and age.[23] The nutritional status was classified as normal (+3 standard deviation [SD] $\leq Z \leq -1$ SD), moderate malnutrition (-1 SD $\leq Z \leq -2$ SD), or severe malnutrition ($Z \geq -3$ SD).

Prescribed ART regimen

The national guidelines for HIV treatment in Nigeria recommend, as first-line ARV drugs for children, zidovudine (AZT) and 3TC plus NVP or EFV, with substitution with stavudine or ABC allowed for toxicity.[24] Second-line ARV drugs include any of the first-line drugs, didanosine (ddI) and ABC or ddI and AZT or ddI and EFV/NVP in combination with the PIs LPV/r or saquinavir/ritonavir.

Identification of potential interactions between co-prescribed and ARV drugs

All co-prescribed and ARV drug pairs were screened for potential interactions using the Liverpool HIV Pharmacology Group website.[25] This website comprises a comprehensive database of over 5,000 drug-interaction pairs and uses a "traffic light" system to flag potential interactions. In order to avoid overestimation of the CSDIs, all interactions flagged as red or amber were further scrutinized, and the quality of evidence underpinning these recommendations was assessed using criteria derived from the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system (http://www.hiv-druginteractions.org/documents/QualityOfEvidence.pdf).[26] CSDIs were defined as those considered to be contraindicated or not recommended without close monitoring, or those requiring a dose adjustment to avoid side effects.[4]

Classification of potential interactions between co-prescribed and ARV drugs

The severity of interactions (CSDIs and non-CSDIs) was rated from A to D and X (Table 1), according to the method of Armahizer et al (A = no known interaction; B = minor/no action needed; C = moderate/monitor therapy; D = major/therapy modification; X = contraindicated/avoid

Table 1 Severity rating of the interactions between antiretroviral drugs and co-prescribed drugs

Rating[a]	Designation	Action	Explanation
Clinically significant drug interaction			
X	Contraindicated	Avoid combination	The drugs are contraindicated for concurrent use.
D	Major	Consider therapy modification	The interaction may be life threatening and/or require medical intervention to minimize or prevent serious adverse events.
C	Moderate	Monitor therapy	The interaction may result in exacerbation of the patient's condition and/or require an alteration in therapy.
Non-clinically significant drug interaction			
B	Minor	No action needed	The interaction would have limited clinical effects. May include an increase in the frequency or severity of the side effects but generally would not require a major alteration in therapy.
A	Unknown	No known interaction	Unknown.

Notes: [a]A = no known interaction; B = minor/no action needed; C = moderate/monitor therapy; D = major/therapy modification; X = contraindicated/avoid combination.[27]

combination).[27] Interactions relating solely to overlapping toxicities, or between co-prescribed ARV drugs such as PI boosting, or involving dermal applications, were excluded. In addition, we excluded from our analysis potential interactions between 3TC and co-trimoxazole due to limited clinical significance suggested by controlled data.[8]

Ethical issues

The study protocol was approved by the research and ethics committee of LUTH. At the point of enrollment on ART, written consent was given by the parents, next of kin, caretakers, or guardians on the behalf of the minors/children for their information to be stored in the hospital database and used for research.

Statistical analyses

All data from the medical records were coded and results presented as median and range, mean ± SD, and frequency distribution with percentage. Patients were grouped according to whether they had a potential drug interaction versus no interaction.

The prevalence of CSDIs across individual NRTIs, non-NRTIs, and PIs were compared by chi-squared test at a significance level of 5%. Multivariate logistic regression was performed with the age, sex, and nutritional status as covariates using the Statistical Package for the Social Sciences ([SPSS] v 16; IBM Corporation, Armonk, NY, USA).

Results

Demographics of the patients

A total of 337 patients were enrolled for ART but only 310 (74.3%), who met the inclusion criteria, were included in the final analysis. The remaining 27 patients were excluded because they had incomplete data documented in their case files, or were lost to follow-up immediately before or after enrollment on ART. The case files of all the 310 patients were reviewed. The patients were comprised of 138 (44.5%) males and 172 (55.5%) females with a median age of 3 (range: 1–15) years, a median weight of 10.4 (7.1–15.1) kg, and a median height of 93.5 (74.0–110.0) cm. The nutritional statuses of the subjects were normal (178; 57.4%) or moderately (39; 12.6%) or severely (93; 30.0%) malnourished. HIV infection was contracted either from mother-to-child transmission (182; 58.8%) or blood transfusion (10; 3.2%). HIV contraction was, however, unknown in 31 (10.0%) cases and not documented in 87 (28.1%) cases.

Prescribed ART regimen

A total of 306 patients (98.7%) were enrolled on first-line ART, comprising AZT–3TC–NVP (279; 91.2%) and AZT–3TC–EFV (27; 8.8%). Four (1.3%) patients were enrolled on a second-line treatment (AZT–3TC–ABC–LPV/r). The first-line ARTs were changed for 66 (21.6%) patients after initial enrollment. Nearly all the patients (64/66; 97%) who switched their ART regimen did so after 1 year of commencing the first-line treatment. Poor adherence and therapeutic failure (60/66; 90.9%), therapeutic failure only (4; 6.1%), and adverse drug reaction (2; 3.0%) were the reasons for changing ARV treatments. The adverse reactions were mainly NVP-induced skin rashes and AZT-induced anemia. None of the adverse reactions were preventable and unrelated to drug–drug interactions. ABC–3TC–LPV/r (20/66; 30.3%), AZT–3TC–ABC–LPV/r (16/66; 24.2%), AZT–3TC–ABC–ddI–LPV/r (10/66; 15.2%), ABC–3TC–NVP (8/66; 12.1%), AZT–ABC–LPV/r (6/66; 9.1%), and AZT–3TC–LPV/r (6/66; 9.1%) were the types of second-line regimen prescribed. All the ARV drugs were prescribed at standard doses recommended by the WHO,[1] irrespective of presence or absence of potential drug–drug interactions.

Co-medications for HIV-infected children on ARV drugs

A wide range of medications were co-prescribed for the patients while on ART regimens. The drugs were used to treat comorbid conditions, opportunistic infections, or concurrent infections. Tuberculosis (35; 11.3%) was the most common opportunistic infection treated in the patients. It was treated with a combination of rifampicin–isoniazid–pyrazinamide for an average of 6 months either before or during ARV treatment. Presumptively diagnosed malaria (208; 67.1%), pneumonia (70; 22.6%), and sepsis (4; 1.3%) were the concomitant infections frequently treated in the patients.

Identified potential interactions between co-prescribed and ARV drugs

Table 2 shows the pattern of ARV drug combinations and the co-prescribed drugs with potential for CSDIs in HIV-infected children. The first-line regimens, AZT–3TC–NVP (309; 67.2%) and AZT–3TC–EFV (65; 14.1%), were frequently associated with CSDIs, followed by a second-line regimen, ABC–3TC–NVP (30; 6.5%).

The prevalence and nature of interactions between the co-prescribed and ARV drugs are presented in Table 3. A total of 596 CSDIs were identified in 208 (67.1%) patients. The majority of the interactions (578; 97.2%) were moderately significant, followed by contraindicated interactions: NVP and rifampicin (8; 1.3%), EFV and artemisinin/amodiaquine (5; 0.8%), and NVP and ketoconazole (4; 0.7%). Excluding the

Table 2 Pattern of ARV drug combinations and the co-prescribed drugs with potential for clinically significant drug interactions in HIV-infected children

ARV and co-prescribed drugs pair	Number of prescriptions N (%)
AZT–3TC–NVP+	
Artemisinin-based combination therapy	162 (35.3)
Fluconazole	55 (12.0)
Prednisolone	26 (5.7)
Ibuprofen	25 (5.5)
Clarithromycin	14 (3.1)
Frusemide	13 (2.8)
Rifampicin	8 (1.7)
Ketoconazole	4 (0.9)
Sulfadoxime/pyrimethamine	2 (0.4)
AZT–3TC–EFV+	
Rifampicin	27 (5.9)
Artemisinin-based combination therapy	18 (3.9)
Loratadine	13 (2.8)
Clarithromycin	5 (1.1)
Sulfadoxime/pyrimethamine	2 (0.4)
ABC–3TC–NVP+	
Artemisinin-based combination therapy	8 (1.7)
Metronidazole	6 (1.3)
Prednisolone	5 (1.1)
Clarithromycin	5 (1.1)
Fluconazole	3 (0.7)
Frusemide	2 (0.4)
Sulfadoxime/pyrimethamine	1 (0.2)
ABC–3TC–EFV+	
Metronidazole	5 (1.1)
Loratadine	2 (0.4)
Sulfadoxime/pyrimethamine	1 (0.2)
AZT–3TC–LPV/r+	
Artemether/lumefantrine	6 (1.3)
Proguanil	1 (0.2)
Ibuprofen	1 (0.2)
Loratadine	1 (0.2)
Furosemide	1 (0.2)
Prednisolone	1 (0.2)
Sulfadoxime/pyrimethamine	1 (0.2)
AZT–3TC–didanosine–LPV/r+	
Artemether/lumefantrine	9 (2.0)
Sulfadoxime/pyrimethamine	2 (0.4)
Proguanil	1 (0.2)
Ibuprofen	1 (0.2)
Loratadine	1 (0.2)
Frusemide	1 (0.2)
Prednisolone	1 (0.2)
Proguanil	1 (0.2)
ABC–3TC–LPV/r+	
Artemether/amodiaquine	4 (0.9)
Metronidazole	2 (0.4)
Proguanil	1 (0.2)
Loratadine	1 (0.2)
Furosemide	1 (0.2)
Prednisolone	1 (0.2)
ABC–3TC–AZT–LPV/r+	
Artemether/amodiaquine	3 (0.7)
Metronidazole	2 (0.4)
Proguanil	1 (0.2)
Loratadine	1 (0.2)
Frusemide	1 (0.2)
Prednisolone	1 (0.2)
Total	460 (100%)

Note: +Indicates that the ART was prescribed along with the other drugs such as fluconazole, prednisolone, etc.

Abbreviations: 3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; AZT, zidovudine; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NVP, nevirapine.

Table 3 Prevalence and nature of the potential clinically significant drug interactions in HIV-infected children on antiretroviral (ARV) therapy

ARV and co-prescribed drug interaction	Frequency of occurrence n (%)	Rating of the clinically significant drug interaction[a]
Nevirapine + artemether/lumefantrine	170 (28.5)	C
Nevirapine + fluconazole	58 (9.7)	C
Zidovudine + fluconazole	55 (9.2)	C
Zidovudine + rifampicin	35 (5.9)	C
Nevirapine + prednisolone	31 (5.2)	C
Zidovudine + ibuprofen	27 (4.5)	C
Efavirenz + rifampicin	27 (4.5)	C
Zidovudine + clarithromycin	24 (4.0)	C
Nevirapine + clarithromycin	19 (3.2)	C
Lamivudine + frusemide	19 (3.2)	C
Nevirapine + furosemide	15 (2.5)	C
Abacavir + metronidazole	15 (2.5)	C
Lopinavir/ritonavir + artemisinin-based combination therapy	15 (2.5)	C
Efavirenz + loratadine	15 (2.5)	C
Efavirenz + artemisinin-based combination therapy	13 (2.2)	C
Nevirapine + rifampicin	8 (1.3)	X
Lamivudine + sulfadoxine/pyrimethamine	8 (1.3)	C
Lopinavir/ritonavir + artemisinin/amodiaquine	7 (1.2)	C
Efavirenz + artemisinin/amodiaquine	5 (0.8)	X
Efavirenz + clarithromycin	5 (0.8)	C
Nevirapine + ketoconazole	4 (0.7)	X
Lopinavir/ritonavir + proguanil	4 (0.7)	C
Lopinavir/ritonavir (solution) + metronidazole	4 (0.7)	C
Lopinavir/ritonavir + loratadine	4 (0.7)	C
Lopinavir/ritonavir + frusemide	4 (0.7)	C
Lopinavir/ritonavir + prednisolone	4 (0.7)	C
Total potential drug–drug interactions identified	596 (100%)	

Notes: [a]C = moderate/monitor therapy; X = contraindicated/avoid combination.[27]

210 CSDIs due to artemisinin-based combination therapy (ACT) in 150 patients, the prevalence of CSDIs reduced from 67.1% to 18.7% in 58 patients.

We considered 70 potential interactions might have occurred in 35 patients resulting in decreased plasma concentration of ARV drugs. Such interactions might have occurred between NVP and rifampicin (8; 1.3%), EFV and rifampicin (27; 4.5%), and AZT and rifampicin (35; 5.9%). Similarly, the interactions between NVP and ACT (210; 35.2%) and between AZT and rifampicin (35; 5.9%) could potentially decrease the plasma concentration of ARV drugs. This is in contrast, however, to the interactions between NVP and fluconazole (58; 9.7%), AZT and fluconazole (55; 9.2%), and NVP and ketoconazole (4; 0.7%), which could potentially increase the plasma concentration of ARV drugs.

The effects of the potential ARV-co-prescribed drug interactions, as well as the alternative drugs to use or the necessary ways to manage the patients for the interactions, are summarized in Table 4.

In Table 5, comparing NRTIs, patients receiving AZT were significantly more likely to be at risk of CSDIs than those on 3TC or ABC (P=0.001). Although there was no statistically significant difference in the risk for CSDIs between NVP and EFV (P=0.723), the large difference in the number of patients on these drugs (287 versus 27 patients, respectively) would make it difficult to draw a firm conclusion on the risk of CSDIs with non-NRTIs. There was a significant difference in the clinically significant interactions associated with the three classes of ARV drugs (P<0.001).

Multivariate logistic regression (Table 6) revealed that the risk for CSDIs was not significantly associated with age (odds ratio [OR] 1.07 [0.92–1.23]; P=0.392), sex (OR 0.89 [0.33–2.38]; P=0.783), and moderate (OR 0.75 [0.19–3.07]; P=0.632) or severe (OR 1.17 [0.38–3.65]; P=0.755) malnourished state of the children.

Discussion

Drug–drug interactions are often serious complications of multiple drug therapies and account for 3%–5% in-patient medication errors in the United States.[31] ARV drugs are among the most therapeutically risky drugs for CSDIs.[8,19] A prevalence of 20%–50% has been reported among cohorts of adult HIV patients in the Netherlands,[18] Kenya,[8] the United Kingdom,[21] Switzerland,[20] and New York state, USA.[4,19] In the present study, the prevalence of CSDI was 67.1%, which is slightly higher than the values reported in other studies involving adult patients.[8,18–21] Differences in the sources of information about CSDIs may have accounted for the variations in the prevalence. Previous studies evaluating interactions between non-ARV drugs have reported discrepancies in the interactions identified by Micromedex® and Lexicomp® databases[27] or Drug Interaction Facts and Micromedex® databases.[32] In addition, concurrent malaria and tuberculosis in the HIV-infected children has necessitated concomitant treatment with ACT and rifampicin-based antituberculosis therapy, and to a great extent, made CSDIs inevitable. Therefore, these classes of drugs have significantly contributed to the high prevalence observed in this study.

ACT was prescribed for over half of the patients and accounted for 40% of the CSDIs. Excluding this class of drug, the prevalence of CSDIs reduced from 67.1% to 18.7% in 58 patients. This suggests that the concurrent diseases in HIV-infected children, as well as their drug utilization pattern, vary from one country to another and may significantly contribute to the varying prevalence of CSDIs. Since ACT remains the first-line antimalarial drug recommended for use in Nigeria,[33] its use for children on ART should be strictly based on laboratory evidence of malaria parasites in blood microscopy. This will, at least, reduce the exposure to ACTs caused by presumptive malaria treatment as noted in the present study. Efforts should also be intensified at preventing malaria in HIV/AIDS-infected children. This measure would include the use of insecticide-treated nets[34] and/or prophylactic antimalarials, such as mefloquine and atovaquone/proguanil.[35] Both mefloquine and atovaquone/proguanil are known to lack clinically significant potential interactions with other ARV drugs, except LPV/r.[36]

A pharmacokinetic study demonstrating two- to three-fold increase in the plasma levels of lumefantrine and decrease in the plasma level of artemether, following coadministration of artemether/lumefantrine and LPV/r in HIV-uninfected adults, has highlighted the need for formal safety analysis of the concomitant therapy.[37] Another pharmacokinetics study involving HIV-infected patients without malaria demonstrated a significantly increased lumefantrine exposure but no increased toxicity when artemether/lumefantrine was coadministered with NVP.[38] Unfortunately, there has been no case report indicating the significance of the interactions between ACTs and ARV drugs in clinical practice. Data are also lacking on the effects of ACT, used concomitantly with ARV drugs, on malaria parasite clearance in HIV-infected patients. Intensive monitoring of patients for possible adverse drug interaction should be instituted during treatment with ACTs. This can be achieved by regular follow-up visits of the patients and a thorough clinical examination during and after treatment with ACTs.

Table 4 Consequences of the antiretroviral (ARV) drug–co-prescribed drug interactions in HIV-infected children and the alternative drugs to use

ARV and co-prescribed drug interaction	Potential clinical effects of the interaction	Alternative drug and/or remark
Nevirapine + artemether/lumefantrine	Decreased extent and rate of absorption of nevirapine and artemether/lumefantrine.[28] Potentially increased treatment failure.[28]	Quinine, but may require clinical and laboratory monitoring of the patient.[25]
Nevirapine + fluconazole	Increased rate and extent of absorption of nevirapine.[28] Decreased half-life of nevirapine, resulting in increased effects.[28] Potentially increased nevirapine effects.[28]	Dosage adjustment of nevirapine or fluconazole is unnecessary; clinical and laboratory monitoring of the patient is required.[28]
Zidovudine + fluconazole	Zidovudine half-life is increased, resulting in increased effects.[28]	Ketoconazole.[25]
Zidovudine + rifampicin	Decreased extent of absorption of zidovudine.[26]	Rifabutin.[28]
Nevirapine + prednisolone	Pyrexia and vomiting.[29]	Dosage adjustment of nevirapine or prednisolone is unnecessary; clinical and laboratory monitoring of the patient is required.[30]
Zidovudine + ibuprofen	Altered bleeding time reported in a patient.[30]	Paracetamol or tramadol.[25]
Efavirenz + rifampicin	Decreased extent and rate of absorption of efavirenz.[28] Decreased efavirenz effects.[28]	Rifabutin.[25]
Zidovudine + clarithromycin	Decreased rate and extent of absorption of zidovudine.[25] Decreased plasma level of zidovudine.[25]	Azithromycin.[25]
Nevirapine + clarithromycin	Decreased rate and extent of absorption of nevirapine.[28] Increased blood level of clarithromycin.[28]	Azithromycin.[25]
Lamivudine + frusemide	Frusemide is a potential substrate and inhibitor of the renal transporters involved in lamivudine elimination.[25]	Dosage adjustment of lamivudine or frusemide is unnecessary in patients with normal renal function, but clinical monitoring may be required.[28]
Nevirapine + frusemide	Nevirapine may potentially interfere with the enzymes involved in the renal elimination of frusemide.[25]	Dosage adjustment of nevirapine or frusemide is unnecessary in patients with normal renal function, but clinical monitoring may be required.[28]
Abacavir + metronidazole	Plasma level of abacavir may be increased.[25]	Dosage adjustment of abacavir or metronidazole is unnecessary. Clinical and laboratory monitoring of the patient may be required.[25]
Lopinavir/ritonavir + artemisinin-based combination therapy	Ritonavir may increase the plasma levels of artemisinins.[25]	Dosage adjustment of lopinavir/ritonavir or artemisinins is unnecessary. Clinical and laboratory monitoring of the patient may be required.[25]
Efavirenz + loratadine	Efavirenz may increase the conversion of loratadine to the active metabolite.[25]	Cetirizine, chlorphenamine, and promethazine.[25] Fexofenadine.[28]
Efavirenz + artemisinin-based combination therapy	Decreased artemether, dihydroartemisinin, and lumefantrine exposures.[25]	Quinine, but its exposure could be decreased.[25] Dosage adjustment of quinine or efavirenz is unnecessary. Clinical and laboratory monitoring of the patient may be required.[25]
Nevirapine + rifampicin	Decreased rate and extent of absorption of nevirapine.[28] Decreased half-life of nevirapine.[28] Potentially decreased nevirapine effects.[28]	Rifabutin.[28]
Lamivudine + sulfadoxine/pyrimethamine	Potentially decreased lamivudine renal elimination as in vitro data suggest that pyrimethamine inhibits the renal transporters involved in lamivudine elimination.[25]	Proguanil.[25] Dosage adjustment of sulfadoxine/pyrimethamine is unnecessary in patients with normal renal function, but clinical monitoring of the patient is required.[25]

(*Continued*)

Table 4 (*Continued*)

ARV and co-prescribed drug interaction	Potential clinical effects of the interaction	Alternative drug and/or remark
Lopinavir/ritonavir + artemisinin/amodiaquine	Ritonavir may increase plasma levels of artemisinins.[25] Lopinavir/ritonavir could potentially increase amodiaquine exposure.[25]	Dosage adjustment of either drugs is unnecessary.[25] Close monitoring for artemisinin toxicity and amodiaquine-related adverse effects are required.[25]
Efavirenz + artemisinin/amodiaquine	Decreased artemether and dihydroartemisinin exposures.[25] Increased amodiaquine exposures.[25]	Quinine, but its exposure could be decreased.[25] Dosage adjustment of quinine or efavirenz is unnecessary. Clinical and laboratory monitoring of the patient may be required.[25]
Efavirenz + clarithromycin	Decreased clarithromycin exposure and effects.[25,28] Increased absorption rate of efavirenz.[25,28]	Azithromycin.[25,28]
Nevirapine + ketoconazole	Decreased rate and extent of absorption of ketoconazole.[28] Potentially decreased ketoconazole effects and increased nevirapine effect.[28]	Efavirenz with fluconazole.[25]
Lopinavir/ritonavir + proguanil	Decreases the extent of absorption of proguanil.[28] Potentially compromises antimalarial activity of proguanil.[28]	Pyrimethamine.[25]
Lopinavir/ritonavir (solution) + metronidazole	Disulfiram reaction (hypotension, headache, nausea, vomiting) due to the alcohol content of the lopinavir/ritonavir solution.[28]	Lopinavir/ritonavir capsule.[28]
Lopinavir/ritonavir + loratadine	May increase loratadine plasma levels, resulting in increased loratadine effects.[25]	Cetirizine or chlorphenamine.[25] Fexofenadine.[28]
Lopinavir/ritonavir + frusemide	Lopinavir/ritonavir may potentially interfere with the enzymes involved in the renal elimination of frusemide.[25]	Dosage adjustment of lopinavir/ritonavir or frusemide is unnecessary in patients with normal renal function but clinical monitoring may be required.[25]
Lopinavir/ritonavir + prednisolone	Increases the extent of absorption of prednisolone.[28] Possibly increased prednisolone effects.[28]	Dose adjustment of lopinavir/ritonavir or prednisolone unnecessary.[28]

Other drugs, including fluconazole (9.7%), prednisolone (5.2%), and clarithromycin (3.2%), were implicated in the drug interactions and accounted for the broad range of CSDIs observed. This is comparable to the pattern of CSDIs reported in a similar study involving adult HIV patients in Kenya,[8] but is in contrast to the findings in adult HIV patients in the United Kingdom, where antidepressants, antibiotics, statins, and recreational drugs were the major suspects for CSDIs.[21]

We identified the potential interactions between ARV drugs and fluconazole, prednisolone, or clarithromycin, namely, between NVP and fluconazole, AZT and fluconazole, LPV/r and prednisolone, NVP and prednisolone, AZT and clarithromycin, NVP and clarithromycin, and EFV and clarithromycin. Fluconazole coadministration has the potential to increase the exposure of NVP[39] or decrease the exposure of AZT;[40] however, the authors[40] noted that the inhibitory effect of fluconazole on AZT was too small to effect a clinically relevant interaction. NVP has the potential to decrease the exposure of prednisolone;[29] in contrast, NVP can increase the exposure of LPV/r.[41] Other studies have also indicated that clarithromycin increases the exposure of EFV[42] but decreases the exposures of NVP and AZT.[43]

Theoretically, all the interactions could result in suboptimal treatment, therapeutic failure, or resistance development. Since the interactions in the present study were moderately significant and required therapy monitoring or adjusting, alternative drugs such as azithromycin could have been used in place of clarithromycin in order to avoid the potential interactions. Presently, there are no alternative drugs to replace fluconazole and prednisolone; therefore, concomitant use of these drugs with the ARV drugs that have potential for interactions requires further evaluation.

Most of the CSDIs identified in this study were moderately significant and necessitated dosage adjustment; however, the Liverpool HIV Pharmacology Group website does not provide clinical relevance or detailed strategies for managing the interactions. This may necessitate clinicians prescribing the ARV and co-prescribed drugs to avoid all drug combinations identified as interacting, when indeed the interactions are

Table 5 Risk of clinically significant drug interactions by individual ARV drug

ARV drug	Total number of patients	Clinically significant drug interactions N (%)[a]	*P*-value
NRTIs			
Lamivudine	310	27 (8.7)	0.001
Zidovudine	310	141 (45.5)	
Abacavir	66	15 (22.7)	
Non-NRTIs			
Nevirapine	287	305 (106)	0.723
Efavirenz	27	66 (244)	
PIs			
Lopinavir/ritonavir	62	42 (67.7)	

Notes: There was a statistically significant difference in the clinically significant interactions associated with the three classes of ARV drugs ($P<0.001$). [a]Based on the number of clinically significant drug interactions relative to the number of patients affected. One or more patients had potential for more than one clinically significant drug interaction.
Abbreviations: ARV, antiretroviral; NRTIs, nucleoside reverse transcriptase inhibitors; PIs, protease inhibitors.

clinically insignificant. Such practice may unnecessarily avert useful therapy options for patients and prevent optimal treatment approaches. Previous studies have documented that many interactions rated moderately significant by Micromedex and Lexicomp databases were found to be clinically insignificant by doctors and pharmacists.[27,44] Clinicians should, therefore, have a good understanding of the opportunistic infections and comorbid conditions associated with HIV infection, and of the necessity to treat patients with a specific drug combination while monitoring for adverse drug interactions.

Some potential CSDIs (NVP and artemether/lumefantrine, EFV and ACT, NVP and rifampicin, EFV and artemisinin/amodiaquine, and NVP and ketoconazole) were rated either as contraindicated or moderately significant interactions. Although it is important to avoid all contraindicated drug interactions, we felt the drugs were prescribed according to the best practice of the clinicians after making a risk-versus-benefit assessment of the situation. In addition, the clinicians may have rated the interactions clinically insignificant or moderately significant 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.[27,44]

Table 6 Multivariate logistic regression of risk for clinically significant drug interactions

Variable	Clinically significant drug interaction		Odds ratio (95% CI)	*P*-value
	No	Yes		
Sample size, n (%)	102 (26.5)	208 (73.5)	–	–
Sex				
Male, n (%)	45 (14.5)	93 (30.0)		
Female, n (%)	57 (18.4)	115 (37.1)	0.83 (0.33–2.38)	0.783
Age (years), mean (SD)	4.34 (3.24)	3.62 (3.25)	1.07 (0.92–1.23)	0.392
Nutritional status				
Normal, n (%)	56 (18.1)	122 (39.3)		
Moderate malnutrition, n (%)	19 (6.1)	20 (6.5)	0.73 (0.19–3.07)	0.632
Severe malnutrition, n (%)	27 (8.7)	66 (21.3)	1.12 (0.38–3.65)	0.755

Abbreviations: CI, confidence interval; SD, standard deviation.

Although many of the previous studies utilized the Liverpool HIV Pharmacology Group drug interaction website,[8] others utilized the Micromedex database,[27] summary of product characteristics,[4] or the United States Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents (DHHS guidelines),[7] we utilized the Liverpool HIV Pharmacology Group database because it is specifically designed for ARV drug interactions, widely used in clinical practice, and requires no subscription fee.

The first-line (AZT–3TC–NVP) and second-line (ABC–3TC–NVP) ART regimens were frequently associated with CSDIs in this study. The use of these regimens with the suspected co-prescribed drugs would require frequent follow-up visits of the patients with regular monitoring for adverse drug interactions. The few CSDIs associated with AZT in this study may suggest an emtricitabine-based regimen as an alternative. Emtricitabine has been authorized for pediatric use in the United States and in the European Union since 2003.[45] Its effectiveness and safety as part of the first-line ART regimen has been reported in children; in addition, it does not interact with any of the cytochrome P450 enzymes.[45]

There were a number of limitations to our study. We specifically assessed the potential for clinically significant drug interactions and did not evaluate adverse clinical outcomes arising from these interactions. The incomplete documentation of the viral loads and liver biochemistry at baseline and follow-up made it difficult to assess the impact of adverse drug interactions. We also did not evaluate the relationship between the risk for CSDIs and response to therapy. We probably underestimated or overestimated the prevalence of CSDIs with ARV drugs due to 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. We also excluded the potential drug interactions between the non-HIV drugs or between ARV drugs, and did not know if the patients were receiving treatment elsewhere other than the HIV clinic. Overall, our findings appear to have overestimated the true prevalence of potentially significant drug interactions in this cohort of patients, due to frequent prescription of ACTs.

The list of interactions involving ARV drugs is extensive and constantly expanding. Therapeutic drug monitoring is necessary to minimize the risk of drug interaction, but lack of facilities would make this approach a non-feasible strategy for managing CSDIs in Nigeria. A complete drug history review and better medication recording, development of a national treatment guideline that would integrate HIV management with other diseases, establishment of a regional network for pediatric pharmacovigilance, access to online databases for drug interactions with ARV drugs, regular training of health care workers on rational prescribing, knowledge of metabolism of the major drug classes, review of the current ART regimen in Nigeria, and familiarization with common interactions involving risk on a country-specific basis are some of the practical steps that could be instituted to reduce the risk of adverse outcomes from CSDIs.

Conclusion

A considerable proportion of children who received ART at the APIN clinic LUTH, Nigeria were at risk of CSDIs with a potential to cause subtherapeutic levels of ARV drugs in some patients as well as sub- or supratherapeutic levels of concomitant drugs. Although ACT used for malaria accounted for a significant proportion of the CSDIs, rifampicin used for tuberculosis was the most frequently involved in contraindicated interaction. Large prospective cohort studies are required to confirm that our findings are generalizable to other pediatric HIV treatment centers in Africa. Increasing the availability of ARV drugs in Nigeria would require strategies to be developed in order to avert important CSDIs, to identify early markers of toxicity, and to manage unavoidable interactions so as to reduce the risk of harm of the ARV drugs.

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Disclosure

The authors report no conflicts of interest in this work.

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