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Original article

Evaluation of cardiotoxicity and other adverse effects associated with concomitant administration of artemether/lumefantrine and atazanavir/ritonavir-based antiretroviral regimen in patients living with HIV

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ABSTRACT

The interplay of artemether-lumefantrine (AL) and atazanavir-ritonavir (ATVr) with Cytochrome P (CYP) 3A4 isoenzyme and QTc-interval may spawn clinically significant drug interactions when administered concomitantly. Cardiotoxicity and other adverse effects associated with interaction between AL and ATVr were evaluated in patients with HIV infection and malaria comorbidity. In a two-arm parallel study design, six doses of AL 80/480 mg were administered to 20 participants [control-arm (n = 10) and ATVr-arm (n = 10)], having uncomplicated Falci-parum malaria, at intervals of 0, 8, 24, 36, 48 and 60 h respectively. Participants in the control arm took only AL while those in ATVr-arm took both AL and ATVr-based ART regimen. Electrocardiography, adverse events monitoring and blood tests were carried out for each of them at pre and post doses of AL. Data obtained were analyzed. QTc-interval was significantly increased in the ATVr-arm (0.4079 ± 0.008 to 0.4215 ± 0.007 s, $p = 0.008$) but not in the control-arm (0.4016 ± 0.018 to 0.4024 ± 0.014 s, $p = 0.962$). All values were, however, within normal range [$0.36 - 0.44 / 0.46$ s (male/female)]. General body weakness and chest pain were new adverse events reported, at post-dose of AL, in the ATVr-arm but not in the control-arm. There was no significant change ($p > 0.05$) in the plasma levels of creatinine, alanine aminotransferase, aspartate aminotransferase and hemoglobin at post-dose compared to pre-dose of AL in both arms of study. Concomitant administration of artemether-lumefantrine with atazanavir-ritonavir-based regimen is potentially cardiotoxic but not associated with clinically significant renal, blood nor liver toxicities. They must be used with caution.

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1. Introduction

Antimalarial and antiretroviral (ARV) drug-drug interaction (Oreagba et al., 2019) in people living with HIV, may aggrandize

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the exacerbation of malaria morbidity already caused by the HIV-associated immunosuppression (Whitworth and Quigley, 2000).

Atazanavir-ritonavir (ATVr)- based ARV regimen is commonly used for the treatment of HIV in Nigeria (Akanmu et al., 2015). The protease inhibitors (PIs) are usually administered with backbone of tenofovir-lamivudine or tenofovir-emtricitabine in a single regimen. (Anafi et al., 2008; Akanmu et al., 2015.) Atazanavir (ATV) is preferred over other protease inhibitors (PIs) because of its metabolic advantages, (Jemsek et al., 2006; Lu et al., 2011; Murphy et al., 2010; Noor et al., 2006) less tendency for showing cross-resistance to other PIs (Kozal, 2004) and simpler dosing frequency (Achenbach et al., 2011).

In Nigeria and other sub-Saharan countries, where co-morbidity of HIV and malaria prevails, (Kwenti, 2018) the concomitant

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administration of the ARV regimen and AL is imminent. This may result in Clinically Significant Drug Interactions (CSDIs) because of their effects on CYP 450 enzymes (Walubo, 2007; Ericsson et al., 2014).

While lumefantrine may not have any impact on the plasma concentration of ATV and ritonavir (RTV) because it neither induces nor inhibits CYP 3A4 isoenzyme, (Ezzet et al., 2000) artemether may reduce their plasma concentration via enzymatic induction of the latter (Burk et al., 2012) which metabolizes both atazanavir (Perloff et al., 2005) and ritonavir. (Kumar et al., 1996) But the interaction is unlikely to have negative impact on the antiretroviral therapy because of the short duration (3 days) of administration of the antimalarial drug.

RTV rarely causes hyperglycemia (Markowitz et al., 1995) and nephrotoxicity (Roling et al., 2006) but commonly causes asthenia, malaise, diarrhea, nausea, vomiting, abdominal pain, dizziness, insomnia, sweating, taste abnormality, hypercholesterolemia, hypertriglyceridemia, elevated transaminases and elevated creatine phosphokinase (Drugs com, 2021 <https://www.drugs.com/sfx/ritonavir-side-effects.html>). While ATV commonly causes hyperbilirubinemias with less effects on glucose and lipid adverse effects compared to other PIs. (Lu et al., 2011; Murphy et al., 2010; Noor et al., 2006) These adverse effects may not be exacerbated by AL which potentially reduces the plasma concentration of the ARV drugs because of the inductive effects (Burk et al., 2012) of artemether on CYP3A4 isoenzyme. However, interaction via additive cardio-toxicity is likely due to the QT-prolongation that ATV and artemether are known to cause. ((Bristol-Myers Squibb Company. BMS-, 2003); Funck-Brentano et al., 2019)

Conversely, ATVr, being an inhibitor of CYP 3A4 isoenzyme, (Moyle and Back, 2001) may increase the plasma concentration of artemether and lumefantrine, which are substrates to the enzyme, (Lefèvre and Thomsen, 1999) thereby enhancing their toxicity. Mild but common adverse effects of artemether-lumefantrine include headache, anorexia, dizziness, asthenia, pyrexia, cough and vomiting while severe but rare ones are QT prolongation, bullous eruption, urticaria, splenomegaly, hepatomegaly, hypersensitivity reaction, and angioedema. (Drugs.com, 2021) <https://www.drugs.com/sfx/artemether-lumefantrine-side-effects.html>. These adverse effects may be exacerbated when co-administered with atazanavir-ritonavir based ART regimen in co-infected patients as a result of the inhibitory effects of atazanavir-ritonavir on CYP3A4 enzyme (Moyle and Back, 2001) which metabolizes artemether and lumefantrine. (Lefèvre and Thomsen, 1999) The toxicity of dihydroartemisinin (DHA) may also be enhanced because of the inhibitory effect of atazanavir on UGT1A1 isoenzyme (Panagopoulos et al., 2017) which metabolizes DHA. In addition, increase in plasma concentration of artemether may further exacerbate its QT-prolongation effect. Similarly, lumefantrine, though, has not been reported to cause QT- prolongation at normal plasma concentration, (Van Vugt et al., 1999) its potential cardiotoxic effect, at higher concentration due to concomitant administration with ATVr-based regimen (Usman et al., 2021), is of utmost concern because of its structural similarity (<https://www.sciencedirect.com/topics/neuroscience/lumefantrine>) with halofantrine, a known cardiotoxic drug. (Bouchaud et al., 2009) A recent pharmacokinetic study (Usman et al., 2021) shows that ATVr increased the exposure and day 7 plasma concentration of lumefantrine by 49.68 and 179.88 % respectively. But the clinical implication of the increase was unknown.

Hence this study was aimed at evaluating the toxicities associated with concomitant administration of artemether-lumefantrine and atazanavir-ritonavir based antiretroviral regimen, which to our knowledge, has not been previously reported.

2. Patients and methods

2.1. Ethics

The research was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The details of the study were explained to the participants and their written informed consents were obtained. Ethical approval was obtained from the Health Research Ethics Committee of the College of Medicine of the University of Lagos (CMUL/HREC/06/18/354: Sept 2018-Sept 2019). The study has also been registered with ClinicalTrials.gov (Clin ClinicalTrials.gov Identifier: NCT04531072).

2.2. Study site

The study was carried out at the Department of Pharmacology, Faculty of Basic Medical Science, College of Medicine of the University of Lagos. Recruitment was done at the APIN clinic of LUTH and Ijede General Hospital, Blood analyses were carried out at the Central Research Laboratory of the College of Medicine of the University of Lagos.

2.3. Study design

An interventional prospective parallel study design aimed at evaluating the toxicities associated with the interaction between AL and ATVr.

Twenty participants were recruited and divided into two groups. The first group (ATVr-arm, n = 10) consisted of participants living with HIV who had been stabilized on ATVr based regimen [ATVr + tenofovir (TDF) + lamivudine (3TC)] for at least three months prior to recruitment and also tested positive for *Plasmodium falciparum* malaria. They were recruited from APIN clinic of LUTH. The second group (Control-arm, n = 10) included participants having uncomplicated falciparum malaria but HIV negative. The latter were recruited from Ijede General Hospital at Ikorodu.

2.4. Inclusion criteria

The inclusion criteria were being an adult male or non-gravid female ≥ 18 years of age, informed written consent, malaria parasitemia (uncomplicated malaria with microscopically confirmed *Plasmodium falciparum* infection), being an HIV 1-infected patient who is registered at APIN Clinic of LUTH (ATVr-arm), HIV negative (Control-arm), participants must be taking only the study drugs and avoid medications that may interfere with research results, CD4 + cells count of > 200 cells/mm³, axillary temperature ≥ 37.5 °C or history of fever within 24 h before visiting the clinic and with, at least, any of the following signs and symptoms of uncomplicated malaria: chills, sweats, headaches, muscle aches, nausea, vomiting, diarrhea, body weakness, poor appetite and pallor. Other patient-related parameters for inclusion in the study were HGB ≥ 8 g/dl and body weight ≥ 35 kg.

2.5. Exclusion criteria

The exclusion criteria were: severe anemia (Hemoglobin levels < 8 g/dl); refusal to give informed consent; withdrawal of consent; known allergy to any of the study drugs; development of complications or severe adverse effects; smokers/alcoholics and users of caffeine, drugs which induce or inhibit CYP3A4 and CYP2B6, herbal medicines, oral contraceptives pills, grape fruits or juice and other illicit drugs; evidence of chronic illnesses such as diabetes, hypertension, psychiatric illnesses; subject taking any drugs or having any condition known to prolong QT-

intervals, signs of severe malaria; being on anti-malarial drugs within four weeks prior to enrolment; and being a pregnant or nursing mother.

2.6. Drug administration and blood sampling

Each participant took, with milk (26 g milk fat per dose), six doses of artemether/lumefantrine 80/480 mg tablets (Coartem 80/480[®]) at intervals of 0, 8, 24, 36, 48 and 60 h respectively from 8 pm on day 1 to 8am on day 4. The first and last doses were given under direct observed therapy (DOT) while the rest were handed over to the participants to be taken on outpatient basis, reminding them with phone call. While the participants in the Control-arm took only artemether-lumefantrine, those in ATVr-arm continued their ATVr-based regimen (atazanavir-ritonavir [300/100 mg] + t enofovir-lamivudine [300/300 mg]), at a dose of one tablet once daily.

Blood samples (2 × 5 mL) were collected, from each participant at pre and post doses of AL, into lithium-heparin (5 mL) and EDTA (5 mL) bottles for blood chemistry and hematology tests respectively. Those collected in lithium-heparin bottles were immediately centrifuged at 4000 rpm at 4 °C for 15 min to obtain their plasma samples which were stored in –80 °C refrigerator until analysis.

2.7. Electrocardiography

Electrocardiography was done twice for all participants, in both arms, at pre and post doses of AL on day 1 and day 4 respectively. The electrocardiogram, on day 4, was obtained at 6 h after the last dose which is the expected time for achievement of maximum plasma concentration of lumefantrine. (Ezzet et al., 2000) The results at pre and post doses of AL were compared using student *t*-test for paired samples in Statistical Package for Social Science (IBM SPSS).

2.8. Blood chemistry test for renal and liver toxicities

Renal and liver toxicities associated with the interaction between AL and ATVr were evaluated by assessing significant change in plasma levels of creatinine and liver enzymes (ALT and AST), respectively, at post-dose (day 4) of AL compared to its pre-dose (day 1).

All biochemical assays were estimated using Roche and Cobas commercial kits and Cobas c311 automated analyzer. The outcome parameters of interest which included plasma levels of creatinine, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were programmed on the machine and plasma samples, obtained after centrifugation of the blood samples collected from each participant, were placed in the sample disks of the analyzer followed by addition of appropriate working reagents for each parameter bearing in mind the volumes needed for calibration.

The reagents used for creatinine assay, following a standard method, (31) included potassium hydroxide (900 mmol/L), phosphate (135 mmol/L), pH ≥ 13.5, preservative, stabilizer, picric acid (38 mmol/L), pH 6.5 and non-reactive buffer. In order to correct for non-specific reaction caused by serum/plasma pseudo-creatinine chromogens including proteins and ketones, the results for serum or plasma were corrected by 26 μmol/L (0.3 mg/dL).

On the other hand, the reagents for the assay of ALT included TRIS buffer (224 mmol/L, pH 7.3 at 37 °C; L-alanine (1120 mmol/L); albumin from bovine (0.25%); LDH from microorganisms (>45 μkat/L); diluent (NaCl 9%), stabilizers and preservative. While the reagents for the assay of AST were TRIS buffer (224 mmol/L), pH 7.3 at 37 °C, L-alanine (1120 mmol/L), bovine albumin (0.25%), LDH from microorganism (≥45 μkat/L), stabilizers, preservative,

2-oxoglutarate (94 mmol/L), NADH (≥1.7 mmol/L) and additive preservative.

After running, the analyzer displayed, on its monitor, the biochemistry assay results which were recorded and subjected to appropriate statistical test using IBM SPSS version 22.

2.9. Haematology

The haemotoxicities associated with the interaction between the ATVr and AL was assessed by determining and comparing the mean hemoglobin levels in the control and test groups at pre- and post-doses of AL. Following collection of blood samples, into EDTA vacutainer bottles, from the participants, the bottles were placed on a vortex mixer to mix the blood uniformly. They were then placed in the sample compartment of the analyzer from where a specified quantity (13 μL) was aspirated and mixed with 3.5 mL of the diluent. The hemoglobin (HGB) level was measured by the colorimetric method using BCE 3200 analyzer at 525 nm wavelength and calculated per the following as follows: HGB (g/L) = Constant X Log10 (Blank Photocurrent/Sample Photocurrent). After determination of the hemoglobin levels, the values obtained at pre and post doses of AL were compared using Student *t* test for paired samples in SPSS.

2.10. Adverse events associated with drug interaction between AL and ATVr

All adverse events reported by the participants, after administration of the first dose of AL, were recorded and compared between the ATVr and Control arms.

2.11. Statistical analysis

Toxicities were evaluated by comparing parameters at pre and post doses of AL. Continuous data that were normally distributed were expressed as Mean ± S.E.M. and analyzed with Students *t*-test for paired samples while categorical data and those that were not normally distributed were presented as median (IQR) and analyzed with Wilcoxon Sign Rank test. Kurtosis and skewness *z*-values (Normal: between –1.96 and + 1.96) as well as Shapiro Wilk and Kolmogorov tests (normal: if *p* > 0.05) were used to determine normality of data. The results were considered to be significant at *p* ≤ 0.05 at 95% confidence level.

3. Results

3.1. Demographics of research participants

Twenty participants, divided into two groups (Control and ATVr arms) of 10 participants per group, were used in the study. The control group consisted of HIV negative participants having uncomplicated falciparum malaria while the ATVr group consisted of patients living with HIV, who had been stabilized on atazanavir/ritonavir-based ART regimen for a minimum of three months in APIN clinic of the Lagos University Teaching Hospital and also having uncomplicated falciparum malaria. All the participants in both groups took six doses of AL 80/480 mg over three days. At the baseline, there was no significant difference in the gender distribution (*p* = 0.63), median weight (*p* = 0.37), median age (*p* = 0.66), mean hemoglobin level (*p* = 0.81), mean creatinine level (*p* = 0.96) and mean QT_c-interval (*p* = 0.75) in both groups. Most of the participants had secondary education [Control (60 %), ATVr (50 %)] and were married [Control (60 %), ATVr (50 %)]. While those in the control group were HIV negative, those in ATVr group were mainly infected through heterosexual contact (70 %) (Table 1).

Table 1
Demographic data of research participants.

Demographic Data	Variable	Participants (Control) n (%)	Participants (ATVr) n (%)	p-value
Sample size		10 (100)	10 (100)	
Age [Years]	Median (IQR)	31 (27–41)	39 (30–50)	0.66
Gender	Male	4 (40)	2 (20)	0.63
	Female	6 (60)	8 (80)	
HIV Status	Positive	0 (0)	10 (100)	
	Negative	10 (100)	0 (0)	
Source of HIV	Heterosexual	0 (0)	7 (70)	
	Blood transfusion	0 (0)	2 (20)	
	Mother to Child	0 (0)	1 (10)	
Marital status	Married	6 (60)	5 (50)	
	Single	4 (40)	1 (10)	
	Separated	0	2 (20)	
	Widowed	0	2 (20)	
Educational level	Primary	1 (10)	1 (10)	
	Secondary	6 (60)	5 (50)	
	Tertiary	3 (30)	3 (30)	
	Illiterate	0	1 (10)	
Baseline body weight (Kg)	Median (IQR)	74.5 (67.25–80.75)	69 (67.75–87.25)	0.37
Baseline HGB ^d	Mean (S.E.M.)	12.92 (0.68)	13.14 (0.55)	0.81
Baseline creatinine level	Mean (S.E.M.)	70.71 (3.86)	71.2 (7.97)	0.96
Baseline QT _c - Interval	Mean (S.E.M.)	0.40 (0.02)	0.41 (0.01)	0.75

n - number of participants, % - percentage of participants, IQR - inter-quartile range, HGB - hemoglobin, S.E.M. - standard error of mean.

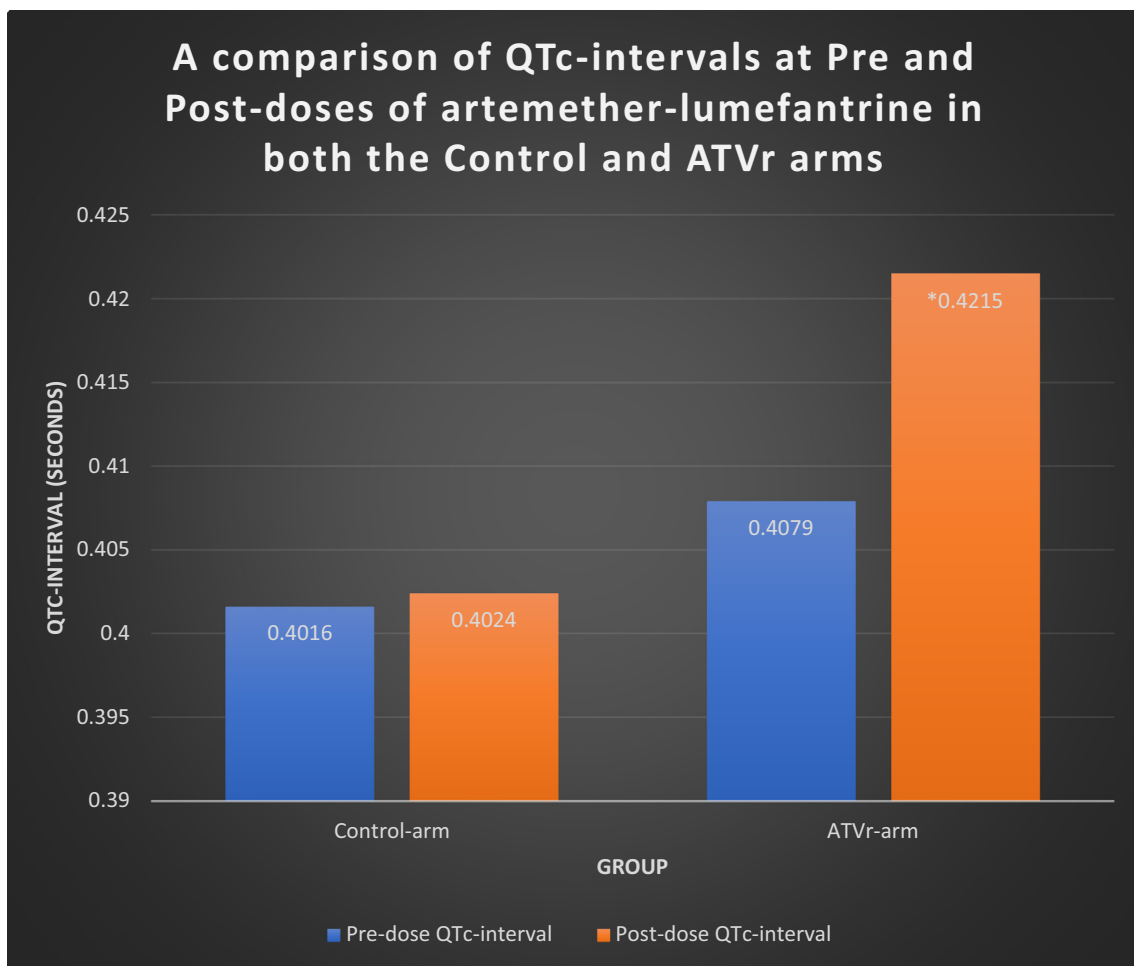


Fig. 1. The effect of interaction between artemether/lumefantrine and atazanavir/ritonavir on QTc-interval. *Significant value at 95% confidence level ($p \leq 5\%$), ATVr- atazanavir-ritonavir, QTc-interval [Normal range: 0.36 – 0.44 / 0.46 s (male/female)]

3.2. Effects of drug interaction between AL and ATVr on cardiotoxicity

The evaluated QTc-interval values were normally distributed as indicated by the Shapiro-Wilk ($p = 0.43$) and Kolmogorov ($p = 0.20$) tests, which at p values > 0.05 ($p > 0.05$) indicate normal distribution. (Shapiro and Wilk, 1965; Lopes, 2011) As well as by the skewness (-0.787) and kurtosis (-0.558) z-scores which fell between an appropriate range (-1.96 and $+ 1.96$) for normal distribution. (Hae-Young, 2013)

Following complete administration of six doses of artemether/lumefantrine, the mean QTc-interval increased in both the control (0.4016 ± 0.018 to 0.4024 ± 0.014 s, $p = 0.962$) and ATVr (0.4079 ± 0.008 to 0.4215 ± 0.007 s, $p = 0.008$) arms. Although the increase was significant, only, in the ATVr-arm, all the values obtained, both at pre and post doses of AL, were within normal range [$0.36 - 0.44 / 0.46$ s (male/female)] (Fig. 1).

On the other hand, ATVr did not cause any significant increase or decrease in the PR-intervals following administration of complete doses of AL. The PR-intervals were within normal ranges ($0.12 - 0.20$ s) in both control ($p = 0.2832$) and ATVr ($p = 0.6193$) arms (Fig. 2).

3.3. Effects of drug interaction between artemether-lumefantrine and atazanavir-ritonavir on liver, renal and haemo toxicities.

The median plasma levels of ALT decreased at post-dose of AL in both the control (pre-dose 14.00 [$10.33 - 20.90$], post-dose 11.20 [$9.4 - 12.25$], $p = 0.066$) and ATVr (pre-dose 15.55 [$11.10 - 26.00$], post-dose $1-2.85$ [$8.05 - 22.48$], $p = 0.009$) arms with all values falling within normal range. On the other hand, the median plasma level of AST, at post-dose of AL, decreased in the control arm (pre-dose 25.05 [$21.38 - 34.78$], post-dose 23.55 [$20.90 - 31.43$], $p = 0.799$) but increased in the ATVr-arm (25.40 [$20.48 - 33.63$] to 32.20 [$20.80 - 41.03$]; $p = 0.262$). Nonetheless, all the values were within normal range (Table 2).

Similarly, the median creatinine levels were within normal range at pre and post doses of AL and there was no significant change in both control {pre-dose 72.60 ($61.50 - 81.08$), post-dose 70.20 ($65.98 - 79.80$), $p = 0.445$ } and ATVr (pre-dose, post-dose, $p = 0.859$) arms. (Table 2).

Likewise, there was no significant change in the median hemoglobin level which increased at post-dose of AL in both the control (pre-dose 12.05 [$11.08 - 14.58$], post-dose 12.70 [$10.83 - 14.03$], $p = 0.475$) and ATVr (pre-dose 12.70 [$11.75 - 14.75$], post-dose 13.75 [$11.18 - 15.70$], $p = 0.646$) arms (Table 2).

3.4. Adverse events associated with interaction between AL and ATVr

The adverse events reported by the participants were few and mild. They included fever, headache, chest pain and body weakness. All the participants (100% , $n = 20$) reported headache and fever, at the pre-dose of AL in both groups, which were reduced to 20% ($n = 4$) of the participants ([Control-arm 1, ATVr-arm 3]) at the post-dose. Chest pain and body weakness were the only new adverse events that were reported by participants in the ATVr-arm at the post-dose of AL without being previously reported at its pre-dose. In the control-arm, 20% of the participants had body weakness at pre-dose of AL which subsided in half of them (10% , $n = 10$) at its post-dose (Fig. 3).

4. Discussion

This is the first study that evaluates the adverse effects associated with interaction between artemether-lumefantrine and atazanavir-ritonavir in people living with HIV in Nigeria.

The participants used in the study were well matched as there was no significant difference ($p > 0.05$) in their baseline (AL pre-dose) age, gender, weight, QTc-interval, HGB, ALT, AST, nor creatinine levels (Table 1). Similar baseline results had been previously reported in another study except for hemoglobin level that was significantly higher in the lopinavir-ritonavir arm. (Byakika-

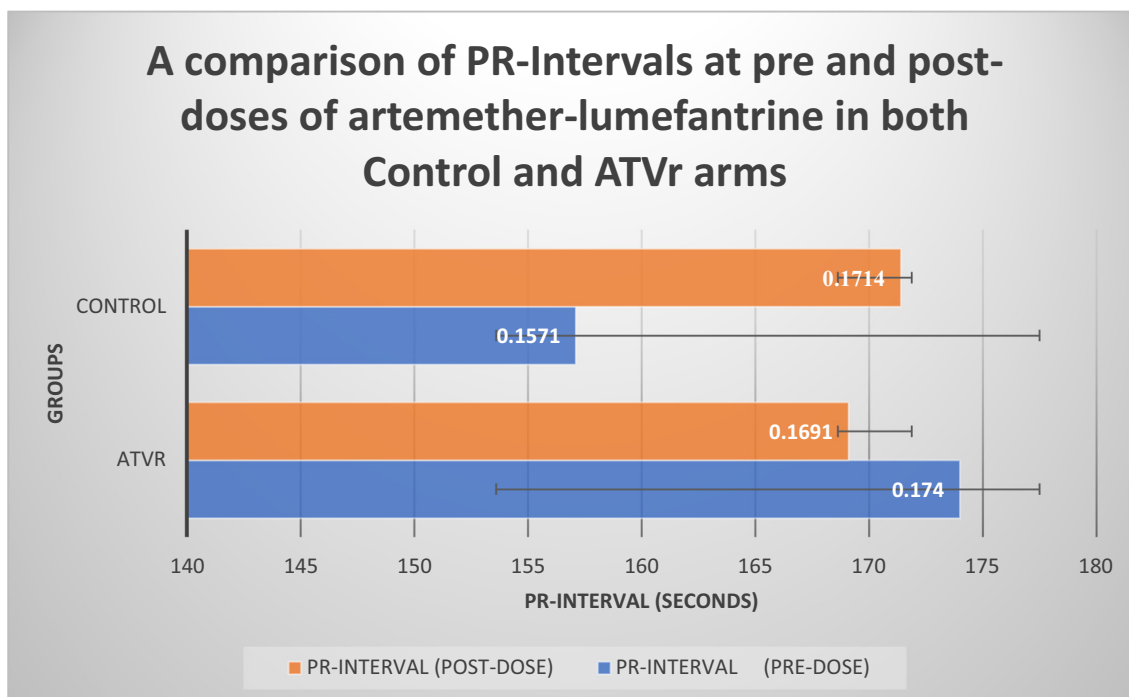


Fig. 2. The effect of interaction between artemether/lumefantrine and atazanavir/ritonavir on PR-interval. ATVr- atazanavir-ritonavir, Control ($p = 0.2832$), ATVr ($p = 0.6193$), confidence level = 95%, PR interval (Normal range: $0.12 - 0.20$ s).

Table 2
The effects of drug interaction between artemether/lumefantrine and atazanavir/ritonavir on the plasma levels of hemoglobin, liver enzymes and creatinine.

Parameters	Group (n = 10)	Pre-dose (Median [IQR])	Post-dose (Median [IQR])	p - value
ALT (U/L)	Control-arm	14.00 (10.33–20.90)	11.20 (9.4–12.25)	0.066
	ATVr-arm	15.55 (11.10–26.00)	12.85 (8.05–22.48)	0.009*
AST (U/L)	Control-arm	25.05 (21.38–34.78)	23.55 (20.90–31.43)	0.799
	ATVr-arm	25.40 (20.48–33.63)	32.20 (20.80–41.03)	0.262
Creatinine (µmol/L)	Control-arm	72.60 (61.50–81.08)	70.20 (65.98–79.80)	0.445
	ATVr-arm	72.45 (50.08–77.00)	62.35 (51.82–93.03)	0.859
Hemoglobin (g/dL)	Control-arm	12.05 (11.08–14.58)	12.70 (10.83–14.03)	0.475
	ATVr-arm	12.70 (11.75–14.75)	13.75 (11.18–15.70)	0.646

n: number of participants in each group/arm, ATVr: atazanavir-ritonavir, SEM: Standard error of mean, *: significant at 0.05 and 95% confidence level. Reference range: Hemoglobin (11 – 16.5 g/dL), creatinine (50 – 140 µmol/L), ALT (5 – 56 U/L), AST (6 – 40 U/L).

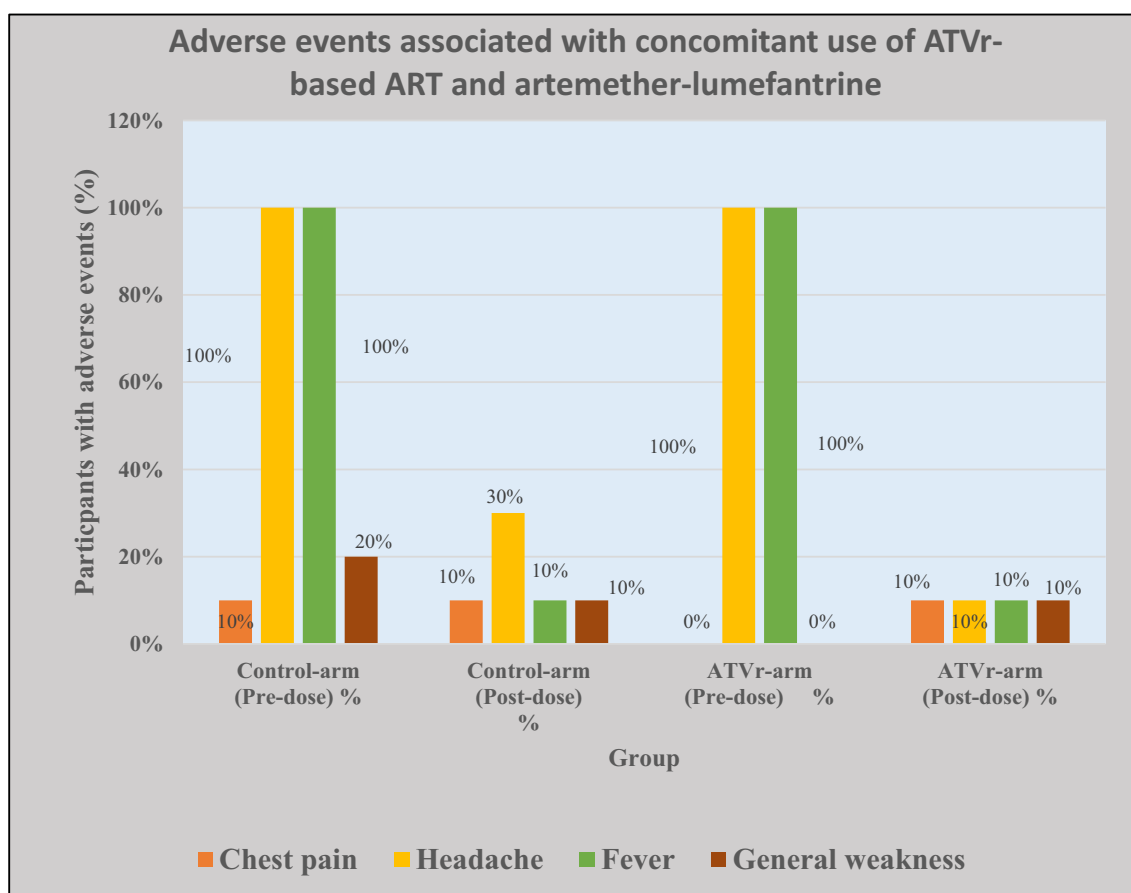


Fig. 3. Adverse events associated with interaction between artemether-lumefantrine and atazanavir-ritonavir.

Kibwika et al., 2012) Difference in type of protease inhibitors used could account for the deviation.

This study ascertained that concomitant administration of AL with ATVr based antiretroviral regimen is potentially cardiotoxic as a result of significant increase ($p = 0.008$) in QTc-interval in ATVr-arm as against the control-arm in which the increase was not significant ($p = 0.962$) at post-dose of AL 80/480 mg tablets. Hence caution should be exercised when administering the combination with another drug that increase QTc-interval. Patients taking the drugs should be monitored for signs of cardiotoxicity. Additive increase in QTc-interval caused by artemether (Funck-Brentano et al., 2019) and atazanavir (Ly and Ruiz, 2007) may be responsible for the results. Although, to our knowledge, the toxicity associated with concomitant administration of AL and ATVr-based ART regimen has not been previously reported, it is notewor-

thy that related studies (Usman et al., 2020; Byakika-Kibwika et al., 2012; Kredo et al., 2015) involving AL and other ritonavir-boosted protease inhibitors have never associated the interaction with cardiotoxicity. This is because other protease inhibitors including lopinavir and ritonavir, unlike atazanavir, (http://www.fda.gov/ohrms/dockets/ac/03/briefing/3950B1_01_BristolMyersSquibb_atazanavir.pdf) are not known to cause QTc-interval prolongation. (Byakika-Kibwika et al., 2011; Charbit et al., 2009) Aside that, the other study (Charbit et al., 2009) made use of a single dose of AL tablet rather than the regular 6 doses, of similar strength (480/80 mg), used in this study. The single dose may not be enough to achieve adequate concentration for a significant cardiac effect of the interaction. Considering the structural similarity of lumefantrine to halofantrine, (<https://www.sciencedirect.com/topics/neuroscience/lumefantrine>) an established cardiotoxic drug,

(Bouchaud et al., 2009) it was thought that increase in plasma concentration of lumefantrine may spawn cardiotoxicity but this has never been the case in previous studies. (Achan et al., 2012; Byakika-Kibwika et al., 2012; Kredo et al., 2015; Usman et al., 2020) Therefore, the significant increase in QTc-interval (Fig. 1) obtained in this study may not be associated with the expected increase in plasma concentration of lumefantrine as a result of inhibitory effects of atazanavir on CYP 3A4 isoenzyme (Moyle and Back, 2001) which metabolizes the antimalarial drug but rather due to additive toxicity cause by atazanavir and artemether both of which are known to prolong QTc-interval (Ly and Ruiz, 2007; Funck-Brentano et al., 2019).

This study has also shown that concomitant administration of AL with ATVr-based ART regimen is not associated with any clinically significant renal, liver nor blood toxicities as indicated by lack of significant change ($p > 0.05$) in the plasma levels of creatinine, ALT, AST and hemoglobin in both arms of study at post dose of AL and all the values obtained were within normal ranges (Table 2). The adverse events were also few and mild. However general weakness and chest pain which are symptoms of cardiotoxicity (https://www.nccn.org/patients/resources/lifewith_cancer/managing_symptoms/cardiac_toxicity.aspx) were experienced, at post-doses of AL, only in the ATVr-arm (Fig. 3) indicating possible cardiac effects. Hence caution must be exercised when administering AL or other drugs that prolong QTc-interval to patients on ATVr-based ART regimen.

Concomitant administration of artemether-lumefantrine with atazanavir-ritonavir-based antiretroviral therapy regimen is not associated with any clinically significant renal, blood nor liver toxicities. However, the combination is potentially cardiotoxic. Caution must be exercised when administering the drugs concurrently.

CRediT authorship contribution statement

Sikiru Olatunji Usman: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing. **Ibrahim Adekunle Oreagba:** Conceptualization, Supervision, Writing – review & editing. **AbdulWasiu Busari:** Conceptualization, Project administration, Writing – review & editing. **Ololade Oluwatosin Adewumi:** Conceptualization, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Michael Rotimi Kadri:** Conceptualization, Data curation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Akinwumi Akinyede:** Conceptualization, Project administration, Supervision, Writing – review & editing. **Yinka Adeyemi Fashina:** Conceptualization, Methodology, Writing – review & editing. **Olayinka Hassan:** Conceptualization, Methodology, Project administration, Validation, Writing – review & editing. **Esther Oluwatoyin Agbaje:** Conceptualization, Validation, Writing – review & editing. **Sulaimon Alani Akanmu:** Conceptualization, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- Achan, J., Kakuru, A., Ikilezi, G., Ruel, T., Clark, T.D., Nsanabana, C., Charlebois, E., Aweeka, F., Dorsey, G., Rosenthal, P.J., Havlir, D., Kanya, M.R., 2012. Antiretroviral Agents and Prevention of Malaria in HIV-Infected Ugandan Children. *N Engl. J. Med.* 367 (22), 2110–2118.
- Achenbach, C.J., Darin, K.M., Murphy, R.L., 2011. Atazanavir/ritonavir-based combination antiretroviral therapy for treatment of HIV-1 infection in adults. *Future Virol.* 6 (2), 157–177. <https://doi.org/10.2217/fvl.10.89>.
- Akanmu, A.S., Usman, S.O., Oreagba, I.A., 2015. Antiretrovirals and Co-prescribed drugs for people living with HIV/AIDS (PLWHA) in a University Teaching Hospital SouthWest Nigeria. *West African J. Pharm.* 26 (2), 103–115.
- Anafi, S.B., Muktar, H.M., Alawode, D.F., 2008. Commonly prescribed drugs in HIV/AIDS and patient's socio-demographic data: a case study of University of Ilorin teaching hospital (UITH), Ilorin Nigeria. *Nigerian J. Pharm. Sci.* 7 (1), 139–145.
- Bouchaud, O., Imbert, P., Touze, J.E., Dodoo, A.NO., Danis, M., Legros, F., 2009. Fatal cardiotoxicity related to halofantrine: a review based on a worldwide safety data base. *Malar J.* 8 (1). <https://doi.org/10.1186/1475-2875-8-289>.
- Bristol-Myers Squibb Company. BMS-232632: atazanavir briefing document May 2003. Available from http://www.fda.gov/ohrms/dockets/ac/03/briefing/3950B1_01_Bristol_MyersSquibb-atazanavir.pdf. Accessed June 21, 2021.
- Burk, O., Piedade, R., Ghebregiorghis, L., Fait, J.T., Nussler, A.K., Gil, J.P., Windshügel, B., Schwab, M., 2012. Differential effects of clinically used derivatives and metabolites of artemisinin in the activation of constitutive androstane receptor isoforms. *Br. J. Pharmacol.* 167 (3), 666–681.
- Byakika-Kibwika, P., Lamorde, M., Lwabi, P., Nyakoojo, W.B., Okaba-Kayom, V., Mayanja-Kizza, H., Boffito, M., Katabira, E., Back, D., Khoo, S., Merry, C., 2011. Cardiac Conduction Safety during Coadministration of Artemether-Lumefantrine and Lopinavir/Ritonavir in HIV-Infected Ugandan Adults. *Chemother. Res. Pract.* 2011, 1–4.
- Byakika-Kibwika, P., Lamorde, M., Okaba-Kayom, V., 2012. Lopinavir/ritonavir significantly influences pharmacokinetic exposure of artemether-lumefantrine in HIV-infected Ugandan adults. *Antimicrob. Agents Chemother.* 67 (5), 1217–1223. <https://doi.org/10.1093/jac/dkr596>.
- Charbit, B., Rosier, A., Bollens, D., Boccara, F., Boelle, P.-Y., Koubaa, A., Girard, P.-M., Funck-Brentano, C., 2009. Relationship between HIV protease inhibitors and QTc-interval duration in HIV-infected patients: a cross-sectional study. *Br. J. Clin. Pharmacol.* 67 (1), 76–82.
- Drugs.com. Artemether-lumefantrine Side Effects. <https://www.drugs.com/sfx/artemether-lumefantrine-side-effects.html>. Accessed August 2021
- Drugs.com. Ritonavir side effects. <https://www.drugs.com/sfx/ritonavir-side-effects.html>. Accessed August, 2021
- Ericsson, T., Sundell, J., Torkelson, A., 2014. Effects of artemisinin antimalarials on Cytochrome P450 enzymes in vitro using recombinant enzymes and human liver microsomes: potential implications for combination therapies. *Xenobiotica* 44 (7), 615–626. <https://doi.org/10.3109/00498254.2013.878815>
- Ezzet, F., van Vugt, M., Nosten, F., Looareesuwan, S., White, N.J., 2000. Pharmacokinetics and pharmacodynamics of lumefantrine (benflumetol) in acute falciparum malaria. *Antimicrob. Agents Chemother.* 44 (3), 697–704. <https://doi.org/10.1128/AAC.44.3.697-704.2000>.
- Funck-Brentano, C., Ouologuem, N., Duparc, S., Felices, M., Sirima, S.B., Sagara, I., Soulama, I., Ouedraogo, J.-B., Beavogui, A.H., Borghini-Fuhrer, I., Khan, Y., Djimé, A.A., Voiriot, P., 2019. Evaluation of the effects on the QT-interval of 4 artemisinin-based combination therapies with a correction-free and heart rate-free method. *Sci. Rep.* 9 (1). <https://doi.org/10.1038/s41598-018-37113-5>.
- Kim, H.-Y., 2013. Statistical notes for clinical researchers: assessing normal distribution (2) using skewness and kurtosis. *Restor. Dent. Endod.* 38 (1), 52. <https://doi.org/10.5395/rde.2013.38.1.52>.
- Jemsek, J.G., Arathoon, E., Arlotti, M., Perez, C., Sosa, N., Pokrovskiy, V., Thiry, A., Soccodato, M., Noor, M.A., Giordano, M., 2006. *Body Fat and Other Metabolic*

- Effects of Atazanavir and Efavirenz, Each Administered in Combination with Zidovudine plus Lamivudine, in Antiretroviral- Naive HIV-Infected Patients. *Clin. Infect. Dis.* 42 (2), 273–280.
- Kozal, M., 2004. Review: Cross-Resistance Patterns Among HIV Protease Inhibitors. *AIDS Patient Care and STDs* 18 (4), 199–208.
- Kredo, T., Mauff, K., Workman, L., 2015. The interaction between artemether-lumefantrine and lopinavir/ritonavir-based antiretroviral regimen. *Br. J. Clin. Pharmacol.* 79 (4), 636–649. <https://doi.org/10.1186/s12879-016-1345-1>.
- Kumar, G.N., Rodrigues, A.D., Buko, A.M., 1996. Cytochrome P450-mediated metabolism of the HIV-1 protease inhibitor ritonavir (ABT-538) in human liver microsomes. *J. Pharmacol. Exp. Ther.* 277 (1), 423–431.
- Kwenti, T.E., 2018. Malaria and HIV co-infection in sub-Saharan Africa: Prevalence, Impact and Treatment Strategies. *Res. Rep. Trop. Med.* 9, 123–136. <https://doi.org/10.2147/RRTM.S154501>
- Lefèvre, G., Thomsen, M.S., 1999. Clinical Pharmacokinetics of Artemether and Lumefantrine (Riamet®). *Clin. Drug Investig.* 18, 467–480.
- Lopes, R.H.C., 2011. Kolmogorov-Smirnov Test. In: Lovric M, ed. *International Encyclopedia of Statistical Science*. Berlin Heidelberg: Springer, 2011. https://doi.org/10.1007/978-3-642-04898-2_326.
- Lu, C.-L., Lin, Y.-H., Wong, W.-W., Lin, H.-H., Ho, M.-W., Wang, N.-C., Hsieh, S.-M., Sheng, W.-H., Hung, C.-C., Chen, M.-Y., 2011. Outcomes of switch to atazanavir-containing combination antiretroviral therapy in HIV-1-infected patients with hyperlipidemia. *J. Microbiol. Immunol. Infect.* 44 (4), 258–264.
- Ly, T., Ruiz, M.E., 2007. Prolonged QT Interval and Torsades de Pointes Associated with Atazanavir Therapy. *Clin. Infect. Dis.* 44 (6), e67–e68.
- Markowitz, M., Saag, M., Powderly, W.G., Hurley, A.M., Hsu, A., Valdes, J.M., Henry, D., Sattler, F., Marca, A.L., Leonard, J.M., Ho, D.D., 1995. A Preliminary Study of Ritonavir, an Inhibitor of HIV-1 Protease, to Treat HIV-1 Infection. *N Engl. J. Med.* 333 (23), 1534–1540.
- Moyle, G.J., Back, D., 2001. Principles and Practice of HIV protease inhibitor pharmaco-enhancement. *HIV MED.* 2, 105–113. <https://doi.org/10.1046/j.1468-1293.2001.00063.x>
- Murphy, R.I., Berzins, B., Zala, C., 2010. Change to atazanavir/ritonavir treatment improves lipids but not endothelial function in patients on stable antiretroviral therapy. *AIDS* 24 (6), 885–890. <https://doi.org/10.1097/QAD.0b013e3283352ed5>.
- Noor, M.A., Flint, O.P., Maa, J.F., 2006. Effects of atazanavir/ritonavir and lopinavir/ritonavir on glucose uptake and insulin sensitivity: demonstrable differences in vitro and clinically. *AIDS* 20 (14), 1813–1821. <https://doi.org/10.1097/01.aids.0000244200.11006.55>.
- Oreagba, I.A., Usman, S.O., Oshikoya, K.A., Akinyede, A.A., Agbaje, E.O., Opanuga, O., Akanmu, S.A., 2019. Clinically significant drug-drug interaction in a large antiretroviral treatment Centre in Lagos, Nigeria. *J. Popul. Ther. Clin. Pharmacol.* 26 (1), e1–e19.
- Panagopoulos, P., Maltezos, E., Hatzakis, A., 2017. Hyperbilirubinemia in atazanavir treated HIV-infected patients: the impact of the UGT1A1*28 allele. *Pharmacogenomics Pers. Med.* 10, 205–208. <https://doi.org/10.2147/PGPM.S107152>.
- Perloff, E.S., Duan, S.X., Skolnik, P.R., Greenblatt, D.J., von Moltke, L.L., 2005. Atazanavir: Effects on p-glycoprotein transport and CYP3A metabolism in-vitro. *Drug Metab and Dispos.* 33 (6), 764–770.
- Roling, J., Schmid, H., Fischereder, M., Draenert, R., Goebel, F.D., 2006. HIV-Associated Renal Diseases and Highly Active Antiretroviral Therapy-Induced Nephropathy. *Clin. Infect. Dis.* 42 (10), 1488–1495.
- Shapiro, S.S., Wilk, M.B., 1965. An analysis of variance test for normality (complete samples). *Biometrika* 52 (3–4), 591–611. <https://doi.org/10.1124/dmd.104.002931>.
- Usman, S.O., Oreagba, I.A., Akinyede, A.A., Agbaje, E.O., Akinleye, M.O., Onwujuobi, A.G., Ken-Owotor, C., Adeuja, O., Ogunfowokan, T., Kogbe, S., Owolabi, E.T., Adeniji, H., Busari, A.W., Hassan, O.O., Abideen, G., Akanmu, A.S., 2020. Effect of nevirapine, efavirenz and lopinavir/ritonavir on the therapeutic concentration and toxicity of lumefantrine in people living with HIV at Lagos University Teaching Hospital. *Nigeria. J. Pharmacol. Sci.* 144 (3), 95–101.
- Usman, S.O., Oreagba, I.A., Kadri, M.R., Adewumi, O.O., Akinyede, A., Agbaje, E.O., Abideen, G., Busari, A.A., Hassan, O.O., Akinleye, M.O., Akanmu, A.S., 2021. Evaluation of the effects of atazanavir-ritonavir on the pharmacokinetics of lumefantrine in patients living with HIV in Lagos University Teaching Hospital. *Eur. J. Clin. Pharmacol.* 77 (9), 1341–1348. <https://doi.org/10.1007/s00228-021-03116-x>.
- Ezzet, F., Looareesuwan, S., Gathmann, I., van Vugt, M., Wilairatana, P., Nosten, F., White, N.J., 1999. No evidence of cardiotoxicity during antimalarial treatment with Artemether-lumefantrine. *Am. J. Trop. Med. Hyg.* 61 (6), 964–967.
- Walubo, A., 2007. The Role of Cytochrome P450 in Antiretroviral Drug Interactions. *Expert Opin. Drug Metab. Toxicol.* 3 (4), 583–598. <https://doi.org/10.1517/17425225.3.4.583>.
- Whitworth, J., Quigley, M.L., 2000. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical episodes in adults in rural Uganda. *Lancet Infect Dis.* 356, 1051–1056. [https://doi.org/10.1016/S0140-6736\(00\)02727-6](https://doi.org/10.1016/S0140-6736(00)02727-6)