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# Significant pharmacokinetic interactions between artemether/lumefantrine and efavirenz or nevirapine in HIV-infected Ugandan adults

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**Objectives:** Co-administration of artemether/lumefantrine with antiretroviral therapy has potential for pharmacokinetic drug interactions. We investigated drug–drug interactions between artemether/lumefantrine and efavirenz or nevirapine.

**Methods:** We performed a cross-over study in which HIV-infected adults received standard six-dose artemether/lumefantrine 80/480 mg before and at efavirenz or nevirapine steady state. Artemether, dihydroartemisinin, lumefantrine, efavirenz and nevirapine plasma concentrations were measured and compared.

**Results:** Efavirenz significantly reduced artemether maximum concentration ($C_{max}$) and plasma AUC (median 29 versus 12 ng/mL, $P<0.01$, and 119 versus 25 ng·h/mL, $P<0.01$), dihydroartemisinin $C_{max}$ and AUC (median 120 versus 26 ng/mL, $P<0.01$, and 341 versus 84 ng·h/mL, $P<0.01$), and lumefantrine $C_{max}$ and AUC (median 8737 versus 6331 ng/mL, $P=0.03$, and 280370 versus 124381 ng·h/mL, $P<0.01$). Nevirapine significantly reduced artemether $C_{max}$ and AUC (median 28 versus 11 ng/mL, $P<0.01$, and 123 versus 34 ng·h/mL, $P<0.01$) and dihydroartemisinin $C_{max}$ and AUC (median 107 versus 59 ng/mL, $P<0.01$, and 364 versus 228 ng·h/mL, $P<0.01$). Lumefantrine $C_{max}$ and AUC were non-significantly reduced by nevirapine. Artemether/lumefantrine reduced nevirapine $C_{max}$ and AUC (median 8620 versus 4958 ng/mL, $P<0.01$, and 66329 versus 35728 ng·h/mL, $P<0.01$), but did not affect efavirenz exposure.

**Conclusions:** Co-administration of artemether/lumefantrine with efavirenz or nevirapine resulted in a reduction in artemether, dihydroartemisinin, lumefantrine and nevirapine exposure. These drug interactions may increase the risk of malaria treatment failure and development of resistance to artemether/lumefantrine and nevirapine. Clinical data from population pharmacokinetic and pharmacodynamic trials evaluating the impact of these drug interactions are urgently needed.

**Keywords:** antimalarial, antiretroviral, malaria, drugs

## Introduction

Malaria and HIV are two infectious diseases causing significant morbidity and mortality. Together they account for >4 million deaths annually worldwide.[1] These two diseases have considerable geographical overlap in sub-Saharan Africa, with significant interactions. HIV increases the risk of malaria infection, severe malaria and death.[2,3] Malaria infection stimulates HIV

replication, causing transient elevation in viral load.[4] Dual infection with HIV and malaria fuels the spread of both diseases in sub-Saharan Africa.[5] Antiretroviral therapy (ART) and co-trimoxazole prophylaxis greatly reduce the risk of malaria in HIV-infected individuals.[6,7] However, once infected with malaria, HIV-infected individuals receive artemisinin-based combination therapy (ACT), often in combination with ART.

Artemether/lumefantrine is the first-line ACT for treatment of uncomplicated malaria in Uganda. A six-dose regimen has excellent efficacy against sensitive and multidrug-resistant falciparum malaria.[8] Following oral administration, artemether is rapidly absorbed, reaching peak plasma concentrations within 2 h post-dose. It is metabolized rapidly via cytochrome P450 (CYP) 2B6, CYP3A4 and possibly CYP2A6 to dihydroartemisinin (DHA), which in turn is converted into inactive metabolites primarily by glucuronidation via uridine diphosphoglucuronyltransferase (UGT) 1A1, 1A8/9 and 2B7. The metabolite DHA reaches peak plasma concentration within 2–3 h post-dosing. Both artemether and DHA have potent antimalarial properties, causing significant reduction in asexual parasite mass of ∼10000-fold per reproductive cycle, with prompt resolution of symptoms.[9,10] Lumefantrine is metabolized by *N*-debutylation, mainly by CYP3A4, to desbutyl-lumefantrine with 5- to 8-fold higher antiparasitic effect than lumefantrine. The key pharmacokinetic determinant of malaria cure following treatment with artemether/lumefantrine is the AUC of lumefantrine.[11] In multidrug-resistant areas, day 7 lumefantrine concentration is a surrogate marker for AUC and a threshold venous plasma concentration of 280 ng/mL has been suggested to predict treatment failure.[11] In a more recent study, patients who had lumefantrine levels <175 ng/mL on day 7 were more likely to experience recrudescence by day 42 following administration of the six-dose regimen.[12]

First-line ART in Uganda and many parts of sub-Saharan Africa comprises efavirenz or nevirapine in combination with two nucleoside reverse transcriptase inhibitors. Efavirenz and nevirapine are substrates and potent inducers of CYP3A4 and 2B6, and co-administration with artemether/lumefantrine therefore creates potential for drug interactions.[13–16]

The potential for pharmacokinetic drug interactions between ART and ACT was demonstrated previously.[17–19] Co-administration of artemether/lumefantrine with nevirapine decreased artemether and dihydroartemisinin exposure with an unexpected increase in lumefantrine exposure in HIV-infected volunteers in South Africa.[20] We hypothesized that co-administration of artemether/lumefantrine with efavirenz or nevirapine reduces artemether and lumefantrine exposure and investigated these interactions in HIV-1-positive patients in Uganda.

## Methods

### Study site

The study was conducted between January 2009 and December 2010 at the Infectious Diseases Institute (IDI) and Mulago Hospital, Kampala, Uganda. The IDI is a regional centre of excellence for HIV/AIDS treatment, prevention, training and research. To date, >20000 HIV-infected patients are registered at the IDI, with >8000 patients taking ART.

### Study design and population

This was a one-sequence cross-over study with efavirenz and nevirapine arms. Participants were screened and enrolled consecutively. They were admitted to the private ward of Mulago Hospital for pharmacokinetic blood sampling. Participants were HIV-1-seropositive ART-naive adults with CD4 count of ≤200 cells/mm$^3$, eligible to start ART according to Uganda's national guidelines. All participants had no evidence of systemic illness and no indication for medications, such as rifampicin, which have known potential for drug interactions with study drugs. We performed screening tests, which included an electrocardiogram, liver and renal function tests, blood smears for malaria parasites and a pregnancy test. All patients with abnormal cardiac, liver or renal function or a positive malaria blood smear, pregnant mothers and those using herbal medication were excluded. All participants took co-trimoxazole daily for prophylaxis.

The study was approved by the Uganda National HIV/AIDS Research Committee (ARC 059) and the Uganda National Council of Science and Technology (HS 196) and was registered with ClinicalTrials.gov (NCT00620438). Study procedures were explained to participants in the local languages. All participants provided written informed consent prior to enrolment. Study procedures were conducted in accordance with Good Clinical Practice standards.

### Study procedures

Participants were instructed to not take any medication other than those prescribed by a study physician. They were encouraged to come to the clinic on appointment days and any day they felt unwell. Adherence to study drugs was assessed using self-report and pill count at each visit. Information on adverse drug events was collected throughout the study period using questionnaires completed by the study team. The study was performed in three phases as described below (Figure 1).

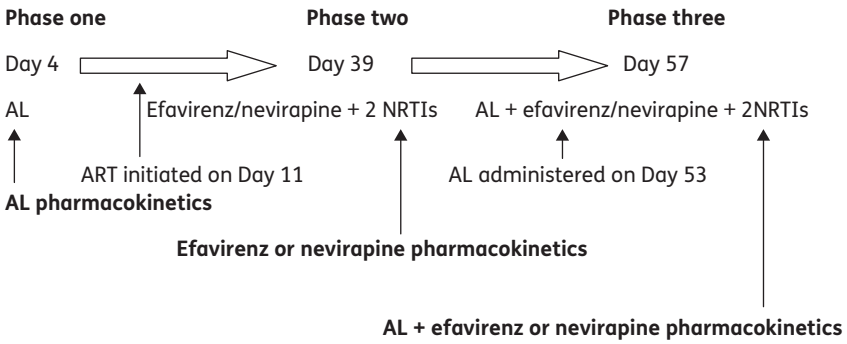


**Figure 1.** Study scheme. AL, artemether/lumefantrine; NRTIs, nucleoside reverse transcriptase inhibitors.

### Phase 1

All participants ($n=60$) received six doses of artemether/lumefantrine, (Coartem®, Novartis Pharma AG, Basel, Switzerland). They received four fixed-dose combination tablets at each dosing time, each tablet containing 20 mg of artemether and 120 mg of lumefantrine. They were given the first five doses of artemether/lumefantrine to administer at home, with instructions to take the second dose 8 h after the first and the rest at intervals of 12 h. The sixth dose was retained to be taken on the morning of sampling. They were encouraged to take each dose with milk and were reminded daily by telephone. On the evening prior to sampling, participants were reminded of their study day appointment, given instructions to eat food, administer medication by 8.00 pm and arrive at the hospital by 7.00 am the following morning in a fasting state.

On the morning of the sampling visit, adherence was assessed and an indwelling cannula was inserted in the forearm. A pre-dose blood sample was drawn for artemether/lumefantrine concentration measurement. Participants received a standardized breakfast with sufficient fat to enhance artemether/lumefantrine absorption.[21] All participants took the sixth artemether/lumefantrine dose immediately after breakfast under direct observation by study staff.

Sampling was performed at 1, 2, 4, 8, 12, 24, 48, 72, 96 and 120 h post-dosing. Lumefantrine's terminal elimination half-life is 4.5 days and its concentration persists in plasma for >20 days;[11] therefore, our sampling schedule permitted estimation of lumefantrine $AUC_{0-last}$, but not clearance and half-life. Four millilitres of blood was collected per sampling time in lithium–heparin bottles. Samples were centrifuged within 30 min at 3000 rpm for 10 min and plasma was stored at −80°C until shipment. Average duration of storage before shipment was 10 months. Samples were shipped in one batch on dry ice to the clinical pharmacology laboratory at the Mahidol-Oxford Tropical Medicine Research Unit, Bangkok, for artemether, dihydroartemisinin and lumefantrine assays.

Participants were asked to return after 1 week for initiation of efavirenz- or nevirapine-containing ART. Nevirapine was administered using the dose escalation schedule of 200 mg daily for 2 weeks followed by 200 mg twice daily and efavirenz at 600 mg daily in combination with zidovudine plus lamivudine twice daily or tenofovir disoproxil fumarate plus emtricitabine once daily for 4 weeks. All participants continued on ART after study completion.

### Phase 2

When participants had attained efavirenz or nevirapine steady state (4 weeks), they were asked to return for sampling for efavirenz or nevirapine concentration measurement. The study procedures in Phase 2 were identical to those in Phase 1 except that participants did not take artemether/lumefantrine. Intensive sampling every 2 h was performed for 12 h for nevirapine and efavirenz and a 24 h sample was drawn for efavirenz. Participants received ART adherence counselling and were told to continue taking their ART as prescribed. They were given appointments to return after 2 weeks for study Phase 3.

### Phase 3

The procedures in Phase 3 were identical to those in Phase 1 except that patients were at efavirenz or nevirapine steady state. All participants received six-dose artemether/lumefantrine and efavirenz- or nevirapine-containing ART. Efavirenz and nevirapine were administered 1 h after artemether/lumefantrine. Intensive sampling as in Phases 1 and 2 was performed after the sixth dose of artemether/lumefantrine. Artemether, dihydroartemisinin, lumefantrine and efavirenz or nevirapine concentrations were measured at the respective sampling schedules described in Phases 1 and 2.

### Artemether, dihydroartemisinin and lumefantrine concentration measurement

Artemether and dihydroartemisinin concentrations were measured using solid-phase extraction and liquid chromatography coupled to tandem mass spectrometry.[22] Total-assay coefficients of variation (CVs) for dihydroartemisinin and artemether during analysis were <5% at all quality-control levels. The lower limit of quantification (LLOQ) for both drugs was set to 1.4 ng/mL.[22]

Lumefantrine concentrations were determined using a solid-phase extraction liquid chromatographic assay with ultraviolet (UV) detection.[23] The CV was <6% at all quality-control levels. The LLOQ was set to 25 ng/mL.[23]

### Nevirapine plasma concentration measurement

Nevirapine concentrations were measured using reverse-phase liquid chromatography with UV detection using a validated method developed at the University of Liverpool.[24] The LLOQ was set to 450 ng/mL. Inter-assay and intra-assay CVs were 8.2% and 6.1%, respectively.

### Efavirenz plasma concentration measurement

Efavirenz concentration was measured by reverse-phase liquid chromatography with UV detection using a validated routine method developed at the Department of Clinical Pharmacology, Karolinska Institute. The method was linear, with a within-day CV of 3.2%, 3.3% and 5.1% at concentrations of 632 ($n=10$), 2528 ($n=10$) and 6320 ng/mL ($n=12$), respectively, and a between-day CV of 4.1% ($n=10$). The LLOQ was set to 110 ng/mL.

### Analytical and pharmacokinetic methods

Non-compartmental analysis was performed using WinNonlin software, version 5.2 (Pharsight Corp., Mountain View, CA, USA). Calculated parameters included maximum observed concentration ($C_{max}$), time to $C_{max}$ ($T_{max}$), minimum concentration prior to next dose ($C_{trough}$), plasma AUC from 0 to last observation or extrapolated to infinity ($AUC_{0-last}$ or $AUC_{0-\infty}$), elimination clearance (CL/F), apparent volume of distribution ($V$/F) and elimination half-life ($t_{1/2}$). The trapezoidal rule (linear up/log down) was used to estimate AUC. All parameters were calculated using actual blood sampling times. Drug concentrations below the LLOQ of the bioanalytical assays were treated as missing data.

Twenty-seven participants provided 80% power to reject the null hypothesis that lumefantrine AUC estimated during administration of artemether/lumefantrine without efavirenz or nevirapine is equivalent to lumefantrine AUC during administration of artemether/lumefantrine with efavirenz or nevirapine. We anticipated a 10% dropout rate and enrolled 30 participants in each arm.

### Statistical analysis

Data were analysed using STATA® version 10.0 (StataCorp, College Station, TX, USA). Baseline characteristics were summarized as medians with IQR and pharmacokinetic parameters as medians with range. Pharmacokinetic parameters were compared using the Wilcoxon matched-pairs signed-rank test. A $P$ value <0.05 was considered statistically significant. Comparisons between treatments were made using individual ratios of pharmacokinetic parameters (i.e. artemether/lumefantrine parameters obtained during co-administration of artemether/lumefantrine with efavirenz or nevirapine compared with parameters obtained during artemether/lumefantrine administration alone). Similarly for efavirenz and nevirapine, individual ratios were calculated (i.e. efavirenz

and nevirapine parameters obtained during co-administration with artemether/lumefantrine compared with parameters obtained during efavirenz or nevirapine administration alone). Individual ratios were calculated for each pharmacokinetic parameter and summarized as medians with range.

## Results

Sixty participants were enrolled; one was discontinued due to non-compliance with study procedures and one developed severe immune reconstitution inflammatory syndrome with tuberculosis following ART initiation and died. Pharmacokinetic data were available for 58 participants: 30 in the efavirenz arm and 28 in the nevirapine arm. Baseline characteristics are shown in Table 1.

All study participants reported 100% adherence to study medication prior to the sampling visit. On the sampling visit, study medication was administered under direct observation by study staff. After administration of fixed-dose combination tablets of artemether/lumefantrine, lumefantrine concentrations were measured and pharmacokinetic parameters calculated for all 58 participants in all three phases; however, 16 participants had artemether and dihydroartemisinin below the LLOQ and were excluded from pharmacokinetic analysis [one participant in Phase 1 and 15 participants in Phase 3 (8 in the efavirenz arm and 7 in the nevirapine arm)].

**Table 1.** Baseline characteristics of study participants

| Parameter | Efavirenz arm ($n=30$) | Nevirapine arm ($n=28$) |
|---|---|---|
| Females, *n* (%) | 19 (63) | 27 (96) |
| Age (years), median (IQR) | 38 (33–43) | 33 (28–36) |
| Weight (kg), median (IQR) | 62 (55–68) | 54 (48–62) |
| Height (cm), median (IQR) | 160 (154–168) | 156 (151–159) |
| BMI (kg/m$^2$), median (IQR) | 23 (20–25) | 21 (19–26) |

BMI, body mass index.

### *Artemether, dihydroartemisinin and lumefantrine pharmacokinetics*

#### *Efavirenz arm*

Co-administration of artemether/lumefantrine with efavirenz significantly reduced pharmacokinetic exposure to artemether ($P<0.01$), dihydroartemisinin ($P<0.01$) and lumefantrine ($P<0.01$) (Table 2 and Figure 2). Artemether CL/F and *V*/F increased with a consequent 59% reduction in $C_{max}$ and 79% reduction in $AUC_{0-last}$. Dihydroartemisinin CL/F and *V*/F increased while $C_{max}$ and $AUC_{0-last}$ were reduced by 78% and 75%, respectively. Lumefantrine $C_{max}$ and $AUC_{0-last}$ were reduced by 28% and 56%, respectively (Table 2).

Day 7 lumefantrine concentrations were lower during co-administration with efavirenz; mean (SD) was 4858 (2398) compared with 7152 (3628) ng/mL without efavirenz ($P<0.01$). However, none of the participants had a day 7 lumefantrine concentration <280 or 175 ng/mL with and without efavirenz.

#### *Nevirapine arm*

Co-administration of artemether/lumefantrine with nevirapine significantly reduced pharmacokinetic exposure of artemether

**Table 2.** Comparison of pharmacokinetic parameters of artemether, dihydroartemisinin and lumefantrine with and without efavirenz

| Parameter | Median (range) | | *P* value | Median (range) of individual ratio |
|---|---|---|---|---|
| | AL | AL plus efavirenz | | |
| Artemether | ($n=22$) | ($n=22$) | | |
| $C_{max}$ (ng/mL) | 29 (10–247) | 12 (2–88) | <0.01 | 0.2 (0.03–2.6) |
| CL/F (L/h) | 591 (80–2273) | 2558 (414–9960) | <0.01 | 3.1 (0.4–35.0) |
| *V*/F (L) | 4523 (374–10402) | 4715 (1078–28925) | 0.02 | 1.6 (0.2–20.0) |
| $t_{1/2}$ (h) | 4 (1–24) | 1 (0.6–4) | <0.01 | 0.5 (0.07–3.1) |
| $AUC_{0-last}$ (ng·h/mL) | 119 (26–917) | 25 (5–185) | <0.01 | 0.1 (0.03–2.3) |
| $AUC_{0-\infty}$ (ng·h/mL) | 135 (35–997) | 31 (8–192) | <0.01 | 0.3 (0.03–2.1) |
| Dihydroartemisinin | ($n=22$) | ($n=22$) | | |
| $C_{max}$ (ng/mL) | 120 (39–230) | 26 (4–114) | <0.01 | 0.2 (0.05–0.9) |
| CL/F (L/h) | 216 (82–382) | 844 (234–5704) | <0.01 | 3.6 (1.2–19.2) |
| *V*/F (L) | 754 (212–1494) | 2082 (608–14013) | <0.01 | 2.6 (1.2–18.6) |
| $t_{1/2}$ (h) | 2 (1–5) | 1 (0.8–3) | <0.01 | 0.6 (0.3–1.1) |
| $AUC_{0-last}$ (ng·h/mL) | 341 (187–908) | 84 (8–321) | <0.01 | 0.2 (0.03–0.8) |
| $AUC_{0-\infty}$ (ng·h/mL) | 352 (199–921) | 90 (13–325) | <0.01 | 0.2 (0.05–0.8) |
| Lumefantrine | ($n=30$) | ($n=30$) | | |
| $C_{max}$ (ng/mL) | 8737 (4073–20470) | 6331 (2996–16576) | 0.03 | 0.7 (0.2–1.7) |
| $AUC_{0-last}$ (ng·h/mL) | 280370 (105127–774338) | 124381 (26992–309305) | <0.01 | 0.4 (0.07–1.3) |

AL, artemether/lumefantrine; $AUC_{0-last}$, plasma AUC from time 0 to the last observation; $AUC_{0-\infty}$, plasma AUC from 0 extrapolated to infinity.

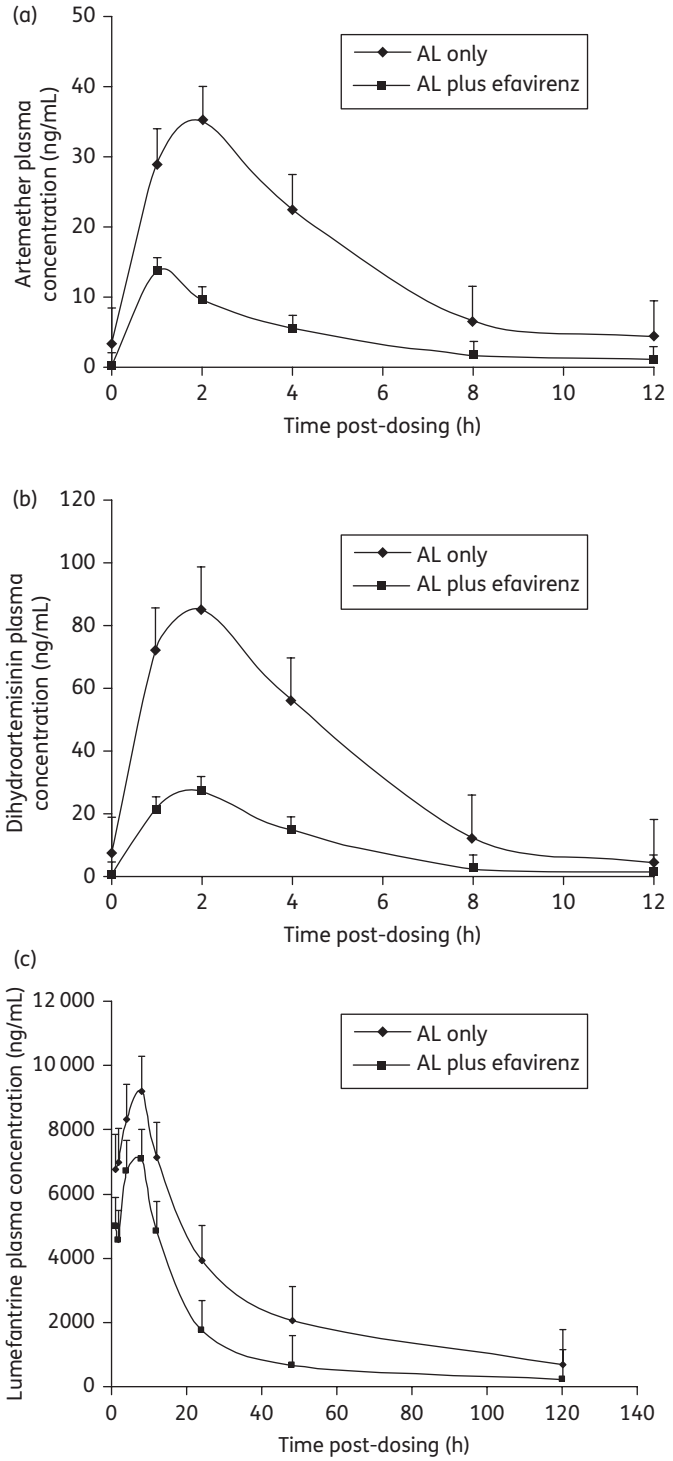


**Figure 2.** Mean plasma concentration versus time of (a) artemether, (b) dihydroartemisinin and (c) lumefantrine with and without efavirenz. AL, artemether/lumefantrine. Vertical bars represent standard errors.

($P<0.01$) and dihydroartemisinin ($P<0.01$) (Table 3 and Figure 3). Artemether CL/F and *V*/F increased while $C_{max}$ and $AUC_{0-last}$ decreased by 61% and 72%, respectively. Dihydroartemisinin CL/F and *V*/F increased while $C_{max}$ and $AUC_{0-last}$ decreased by 45% and 37%, respectively.

Lumefantrine exposure was non-significantly reduced by nevirapine ($P=0.4$) (Table 3). There was no difference in day 7 lumefantrine concentration with or without nevirapine, for which the mean (SD) was 6820 (4595) compared with 7547 (3438) ng/mL ($P=0.2$). None of the participants had day 7 lumefantrine concentration less than the threshold of 280 ng/mL or 175 ng/mL with or without nevirapine.

### *Efavirenz and nevirapine pharmacokinetics*

Co-administration with artemether/lumefantrine did not affect efavirenz exposure ($P=0.7$), but significantly reduced nevirapine $C_{max}$ and $AUC_{0-last}$ by 42% ($P<0.01$) and 46% ($P<0.01$), respectively (Table 4).

Median (IQR) efavirenz $C_{trough}$ was not affected by co-administration with artemether/lumefantrine [4.2 (1.3–4.2) versus 3.8 (2.1–4.6) μg/mL, $P=0.7$]. Median (IQR) nevirapine $C_{trough}$ was reduced during co-administration with artemether/lumefantrine [6406 (3364–8455) versus 4382 (2807–6188) ng/mL, $P=0.026$]. Two of 28 participants (7%) compared with 7 of 28 (25%) had nevirapine $C_{trough}$ below the minimum effective concentration of 3000 ng/mL during co-administration of nevirapine without and with artemether/lumefantrine, respectively.

## Discussion

We investigated interactions between artemether/lumefantrine and efavirenz or nevirapine in HIV-infected Ugandan adults. Co-administration of artemether/lumefantrine with efavirenz or nevirapine significantly reduced artemether and dihydroartemisinin exposure while lumefantrine exposure was significantly reduced by efavirenz and non-significantly reduced by nevirapine.

Our data show a similar trend, but with a different magnitude, to data from a study by Huang *et al.*[25] We found significant reductions in artemether, dihydroartemisinin and lumefantrine exposures with no effect on efavirenz exposure when artemether/lumefantrine was co-administered with efavirenz. Huang *et al.*[25] demonstrated a significant decrease in dihydroartemisinin exposure and a trend towards decreased artemether and lumefantrine exposure with no significant effect on efavirenz exposure. The differences in magnitude of data between the two studies are possibly due to differences in the study population and sample size. We studied 30 HIV-infected adults while Huang *et al.*[25] evaluated 6 healthy adults.

In contrast, our data on co-administration of artemether/lumefantrine with nevirapine show some differences from previously published data.[20] We demonstrated significant decreases in artemether and dihydroartemisinin, a similar trend to what was shown by Kredo *et al.*;[20] however, the effect on lumefantrine was different in the two studies, with a non-significant decrease shown by our study compared with an increase demonstrated by Kredo *et al.*[20] Reasons for the differences are unclear, but may arise from inter-individual variability due to differing genetics, disease status and study design.[26] Inter-individual variability occurs more commonly with the parallel study design utilized in the study published by Kredo *et al.*[20] We minimized inter-individual variability using a cross-over design and restrictive eligibility criteria. Our study participants were all HIV-infected with

**Table 3.** Comparison of pharmacokinetic parameters of artemether, dihydroartemisinin and lumefantrine with and without nevirapine

| Parameter | Median (range) | | *P* value | Median (range) of individual ratio |
|---|---|---|---|---|
| | AL | AL plus nevirapine | | |
| Artemether | (*n*=21) | (*n*=21) | | |
| $C_{max}$ (ng/mL) | 28 (3–254) | 11 (3–232) | <0.01 | 0.3 (0.04–2.7) |
| CL/F (L/h) | 601 (102–7271) | 1983 (119–9267) | <0.01 | 3.5 (0.6–20) |
| *V*/F (L) | 4095 (866–18886) | 7748 (429–37946) | <0.01 | 2.0 (0.2–9.6) |
| $t_{1/2}$ (h) | 4 (1–21) | 2 (0.3–13) | 0.04 | 0.5 (0.1–2.0) |
| $AUC_{0-last}$ (ng·h/mL) | 123 (7–756) | 34 (6–653) | <0.01 | 0.2 (0.04–1.5) |
| $AUC_{0-\infty}$ (ng·h/mL) | 133 (11–781) | 40 (8–670) | <0.01 | 0.2 (0.05–1.5) |
| Dihydroartemisinin | (*n*=21) | (*n*=21) | | |
| $C_{max}$ (ng/mL) | 107 (55–217) | 59 (16–222) | <0.01 | 0.5 (0.2–1.5) |
| CL/F (L/h) | 201 (96–341) | 327 (111–1206) | <0.01 | 1.6 (0.6–3.9) |
| *V*/F (L) | 750 (220–1767) | 930 (284–2640) | 0.02 | 1.2 (0.3–3.2) |
| $t_{1/2}$ (h) | 2 (1–6) | 1 (1–3) | <0.01 | 0.7 (0.3–1.4) |
| $AUC_{0-last}$ (ng·h/mL) | 364 (216–780) | 228 (59–674) | <0.01 | 0.5 (0.2–1.5) |
| $AUC_{0-\infty}$ (ng·h/mL) | 379 (224–794) | 233.34 (63–683) | <0.01 | 0.6 (0.2–1.5) |
| Lumefantrine | (*n*=28) | (*n*=28) | | |
| $C_{max}$ (ng/mL) | 10000 (2935–18489) | 7591 (3084–30572) | 0.6 | 1.0 (0.4–1.9) |
| $AUC_{0-last}$ (ng·h/mL) | 291671 (79510–699798) | 229605 (77969–760297) | 0.4 | 0.8 (0.3–2.1) |

AL, artemether/lumefantrine; $AUC_{0-last}$, plasma AUC from time 0 to the last observation; $AUC_{0-\infty}$, plasma AUC from 0 extrapolated to infinity.

CD4 counts <200 cells/mm$^3$. Kredo *et al*.[20] conducted a parallel study design with HIV-infected ART-naive participants and those stable on ART, with CD4 counts >200 cells/mm$^3$. These differing data suggest the need for further evaluation of these interactions and their clinical implications.

Artemether metabolism is catalysed by CYP3A4, CYP2B6, 2C9 and 2C19[27] to dihydroartemisinin. Dihydroartemisinin is converted into inactive metabolites via UGT, mainly UGT1A9 and 2B7.[11,28,29] Artemether exhibits autoinduction of CYP3A4 with subsequent reduction in exposure with repeated dosing.[9,30] Lumefantrine is metabolized mainly by CYP3A4 to desbutyllumefantrine; however, systemic exposure to desbutyllumefantrine is <1% of exposure to lumefantrine.[27]

Without the interacting drug, the artemether exposure observed in our study was lower than that observed in previous studies conducted among Pakistani,[31] Thai,[32] Malaysian[33] and Chinese[30] populations with and without malaria, but dihydroartemisinin exposure was comparable. Artemether shows a large variability within and between different populations; however, it is possible that the difference in exposure is due to differences in ethnicity and disease state. Our study participants were all HIV infected and of African origin, unlike the participants in the previous studies, who were mostly healthy volunteers. Assessment of the effect of HIV upon drug pharmacokinetics is important.

Co-administration of artemether/lumefantrine with efavirenz or nevirapine reduced plasma concentrations of artemether, dihydroartemisinin and lumefantrine, with more marked reductions for artemether and dihydroartemisinin and undetectable levels in some participants. The reduced exposure appears to be mediated through a pharmacokinetic interaction between artemether/lumefantrine and efavirenz or nevirapine, with efavirenz demonstrating stronger interaction potential. Our study was not designed to investigate the mechanisms of interaction. Previous studies have demonstrated induction of metabolism through mechanisms involving both decreased enzyme degradation and enhanced protein synthesis by increasing transcriptional activation of messenger RNA. The human nuclear pregnane X receptor (hPXR) and the constitutive androstane receptor (hCAR) regulate expression of CYP3A4 and 2B6 genes. Trans-activation of these receptors leads to up-regulation of CYP3A4 and 2B6 activity.[34–36] Efavirenz and nevirapine activate hPXR and hCAR, which markedly increase the functional activity of CYP3A4 and 2B6.[36,37] Efavirenz has mixed effects on CYP3A4, with inhibition during acute exposure and induction during chronic exposure.[15] Induction is more likely in this study, given that we measured concentrations at steady state. Activation of hPXR and hCAR can induce specific UGT1A isoforms,[38] which likely explains the reduction in dihydroartemisinin exposure.

During malaria treatment, parasite clearance is dependent on artemether and dihydroartemisinin exposure within the first 48 h, and lumefantrine clears residual parasites.[9,11,39] Reduced artemether, dihydroartemisinin and lumefantrine exposure may predispose to slow parasite and symptom clearance and treatment failure with the risk of development of resistance. This is of particular concern in HIV-infected individuals who are at risk of a high malaria parasite count,[2,40] an independent predictor of antimalarial treatment failure.[41] However, extrapolation of our data to clinical relevance should be performed with caution and in consideration of changes in drug bioavailability during the acute malaria disease state. Previous studies demonstrated low bioavailability of artemether/lumefantrine during acute malaria states and higher concentrations during recovery due

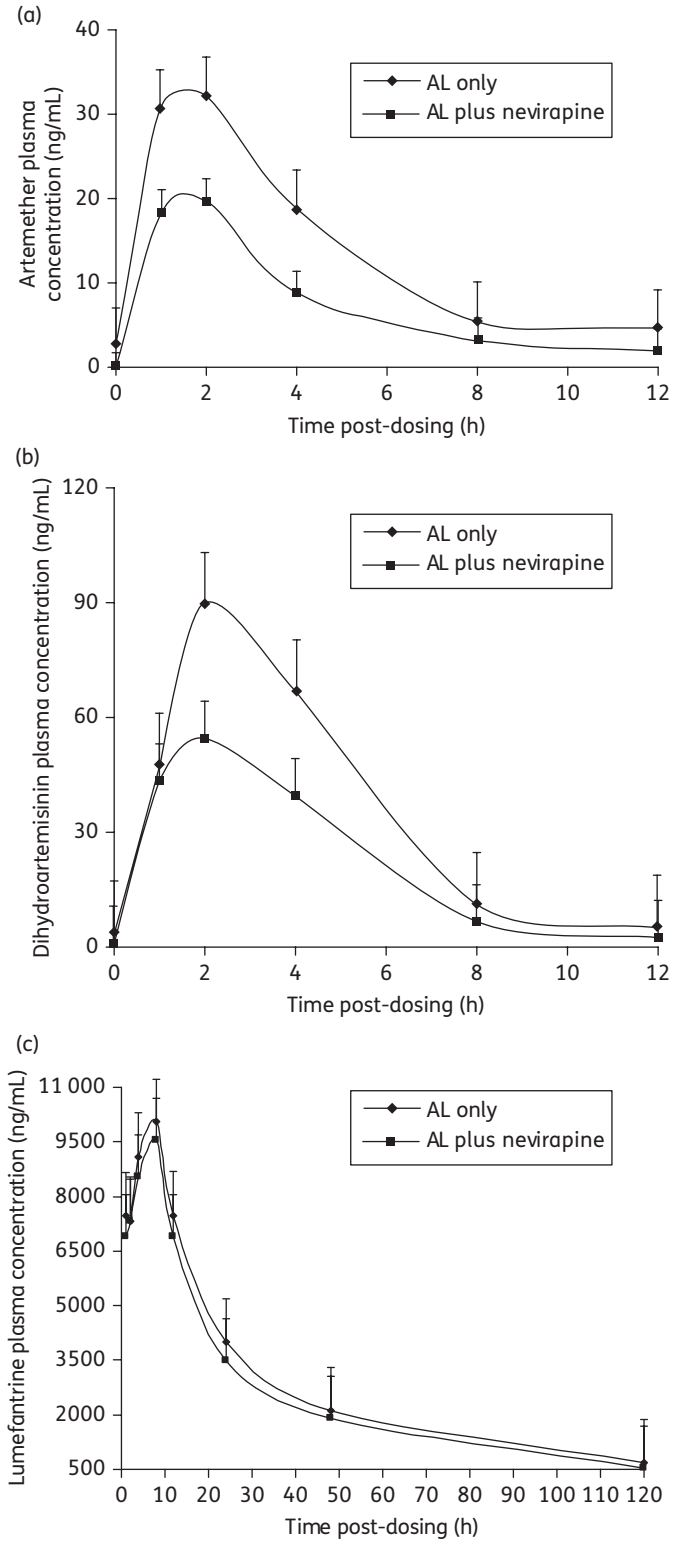


**Figure 3.** Mean plasma concentration versus time of (a) artemether, (b) dihydroartemisinin and (c) lumefantrine with and without nevirapine. AL, artemether/lumefantrine. Vertical bars represent standard errors.

**Table 4.** Comparison of pharmacokinetic parameters of efavirenz and nevirapine with and without artemether/lumefantrine

| Parameter | Median (range) | | *P* value | Median (range) of individual ratio |
|---|---|---|---|---|
| | no AL | AL co-administered | | |
| Efavirenz | ($n$=30) | ($n$=30) | | |
| $C_{max}$ (ng/mL) | 1199 (580–14818) | 1174 (325–971347) | 0.8 | 1.0 (0.1–3.8) |
| $AUC_{0-last}$ (ng·h/mL) | 627 (225–7986) | 652 (45–8711) | 0.7 | 0.7 (0.1–3.8) |
| Nevirapine | ($n$=28) | ($n$=28) | | |
| $C_{max}$ (ng/mL) | 8620 (3454–18079) | 4958 (1563–12814) | <0.01 | 0.5 (0.1–1.7) |
| $AUC_{0-last}$ (ng·h/mL) | 66329 (28128–141100) | 35728 (6382–102055) | <0.01 | 0.6 (0.1–1.2) |

AL, artemether/lumefantrine; $AUC_{0-last}$, plasma AUC from time 0 to the last observation.

to improvement in food intake and changes in volume of distribution.[28,42] Our data suggest that drug interactions that result in reduced antimalarial exposure may result in poor malaria treatment outcomes. In anticipation of decreased artemether/lumefantrine exposure, we excluded patients with malaria from our study, so the findings cannot be directly extrapolated to this population.

Nevirapine exposure was significantly reduced during co-administration with artemether/lumefantrine, possibly due to effects of autoinduction of CYP3A4.[43] However, artemether also induces CYP3A4[27] and therefore could have contributed to this effect. In Uganda nevirapine is administered to patients for whom efavirenz is contraindicated, such as children weighing <10 kg or younger than 3 years and women of reproductive age. Children below 5 years and pregnant mothers have increased risk of malaria. Co-administration of artemether/lumefantrine with nevirapine is highly likely in this population. Recurrent malaria attacks and recurrent co-administration of artemether/lumefantrine with nevirapine may predispose to intermittent sub-therapeutic nevirapine concentrations, which may predispose to increased risk of ART failure with risk of development of resistance to nevirapine. Therefore, further evaluation of the clinical impact of this interaction is urgently needed.

### *Conclusions*

Co-administration of artemether/lumefantrine with efavirenz or nevirapine resulted in reductions in artemether, dihydroartemisinin, lumefantrine and nevirapine pharmacokinetic exposure, which are likely to increase the risk of malaria treatment failure and the development of resistance to artemether/lumefantrine and nevirapine. Monitoring of artemether/lumefantrine treatment response among HIV–malaria co-infected patients receiving efavirenz or nevirapine is recommended. Clinical data from population pharmacokinetic and pharmacodynamic trials evaluating the impact of these drug interactions are urgently needed.

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## Transparency declarations

None to declare.

### *Author contributions*

P. B.-K., M. L. and C. M. contributed to the design and conduct of the study. P. B.-K., M. L., J. M. and L. N. participated in recruitment of participants and data collection. R. N., M. N., W. H. and N. L. performed the bioanalytical assays. P. B.-K., J. T., N. L. and P. J. de V. analysed and interpreted the data. H. M.-K., E. K., N. P., M. R., P. J. de V., S. K., D. B. and C. M. participated in training the study staff and provided scientific support. P. B.-K. drafted the first version and all authors reviewed and approved the manuscript for submission.

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