Title: Drug-drug Interactions between Lumefantrine and Commonly-used Antiretroviral Treatment: An Individual Participant Data Population Pharmacokinetic Meta-Analysis.

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Treating malaria in HIV co-infected individuals should consider potential drug-drug interactions. Artemether-lumefantrine is the most widely recommended treatment for uncomplicated malaria globally. Lumefantrine is metabolized by CYP3A4, an enzyme that commonly-used antiretrovirals often induce or inhibit. A population pharmacokinetic meta-analysis was conducted using individual participant data from ten studies, with 6,100 lumefantrine concentrations from 793 non-pregnant adult participants (41% HIV-malaria co-infected, 36% malaria-infected, 20% HIV-infected, and 3% healthy volunteers). Lumefantrine exposure increased 3.4-fold with co-administration of lopinavir/ritonavir-based antiretroviral therapy (ART), while it decreased by 47% with efavirenz-based ART and by 59% in the patients with rifampicin-based anti-tuberculosis treatment. Nevirapine- or dolutegravir-based ART and malaria- or HIV-infection were not associated with significant effects. Monte Carlo simulations showed that those on concomitant efavirenz or rifampicin have 49% and 80% probability of day-7 concentrations <200 ng/mL respectively, a threshold associated with an increased risk of treatment failure. The risk of achieving sub-therapeutic concentrations increases with larger body weight. An extended 5-day and 6-day artemether-lumefantrine regimen is predicted to overcome these drug-drug interactions with efavirenz and rifampicin respectively.
Main text (4116 words)

Introduction

Malaria is responsible for the heaviest burden of all parasitic infections, with an estimated 219 million cases and 435,000 deaths reported worldwide in 2017. The vast majority of malaria deaths (~93%) occurred in Sub-Saharan Africa region. Due to the substantial geographical overlap between malaria and HIV, many patients require concomitant treatment with both antimalarial drugs and antiretroviral drugs (ARVs). This creates a potential for drug-drug interactions, which may affect the antimalarial treatment outcome. Artemether-lumefantrine (AL) is the most widely used first-line treatment for uncomplicated *falciparum* malaria globally. Artemether is rapidly converted to its active metabolite dihydroartemisinin, which rapidly reduces the parasite biomass with a short terminal half-life of 1.5-2 h, whereas lumefantrine displays a longer terminal half-life of 3-5 days and is responsible for clearing the remaining parasites to prevent recrudescence. The absorption of lumefantrine is readily saturable (i.e. dose-limited) and markedly affected by food, as co-administration of fat increases its absorption. Lumefantrine is highly protein-bound, mostly to high-density lipoproteins. It is mainly metabolized by CYP3A4 to desbutyl-lumefantrine, a compound that appears to be more active against malaria than lumefantrine. However, since systemic lumefantrine exposure is 85- to 300-fold higher than desbutyl-lumefantrine, lumefantrine is considered responsible for most antimalarial activity. Many of the first- and second-line ARVs currently used in developing countries affect the expression or activity of the CYP3A4 enzyme. Ritonavir is a potent inhibitor of CYP3A4, while efavirenz and nevirapine are both inducers, the latter with a weaker induction capacity than the former. Various studies have reported that lumefantrine exposure is significantly decreased when co-administered with efavirenz-based antiretroviral therapy (ART) and increased when given with lopinavir/ritonavir-based ART. Results are inconsistent in the few studies...
investigating the effect of nevirapine-based ART on lumefantrine exposure, showing increased, decreased or no effect on lumefantrine exposure. (13–18) Dolutegravir-based ART is being rapidly adopted as first-line HIV treatment; Dolutegravir is an HIV-integrase inhibitor reported to have minimal effects on CYP3A4 and a study has shown that DTG-based ART did not alter lumefantrine exposure significantly. (19, 20) Additionally, no information is available on whether malaria or HIV disease may affect lumefantrine pharmacokinetics.

The purpose of this meta-analysis was to pool available clinical data to characterize the effect of ARV drug-drug interactions with artemether-lumefantrine and to identify any other significant covariates affecting lumefantrine concentrations. This meta-analysis did not simply collate aggregate results from individual studies, but jointly re-analyzed the individual participant data, using a with population pharmacokinetic modeling approach. This technique can identify and quantify the different sources of variability in the data, thus separating the random unexplained differences between participants and studies from systematic effects, such as those associated with patient characteristics (e.g., weight or age), drug-drug interactions and/or disease effects. With an increased and diverse study population and a larger variability in treatment scenarios obtained when pooling individual participant data from different studies, it is possible to quantify the extent of drug-drug interactions and other covariates more robustly than in the individual primary studies.

**Results**

**Data summary**

A total of 16 artemether-lumefantrine pharmacokinetic studies were identified in a literature review and invited by WorldWide Antimalarial Resistance Network (WWARN) to contribute
to the individual patient data (IPD) meta-analysis. Studies addressing the pharmacokinetics of lumefantrine in pregnant women and children were not included as it was beyond the scope of this meta-analysis. WWARN received and curated data from 11 artemether-lumefantrine pharmacokinetic studies, 9 from Africa and 2 from the USA, but one USA study only contributed summary values (not individual patient data) and was excluded. Thus, the IPD meta-analysis consisted of 10 clinical studies with 793 non-pregnant adult participants and 6,100 measured lumefantrine concentrations. Out of these, the concentrations in 341 (5.59%) samples were below the lower limit of quantification (LLOQ). All participants were non-pregnant adults treated with artemether/lumefantrine (Coartem®, Novartis Pharma AG). The distribution of participants and their demographic characteristics across different studies are presented in Table 1, while an overview of the studies included is provided in Table 2.

### Population Pharmacokinetics of Lumefantrine

**Structural model and effect of body size**

The population pharmacokinetics of lumefantrine was best described with a three-compartment disposition model (objective function value reduction, ΔOFV, of 930 points when comparing to a two-compartment model, p<0.001) with first-order elimination and transit compartment absorption (ΔOFV = 2,616 when compared to a more traditional first-order absorption, p<0.001). Final pharmacokinetic parameter estimates are presented in Table 3 and a visual predictive check (VPC) stratified by study and treatment arm is provided in Figure 1, showing an adequate model fit to clinical data. Allometric scaling using total body weight was included in the model for all disposition parameters to adjust for differences in body size. The use of fat-free mass or normal fat mass as alternative body size descriptors did not improve the model fit significantly compared to the use of total body weight. (21) In a
typical patient weighing 57 kg, the apparent clearance (CL) was 3.28 L/h [3.14 - 3.46] (Table 3).

**Drug-drug interactions**

Co-administration of lopinavir/ritonavir-based ART increased lumefantrine exposure substantially; the area under the curve (AUC) was nearly 3.4-fold higher, due to 50.1% slower clearance (ΔOFV = 220, p<0.001) and 67.2% increased bioavailability (ΔOFV 40, p<0.001). Lopinavir/ritonavir-based ART was also found to slow down the rate of absorption by 47.6% (ΔOFV = 33, p<0.001). Efavirenz-based ART significantly increased the clearance of lumefantrine by 89.9% (ΔOFV = 308, p<0.001), thus resulting in 47% lower AUC.

Rifampicin-based anti-tuberculosis treatment increased lumefantrine clearance by 142% (ΔOFV = 87, p<0.001) thus reducing AUC by 59%. A small number of patients (n=4) was administered both rifampicin and efavirenz, and there was trend towards an even higher clearance of lumefantrine, but this was not statistically significant and was not retained in the final model. Dolutegravir-based ART didn’t alter the lumefantrine exposure. Discordant trends towards slightly higher or lower exposure in the nevirapine-based ART arms were found in the different studies, but no significant effect was found in the combined data after adjusting for other factors (below).

**HIV and malaria disease effects**

After adjusting for the substantial drug-drug interactions above (and other effects explained below), the IPD meta-analysis also tested for any malaria and HIV disease effects, but none was identified. The HIV+ but ART-naive participants from SEACAT showed a trend towards moderately increased clearance of lumefantrine, but the same trend was not found with the HIV+ ART-naive participants in the other studies. As the magnitude of this effect was small and not consistent across studies, it was not retained in the final model. Similarly, no
A significant consistent difference in pharmacokinetic parameters was found that could be ascribed to malaria-infection.

Study and other covariate effects

Diurnal variation: After adjusting for the effects described above, significant differences in drug concentrations remained between the studies and, when data were available, between profiles collected after morning or evening doses. These differences were well captured in the model using categorical covariate effects on relative bioavailability (i.e. separate values of bioavailability on specific dosing occasions). The highest bioavailability was observed in the InterACT and the SEACAT studies for the evening doses (with no significant difference between these two studies) and this was chosen as the reference value (fixed to 1) to which the bioavailability of other doses was compared. In the SEACAT studies, the relative bioavailability was 48.6% lower for the first (morning) dose (ΔOFV = 63, p<0.001) and 74% lower for the consecutive morning doses (ΔOFV =280, p<0.001). The value of relative bioavailability in the Ugandan studies was similar and found to be 26.9% lower than the reference (ΔOFV =31, p<0.001), while the value was 58.1% lower than the reference (ΔOFV =18, p<0.001) for the 6th (morning) AL dose in the Nigeria study 1. Lumefantrine bioavailability in the US healthy volunteer study was not significantly different from the reference group.

Matrix effect: Lumefantrine concentrations in both arms of Nigeria study 2, which was the only study measuring concentrations from whole blood samples (as opposed to venous plasma samples), were much higher than in all other studies. A scaling factor of 2.21-fold was included to account for this matrix effect (ΔOFV =122, p<0.001), which is consistent with previous reports (22, 23).
Dosing time: The pre-dose (i.e. morning samples before the 6th dose) concentrations in Nigeria study 1 and the US healthy volunteer study were higher and inconsistent with the profile collected after the observed 6th dose. The actual dosing time of the previous (5th) dose was not reported, so had been imputed to exactly 12 hours before the morning dose. We adjusted for this by estimating a delay in the absorption for this specific occasion, ~4.3 hrs (ΔOFV =17, p<0.001).

Weight-adjusted dose: Finally, a negative trend between bioavailability and mg/kg dose was detected in the ART naïve arms of SEACAT, InterACT, and for the AL-only arm of Uganda Clinical study 1. However, this trend was not present in the other studies and arms and was not significant in the model when tested overall.

Simulations on the attainment of therapeutic Day 7 concentrations

The Monte Carlo simulations from the final model (Table 4 and Figure 2) show how body weight and different co-treatments for HIV and tuberculosis affect lumefantrine concentrations and the probability of achieving the purported therapeutic concentration threshold of ≥200 ng/mL. (22) A typical 57-kg participant (median body weight in the study) is predicted to achieve satisfactory day-7 concentrations when treated with AL alone or concomitantly with nevirapine or dolutegravir and largely exceed them if on lopinavir/ritonavir. On the other hand, the same patient has 49% and 80% probability of not achieving day-7 concentration above the target when co-treated with efavirenz or rifampicin, respectively. Additionally, participants with larger body weight are predicted to have lower exposures. The effect of body size on target attainment is modest when AL is used alone or with nevirapine or dolutegravir, but it becomes critical for participants of larger weight co-treated with efavirenz or rifampicin. Our model predicts that the risk of day-7 concentrations below the target increases to 62% and 87% for an 80-kg patient on efavirenz or rifampicin,
respectively. The use of a 4-day regimen of AL is predicted to reduce the risk of sub-therapeutic day-7 concentration to 18% and 50% for a typical 57-kg patient on efavirenz or rifampicin, respectively, and these probabilities drop further to 3% and 16% with a 5-day regimen. Simulations showed that a 6-day regimen of AL was necessary to reduce the risk of sub-therapeutic day-7 concentration to 2% for a typical 57-kg patient on rifampicin. For an 80-kg patient, a longer 5-day and 6-day regimen for efavirenz or rifampicin co-treatment, respectively, reduces the risk of sub-therapeutic concentrations to 5% and 2%.

Discussion

In this IPD meta-analysis of lumefantrine pharmacokinetics, we quantified the effect of commonly prescribed ARTs on lumefantrine exposure. To the best of our knowledge, this is the largest IPD meta-analysis of drug-drug interactions of lumefantrine with antiretrovirals to date, combining 6,100 concentrations from 793 adults in 10 studies, 9 from sub-Saharan Africa and 1 from North America. Although most included studies were from Africa, they were carried out in different regions, and the continent is known for its genetic diversity, (24) so we believe that significant genetic differences are represented in our pooled analysis. The pooling of individual participant data allowed us to re-evaluate and characterize the various drug-drug interactions and other covariate effects more robustly and reliably than in any single study. This was accomplished thanks to the larger sample size, and to the flexibility of population pharmacokinetic modeling, which is able to adjust for study-specific differences and the known effects such as patient body size, and separately investigate the drug-drug interactions and disease effects across the different studies. The pooling of data from different studies allowed us to investigate the effect of malaria and HIV infection on lumefantrine exposure and, reassuringly, no effect was found.
The primary aim of this pooled analysis was to characterize the effect of lopinavir/ritonavir-, efavirenz-, dolutegravir-, and nevirapine-based ART on lumefantrine exposure. Lumefantrine exposure is a key determinant of artemether-lumefantrine treatment success, so increased exposure might be associated with a higher cure rate and/or a longer post-treatment prophylactic period (25, 26), while a decrease in concentrations increases the risk of treatment failure.

Lopinavir/ritonavir-based ART increased the exposure of lumefantrine by 3.4-fold and slowed absorption, delaying the time of peak concentration. Lopinavir/ritonavir is a potent inhibitor of CYP3A4 isoenzyme, which explains the increased exposure of lumefantrine when it is co-administered, confirming previous findings from individual studies (8–10, 16).

The safety of this increased lumefantrine exposure with lopinavir/ritonavir-based ART is reported in detail elsewhere; in short, there were no serious adverse events and no clinically significant safety concerns raised (10, 26, 27).

Efavirenz-based ART increased the clearance of lumefantrine, thus decreasing exposure by 47%, confirming previous reports and the known effect of efavirenz as a potent inducer of CYP3A4 (11, 12, 17, 26). The findings from this pooled analysis are consistent across studies and provide a more robust estimate since they are based on a larger number of participants and study settings, and was able to demonstrate the particular importance of this interaction in larger adults.

Rifampicin-based tuberculosis treatment was found to decrease lumefantrine exposure by 59%, which was expected, since rifampicin is known to be a potent inducer of CYP3A4 and previous physiologically-based pharmacokinetic modelling had predicted this in silico (28).

Clinically, the interaction has been shown in a small study in HIV-infected malaria-uninfected adults (29), which in this analysis was pooled with data from patients on...
rifampicin co-treatment from InterACT, thus confirming and making the result more robust. Of the 13 participants on rifampicin included in our analysis, four were co-treated with efavirenz, while the rest were not on ART. There was a non-statistically significant trend towards an even stronger effect on clearance when both efavirenz and rifampicin were combined, but the limited sample size limited our ability to robustly characterise this interaction and this was not included in the final model. Further studies are needed to accurately characterize this clinically significant interaction.

Dolutegravir-based ART had no significant effect on lumefantrine exposure, which suggests that standard doses of AL can be co-administered safely. This finding is of importance considering the rapid adoption of DTG-based ART as first line treatment.

Nevirapine-based ART had no significant interaction with lumefantrine in our IPD meta-analysis overall. Nevirapine is reported to be an inducer of CYP3A4 isoenzyme, but the extent of induction is generally considered to be smaller than that of efavirenz,(7, 12), with some studies, such as Mouly et al. (30), reporting no induction of nevirapine on CYP3A4 enzymes. Previous reports show inconsistent results regarding the effect of nevirapine on lumefantrine exposure, including the studies contributed to this pooled analysis, but the magnitude of any interaction shown was relatively small. Non-compartmental analyses in Uganda Study 2 and Nigeria Study 1 reported reduced lumefantrine exposure with nevirapine. The SEACAT study showed that nevirapine-based ART causes a moderate increase in lumefantrine bioavailability (+36%), with similar findings in Nigeria study 2. The difference in findings in the IPD meta-analysis with and between individual previous studies may be explained by their including effects of between-occasion variability on bioavailability while our IPD meta-analysis could identify and characterize the effect of food (fat) co-administration increasing lumefantrine exposure. Accounting for these potential differences between the studies on lumefantrine exposure was necessary for better characterization of the
drug-drug interactions. After adjusting for this biologically plausible effect, no effect of nevirapine-based ART on lumefantrine exposure was found in the IPD meta-analysis. This also points to the importance of standardizing food co-administration when lumefantrine pharmacokinetics is investigated.

Simulations from the model helped us to identify participants who are at the highest risk of sub-therapeutic concentrations. Most participants treated with AL alone or in combination with nevirapine are predicted to achieve day-7 concentrations above the therapeutic target of 200 ng/mL. However, larger participants are at relatively higher risk of sub-therapeutic day-7 concentrations, e.g. an 80-kg patient on the standard regimen of AL alone or with nevirapine has 2% risk of day-7 concentrations below the target. This finding is in line with previous studies reporting that participants with body weight ≤ 65 kg had a better therapeutic outcome compared to those who weighed > 65 kg.(31, 32) In this IPD meta-analysis, the effect of body size was successfully described using allometric scaling and no difference in pharmacokinetic parameters remained between participants ≤ 65 kg and >65 kg. The increase in concentrations due to lopinavir/ritonavir-based ART resulted in day-7 levels well above the target in all participants. However, a significant proportion of participants co-treated with efavirenz or rifampicin have day-7 concentrations below 200 ng/mL, and this risk is exacerbated in participants with larger body weight.

As demonstrated in previous studies, the exposure of artemether, the companion drug of lumefantrine, was lowered by concomitant administration of efavirenz or rifampicin, but not with lopinavir/ritonavir.(11, 12, 26) This may further increase the risk of artemether-lumefantrine treatment failure in those on concomitant efavirenz or rifampicin and may hasten the development of artemisinin and/or lumefantrine resistance. Hyperparasitemia is another important risk factor for artemether-lumefantrine treatment failure.(22) Drug interactions with efavirenz and rifampicin, particularly in participants with other risk factors
such as large body weight or hyperparasitemia, are of particular concern given the high prevalence of molecular markers \textit{mdr}86N and \textit{crt}76K associated with reduced lumefantrine susceptibility (33–35) and that artemisinin resistance has been confirmed in at least six countries in south-east Asia.\textsuperscript{(36, 37)}

Alternative dosing regimens for AL are needed to balance the effect of these drug-drug interactions and ensure successful therapeutic outcomes. Unfortunately, simply increasing the number of tablets administered at each dose is precluded by lumefantrine absorption being readily saturable and dose-limited with the currently available formulations.\textsuperscript{(16)} The use of new formulations as proposed by Jain \textit{et al.} may present a valuable alternative to circumvent this decreased exposure of lumefantrine.\textsuperscript{(38)} A recent study by Tun \textit{et al.} and Onyamboko \textit{et al.} where the standard 3-day course of AL was compared to the extended 5-day regimen reported that the extended regimen was well tolerated.\textsuperscript{(39, 40)} The simulations from this analysis predict that an extended 5- or 6-day AL regimen overcomes the effect of drug-drug interactions with efavirenz and rifampicin, respectively, reducing the chances of sub-therapeutic concentrations from $\geq 60\%$ to under 5\%, even for an 80-kg person. Prospective clinical drug-drug interaction studies are needed to evaluate whether these extended regimens of AL or a new lumefantrine formulation can compensate adequately for the effects of interacting drugs such as efavirenz and rifampicin.

\textit{Limitations}

The pooling of data from diverse studies also presented some challenges in the IPD meta-analysis. We adjusted the differences between the studies and occasions according to the available information on food intake with the dose, but the influence of any undocumented confounding factors cannot be excluded, as is always the case in pooled analyses. Further studies are recommended to accurately quantify the effect of concomitant food co-
administration and diurnal variation on lumefantrine exposure. The uncertainty in the time of
dosing history for the Nigeria study 1 and the US healthy volunteer study, and the different
matrix of drug concentration measurement in Nigeria study 2 were the other hurdles faced.
However, the inclusion in the model of the estimation of time of the previous dose and a
matrix scaling factor have mitigated the consequences of this uncertainty and allowed us to
include these two datasets in our analysis.

Conclusion

A model-based IPD meta-analysis was performed to describe the population
pharmacokinetics of lumefantrine using data from multiple studies and robustly characterize
drug-drug interactions between lumefantrine and commonly used anti-retroviral drugs. No
significant effect of nevirapine- and dolutegravir-based ART co-administration, malaria, or
HIV disease were found. Lopinavir/ritonavir-based ART dramatically increased lumefantrine
exposure, while efavirenz-based ART and rifampicin-based anti-tuberculosis treatment
significantly reduced lumefantrine exposure significantly, particularly in large adults. This
warrants further prospective investigation to inform dose modifications given that
lumefantrine absorption is readily saturable and dose-limited. Various approaches such as
extended 5- or 6-day regimen of AL for participants on efavirenz-based ART or rifampicin-
based anti-tuberculosis treatment or new formulations of lumefantrine need to be evaluated to
ensure optimal artemether-lumefantrine treatment response. In the interim, full adherence to
AL administered with dietary fat and closer monitoring of treatment response is required in
these participants.

Materials and methods
Data acquisition

A search was conducted in PubMed, EMBASE, clinicaltrials.gov, Google Scholar, various conference proceedings and in the Worldwide Antimalarial Resistance Network (WWARN) pharmacology publication database to identify relevant antimalarial clinical studies published between 1990 and 2016. The search strategy used key terms “lumefantrine pharmacokinetics” or “lumefantrine concentration”, “clinical study” and “HIV” or “antiretroviral”. Inclusion criteria permitted data sets of participants treated with at least one dose of artemether-lumefantrine with or at risk of malaria OR healthy volunteers who were HIV infected or uninfected and/or treated with antiretroviral/s, and with at least one or more post-dose concentration(s) of lumefantrine (+desbutyl-lumefantrine) measured. Under the auspices of the WWARN, corresponding authors of relevant studies were invited to participate in this IPD meta-analysis (http://www.wwarn.org/working-together/study-groups/lumefantrine-arv-pkpd-study-group). WWARN is a collaborative data sharing platform which provides an opportunity to share data and results from studies in the field of anti-malarial treatment.(41) Participating authors agreed to the WWARN terms of submission,(42) which ensure that all data uploaded were anonymized and obtained with informed consent, and in accordance with any laws and ethical approvals applicable in the country of origin. The WWARN semi-automated data management, curation, and analysis tools converted submitted data into a set of defined data variables in a standard format, following the WWARN clinical and pharmacology data management and statistical analysis plans.(43, 44) Individual study protocols were available for all trials included, either from the publication or as a metafile submitted with the raw data.

Population pharmacokinetic modeling
The population pharmacokinetics of lumefantrine was described using nonlinear mixed-effects modeling in the software NONMEM (version 7.4.2) and the algorithm first-order conditional estimation with eta-epsilon interaction (FOCE-I). Various tools such as Perl speaks NONMEM (PsN version 4.7.12), Pirana, and Xpose were used to aid the model development and to generate model diagnostics. R software was used to generate plots and to perform post modeling analyses.

Various structural models were attempted, from one- to three-compartment disposition with 1st-order elimination and 1st-order absorption, testing the inclusion of lag time or a chain of transit compartments to describe the delay in the onset of absorption. Both the between-subject variability and between-occasion variability were assumed to be log-normally distributed. Another level of variability i.e. the between-visit variability (BVV) was introduced to capture the difference between phase 1 and phase 2 in SEACAT 2.4.2, Uganda studies, and the healthy volunteer study from the USA. Allometric scaling was used to adjust for the effect of body size on disposition parameters with allometric exponents were fixed to 0.75 for clearance parameters and 1 for volumes of distribution. Besides total body weight, fat-free mass and normal fat mass were tested as alternative descriptors to characterize the size of drug-clearing organs and blood flows through them and to explore the possibility that lumefantrine may distribute differentially between muscle or fat tissue. A combined additive and proportional error model was used to describe residual unexplained variability. All samples with concentrations below the limit of quantification (BLQ) were handled with the M6 method as described by Beal. I.e. BLQ samples were replaced with half of the LLOQ value, except for consecutive values in a series, where the trailing BLQ values were omitted from the model fit but was included in simulation-based diagnostic plots, such as VPC’s. Model development and the inclusion of parameter-covariate relationships was guided by drops in the NONMEM OFV, assumed to be $\chi^2$-square distributed and thus...
using 3.84 points drop as significant at p<0.05 for the inclusion of a single parameter in a nested model), inspection of diagnostic plots including visual predictive checks,(51) and considering at each step the physiological and scientific plausibility of the proposed change. The robustness of the parameter estimates of the final model was assessed using the sampling importance resampling (SIR) method.(52)

The strategy used for the inclusion of data from each single study into the joint model was based on the one proposed by Svensson et al.(53) The data from each study was first briefly explored separately and included one-by-one, starting from the SEACAT studies, which were analyzed first since they provided richly sampled pharmacokinetic profiles and had accurate recording of time and concentration for all doses. Further studies were included step-wise and significant parameter-covariate relationships were explored. If after testing all the known/observed covariates, a systematic bias could still be seen in the model prediction of the newly-added study, a study-effect was included to adjust for the unexplained difference and prevent it from skewing the estimates of other covariate effects.

Monte Carlo simulations (n=10,000) based on the final model were used to predict the lumefantrine concentrations achieved with the current dosing recommendations in participants of different body weight and co-treated with different concomitant medications. To evaluate the expected effect of the pharmacokinetic differences on the therapeutic outcome, we calculated the probability of target attainment in the various scenarios using the suggested value of lumefantrine day-7 concentrations above 200 ng/mL, which has previously been associated with better cure rates.(22)

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**Author Contributions:** K.B. and P.D. designed the research. J.F. and P.D. performed the research and analysed the data. J.F., P.D., and K.B., wrote the manuscript. L.W. managed the collation and curation of data. T.K., L.V., R.H., P.B., M.L., M.L., S.W., I.C., C.S., C.M., K.S., N.N., M.M., S.K., I.B., S.P., F.A., J.T., contributed individual participant data for the pooled analysis. All authors reviewed the manuscript critically for important intellectual content and approved the final version submitted.

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Table 1: Distribution of patient and their characteristics across the studies included in the analysis

| Study [Study name] | Participants (samples) | Malaria  | HIV      | ART  | Weight (male/female) | Fat free mass (male/female) | Age (male/female) | Sex (male/female) |
|--------------------|------------------------|----------|----------|------|----------------------|-----------------------------|-------------------|------------------|
| Kredo et al. (2011, 2016) [SEACAT 2.4.1 & 2.4.2] | 55 (1,908) | Not infected | Positive | 59.0 (45.5 - 88.0) | 41.1 (31.3 - 59.7) | 32 (19.6 - 60.9) | 10/45 |
| a) HIV+, malaria-uninfected, not on ART | 18 (569) | Not infected | Positive | None | 58.0 (52.0 - 88.0) | 37.8 (34.3 - 51.9) | 27.6 (19.6 - 39.6) | 1/17 |
| b) HIV+, malaria-uninfected on NVP-based ART | 18 (449) | Not infected | Positive | NVP | 58.5 (45.5 - 80.0) | 39.2 (31.3 - 59.6) | 32.2 (28.1 - 60.9) | 3/15 |
| c) LPV/r Phase 1 – Single dose of AL | 18 (378) | Not infected | Positive | LPV/r | 60.5 (46.0 - 85.0) | 43.8 (31.9 - 52.5) | 36.9 (28.1 - 44.6) | 6/12 |
| d) Phase 2 – Multiple doses of AL | 16* (512) | Not infected | Positive | LPV/r | 62.0 (50.0 - 85.0) | 44.5 (34.2 - 54.5) | 37.4 (30.1 - 44.9) | 5/11 |
| Study            | Phase                                         | ART Type                  | N (%) | Not infected | Positive | Pos & Neg | Pos | Neg | Pos & Neg | N (%) | Not infected | Positive | Pos & Neg | N (%) | Not infected | Positive | Pos & Neg | N (%) | Not infected | Positive | Pos & Neg | N (%) |
|------------------|-----------------------------------------------|---------------------------|-------|--------------|----------|-----------|--------|-----|-----------|-------|--------------|----------|-----------|-------|--------------|----------|-----------|-------|--------------|----------|-----------|-------|
| Study 1          |                                               |                           |       |              |           |           |        |     |           |       |              |           |           |       |              |           |           |       |              |           |           |       |
| a) HIV+, malaria-uninfected, not on ART | 13 (116)                                     | Not infected              | Positive | None         | 64.0     (50.0-81.0) | 41.8     (34.1-51.9) | 34.0   (24.0-51.0) | 4/9 |
| b) HIV+, malaria-uninfected, on LPV/r-based ART | 18 (170)                                     | Not infected              | Positive | LPV/r        | 64.5     (45.0-86.0) | 45.5     (31.7-47.4) | 37.5   (25.0-44.0) | 8/10 |
| Study 2          |                                               |                           |       |              |           |           |        |     |           |       |              |           |           |       |              |           |           |       |              |           |           |       |
| Phase 1 - HIV+, malaria-uninfected, not on ART | 59 (524)                                     | Not infected              | Positive | None         | 56.0     (42.0-91.0) | 45.4     (36.5-57.9) | 36.0   (20.0-70.0) | 12/47 |
| Phase 2a - HIV+, malaria-uninfected, on NVP-based ART | 28 (249)                                     | Not infected              | Positive | NVP          | 54.5     (42.0-78.0) | 44.6     (36.6-55.5) | 33.5   (20.0-62.0) | 1/27 |
| Phase 2b - HIV+, malaria-uninfected, on EFV-based ART | 30 (265)                                     | Not infected              | Positive | EFV          | 62.0     (43.0-91.0) | 48.7     (37.6-57.9) | 38.0   (23.0-70.0) | 11/19 |
| Parikh et al. (2015) (14) | 11 (164)                                     | Not infected              | Positive | NVP          | 66.0     (56.0-92.0) | 44.3     (36.8-56.9) | 37.0   (31.0-60.0) | 2/9 |

InterACT study (54) [InterACT] 441 (1,749) Infected Positive & Negative 53.0 (30.0-96.0) 38.6 (24.7-66.6) 38.0 (14.0-59.0) 252/189

Byakika-Kibwika, P et al. (2012) (9, 17) [Uganda study 1 & study 2] 90 (1,324) Not infected Positive 60.5 (42.9-71) 39.51 (29.3-60.1) 36.0 (20.0-70) 24/66

Parikh et al. (2015) (14) [Nigeria Study 1] HIV+, malaria-uninfected, on NVP- 11 (164) Not infected Positive NVP 66.0 (56.0-92) 44.3 (36.8-56.9) 37.0 (31.0-60.0) 2/9
# 15 subjects were recruited in both phases

Only 58 patient’s data were available for Phase 2 of Uganda study

The information on age was available for 76 participant’s and the height measurement was missing for all the participants, therefore the fat-free mass was not calculated

| Study (and type) | HIV status | Malaria status | ART | Age (range) | Height (range) | Fat-free mass (range) |
|------------------|------------|----------------|-----|-------------|----------------|-----------------------|
| Nigeria Study 2  | HIV-, malaria-infected | not on ART | 99 (99) | 65.0 (25.0-97.0) | NA | 37.5 (17.0-49.5) |
| Uganda study 3   | HIV-, malaria-uninfected, participants | on RIF based ART treatment | 5 (110) | 61.0 (41.5-69.0) | 39.9 (30.3-48.6) | 30.0 (23.0-50.0) |
| Uganda study 4   | HIV-, malaria-uninfected, participants | on DTG based ART treatment | 14 (361) | 57.8 (45.0-76.0) | 49.1 (32.3-56.9) | 29.0 (19.0-32.0) |

NVP – Nevirapine, LPV/r – Lopinavir/ritonavir, EFV – Efavirenz, RIF – Rifampicin, DTG – Dolutegravir

677  # 15 subjects were recruited in both phases
678  $ Only 58 patient’s data were available for Phase 2 of Uganda study 2
679  ¥ The information on age was available for 76 participant’s and the height measurement was missing for all the participants, therefore the fat-free mass was not calculated
680  681  Weight, fat-free mass and age are reported as median (range)
682  683  NVP – Nevirapine, LPV/r – Lopinavir/ritonavir, EFV – Efavirenz, RIF – Rifampicin, DTG – Dolutegravir
684  685  686
Table 2: Summary of the study pharmacokinetic protocols

| Study Name          | Country    | Treatment (protocol)                                                                 | Sampling Schedule (Protocol)                                                                 | Sample collection | Sample assay method (LLOQ)              |
|---------------------|------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-------------------|----------------------------------------|
| SEACAT 2.4.1(15)    | South Africa | Coartem® 480 mg twice daily for 3 days (0, 8, 24 h, thereafter 12-hourly) taken with 40 mL of soya milk (0.8 g fat) and, for all doses except the second, a meal containing 6 g of fat within 1 h of each dose | 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 14, 24, 30, 36, 42, 48, 54, 60, 61.5, 62, 63, 64, 65, 66, 68, 70, 72, 96, 120, 144, 168, 336, and 504 h after the 1st dose | Plasma from venous blood | LC-MS/MS (20 ng/mL)                        |
| SEACAT 2.4.2(10)    | South Africa | Phase 1 - Coartem® 480 mg single dose taken with 40 mL of soya milk (0.8g fat) and a meal containing 6 g of fat within 1 h of dose administration | 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 14, 24, 30, 36, 42, 48, 54, 60, 72, 96, 120, 144, 168, 336, and 504 h after the 1st dose | Plasma from venous blood | LC-MS/MS (20 ng/mL)                        |
|                     |            | Phase 2 - Coartem® 480 mg twice daily for 3 days (0, 8, 24 h, thereafter 12-hourly) taken with 40 mL of soya milk (0.8g fat) and, for all doses except the second, a meal containing 6 g of fat within 1 h of each dose | 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 14, 24, 30, 36, 42, 48, 54, 60, 61.5, 62, 63, 64, 65, 66, 68, 70, 72, 96, 120, 144, 168, 336, and 504 h after the 1st dose | Plasma from venous blood | LC-MS/MS (20 ng/mL)                        |
| InterACT(54)        | Tanzania   | Coartem® 480 mg twice daily for three days, taken with yogurt                         | Day 3, 7, 14, 28 and 42 after the 1st dose                                                 | Plasma from venous blood | LC-MS/MS (20 ng/mL)                        |
| Uganda study 1(9)   | Uganda     | Coartem® 480 mg single dose taken with standard Ugandan breakfast                     | 0, 1, 2, 4, 6, 8, 12, 24, 48, and 72 h after the 1st (single) dose                          | Plasma from venous blood | LC-MS/MS (25 ng/mL)                        |
| Uganda study 2(17)  | Uganda     | Coartem® 480 mg twice daily for 3 days taken with standard Ugandan breakfast           | 0, 1, 2, 4, 8, 12, 24, 48, 72, 96 and 120 h after the 6th (and last) dose                   | Plasma from venous blood | LC-MS/MS (25 ng/mL)                        |
| Nigeria Study 1(14) | Nigeria    | Coartem® 480 mg twice daily for 3 days with standard Nigerian meal 30-60 min post dose | 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72 and 96 h after the 6th (and last) dose | Plasma from venous blood | HPLC (50 ng/mL)                          |
| Study                          | Country | Treatment                  | Time Points After Dose | Sample Type                           | Detection Method   |
|-------------------------------|---------|----------------------------|------------------------|---------------------------------------|--------------------|
| Nigeria Study 2 (18)          | Nigeria | Coartem® 480 mg twice daily for 3 days with advice to eat before medication | Day 7 after the 1st dose | Capillary whole blood from a finger prick spotted on a dried blood spot. | LC-MS/MS (1000 ng/mL) |
| US healthy volunteer study (8)| USA     | Coartem® 480 mg twice daily for 3 days with advice to take all drugs with a meal | 0, 0.5, 1, 2, 4, 6, 8, 12, 24, 48, 72, 96, 120, 168, 216, 264 h after the 6th (and last) dose | Plasma from venous blood | LC-MS/MS (1.43 ng/mL) |
| Uganda study 3 (29)           | Uganda  | Coartem® 480 mg twice daily for 3 days taken with standard Ugandan breakfast | 0, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 192, 480, and 600 h after the 6th (and last) dose | Plasma from venous blood | LC-MS/MS (25 ng/mL) |
| Uganda study 4 (20)           | Uganda  | Coartem® 480 mg twice daily for 3 days taken with standard Ugandan breakfast | 0, 1, 2, 4, 8, 12, 24, 48, 72, 96, 168, and 264 h after the 6th (and last) dose | Plasma from venous blood | LC-MS/MS (25 ng/mL) |

a – The samples from 61.5 to 70 hours were not drawn for the single-dose phase of SEACAT 2.4.2

LC-MS/MS - Liquid chromatography-tandem mass spectrometry; HPLC - High performance liquid chromatography; LLOQ – Lower limit of quantification
### Table 3: Final lumefantrine population pharmacokinetics parameter estimates

| Parameter                                                                 | Typical value | 95% CI          | BSV¹, BVV⁺⁺⁺ or BOV⁺⁺⁺ (CV%) | 95% CI          |
|--------------------------------------------------------------------------|---------------|-----------------|------------------------------|-----------------|
| Clearance (L/h) [CL]                                                     | 3.28          | 3.14; 3.46      | 20.8⁺⁺⁺                      | 18.1; 23.1      |
| Central volume of distribution (L)                                       | 60            | 56.3; 63.9      |                              |                 |
| Relative oral bioavailability [F]                                        | 1 FIX         | -               | 30.2⁺⁺⁺                      | 25.4; 35.6      |
| Mean absorption transit time (h)                                         | 2.86          | 2.74; 2.94      | 31.9⁺⁺⁺                      | 28.8; 35.1      |
| Number of hypothetical transit compartments                              | 7.58          | 7.06; 8.10      |                              |                 |
| First-order absorption rate constant (1/h) [Ka]                         | 0.727         | 0.62; 0.83      | 73.8⁺⁺⁺                      | 67.5; 80.8      |
| Intercompartmental clearance between central and first peripheral compartment (L/h) | 0.63         | 0.60; 0.67      | 29.1⁺⁺⁺                      | 26.1; 32.4      |
| Volume of distribution of the first peripheral compartment (L)          | 182           | 171; 195        |                              |                 |
| Intercompartmental clearance between central and second peripheral compartment (L/h) | 1.55         | 1.43; 1.72      |                              |                 |
| Volume of distribution of the second peripheral compartment (L)         | 39.1          | 37.1; 41.2      |                              |                 |
| Additive error (ng/mL)                                                  | 32.9          | 33.2; 33.5      |                              |                 |
| Proportional error (%)                                                  | 14.2          | 13.9; 14.4      |                              |                 |
| Efavirenz on CL (%)                                                      | +89.9         | 81.1; 99.7      |                              |                 |
| Lopinavir/ritonavir on CL (%)                                            | -50.1         | -53.0; -46.4    |                              |                 |
| Lopinavir/ritonavir on F (%)                                             | +67.2         | 49.1; 88.9      |                              |                 |
| Lopinavir/ritonavir on Ka (%)                                            | -47.6         | -56.5; -37.4    |                              |                 |
| Rifampicin-based TB treatment on CL (%)                                  | +142          | 111; 180        |                              |                 |
| First dose in SECAT on F (%)                                             | -48.6         | -54.9; -41.7    |                              |                 |
| Consecutive morning doses in SEACAT on F (%)                             | -77.2         | -80.7; -73.8    |                              |                 |
| Uganda studies on F (%)                                                 | -26.9         | -32.3; -20.7    |                              |                 |
| Nigeria study 1 on F (%)                                                | -60.8         | -73.2; -47.3    |                              |                 |
| Delay for unobserved dosea (h)                                          | 4.30          | 2.84; 5.73      |                              |                 |
| Scaling factor for DBS concentrationsb (-fold)                           | 2.28          | 2.05; 2.55      |                              |                 |
BSV - between-subject variability; BVV – between-visit variability; BOV - between-occasion variability – All are expressed as approximate coefficient of variation (%CV).

The typical values of all clearances and volumes of distribution were allometrically scaled with body weight and the typical values reported are for a patient with body weight 57 kg.

a - This delay in absorption/dosing time applies to the unobserved dose prior to the PK visit in the Nigeria Study 1 & Healthy volunteer study USA.

b - Scaling factor adjusting for the difference between concentrations from DBS (Nigeria Study 2) and plasma (all other studies).

95% CI of parameter estimates computed with sampling importance resampling (SIR) on the final model.
Table 4: Simulated day-7 concentration of Lumefantrine with various drug-drug interactions in the analysis

| Typical patient with body weight | Lumefantrine alone or with Nevirapine/Dolutegravir (ng/mL) | Lumefantrine + Lopinavir/ritonavir (ng/mL) | Lumefantrine + Efavirenz (ng/mL) | Lumefantrine + Rifampicin (ng/mL) |
|---------------------------------|-----------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                 | 3-day regimen of AL                                  | 3-day regimen of AL              | 3-day regimen of AL              | 3-day regimen of AL              |
| 40-kg person                    | 999 [670-1,476] (0%)                                 | 5.823 [4,123-8,186] (0%)         | 250 [162-382] (37%)              | 144 [94-222] (69%)               |
|                                 |                                                     |                                 | 410 [276-606] (11%)              | 243 [161-362] (38%)              |
|                                 |                                                     |                                 | 700 [483-1,003] (1%)             | 419 [286-610] (10%)              |
|                                 |                                                     |                                 |                                 | 812 [563-1,169] (0%)             |
| 57-kg person                    | 811 [548-1,194] (1%)                                 | 4.626 [3,294-6,407] (0%)         | 203 [132-310] (49%)              | 118 [77-182] (80%)               |
|                                 |                                                     |                                 | 336 [228-498] (18%)              | 201 [135-299] (50%)              |
|                                 |                                                     |                                 | 576 [401-836] (3%)               | 343 [236-497] (16%)              |
|                                 |                                                     |                                 |                                 | 656 [459-941] (2%)               |
| 80-kg person                    | 671 [459-987] (2%)                                   | 3.686 [2,669-5,058] (0%)         | 166 [110-253] (62%)              | 99 [65-151] (87%)                |
|                                 |                                                     |                                 | 279 [191-414] (28%)              | 166 [113-246] (62%)              |
|                                 |                                                     |                                 | 479 [332-684] (5%)               | 282 [197-413] (26%)              |
|                                 |                                                     |                                 |                                 | 547 [378-776] (3%)               |

Values are reported as median and interquartile range within square brackets, while the values in brackets refer to the percentage of individuals below the day-7 threshold of 200 ng/mL after simulations (n=10,000).

57 kg was the median weight in the study.
Figure 1: Visual predictive check of lumefantrine concentrations vs. time, stratified by study and treatment arm.
The observed lumefantrine concentrations (in the log scale) vs. time after the first dose are displayed as blue dots. The solid and dashed lines are the 50th, 5th, and 95th percentiles of the observed plasma concentration, while the shaded areas are the 90% confidence intervals for the same percentiles, as predicted by the model. The three panels correspond to the data collected from 0-24 hours, 25-220 hours and 221-1,175 hours after the first dose respectively.

CTRL – Control arm; Ph – Phase
Figure 2: Simulated day-7 concentration of Lumefantrine with various drug-drug interactions in the analysis.

The box represents the 25th to 75th percentile, and the whiskers the 2.5th to 97.5th percentile of the simulated day-7 concentration after Monte Carlo simulations (n=10,000). The dashed line at 200 ng/mL denotes the suggested threshold.