**Supplement**

**Methods**

Tororo is a high transmission area with an annual entomological inoculation rate up to 562 infective bites per person per year) [1]. For the randomized controlled trial, convenience sampling was utilized for infants presenting to antenatal clinics for routine care. Eligibility criteria included the following: i) living within 30 km of the study site, ii) documented human immunodeficiency virus (HIV) status of the mother and child, iii) breastfed if HIV-exposed (defined as children of an HIV-infected mother), and iv) agreement to come to the clinic for any illness and avoid medications outside of the study clinic. All participants were given an insecticide-treated bednet at enrolment. No additional medications with antimalarial activity, or known hepatic enzyme inhibitors or inducers, were administered to patients during the study, with the exception of daily TS prophylaxis and ART. During the last month of the PK study, only day 7 lumefantrine levels were obtained from participants (n=31). All parents or guardians provided informed consent. Ethical approval for the PK/PD study was obtained from the Uganda National Council of Science and Technology, the Makerere University Research and Ethics Committee, the University of California San Francisco Committee on Human Research. The study was reviewed in accordance with CDC human subjects review procedures and was determined that CDC investigator was not engaged in the research per HHS guidelines.

**Population Pharmacokinetic analysis**

Whole blood was allowed to dry on the pretreated filter paper and was stored in the dark at -4 ºC for a maximum of 3 weeks, and later transferred to -70 ºC until shipment on dry ice to the laboratory of Dr. Yngve Bergqvist. Extracted lumefantrine was further purified using solid-phase extraction and quantified with high performance liquid chromatography [2].Parameters were estimated by computing the maximum likelihood estimator of the parameters by linearization and importance of sampling using the stochastic approximation expectation maximization (SAEM) algorithm combined with a Markov Chain Monte Carlo (MCMC) procedure. Unless otherwise noted (Results section), all measurements, including those below 52 ng/mL were included in the analysis due to the large number of samples below LLOQ and LOD. Although an exact value was unavailable for data below LOD, the contribution to the likelihood of an outcome being less than LOD was computed and coded as left-censored, allowing these data to inform the model [3, 4]. Due to the sparsity of the data, IIV and IOV of *Q*/*F* and *V*2/*F* were each fixed to be 50% (CV). Correlation among *CL/F*, *V*1*/F*, *Q/F* and *V*2/*F* was introduced through the allowance of IOV and IIV variability in *F* (the typical value of which was fixed to 1). The data did not support full covariance matrixes. A combined additive plus proportional error model was used for residual variability, though other models were tested.

The relationship between continuous covariates and PK parameters were taken to be nonlinear and centered about the median values; the exception was for the final model in which weight and age were centered around the values of a one-year old, for ease of interpretation. Model building was guided by the plausibility of the estimates, minimum objective function value (OFV), Akaike Information Criterion, Bayesian Information Criteria, visual inspection of diagnostic plots and precision of parameter estimates. The initial model development used less rigorous criteria for statistical significance (a p-value of 0.05 for change in OFV when adding a covariate-parameter pair). The criteria for statistical significance with the final step (stepwise deletion) required, however, a 95% confidence interval of the parameter in the full model which excluded the null value, as well as a change in the OFV corresponding to a p-value of 0.005 upon its deletion.

**Results**

***Population PK data and modeling***

PK data from 5 episodes (n=5 individuals) of infection with *Plasmodium ovale* and 9 episodes (n=9 individuals) of infection with *Plasmodium malariae* were included in the PK analysis, after the influence of species type on PK parameters was ruled-out as being statistically significant. There were 56 PK data points (6.4%) excluded from the dataset. Eight episodes (n=8 samples) were excluded due to the absence of information regarding dosing time prior to day 7 concentrations only. Nine episodes (44 samples in total) were excluded due to detectable concentrations (ranging from 78 to 4473 ng/ml) prior to the 1st dose on the day of diagnosis; either prior dosing data were missing for these records or a previous concentration (from an earlier episode studied for PK) was considerably lower and there was no intervening dose. One additional episode (n=4 samples) was excluded from the analysis due to inconsistencies in the concentrations between day 7 and 14. One hundred eighty-eight samples (23.3%) were less than the LOD, but were retained in the analysis as informatively censored. Twenty-one of these samples were obtained on day 7 and the remainder on day 14. Only 25 of 197 (12.7%) analyzed PK data from day 14 had concentrations above the LOD; those concentrations ranged from 59 to 456.4 ng/mL, with a median of 133.8 ng/mL.

Overall, 80 episodes of malaria in 47 children were associated with concurrent daily TS administration and 16 episodes occurred in 9 HIV-infected children (15 of which were associated with concurrent ARV use) (Supplementary Figure 1). Of note, during the last month of the PK study, only day 7 lumefantrine levels were obtained from all enrolled participants. The actual (recorded) collection time [median (IQR)] on day 3 was 2.86 (2.80, 2.93) days after the first dose and on day 7 (when recorded) was 6.89 (6.82, 6.94) days post-first dose.

In earlier stages of the model building, there was a suggestion that parasite density may have an influence upon either or both volumes of distribution; this covariate was not significant, however, in the last step.

**Pharmacodynamic data**

Of the 249 episodes enrolled in the PK/PD study, 222 episodes in 100 children were analyzed for 28-day outcomes. Twenty-seven episodes were not included in the PD analysis due to infection with non-*P. falciparum* species (n=14), elevated pre-1st dose concentrations (n=9), lack of outcome classification (n=3), and medication noncompliance (n=1). j

**Supplemental Figure S1. HIV and TS status of PK study participants**

**Supplemental Figure S2a-S2c. Individual and population predictions of lumefantrine concentration by individual and occasion**

Individual (red line) and population (green line) predictions of lumefantrine capillary whole blood concentration by individual and occasion superimposed on the data. The red \* represents individual predictions for concentrations below the limit of detection, 52 ng/mL, and the blue + represents the measured values of all other concentratrations.

**Supplemental Figure S3. Cumulative risk of recurrent malaria by day 63 following treatment with artemether-lumefantrine stratified by TS status and lumefantrine concentration of 200 ng/mL**

Cox proportional hazards risk adjusted for repeated measures, age, residence, underweight status, parasite density and hemoglobin on the day of diagnosis; stratified by TS status and capillary whole blood lumefantrine threshold of 200 ng/mL.

**Supplemental Figure S1**

**Supplemental Figure S2a-c**

**Supplemental Figure S3**

**References**

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4. Samson A, Lavielle M, Mentre F. Extension of the SAEM algorithm to left-censored data in nonlinear mixed-effects model: Application to HIV dynamics model. Computational Statistics and Data Analysis **2006**; 51:1562-74.