SUPPLEMENTAL MATERIAL

Supplemental Methods: Population PK Model Development and Evaluation

To create the dosing dataset, the HCQ dose and dosing interval reported at each visit were carried forward until the next clinic visit. Dosing at the first visit was assumed to start 3 months prior to the first clinic visit, consistent with study inclusion criteria. In instances where there was a discrepancy in the dosing record or atypical PK profiles, adjudication of dosing records was conducted by a study rheumatologist using the totality of available EMR progress notes, pharmacy refill information, drug concentrations, and patient-reported history. For HCQ samples below the quantifiable limit (10 ng/mL), we imputed a value of 5 ng/mL.

To develop the structural model, we explored one- and two-compartment PK models with proportional, additive, and proportional-plus-additive residual error models. Due to the sparse sample collection, we fixed the lag time to 0.4 hours [1, 2] and the absorption rate constant to 1.4/hr. Initially, between-subject variability was estimated on all parameters. Thereafter, between subject variability was removed on parameters with high shrinkage (>40%). The final structural model was determined using the objective function value (OFV), diagnostic plots, biologic plausibility of parameter estimates, and model precision. The OFV was the model's -2 log likelihood. The diagnostic plots included individual and population predictions vs. observed concentrations, conditional-weighted residuals vs. time and predictions, and conditional weighted residuals vs. standard normal quantiles.

We explored the following covariates for their effect on PK parameters: trimester, pregnancy duration, and the effect of weight on HCQ apparent volume of distribution. In addition, we evaluated lupus nephritis (LN) within the past 3 years (binary), trimester, pregnancy duration, weight, and creatinine clearance as potential covariates to explain between-subject variability in apparent HCQ clearance. Creatinine clearance was calculated as: (((140 - age)*Weight)/(72*serum creatinine)*0.85). The mathematical functions used to evaluate covariate relationships are noted in **Supplemental Table 2**. These covariates were chosen for testing based on: 1) physiologic plausibility; 2) prior published literature; and 3) observed trends in the dataset on between-subject variability vs. covariate plots/boxplots. We conducted a stepwise covariate search using a forward inclusion threshold of $p<0.1$ and backward elimination threshold of $p<0.05$. These p-values correspond to a change in the model's OFV by 2.706 and 3.841, respectively, for 1 degree of freedom. For missing weight, we imputed the closest known weight for each patient. For missing serum creatinine, we imputed the median population value.

To evaluate model performance, we used the final PK model to conduct Monte Carlo simulations and generated the 95% confidence intervals for PK parameter estimates (1000 replicates of nonparametric bootstrapping). In addition, we used proportional prediction-corrected visual predictive checks (pcVPCs) to compare observed vs simulated results. To conduct the simulations for the pcVPC, we used the same covariates and dosing observed in the PK study population.

Supplemental Table 1. Parameter estimates for the final population PK model

Parameter	Estimate	CV (%)	2.5th %ile	Bootstrap* Median	97.5th %ile
Structural Model					
Ka (1/hr)	1.4	(fixed)	-	-	-
CL/F (L/hr), postpartum	31.4	19.5	22.6	31.5	45.3
V/F (L/70kg)	21,041	43.4	8,497	20,468	32,200
Tlag (hr)	0.4	(fixed)	-	-	-
Weight on V/F	2.4	35.3	1.17	2.41	3.73
Trimester on CL/F	0.34	56.6	0.03	0.33	0.59
Inter-Individual Variability (%CV)					
CL	34.7				
Residual Error					
Proportional error (%)	20.4		14.1	19.7	26.0

K_a: Absorption rate constant; CL/F: apparent clearance; V/F: apparent volume of distribution; Tlag: Lag time after oral administration; CV: Coefficient of variation calculated as 100* standard error/parameter value. Weight on V/F defined as: $V/F = tvV * (Weight/70kg)^{\theta}$; Trimester on CL/F defined as: $CL/F = tvCL*Trimester^{\theta}$,where tv is the typical value of the parameter for the population

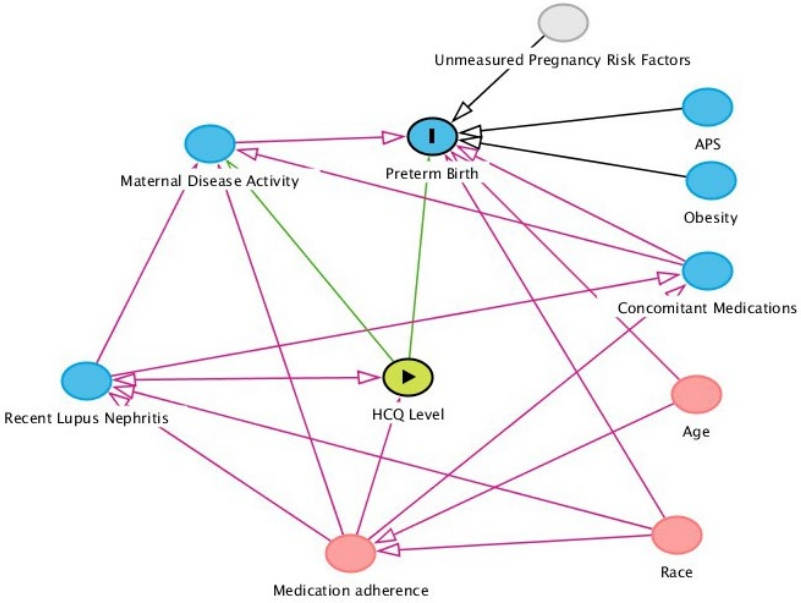
Supplemental Table 2. Results of covariate search

Description	Population model[a]	OFV	ΔOFV[b]
Basic models			
1 Compartment Proportional error		679.154	-
Forward Step 1			
Lupus Nephritis on CL	$CL/F = tvCL*exp(^{\theta}(Lupus\ Nephritis==1)$	679.152	-0.002
Weight on CL	$CL/F = tvCL * (Weight/70)^{\theta}$	676.326	-2.828
Creatinine Clearance on CL	$CL/F = tvCL * (creatinine\ clearance)^{\theta}$	678.881	-0.273
Weeks Gestation on CL	$CL/F = tvCL*weeks\_gestation^{\theta}$	679.930	0.776
Trimester on CL (categorical)	$CL/F = tvCL*exp(^{\theta}(Trimester==1) * exp(^{\theta}(Trimester==2)) * exp(^{\theta}(Trimester==3))$	672.463	-6.691
Trimester on CL (power)	$CL/F = tvCL*Trimester^{\theta}$	676.750	-2.404
Trimester on CL (exponential)	$CL/F = tvCL*exp((Trimester* ^{\theta})$	676.176	-2.978
Weight on V	**$V/F = tvV * (Weight/70)^{\theta}$**	**669.939**	**-9.215**
Weeks Gestation on V(continuous)	$V/F = tvV*weeks\_gestation^{\theta}$	679.930	0.776
Trimester on V (categorical)	$V/F = tvV*exp(^{\theta}(Trimester==1)) * exp(^{\theta}(Trimester==2)) * exp(^{\theta}(Trimester==3))$	677.247	-1.907
Trimester on V (power)	$V/F = tvV*Trimester^{\theta}$	678.567	-0.587
Forward Step 2			
Weight on V, Lupus Nephritis on CL	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL*exp(^{\theta}(Lupus\ Nephritis==1)$	669.887	-0.052
Weight on V, Weight on CL	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL * (Weight/70)^{\theta}$	667.857	-2.082
Weight on V, Creatinine Clearance on CL	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL * (creatinine\ clearance)^{\theta}$	669.694	-0.245
Weight on V, Weeks Gestation on CL	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL*weeks\_gestation^{\theta}$	679.930	9.991
Weight on V, Trimester on CL (categorical)	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL*exp(^{\theta}(Trimester==1) * exp(^{\theta}(Trimester==2) * exp(^{\theta}(Trimester==3))$	663.934	-6.005
Weight on V, Trimester on CL (power)	**$V/F = tvV * (Weight/70)^{\theta}$** **$CL/F = tvCL*Trimester^{\theta}$**	**664.502**	**-5.437**
Weight on V, Trimester on CL (exponential)	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL*exp((Trimester* ^{\theta})$	669.521	-0.418

Weight on V, Weeks Gestation on V	$V/F = tvV * (Weight/70)^{\theta}$ $*weeks\_gestation^{\theta}$ $CL/F = tvCL$	679.930	9.991
Weight on V, Trimester on V (categorical)	$V/F = tvV * (Weight/70)^{\theta}$ $*exp(^{\theta}(Trimester==1) *$ $exp(^{\theta}(Trimester==2) *$ $exp(^{\theta}(Trimester==3))$ $CL = tvCL*$	666.799	-3.14
Weight on V, Trimester on V (power)	$V/F = tvV * (Weight/70)^{\theta} *Trimester^{\theta}$ $CL/F = tvCL$	669.557	-0.382
Forward Step 3			
Weight on V, Trimester on CL (power), Lupus Nephritis on CL	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL*Trimester^{\theta} *exp(^{\theta}$(Lupus Nephritis==1)	663.935	-0.567
Weight on V, Trimester on CL (power), Weight on CL	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F\ CL = tvCL *Trimester^{\theta} *$ $(Weight/70)^{\theta}$	664.462	-0.04
Weight on V, Trimester on CL (power), Creatinine Clearance on CL	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL *Trimester^{\theta} *$ (creatinine clearance) $^{\theta}$	664.139	-0.363
Weight on V, Trimester on CL (power), Weeks Gestation on CL	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL*Trimester^{\theta}$ $*weeks\_gestation^{\theta}$	679.930	15.428
Weight on V, Trimester on CL (power), Trimester on CL (categorical)	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL*Trimester^{\theta}$ $*exp(^{\theta}(Trimester==1) *$ $exp(^{\theta}(Trimester==2) *$ $exp(^{\theta}(Trimester==3))$	663.934	-0.568
Weight on V, Trimester on CL (power), Trimester on CL (exponential)	$V/F = tvV * (Weight/70)^{\theta}$ $CL/F = tvCL*Trimester^{\theta}$ $*exp((Trimester*\ ^{\theta})$	664.258	15.428
Weight on V, Trimester on CL (power), Weeks Gestation on V	$V/F = tvV * (Weight/70)^{\theta}$ $*weeks\_gestation^{\theta}$ $CL/F = tvCL*Trimester^{\theta}$	679.930	-2.516
Weight on V, Trimester on CL (power), Trimester on V (categorical)	$V/F = tvV * (Weight/70)$ $*exp(^{\theta}(Trimester==1) *$ $exp(^{\theta}(Trimester==2) *$ $exp(^{\theta}(Trimester==3))$ $CL/F = tvCL*Trimester^{\theta}$	661.986	-0.182
Weight on V, Trimester on CL (power), Trimester on V (power)	$V/F = tvV * (Weight/70)^{\theta} *Trimester^{\theta}$ $CL/F = tvCL*Trimester^{\theta}$	664.320	-0.567
Backward Elimination			
Remove Weight on V	$V/F = tvV$	676.750	12.248

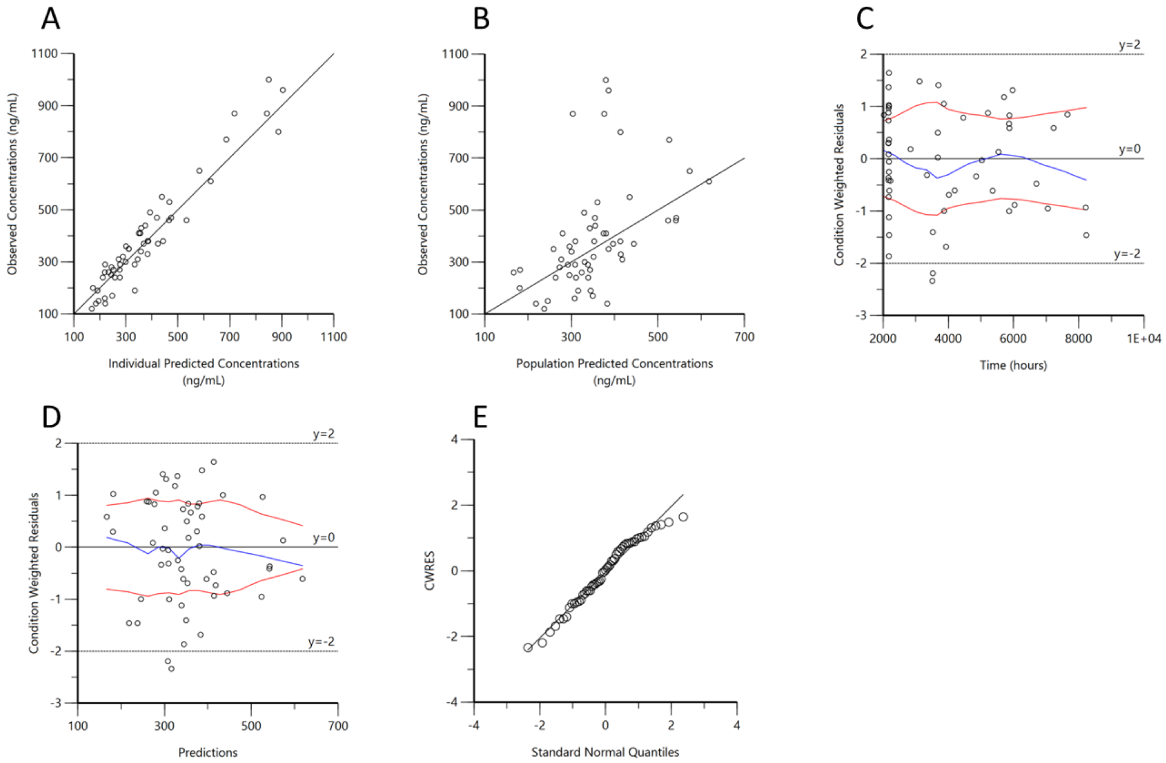
	CL/F = tvCL*Trimester$^{\theta}$ *exp($^{\theta}$(Lupus Nephritis==1)		
Remove Trimester on CL	V/F = tvV * (Weight/70) $^{\theta}$ CL/F = tvCL	669.93	5.428
Final model			
Weight on V, Trimester on CL (continuous)	**V/F = tvV * (Weight/70) $^{\theta}$ CL/F = tvCL*Trimester$^{\theta}$**	**664.502**	**-14.652**

Supplemental Figure 1. Directed acyclic graph (DAG) for preterm birth



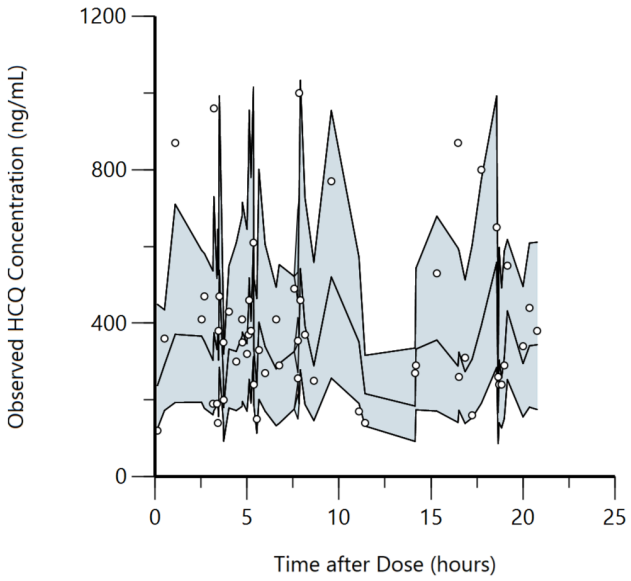
Green circle with black triangle: Exposures of interest. Blue circle with vertical line: Outcomes of interest. Pink circles: ancestors of exposure and outcome. Empty blue circle: ancestor of outcome only. Light grey circles: Unobserved variable. APS:Antiphospholipid antibody syndrome. DAGs were produced using software available at: daggity.net (Reference: Textor et al. International Journal of Epidemiology 45(6):1887-1894, 2016).

Supplemental Figure 2. Diagnostic plots for the final population PK model



A: Observed concentrations vs individual predicted concentrations; B: Observed concentrations vs population predicted concentrations. The solid black line in A and B is the line of unity; C: Conditional weighted residuals vs time; D: Conditional weighted residuals vs predictions. The blue line represents LOESS [locally weighted scatterplot smoothing] curve for all data, whereas the red lines represents a LOESS curve using the absolute value of the data (above 0) and it's negative reflection (below 0).E: Condition weighted residuals vs standard normal quantiles.

Supplemental Figure 3. Prediction-corrected visual predictive check



Empty black circles represent observed HCQ concentrations; the gray shaded region represents the 90% prediction interval with the black lines representing the 5th, 50th, and 95% predicted quantiles.

Supplemental References

1. Lim HS, Im JS, Cho JY, et al. Pharmacokinetics of hydroxychloroquine and its clinical implications in chemoprophylaxis against malaria caused by Plasmodium vivax. *Antimicrob Agents Ch* 2009;53:1468–75.
2. Morita S, Takahashi T, Yoshida Y, et al. Population pharmacokinetics of hydroxychloroquine in Japanese patients with cutaneous or systemic lupus erythematosus. *Ther Drug Monit* 2016;38(2):259–67.