Supplementary methods:

Reasons for study withdrawal

Three HIV-uninfected women in the q8wk arm who did not deliver were withdrawn from the study because they could not be located for more than 60 days. One HIV-uninfected woman in the q4wk arm was withdrawn because she moved out of the study area.

Outliers excluded:

A day 28 trough of 306 ng/mL was excluded given the average trough value for this patient was 7 ng/mL. The second sample excluded was a 6 hr intensive sample below the LLOQ for which every other sample in the participant's intensive profile was above the LLOQ.

BMI as a surrogate marker for malnutrition:

To explore how weight gain could change BMI for a hypothetical malnourished woman over the second and third trimesters of pregnancy we used weight gain guidelines from the Institute of Medicine (1). We needed to establish if it is therefore reasonable to believe the low BMI women in our trial were malnourished at 28 weeks gestation and to determine what range of continuous BMIs could be expected from a malnourished woman if she gained the ideal amount of weight (Figure S3)(1). Weight gain guidelines do not exist for the first trimester so to overcome this knowledge gap while exploring realistic scenarios we selected a woman from our trial who was enrolled early in the second trimester (at 14 weeks gestation) with a BMI of 18.3 kg/m^2 as she

would be considered malnourished based on pre-pregnancy guidelines (BMI of <18.5 kg/m^2 is considered malnourished). Our derived BMI trajectories, assuming the minimal (0.45 kg/week) and maximal (0.6 kg/week) recommended weight gain, resulted in a week 28 BMI of 20.5 and 21.5 kg/m^2, respectively. The more conservative cutoff of 20.5 kg/m^2 was used when plotting our data but likely underestimates the number of women malnourished given that recent studies report up to 62% of Ugandan women gain inadequate weight during pregnancy (2).

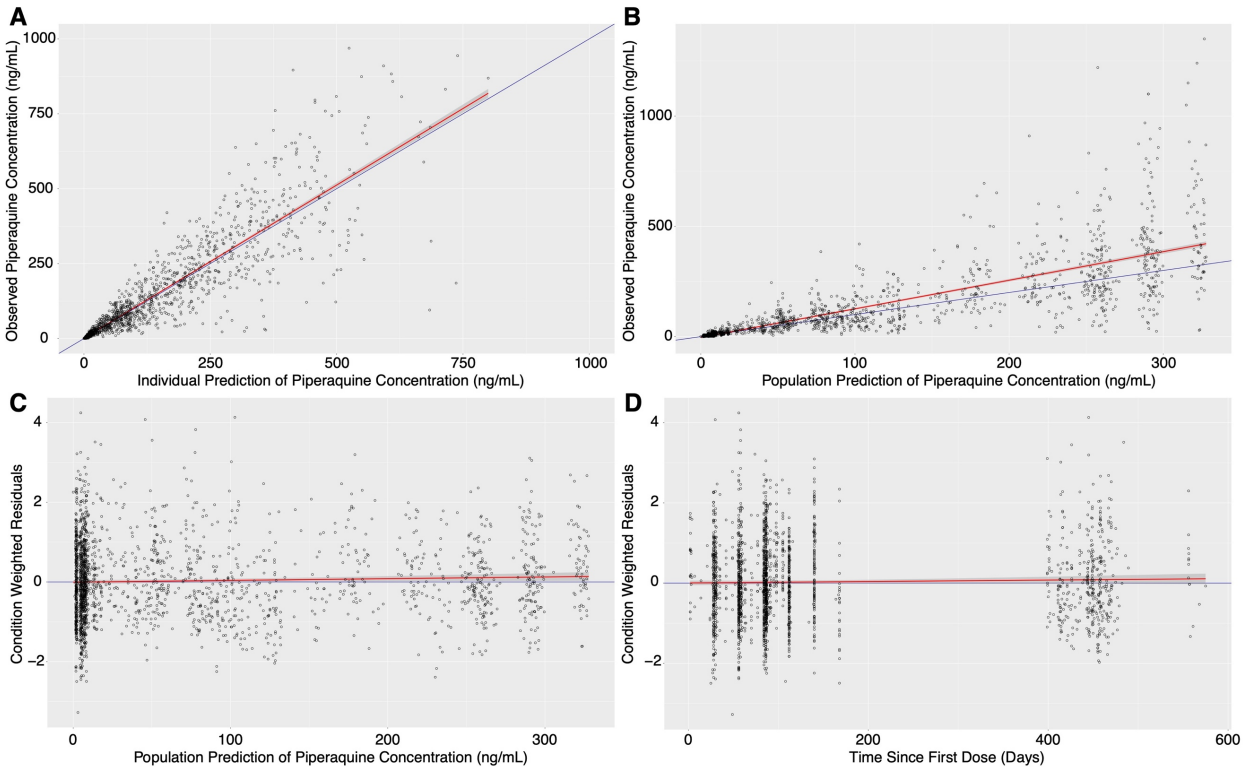
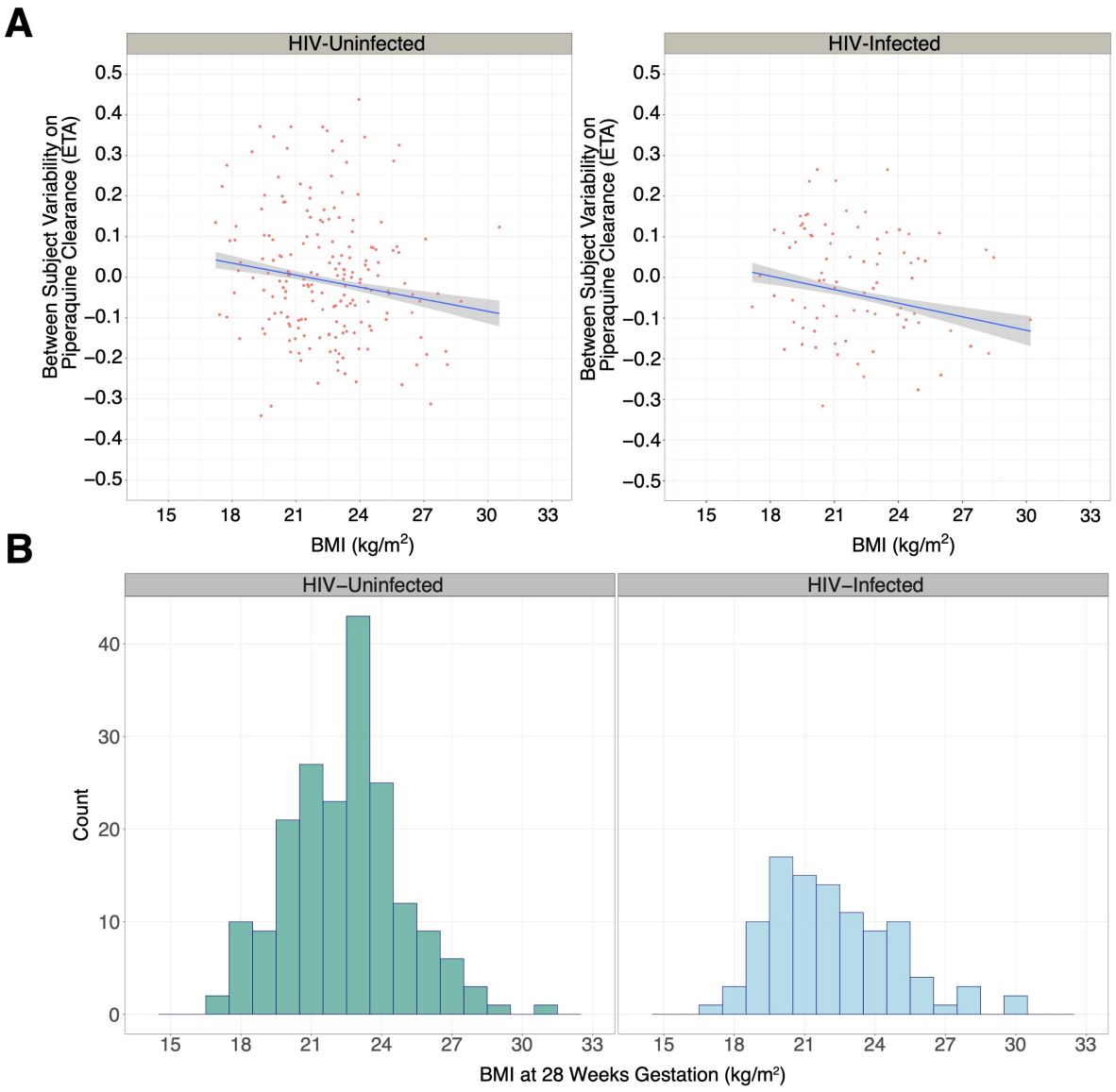


Figure S1. Goodness-of-fit plots for the final PQ model. **A**. Individual predictions versus observations. **B**. Population model predictions versus observations. **C**. Population model predictions versus conditional weight residuals **D**. Time after the first dose versus conditional weight residuals. Each black circle represents one observation. Each black line is the line of unity, and each red regression line is the model based locally weighted least-squares.



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41 **Figure S2. BMI at 28 weeks gestation**. **A.** The linear relationship between PQ

42 clearance variability and BMI at 28 weeks gestation stratified based on HIV status. Each

43 red circle represents one woman in the study. **B.** The distribution of BMI values at 28

44 weeks gestation. The median and interquartile range are 21.5 (19.4 – 22.7) kg/m^2 and

45 22.4 (20.1 – 24.1) kg/m^2 for HIV-uninfected and -infected women, respectively.

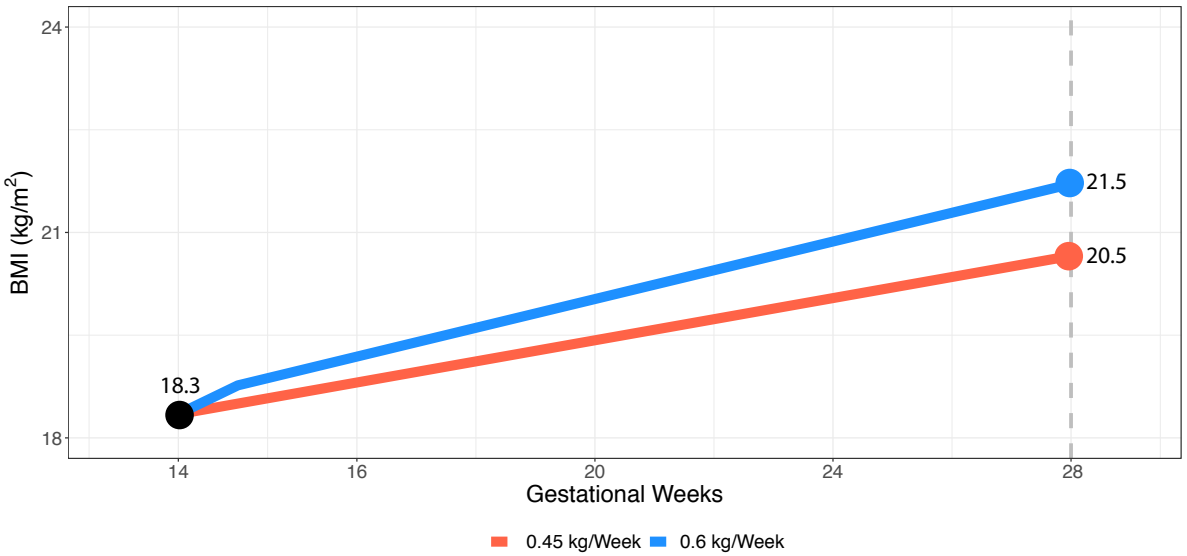

Figure S3. Second trimester BMI. Anticipated changes in BMI over the second trimester as a function of recommended weight gain guidelines during the second trimester from the Institute of Medicine (1). The minimal (0.45 kg/week) and maximal (0.6 kg/week) recommended weight gain are plotted. The week 14 BMI value (18.3 kg/m^2) was chosen based on a study participant's value.

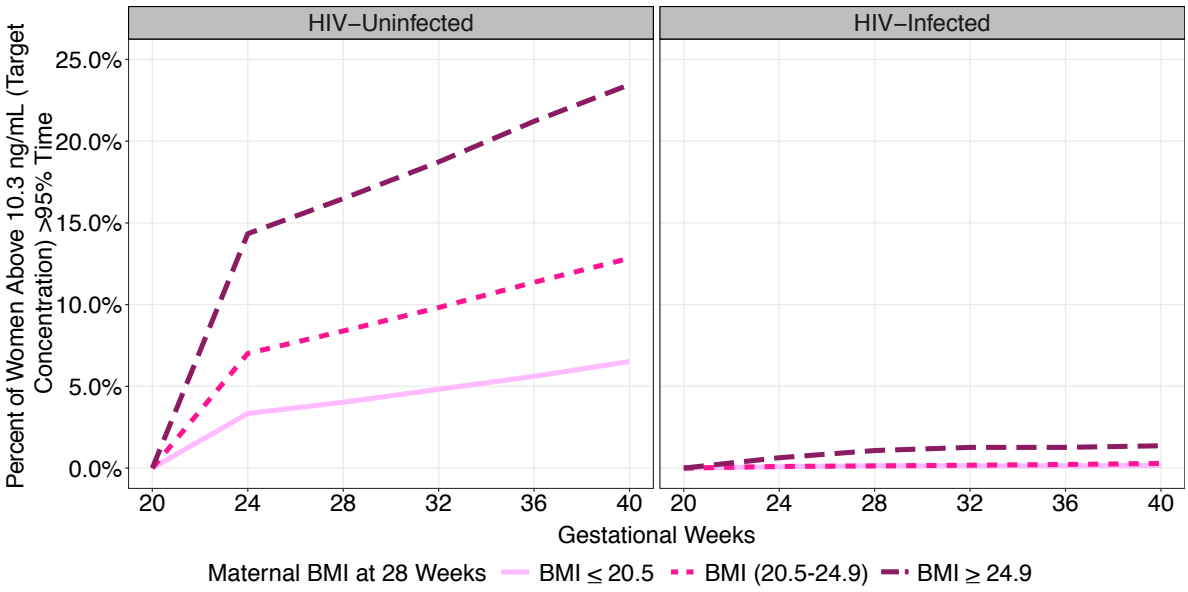

Figure S4. Weight based dosing simulations. Percent of women achieving protection based on HIV status for a monthly prevention regimen using weight-based dosing guidelines (3). Protection was defined as sustaining a PQ concentration of 10.3 ng/mL or greater for 95% of their pregnancy.

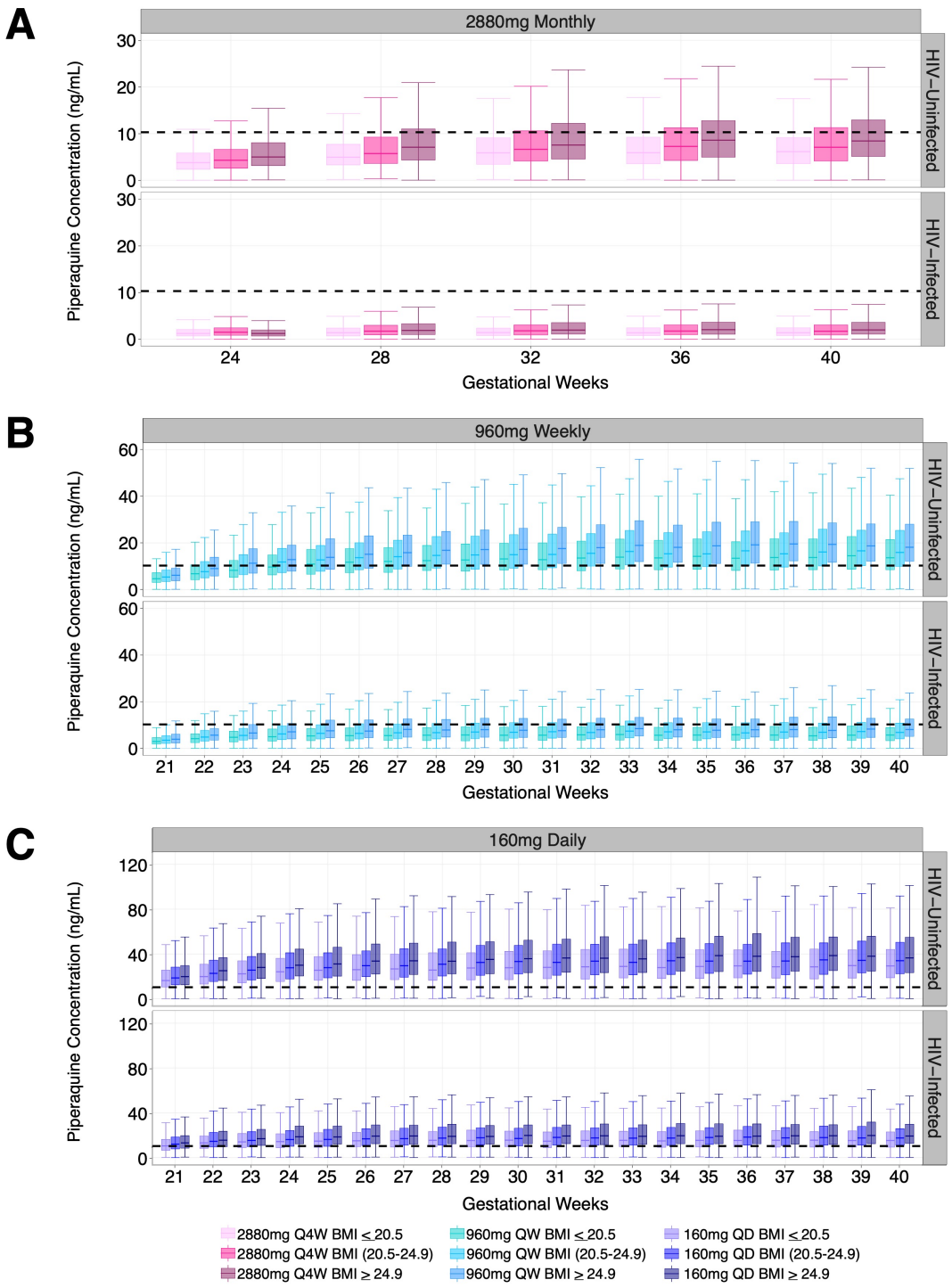

Figure S5. Simulated concentrations for alternative IPTp dosing regimens.

Simulated PQ concentrations over pregnancy stratified based on HIV status and week 28 BMI. Weekly and daily regimens are displayed with day 7 levels while the monthly

regimen is displayed with day 28 levels. The dashed line at 10.3 ng/mL marks the previously defined threshold for malaria protection in pregnant women (4). Q4W: doses given every four weeks; QW: doses given every week; QD: doses given daily.

Table S1. Maximum concentration and change in QTc interval for simulated dosing regimens

Regimen	HIV-Uninfected		HIV-Infected	
	Maximum concentration (ng/mL) [median (SD)]	Change in QTc (msec) [median (SD)]	Maximum concentration (ng/mL) [median (SD)]	Change in QTc (msec) [median (SD)]
2880 mg Monthly	289 ± 126	14.4 ± 6.31	243 ± 113	18.7 ± 8.67
960 mg Weekly	231 ± 107	11.5 ± 5.35	204 ± 89	15.7 ± 6.87
160 mg Daily	71 ± 34	3.53 ± 1.69	48 ± 25	3.67 ± 1.91

Table S2. Study participant characteristics for intensive PK sampling cohort

Characteristics	HIV-Uninfected Pregnant		HIV-Infected Pregnant
	DHA-PQ every 8 weeks (n = 17)	DHA-PQ every 4 weeks (n=13)	DHA-PQ every 4 weeks (n=28)
Age in years, [median (2.5-97.5% percentile)]	21 (18-29)	23 (20-30)	30.3 (18.2-40.4)
Gestational age in weeks, no.(%)			
16 wk	15 (88.2)	12 (92.3)	8 (28.6)
>16 to 20 wk	2 (11.8)	1 (7.7)	10 (35.7)
> 20 to 24 wk	0 (0)	0 (0)	8 (28.6)
>24 to 28 wk	0 (0)	0 (0)	2 (7.1)
Gravidity, no.(%)			
1	4 (23.5)	2 (15.4)	5 (17.9)
2	6 (35.3)	5 (38.5)	3 (10.7)
≥ 3	7 (41.2)	6 (46.1)	20 (71.4)
Weight in kg, [median (2.5-97.5% percentile)]	58.3 (49.1-76.8)	57.0 (47.3-79.2)	57.6 (43.3-71.8)
Height in cm, [median (2.5-97.5% percentile)]	162 (152-172)	165 (157-177)	163 (146-174)
BMI in kg/m^2, [median (2.5-97.5% percentile)]	22.3 (19.0-26.4)	21.7 (17.3-25.3)	22.0 (18.5-26.4)
Low BMI at enrollment, no.(%)***	1 (5.9)	4 (30.8)	3 (10.7)
Low BMI at 28 weeks gestation, no.(%)***	2 (11.8)	4(30.8)	10 (35.7)

DP; Dihydroartemisinin-piperaquine;
*** Low BMI at enrollment is defined as a BMI of less than 18.5 kg/m^2. At 28 weeks low BMI is defined as a BMI of 20.5 kg/m^2 or less to account for weight gained during pregnancy.

References:

1. Rasmussen KM, Yaktine AL (ed). 2009. Weight Gain During Pregnancy: Reexamining the Guidelines. National Academies Press Washington (DC).
2. Wanyama R, Obai G, Odongo P, Kagawa MN, Baingana RK. 2018. Are women in Uganda gaining adequate gestational weight? A prospective study in low income urban Kampala. Reprod Health 15:160.
3. World Health Organization. 2015. Guidelines for the treatment of malaria 3rd ed. Geneva.
4. Savic RM, Jagannathan P, Kajubi R, Huang L, Zhang N, Were M, Kakuru A, Muhindo MK, Mwebaza N, Wallender E, Clark TD, Opira B, Kamya M, Havlir DV, Rosenthal PJ, Dorsey G, Aweeka FT. 2018. Intermittent Preventive Treatment for Malaria in Pregnancy: Optimization of Target Concentrations of Dihydroartemisinin-Piperaquine. Clin Infect Dis 67:1079-1088.