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Pharmacokinetics of piperaquine when used as malaria chemoprevention in HIV-infected children on antiretroviral therapy in Uganda

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Introduction

- Dihydroartemisinin-piperaquine (DHA-PPQ) is increasingly used for malaria treatment and considered for malaria chemoprevention.
- These regions are often co-endemic for both malaria and HIV
- PPQ is metabolized by cytochrome p450 CYP3A4 leading to drug-drug interactions (DDI) between DHA-PPQ and antiretroviral therapy when co-administered.
- Suboptimal or elevated pharmacokinetic (PK) exposure may result with efavirenz (EFV)- and lopinavir/ritonavir (LPV/r)-based antiretroviral therapy, respectively, compromising efficacy, toxicity, and risking the emergence and/or spread of drug resistance.
- Dolutegravir (DTG), which is currently the most widely used antiretroviral in sub-Saharan Africa, has not been extensively evaluated for DDIs.

Method

- *Clinical trial design*: We conducted a prospective open-label PPQ PK study in the context of EFV-, LPV/r- and DTG-based antitretroviral regimens among HIV-infected Ugandan malaria-uninfected children alongside HIV-uninfected controls.(**Figure 1**). DHA-PPQ was given once daily for 3 days at the WHO weight-based recommended dose.

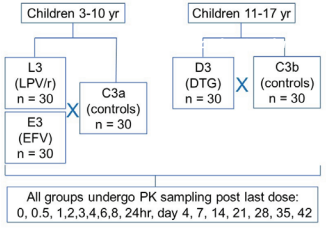

Figure 1. Study population

- *Determination of PPQ concentration*: A validated LC-tandem mass method was used to determine [PPQ][1]. The calibration range was 0.5- 250 ng/mL.
- *PK data analysis*: Noncompartmental analysis was performed with Phoenix WinNonlin version 8.3.1 (Certara, Princeton, NJ) using the linear up log down trapezoidal rule. PK parameters C_{max}, T_{max}, T_{half}, $AUC_{0\text{-}21d}$, $AUC_{0\text{-}28d}$, and $AUC_{0\text{-}42d}$ were calculated for comparison. STATA version SE14.1 was used for the statistical analyses.

Results

Two control groups were used: the older children for DTG and younger children for LPV/r and EFV (**Table 1**). PK data are shown in **Table 2-3** and **Figure 2. The box plot for day 28 and 42 PPQ** are shown in **Figure 3 and 4**.

Table 1. Demographic data of study participants

	Controls		Concomitant ART		
	10-17yr (n=30)	3-10yr (n=30)	DTG (n=30)	LPV/r (n=30)	EFV (n=30)
Age (yr) Median(IQR)	15 (13.8 – 16.3)	7.4 (6.0 – 8.7)	15.3 (13.6 - 17.1)	7.1 (6.0 – 8.7)	7.9 (6.6 – 9.1)
Weight (kg) Median (IQR)	42.4 (35.4 – 53.5)	23.6 (21.4 – 27.9)	48.7 (38.7 – 53.4)	19 (17.4 – 22.5)	21.4 (18 – 26.2)
Height (cm) Median(IQR)	152.5 (148.8 – 160.3)	123 (118.8 – 130.3)	154 (147.8 – 163.3)	115 (108.2 – 123.6)	119.8 (112.3 – 128.4)
BMI (kg/m2) Median(IQR)	18.1 (16.1 – 19.6)	15.6 (14.9 – 16.3)	20 (12.9 – 20.8)	14.8 (14.4 – 15.1)	15.1 (14.6 – 15.8)
Hemoglobin (g/dL)	12.7 (12.0 – 13.6)	11.9 (10.8 – 12.7)	13.8 (12.6 – 15.5)	12.9 (11.8- 13.6)	12.5 (11.9 – 13.0)
Male n(%)	13 (43.3)	19 (63.3%)	17(56.7%)	15 (50%)	11 (36.7)
DHA (mg/kg/dose)	2.2 (1.7 - 3.4)	2.7 (2.4 - 3.8)	2.4 (1.7 - 3.1)	3.0 (2.4-3.5)	3.1 (2.5 - 3.5)
Total weight adjusted DHA (mg/kg	6.5 (5.2 - 10.2)	8.2 (7.1 - 11.4)	7.3 (5.0 - 9.4)	8.9 (7.1 -10.5)	9.2 (7.4 - 10.5)
PQ (mg/kg/dose)	17.4 (13.9 -27.3)	22.0 (18.9 - 30.5)	19.4 (13.2 - 25.1)	23.6 (18.9 - 27.9)	24.7 (19.7 - 28.1)
Total weight adjusted PQ (mg/kg)	52.2 (41.7 - 81.8)	65.9 (56.8 - 91.4)	58.2 (39.7 - 75.2)	70.9 (56.8 - 83.7)	74.0 (59.0 - 84.2)

Table 2. PK parameters of piperaquine in children in the context of DTG-based antiretroviral therapy

	HIV+ children (DTG)	HIV- children Control		
PK parameters	GM; 90%CI (n=30)	GM; 90%CI (n=30)	GMR	P value
C_{max}, ng/mL	285 (224, 363)	272 (221, 334)	1.05	0.73
T_{max}, hr	3.04 (2.94, 6.02)	4.02 (3.00, 6.05)	1.320	0.16
$t_{1/2}$,hr*	434 (386, 487)	400 (346, 461)	1.090	0.4
$AUC_{0\text{-}day21}$, hr·ng/mL	11.5 (9.24, 14.3)	14.7 (12.5, 17.2)	0.782	0.16
$AUC_{0\text{-}day28}$, hr·ng/mL	12.7 (10.3, 15.7)	16.4 (14.1, 19.1)	0.774	0.13
$AUC_{0\text{-}day42}$, hr·ng/mL	14. 9(12.0, 18.2)	19.2 (16.6, 22.2)	0.776	0.1
C_{7d_cap}, ng/mL	39.1 (31.8, 48.0)	37.2 (29.4, 47.0)	1.050	0.68
C_{21d_cap}, ng/mL	14.0 (11.8, 16.5)	18.1 (15.5, 21.1)	0.773	0.081
C_{28d_ven}, ng/mL	5.44(4.23, 6.68)	8.01 (6.90, 9.30)	0.679	0.0199
C_{42d_ven}, ng/mL	5.01 (4.12, 6.10)	13.8 (11.0, 17.2)	0.363	<0.0001

Note: GM: geometric mean; CI: confidence interval; GMR: geometric mean ratio (DTG/control);
* n=29 for DTG and 26 for control. Tmax was median (IQR)

Table 3. PK parameters of piperaquine in children in the context of LPV/r- and EFV-based antiretroviral therapy.

	HIV+ children		HIV- children	GMR (p value)	
PK parameters	EFV (n=30)* GM; 90%CI	LPV (n=30) GM; 90%CI	Control (n=30) GM; 90%CI	EFV/control	LPV/control
C_{max}, ng/mL	243 (202, 292)	491 (397, 608)	218 (175, 272)	1.11 (0.53)	2.25 (0.0001)
T_{max}, hr	4.02 (2.97, 6.05)	3.04 (2.00, 6.02)	3.00 (2.98, 6.10)	1.34 (0.41)	1.01 (0.98)
$t_{1/2}$, hr**	209 (179, 244)	414 (364, 471)	435 (377, 502)	0.480 (<0.0001)	0.952 (0.49)
$AUC_{0\text{-}day21}$, hr·ng/mL	4.17 (3.56, 4.88)	36.7 (30.7, 44.0)	11.2 (9.71, 12.9)	0.372 (<0.0001)	3.28 (<0.0001)
$AUC_{0\text{-}day28}$, hr·ng/mL	4.33 (3.71, 5.06)	41.6 (34.8, 49.9)	12.5 (10.9, 14.4)	0.346 (<0.0001)	3.33 (<0.0001)
$AUC_{0\text{-}day42}$, hr·ng/mL	4.47 (3.83, 5.22)	49.7 (41.7, 59.2)	14.6 (12.7, 16.7)	0.306 (<0.0001)	3.40 (<0.0001)
C_{7d_cap}, ng/mL	8.16 (6.88 (9.69)	119 (96.2, 146)	28.7 (24.4, 33.7)	0.284 (<0.0001)	4.15 (<0.0001)
C_{21d_cap}, ng/mL	2.24 (1.76, 2.88)	47.0 (37.7, 58.6)	14.9 (12.9, 17.1)	0.150 (<0.0001)	3.15 (<0.0001)
C_{28d_ven}, ng/mL	1.03 (0.873, 1.22)	17.6, 13.6, 22.8)	6.41 (5.38, 7.65)	0.161 (<0.0001)	2.75 (<0.0001)
C_{42d_ven}, ng/mL	0.757 (0.645, 0.888)	17.8 (14.9, 21.3)	9.34 (7.35, 11.9)	0.081 (<0.0001)	1.91 (0.0006)

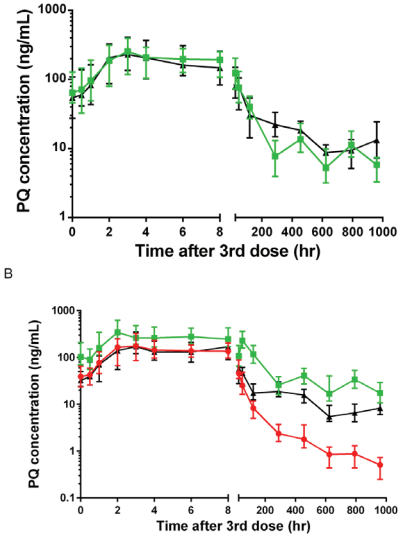

Figure 2. Mean plasma concentration versus time profile for PPQ in children. Top panel: Control (black line), DTG (green line). Bottom panel: Control (black line), LPV/r (green line) EFV (red line), data represent geometric mean, error bars represent 95% confidence interval.

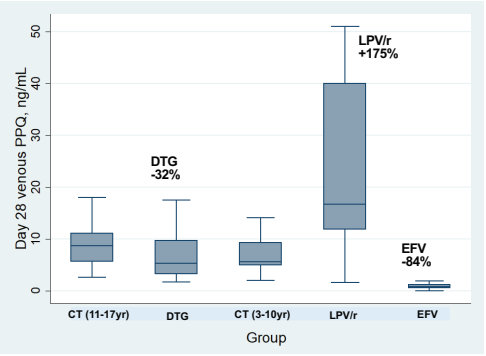

Figure 3. Box plot of day-28 PPQ in children receiving DHA-PPQ as chemoprevention with concomitant antiretroviral regimens. CT (11-17 yr), DTG controls; DTG, dolutegravir; CT (3-10yr), controls for LPV/r and EFV; LPV/r, lopinavir/ritonavir; EFV, efavirenz.

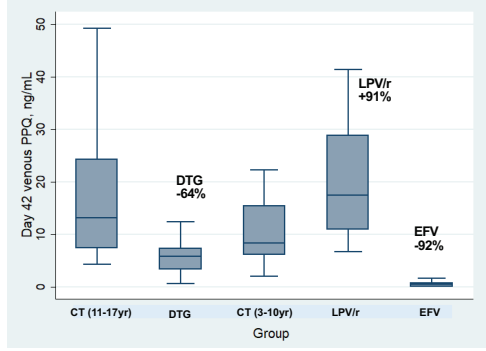

Figure 4. Box plot of day-42 PPQ in children receiving DHA-PPQ as chemoprevention with concomitant antiretroviral regimens. CT (11-17 yr), DTG controls; DTG, dolutegravir; CT (3-10yr), controls for LPV/r and EFV; LPV/r, lopinavir/ritonavir; EFV, efavirenz.

Conclusions

1. DTG did not impact PPQ total exposure but decreased terminal PPQ exposure by 1.3- to 2.8-fold.
2. LPV/r *increased* total PPQ exposure by 3.3 fold and increased terminal PPQ by 2- to 4-fold.
3. EFV *decreased* total PPQ exposure by 3-fold and decreased terminal PPQ even more significantly by 7- to 10-fold.
4. The impact of DTG and EFV on terminal PPQ *increased* over time, but the impact of LPV/r on terminal PPQ *diminished* over time.
5. HIV-infected children on EFV- and LPV/r-based antiretroviral regimens have opposing effects on PQ exposure, which may impact efficacy and toxicity, respectively, while reductions in the terminal PQ exposure in those on DTG may reduce the duration of post-treatment malaria chemoprophylaxis.

References and Funding

1. Kjellin, et al. Bioanalysis, 2014, 6 (23):3081-3089.

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