Changes in Doravirine Pharmacokinetics During Pregnancy: A Longitudinal Single Dose Study

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BACKGROUND

- Pregnancy-induced physiologic changes can significantly alter the pharmacokinetics (PK) of antiretrovirals (ARV), potentially impacting HIV control and vertical transmission
- Doravirine (DOR), a once-daily potent NNRTI with a strong safety profile, could be used during pregnancy if data were available to optimize dosing strategies during gestation, but post-marketing pregnancy PK data often lags by years post-approval
- This study described a novel single-dose (SD) PK approach to describe total and protein-unbound DOR PK in blood plasma of women living with HIV during the 2nd trimester, 3rd trimester, and post-partum

METHODS

- Single-center, phase IV, SD, longitudinal study conducted in pregnant women living with HIV (NCT04900974/IND151534)
- Pregnant women with a single gestation and normal renal function were enrolled if adherent to ARVs (HIV RNA < 50 for 3 months prior) with no drug-drug interaction risk with DOR
- Intensive SD 72hr PK profiles of DOR 100mg were performed during the 2nd (20-26wk) and 3rd (30-34wk) trimester and postpartum (4-8wk)
- Total and protein-unbound DOR concentrations were measured by validated LC-MS/MS methods with lower limits of quantification at 3 and 0.3ng/mL, respectively
- Noncompartmental PK parameters were calculated using Phoenix WinNonlin v8.6; comparisons were made using Friedman's and post hoc Wilcoxon signed-rank with Bonferroni adjustment
- Steady-state (SS) drug exposure was estimated from terminal elimination rate calculations
- Data are presented as median(range)

Significant declines in **total** and **unbound doravirine C_{24h}** were noted during pregnancy.

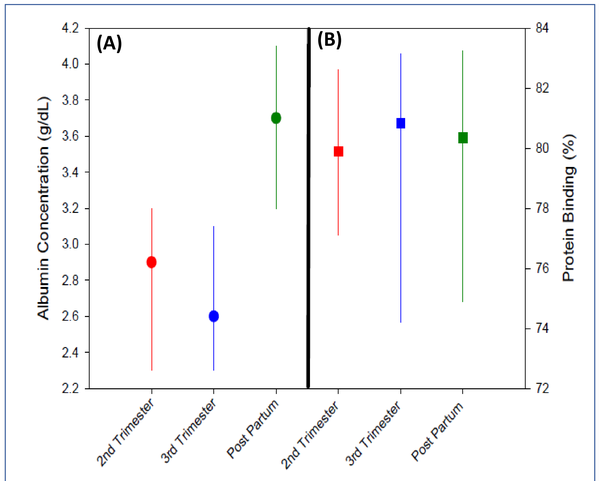


Figure 1. (A) Median (range) observed albumin concentrations across visits. (B) Median (range) DOR Protein Binding (%) across visits.

Table 1: SD and Estimated SS Doravirine PK Parameters During and After Pregnancy (n=5)

		2nd Trimester (20-26wks)	3rd Trimester (30-34wks)	Post Partum (4-8wks)	Friedman's p-value
SD Total Drug Concentration	C_{max} (ng/mL)	1,340 (884-1,420)	928 (717-1,500)	1,060 (521-1720)	0.4
	C_{24h} (ng/mL)	210 (86-292)	172 (82-330)	425 (174-475)	0.01
	AUC_{24h} (ng*h/mL)	12,219 (7,981-13,298)	9,117 (8,318-12,772)	15,880 (6,094-20,317)	0.2
Estimated SS Total Drug Concentration	C_{24h} (ng/mL)	290 (119-403)	237 (113-455)	587 (240-656)	N/A
Protein Unbound Drug Concentration	C_{max} (ng/mL)	252 (194-299)	192 (137-303)	210 (103-350)	0.2
	C_{24h} (ng/mL)	38 (18-65)	32 (16-65)	78 (35-97)	0.007
	AUC_{24h} (ng*hr/mL)	2,402 (1,707-2,576)	1,701 (1,595-2,653)	3,156 (1,261-3,673)	0.2
Estimated SS Protein Unbound Drug Concentration	C_{24h} (ng/mL)	52 (25-90)	44 (22-90)	108 (48-134)	N/A

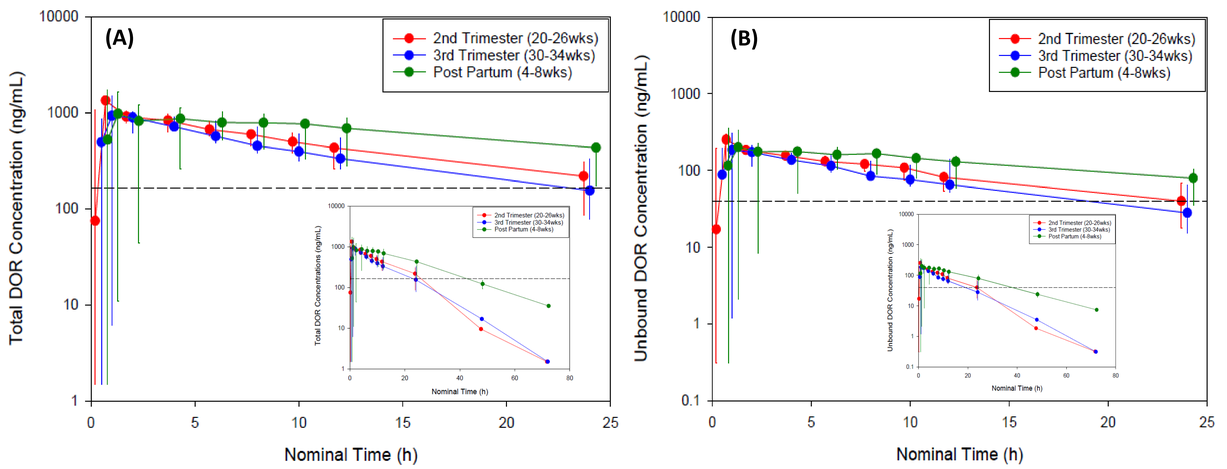


Figure 2. Median (range) observed plasma DOR concentration vs nominal time profiles (jittered for clarity). (A) Total concentrations relative to PA IC90 (---166ng/mL). (B) Unbound concentrations relative to IC90 (--- 40ng/mL). Inset graphs span 0-72hrs.

RESULTS

8 subjects were screened, 7 enrolled and 5 (1 White, 3 Hispanic, 1 Black) aged 28 (21-30)yrs with a BMI of 37 (26-49)kg/m^2 completed the study. Of those completing, 4 were prescribed TAF/FTC/BIC, and 1 was taking TDF/FTC/DTG. No AEs were noted. Albumin declined to a low of 2.6 (2.3-3.1)g/dL in the 3rd trimester, but no consistent or significant DOR protein binding changes were noted (Figure 1). SD PK profiles are summarized in Figure 2 and PK parameters are summarized in Table 1. Friedman's noted statistically significant differences in C_{24h}; however, no significant differences were found with post-hoc analysis. SS C_{24h} estimates in Table 1 were calculated using an accumulation ratio of 1.38.

CONCLUSIONS

SD PK data of DOR were collected safely. Significant declines were noted in total and unbound C_{24h} in the 2nd and 3rd trimesters compared to post-partum. While calculated SS C_{24h} concentrations are within previously identified effective concentration ranges (PMCID6437494), it would be prudent to closely monitor HIV RNA in pregnant women until clinical data (NCT05630638) are available.

PLAIN LANGUAGE SUMMARY

During pregnancy, compared to post-partum, the amount of doravirine in the body is noticeably lower by the end of the dosing interval, especially in the third trimester. Therefore, it is important to monitor HIV RNA closely until clinical data are available to determine if dose increases are necessary.

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