PBPK Modeling of Extended-Release MK-2048 Formulations for HIV Pre-Exposure Prophylaxis in Non-Human Primates

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Introduction

- Human immunodeficiency virus (HIV) remains a significant global health challenge that disproportionately affects young women in sub-Saharan Africa
- Long-acting pre-exposure prophylaxis (PrEP) vaginal dosage formulations, such as MK-2048 film or rings, are a promising strategy for HIV prevention, offering the potential for improved adherence and efficacy compared to oral dosing regimens
- The macaque non-human primate (NHP) animal model can be utilized to assess the application, formulation, efficacy, and safety of MK-2048, a second-generation integrase inhibitor
- Physiologically-based pharmacokinetic (PBPK) modeling is a valuable tool for evaluating the pharmacokinetic properties of these formulations and translating animal models to predict human concentrations

Aims

- By integrating PBPK modeling with NHP studies, we aim to provide insights into factors influencing drug absorption, distribution, and release kinetics in the vaginal fluid, vaginal tissue and plasma of NHPs; therefore, informing formulation optimization and dosing strategies for enhanced HIV prevention in at-risk populations

Methods

- Macaque non-human primate (NHP) studies involved the administration of extended-release vaginal PrEP formulations containing MK-2048 or MK-2048/Vicriviroc (MK-2048A)
- The PBPK model utilized ordinary differential equations to characterize the amount of MK-2048 drug in the blood, vaginal space, and various tissues after vaginal administration
- The model utilized the Kay et al. dapivirine PBPK model as a foundation and was modified to simulate the PK profiles of MK-2048 in NHPs using the mrgsolve package in R
- The PBPK model integrated drug-specific characteristics of MK-2048, such as protein binding, ionization, and release kinetics, alongside NHP specific physiological parameters
- After the initial adjustments to the PBPK model parameters were made, they were fixed for following simulations

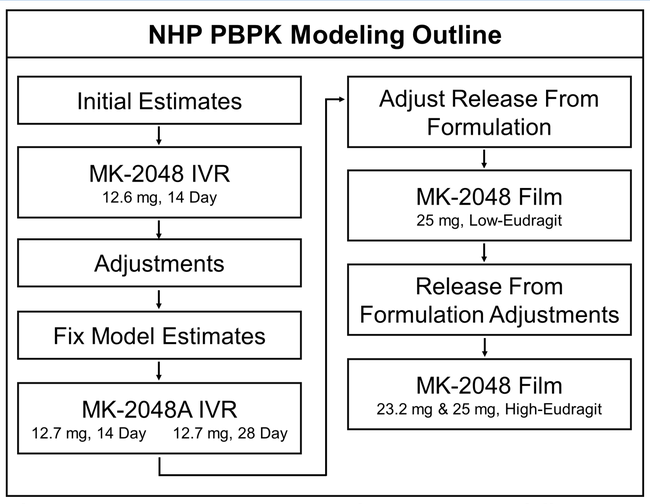

Figure A: Macaque Non-Human Primate PBPK Modeling Outline

Results

- The developed PBPK model successfully captured the pharmacokinetic profiles of MK-2048 in vaginally administered extended-release PrEP formulations in NHP models, demonstrating good agreement with observed data
- Model validation using different NHP study data confirmed the robustness and reliability of the PBPK model in predicting MK-2048 pharmacokinetics in the vaginal space and plasma
- Key adjustments to the model to capture the observed data include 1) drug species capable of moving throughout the vaginal space, 2) the first order permeation rate constants within the vaginal space, 3.) clearance parameters, 4) first order release from film formulation

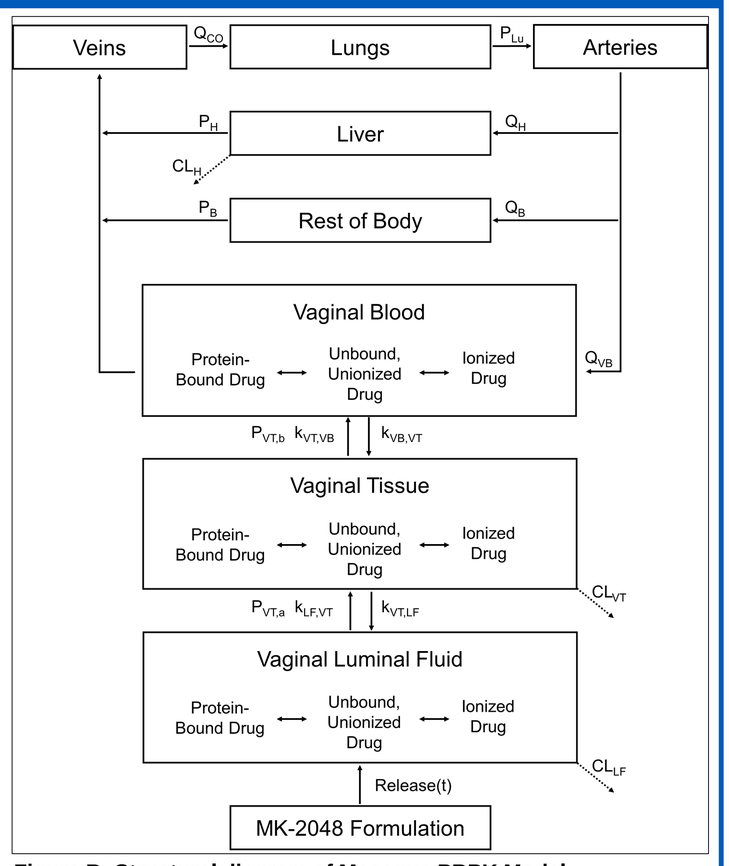

Figure B: Structural diagram of Macaque PBPK Model
LF: Luminal Fluid, VT: Vaginal Tissue, VB: Vaginal Blood, B: Rest of Body, H: Liver, Lu: Lungs, Q_i : Blood flow rate, CO: Cardiac Output, P_i: Partition coefficient, k_i: Permeation rate constant, CL_i: Clearance, Release(t): Release rate function of vaginal film or ring

Results

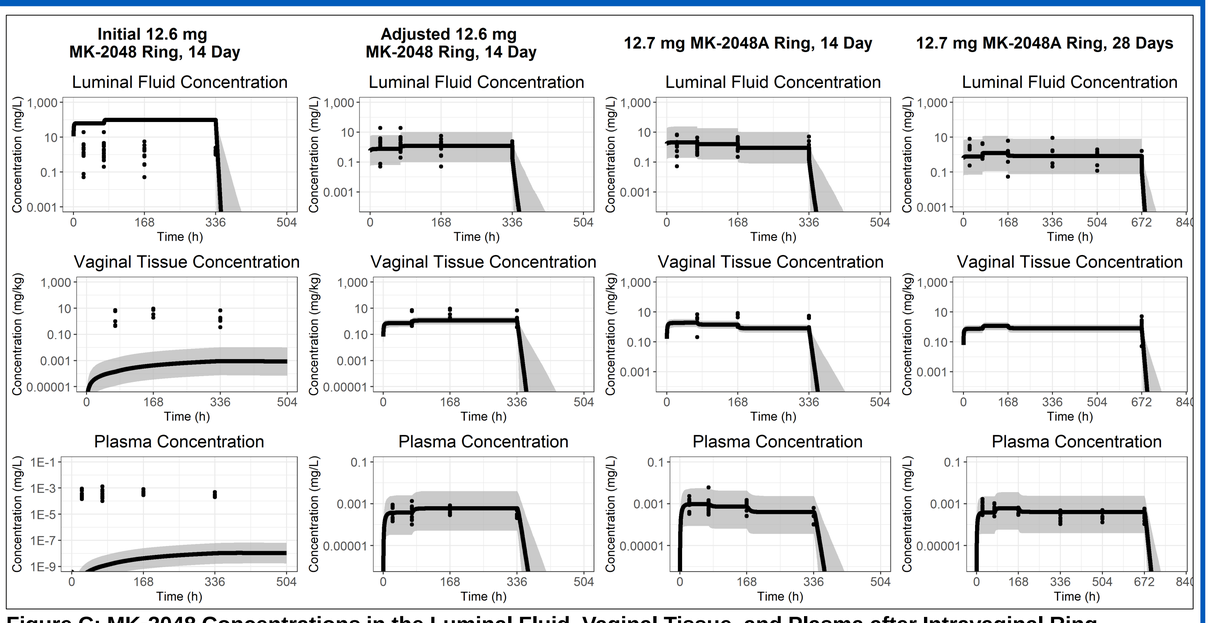

Figure C: MK-2048 Concentrations in the Luminal Fluid, Vaginal Tissue, and Plasma after Intravaginal Ring Administration in Macaques

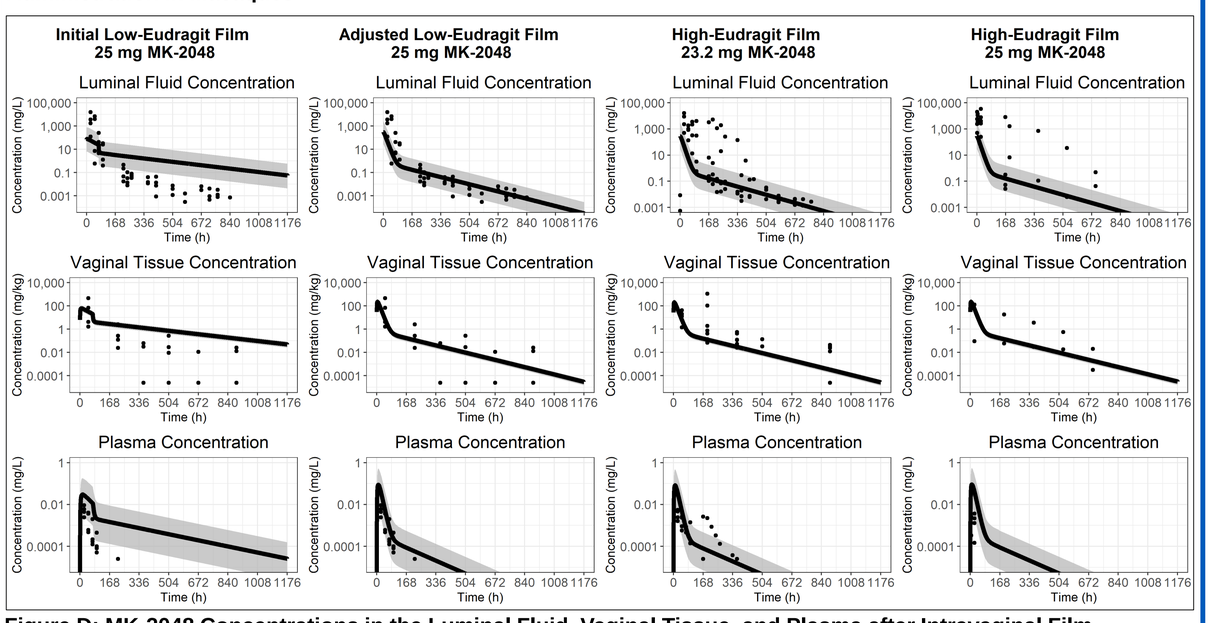

Figure D: MK-2048 Concentrations in the Luminal Fluid, Vaginal Tissue, and Plasma after Intravaginal Film Administration in Macaques

Description		Initial Estimate	Final Estimate
Rate Constants (h^{-1})	$k_{LF,VT}$	0.0003	0.7
	$k_{VT,LF}$	0.0008	0.6
	$k_{VT,VB}$	0.0008	0.05
	$k_{VB,VT}$	0.0003	0.04
Clearance (L/h)	CL_H	0.21	1.2
	CL_{VT}	0	0.005
Tissue to Plasma Partition Coefficient	$P_{VT,a}$	0	140
Release From Film Rate (h^{-1})	$k_{Film1\ (0\text{-}72h)}$	0.019	
	$k_{Film2\ (\geq 72h)}$	0.004	
	k_{Film1}		0.09
	k_{Film2}		0.085

Table 1: Initial and Final Estimates

Description		Mean Value	CV%
Weight (kg)	BW	7.8	
Volume (L)	V_{LF}	7.0E-05	100
	V_{VT}	0.0125	100
	V_{VB}	0.0025	0
	V_{Lu}	0.06	0
	V_H	0.21	0
	V_B	6.99	0
	V_{Veins}	0.35	0
	$V_{Arteries}$	0.17	0
Specific Cardiac Output (L/h/kg)		7.46	
Blood Flow Rate (L/h)	Q_{CO}	58.2	0
	Q_{VB}	0.015	0
	Q_H	19.6	0
	Q_B	38.6	0
Clearance (L/h)	CL_H	1.2	0
	CL_{VT}	0.005	0
	CL_{LF}	7.0E-5	0

Table 2: Mean Macaque Physiological Parameters

Description		Value	CV%
pH	LF	6.25	10
	Body	7	10
LogP		2.5	0
pKa		9.79	0
Rate Constants (h^{-1})	$k_{LF,VT}$	0.7	30
	$k_{VT,LF}$	0.6	30
	$k_{VT,VB}$	0.05	30
	$k_{VB,VT}$	0.01	30
Protein Binding (%)	Plasma	97.5	0
	LF	98.3	0
	VT	85.0	0
Tissue to Plasma Partition Coefficient	P_H	0.26	30
	P_B	0.39	30
	P_{Lu}	0.42	30
	$P_{VT,a}$	140	30
	$P_{VT,b}$	0.18	30

Table 3: Mean Macaque Pharmacokinetic Parameters

Conclusion

- This research highlights the utility of PBPK modeling to help understand the pharmacokinetic behavior of vaginally administered extended-release PrEP formulations containing MK-2048 in NHPs
- Integrating mechanistic insights from PBPK models with experimental data from NHP studies facilitates the rational design and optimization of PrEP formulations for enhanced HIV prevention efficacy in humans
- Leveraging NHP models to scale these findings to human populations presents a robust approach for translating preclinical data into clinically relevant strategies
- This integrated methodology emphasizes the relationship among formulation characteristics, vaginal physiology, and dosing regimens in extended-release PrEP strategies with MK-2048 and other vaginally administered formulations
- In the future, continued development and refinement of this PBPK model are essential for translating these insights into improvements in HIV prevention strategies

References

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