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Population PK Modeling of Dapivirine Released from Vaginal Rings

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Introduction

Dapivirine is a non-nucleoside reverse transcriptase inhibitor with potent antiviral activity against HIV-1. International Partnership for Microbicides (IPM) has developed a vaginal ring containing dapivirine (25 mg) to reduce the risk of HIV infection through sexual intercourse for women. These rings are placed in the upper third of the vagina resulting in a sustained release of dapivirine for at least a month. In six Phase 1 to Phase 3 clinical trials (IPM 013, IPM 024, IPM 027, IPM 028, IPM 031 and IPM 034) vaginal fluid concentrations of dapivirine were collected from the area of the introïtus and cervix by means of tear test strips. In addition plasma samples were collected. These data were analyzed simultaneously by a population PK approach. The analysis was based on 35993 samples originating from 1464 healthy, HIV-1 negative women.

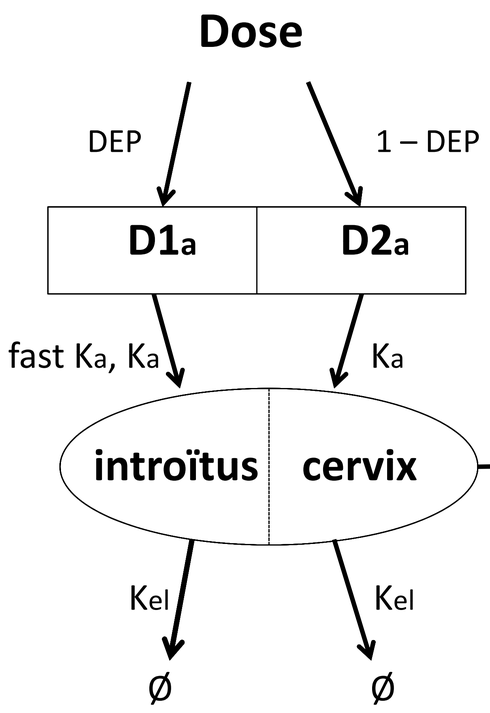
Objectives

A population PK model was built to describe the time course of vaginal fluid (introïtus and cervix) and plasma concentrations of dapivirine:

- to provide a robust aggregate for exposure from vaginal rings across the Phase 1 to Phase 3 clinical trials;
- to characterize change in exposure under different conditions or special populations.

PK model: Fluid & Fluid-Plasma

- Distribution of dapivirine to the introïtus and cervix is described by a first-order release process
- The absorption process is modeled according to a first-order process with the same estimate of rate for both fluid compartments
- During the first eight hours a faster estimate of absorption was used for introïtus (fast Ka)
- Elimination was captured by a first-order process



Implementation in NONMEM

- DEP: depot fraction going into introïtus
- D1a, D2a: depot compartments for introïtus and cervix
- Ka: first order absorption rate constant
- fast Ka : faster estimate of absorption
- Kel: first order elimination rate constant
- Ratio,pl/fl: ratio of plasma over fluid concentrations

Software

Non-linear mixed effects modeling was performed using NONMEM (v7.3.0, Method FOCE INTER) with gfortran (v5.4.0) together with PsN (v4.6.0) and R (v3.2.3).

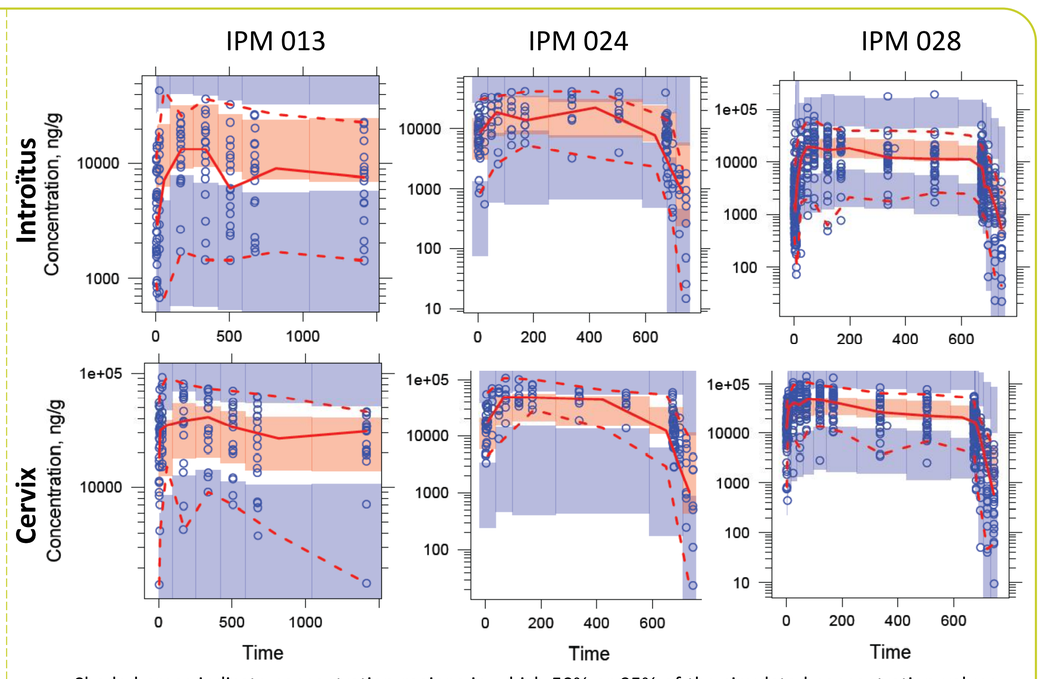
Results Fluid Model

- SCM analysis revealed that weight, age, height, pH of vaginal fluid and research center ID were statistically significant on V; and weight, age, height and bilirubin concentration were significant on Kel
- Simulations showed that only pH of vaginal fluid and research center ID were of a clinically significant effect size
- Refinement of the pruned final SCM model resulted in successful minimization and covariance steps
- Fixed and random effects parameters were estimated with good precision (CV<25%)
- Beside a slight bias due to lack of data in the initial phase, diagnostic plots showed no relevant bias
- VPCs showed that observed concentrations during ring use are predicted well
- Bootstrap results were in good agreement with the results directly obtained from NONMEM

Parameter	Estimate	IIV
Kel [h^{-1}]	0.0326	0.732
V/F [g]	11.1	0 FIX
Ka [h^{-1}]	0.000444	0.722
DEP [ratio]	0.360	0.947
fastKa [ratio]	3.03	0 FIX
V-pH	0.164	-
Vrel,Ed.	0.289	-
Vrel,Pi.	0.655	-
σ (ratio)	6.25	-
σ (introïtus)	0.712	-
σ (cervix)	0.744	0.316

*DEP on a linear scale

Final estimates of the fixed and random parameters and σ denotes the variance of the residual error at the two sample sites.



Shaded areas indicate concentration regions in which 50% or 95% of the simulated concentration values are contained. Red lines indicate calculated median and 95% coverage intervals, and circles display measured concentration values.

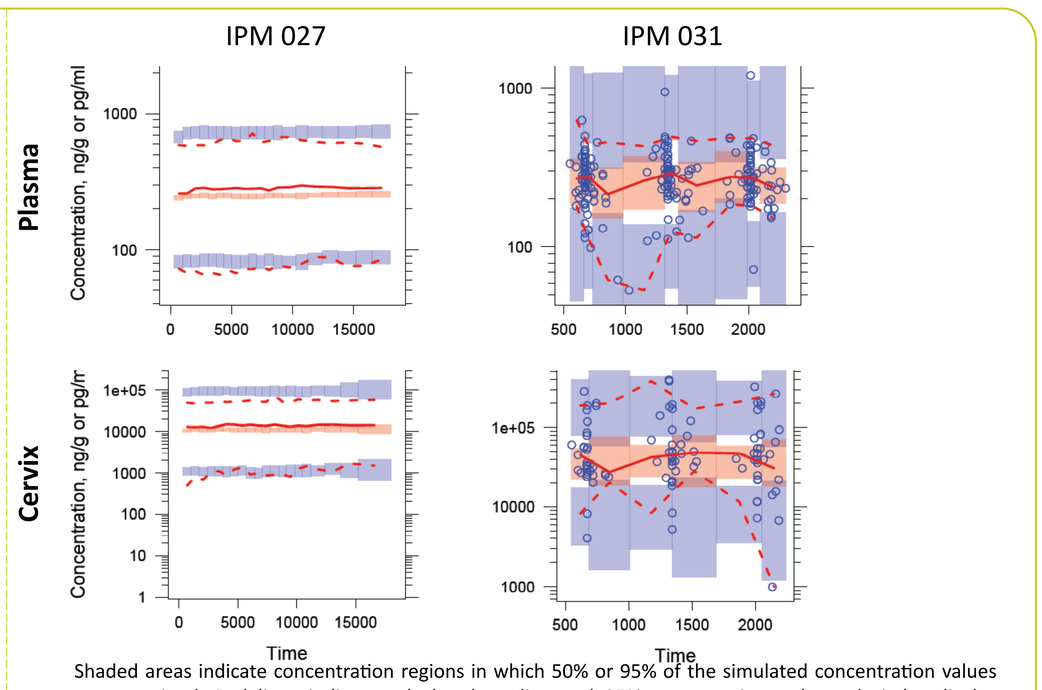
Results Fluid-Plasma Model

- To obtain successful minimization, deselection of richly sampled clinical trials and removal of plasma distribution kinetics were necessary
- Assuming a steady-state concentration ratio between plasma and fluid resulted in successful covariance steps
- Parameters were well estimated with relative standard errors generally below 25% with the exception of V (33.1%)
- VPC's for IPM 031 showed slight and more severe underpredictions for cervix and plasma respectively
- VPC's for IPM 027 showed underprediction but uncertainty in predictions was much smaller
- Bootstrap results were in good agreement with the results directly obtained from NONMEM

Parameter	Estimate	IIV
Kel [h^{-1}]	0.00546	0.248
V/F [g]	30.1	0 FIX
Ka [h^{-1}]	0.000693	0.334
DEP [ratio]	0.838	0.756
Ratio pl/fl	3.51	0 FIX
Vrel,Pi.	0.505	-
λ box-cox, IIV (ε (cervix))	1.16	-
Ifrel,IPM031	-1.82	-
σ (plasma)	0.336	0.307
σ (cervix)	0.782	0.303

*DEP on a linear scale

Final estimates of the fixed and random parameters and σ denotes the variance of the residual error at the two sample sites.



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Conclusion

Vaginal fluid concentrations of dapivirine at the introïtus and cervix could be described adequately by a non-linear mixed effects model. The pH of vaginal fluid was included as a covariate and resulted in a 22% reduction in exposure at the 90th percentile of the population. Reduced exposure at two South-African study sites (29% and 66%) might be explained by different adherence patterns of ring use that may vary according to local culture e.g. vaginal practices. A fluid-plasma link model was developed but did not perform optimally. It nevertheless yields potentially useful post hoc estimates and provides reasonable simulation properties.

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