Physiologically based pharmacokinetic modelling to support design of microarray patches delivering antiretroviral drugs to HIV positive children

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Objective

To inform islatravir (ISL) microarray patch (MAP) design and dosing regimen needed to achieve a therapeutic target concentration of islatravir-triphosphate (ISL-TP) in children living with HIV, from neonates to adolescents, by developing a physiologically based pharmacokinetic (PBPK) model of ISL.

Background

Children and adolescents living with HIV often face significant barriers in accessing treatments, with only 43% of the 1.5 million affected individuals able to receive adequate care [1]. Consequently, this population experiences a higher mortality rate. Microarray patches (MAPs) are a novel method for administering Antiretroviral (ARV) drugs to children in low- and middle-income countries that could potentially alleviate challenges related to user compliance, the need for refrigeration, and the development of formulations suitable for pediatric use.

Data and methods

A rat PBPK model was developed describing the distribution and elimination of ISL in PK-Sim® after intravenous (IV) administration using physicochemical data, *in vitro* data and parametrized towards rat IV data. We then extended the PBPK model with a dermal module in MoBi®, based on Rajoli *et al.* [2] and illustrated in Figure 1.

Intradermal diffusion:

- Drug in the microneedle is released only to the corresponding skin layer (SC, VE or DE) and hair follicles (HF)
- Release rate is a function of the needle lateral surface area (SA).
- Drug in the lesser-vascularized tissues as SC and VE will firstly dissolve from the needle in the skin layer and then permeate the underlying layers until DE. The drug in DE is directly released into the systemic circulation.
- A fraction of the drug released in SC and VE will be redirected to the HF.
- Permeability rate and drug partition coefficients were derived using quantitative structure–property relationships (QSPR) as in Gajewska *et al.* [3].

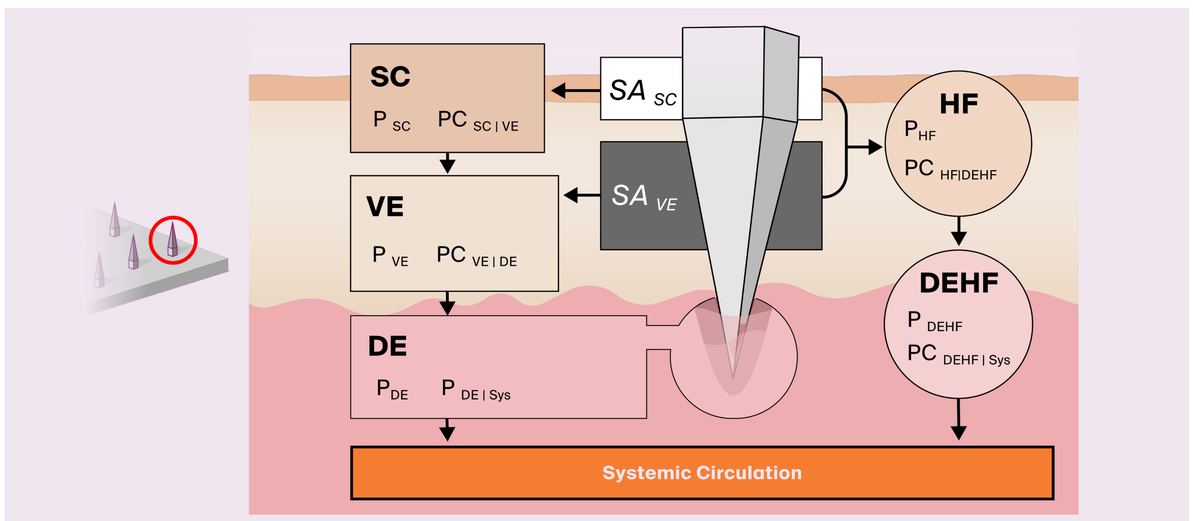

Figure 1. Schematic representation of the dermal model. Stratum corneum (SC), Viable epidermis (VE), Hair follicle (HF), Dermis (DE) and Dermis associated to HF (DEHF).

The drug release rates from the MAP needles to the skin sub-layers were described according to an empirical double-Weibull function (Equation 1). The release function parameters were identified by optimizing parameters (Table 1) towards pre-clinical MAP data (Figure 2) from Sprague Dawley Rat .

The resulting rat PBPK model was then extrapolated to human children by scaling anatomical and physiological parameters and implementing an age dependency on the thickness of different skin layers, as illustrated in Yun *et al.* [4].

Conclusions

- This analysis suggests MAPs are a viable drug delivery system for ISL, given the reasonable patch size, in children living with HIV.
- Use of ISL MAPs could improve both access and adherence to HIV treatment for this population.

Table 1. Double Weibull parameters describing Islatravir rat release profile.

Name	Value	Units
β_1	3.18	-
β_1	0.46	-
$Diss.Time_1$	24.7	Day
$Diss.Time_2$	158	Day
f_1	0.2	-

Equation 1. Double Weibull.

$$M1 = 1-\exp(-(t/\alpha_1)^{\beta 1})$$
$$M2 = 1-\exp(-(t/\alpha_2)^{\beta 2})$$
$$M = M1*f1+M2*(1-f1)$$

Where

$$\alpha = 1/Diss.Time^{\beta}$$

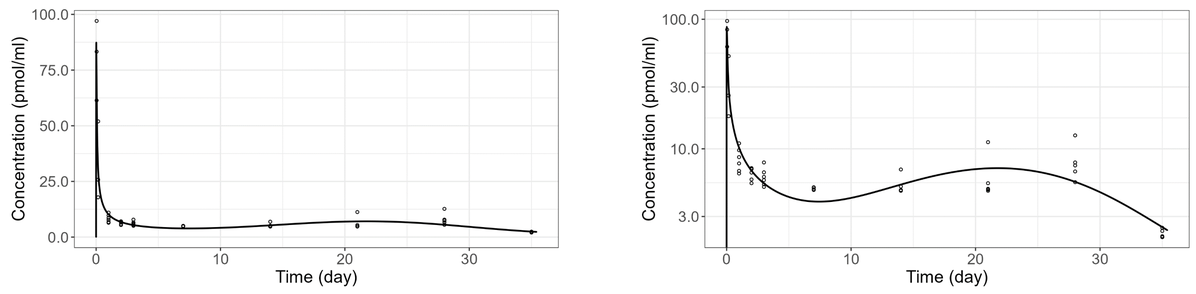

Figure 2. ISL plasma concentration in rats (left: linear scale; right: log scale) after MAPs administration (Dose = 2.66 mg/MAP, MAP = 4). Observations represented by dots and solid lines show the simulated profile.

Results

The paediatric PBPK model for ISL was used to simulate pharmacokinetic (PK) profiles after monthly administration of ISL-MAPs to human children of different weight groups (Figure 3), and the dose (i.e., number of MAPs) to achieve ISL-TP therapeutic target concentration was estimated (Table 2).

The ISL release profile required the definition of an onset day from which the whole-blood concentration of ISL-TP was above the therapeutic target. The accumulation ratio was calculated between the trough concentration at day 90 and day 30, indicating a 33% accumulation.

Table 2. Islatravir MAPs dosing per weight bands with onset defined at day 5 after administration.

Weight [kg]	MAPs [-]	Dose [mg]	Area [cm^2]
3 to 6	0.6	1.6	0.3
6 to 10	1.3	3.5	0.7
10 to 14	1.9	5.1	1
14 to 20	2.5	6.7	1.3
20 to 25	3.3	8.8	1.7
25 to 35	4.3	11.4	2.2
Above 35	6.6	17.6	3.3

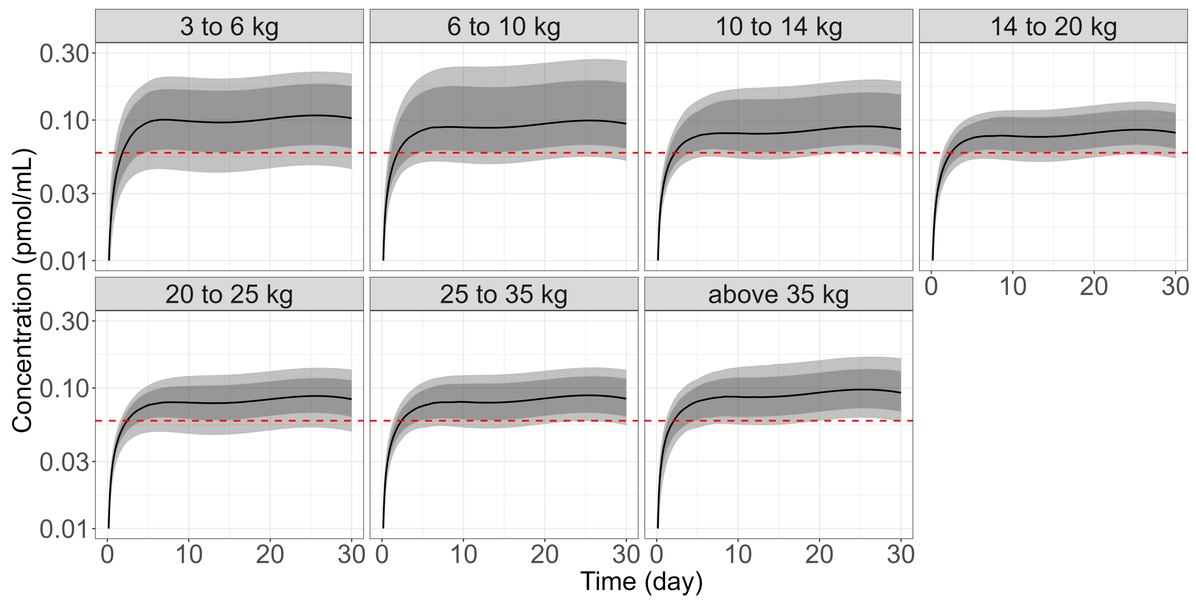

Figure 3. ISL-TP whole blood concentration after application of MAP to children in different weight bands. Solid line, dark shaded area and light shaded area represent the simulated median, the 10-90% quantiles and the 2.5-97.5% quantiles of the PBPK model for a virtual population (n=200). Red dotted line indicates therapeutic target concentration of 0.0585 pmol/ml of blood.

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