Pediatric PBPK Scaling Model for a novel Long-Acting Injectable 3-HIV Drugs in Combination

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BACKGROUND

- TLC-ART101 product contains **3 HIV Drugs (lopinavir, LPV; ritonavir, RTV, Tenofovir, TFV)** assembled in stable nanosuspension for monthly subcutaneous dosing.
- TLC-ART101 in **Phase 1** Study (*NCT06850728*).
- The Drug-combination-Nano-Particles (**DcNP**) allow for existing drug substances to become long-acting injectable ART (LA)
- In nonhuman primates (NHP), long-acting PK **mechanisms** have been verified in Physiologically based Pharmacokinetic models **(PBPK)** [1-3]
- LPV, RTV, and TFV in TLC-ART 101 are quickly absorbed by the lymphatic system, with excess appearing later in the blood (Class II). DcNP's long-acting release differs from traditional dissolution-based formulations (Class I).
- Traditional slow or controlled release rates (e.g., observed for nanocrystal or encapsulated drug) *in vitro* do not appear to relate to long-acting plasma kinetics of TLC-ART 101.
- Several works [1-3] have verified distinct drug-carrier-complex distribution and retentions in lymph nodes of TLC-ART 101 in DcNP in previously reported **MBPK and PBPK** models for the 3 HIV drug levels in the **lymph**, **plasma,** and **cells** of interests (validated with NHP data).



4 bottles
LPV/RTV liquid

+



30 TFV tablets
In TDF

=

All-in-one monthly

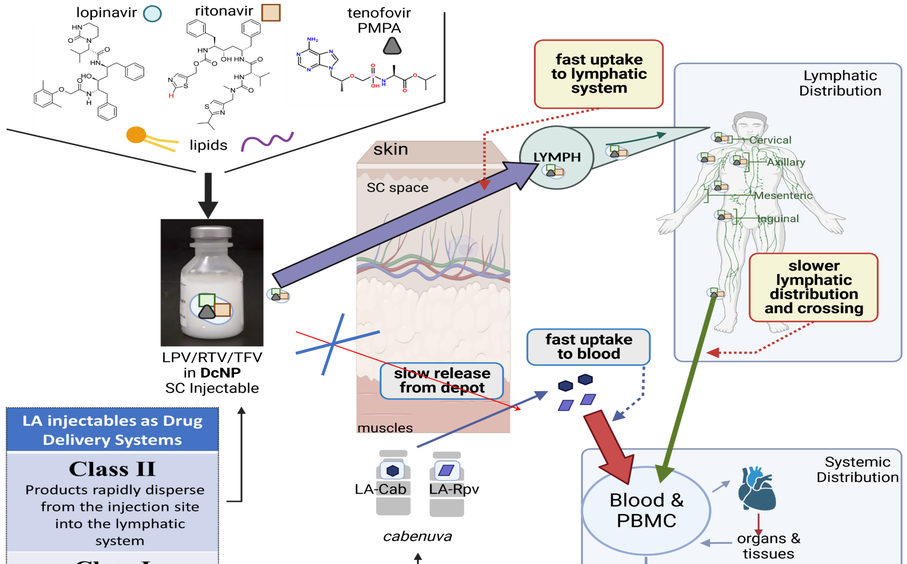
1 TLC-ART 101 Injection
(LPV/RTV/TFV)

METHODS/APPROACH

- PBPK models were validated with juvenile NHP PK data collected with Free vs DcNP dosage form.
- Scaled for each age-weight band according to developmental changes in blood flow and tissue/organs.
- Assuming equivalent plasma/drug exposure and based on developmental changes in blood flow and metabolic or elimination clearance, dose for each age-weigh band is derived.
- Weight-based dose estimates were used for comparison.
- Due to the drug-carrier-complex stability and rate control step of drug release is after distribution to lymph nodes, the classical sustained-slow-release rate driven long-acting PK no-longer applicable.
- Thus, we proposed and defined two distinct classes of LA products (and described them in detail in this abstract and on ref [3]).

OBJECTIVES

Using this PBPK model that enable simulating plasma and cell kinetics, the objectives are to further validate the model for the 3 HIV drugs combined in injectable dosage form that may be considered for **children** living with HIV.



Class I & Class II LA Product Characteristics

Long-acting injectables product classified by pharmacokinetic mechanism generating plasma extended permanence [3]

Long-acting Mechanism	Class I	Class II
Type	Depot drugs.	Drug-carrier-complex.
Distinction	Access blood by depot release.	Access blood by lymphatic transport.
Administration	IM/SC	SC
Injection site residence	$T_{1/2}$~ 1-3 months.	$T_{1/2}$ ~ 1-3 days.
PK rate-limiting step	Absorption; Release from depot ("flip-flop" PK).	Absorption; Lymphatic transport; lymph node cells distribution; Clearance; Stable carriers limit metabolic and filtration accessibility.
IVIVC predictivity	Simple; *ivivc* OK from AE tests.	Complex; Seldom *ivivc* works.
PK modeling approach	3-compartment empirical; Simple vascular (minimal) PBPK.	Mechanism-based-PK or lymphatic PBPK with 3 layers: lymphatic carrier model; carrier vascular model; free drug model.[2]
Single or Multiple (API) drug	Typically, single API.	Single (eg, mAb) and multiple (eg, DcNP).
Examples	LA-progesterone/-risperidone; LA-cabotegravir/-rilpivirine, LA-lenacapavir.	LA-mAb, IFN-gamma; acylated insulin/GLP1 micelles; LA-LRT (TLC-ART 101).

Abbreviations. ***PBPK****: Physiologically-based Pharmacokinetic model.* ***LPV****: lopinavir;* ***RTV****: tenofovir;* ***TFV****: tenofovir (PMPA);* ***IM****: intramuscular;* ***SC****: subcutaneous;* ***ivivc****: in-vitro to in-vivo correlation;* ***DDI****: drug-drug interaction (RTV perpetrator; LPV victim);* ***TLC-ART 101****: Targeted Long-Acting Antiretroviral Therapy product '101';* ***NHP****: non-human primates (macaques);* ***DcNP****: Drug-combination Nanoparticles;* ***LA****: long-acting;* ***BW****: body-weight dose scaling;* ***AE****: association efficiency;* ***LA-LRT****: long-acting lopinavir-ritonavir-tenofovir.*

RESULTS

- **PBPK model developed for injectable HIV drug combo to enable physiological dose-scaling in pediatric.**
- **Dosing guidelines by age and weight provided (Table 1).**
- **More realistic PBPK-proposed doses are lower than body-weight ones, especially in the youngest (e.g., infants may need 3/5-fold lower mg than adolescents or <10-folds than adults).**
- **Low-to-none drug-drug interactions (DDI) due to RTV presence are expected in pediatrics, as studied in [3] .**
- **Lymphatic and mononuclear cell concertation predictions for all 3-drugs are possible in pediatrics, as demonstrated in [2,3].**

Table 1. Entry safe dosing in pediatrics by age/weight bands for TLC-ART101 long-acting monthly injectable. Body-weight (allometry) vs PBPK dose proposals.

Age/weight band	lopinavir		ritonavir		tenofovir	
Adults [a]	*16 mg*		*4.1 mg*		*9.2 mg*	
	BW	PBPK	BW	PBPK	BW	PBPK
10-18y, or>30kg	9.0 mg	10 mg	2.0 mg	2.0 mg	4.2 mg	4.5 mg
6-14y, or 20-30kg	7.0 mg	4.1 mg	1.9 mg	1.7 mg	3.5 mg	3.8 mg
3-6y, or 14-20kg	5.0 mg	3.5 mg	3.0 mg	2.5 mg	3.0 mg	2.0 mg
1-3 y, or 10-14kg	3.0 mg	0.65 mg	2.0 mg	0.65 mg	1.8 mg	0.8 mg

a. First-in-human entry doses that proved safe (preliminary results from *nct06850728*)

INFERENCE

- **Entry safety pediatric dosing for TLC-ART-101 are proposed with PBPK model validated with NHP data and integrating metabolic changes in developmental stage of children**
- **PBPK modeling for Class II showcased including of lymphatic system, mononuclear cells, organ/lymphatic system maturations and drug-drug interactions**

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