Transformation of 3 current *short-acting* HIV drugs, Tenofovir, Lamivudine and Dolutegravir (TLD) into a novel, *all-in-one long-acting* TLD 3-drug-combination in a single injectable dosage that produces extended pharmacokinetics

Zachary R Stephen, Simone Perazzolo, Jason Lo, Xiaolin Xu, Yuqian Zhao, Masa Eguchi, Matthew Hartman, Christine Jonsson, Ann C Collier, Ann J Melvin, **Rodney JY Ho**

Rodney JY Ho-Presenter

INTRO

- **Long-acting Cabenuva** contains two HIV drug products, LA-cabotegravir + LA rilpivirine given in 2 injections
- **Long-acting HIV treatment** with Cabenuva is considered a game-changer to overcome pill fatigue and remain undetectable for People living with HIV
- **The two drugs** in Cabenuva LA-CAB and LA-RPV are given in 2 injections in the buttock muscles in clinics

OBJECTIVES

To develop a Next-Gen long-acting TLD 3-HIV drug combination product in a single subcutaneous injection for PLWH worldwide

METHODS

- The 3 drugs in TLD (tenofovir, lamivudine and dolutegravir) are stabilized with two lipid excipients under a controlled process to produce a ***Drug-combination Nano-Particle (DcNP)** product.
- The TLD-in-DcNP dosage form is stable and scalable to support pharmacokinetic studies in primates
- TLD-in-DcNP is evaluated for the optimal composition, particle size, suitability for scale up and proceeding to primate study
- The optimized TLD-in-DcNP injectable dosage form is given subcutaneously to non-human primates, *M. Nemestrina* under institutional (IACUC) approved protocol.
- A single subcutaneous dose of TLD-in-DcNP (6.2/5/10) mg/kg is given to NHP and plasma time-course is determined.

RESULTS

The optimal preparation of TLD-in-DcNP formulation process includes

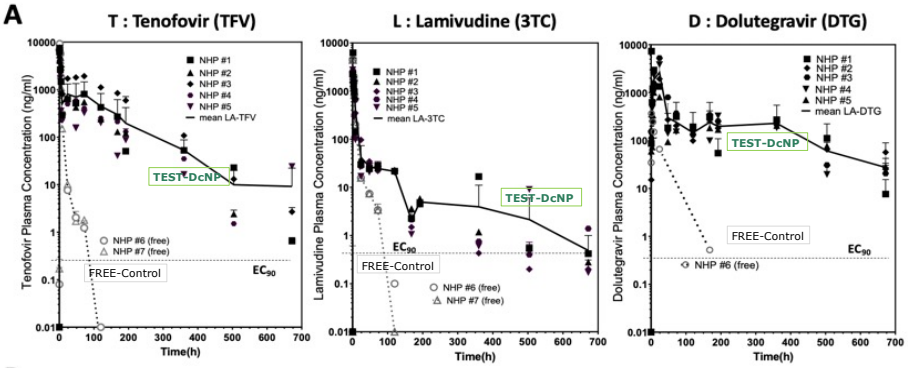
- Dissolving TLD with two lipid excipients in buffered alcoholic solution
- Controlled solvent removal to produce TLD-DcNP powder product
- Resuspend in sterile buffered-saline
- Size reduction by homogenization
- Final sterile product with 60-80nm TLD-in-DcNP, which is stable in suspension

Oral 3-drug Short-Acting-TLD are transformed with DcNP* into a Long-Acting 3-HIV-drug-combination product for subcutaneous self-dosing

About UW Targeted Long-acting Combination Anti-Retroviral Therapeutic program

The TLD-in-DcNP formulation exhibits a long-acting plasma time-course for all 3-drugs

A



B

Parameters	Tenofovir (TFV) DcNP	Tenofovir (TFV) Free	Lamivudine (3TC) DcNP	Lamivudine (3TC) Free	Dolutegravir (DTG) DcNP	Dolutegravir (DTG) Free
Time-to-peak (hr) [a]	**1.0**	1.0	**1.0**	1.0	**16** ± 4.0	1.0
C_{max} (µg/mL)	**6.1** ± 0.7	6.7	**3.0** ± 0.8	2.1	**2.0** ± 1.2	0.37
$AUC_{0\text{-}4w}$ (hr•µg/mL)	**146** ± 41	21	**20** ± 2.0	9.5	**173** ± 19	8.5
AUC ratio (DcNP/Free)	**7.0**		**2.1**		**20**	
$t_{1/2,z}$ (hr)	**88** ± 35	8.6	**74** ± 16	8.9	**112** ± 34	19

TLD in DcNP form and free mixture TLD were both given SC and scaled at same dose of 6.2, 5.2 and 10 mg/kg, for TFV, 3TC, and DTG, respectively. NCA values are given as mean ± SEM

Table 1. TLD concentration ratio between PBMC and plasma when TLD is formulated in DcNP (*TLD-in-DcNP*)

	PBMC/plasma drug ratio in NHP dosed with *TLD-in-DcNP*					
	Tenofovir (T)		Lamivudine (L, 3TC)		Dolutegravir (D)	
N of NHP	48 h	168 h	48 h	168 h	48 h	168 h
2	2.1	3.3	1.1	3.6	29	5.2
2	1.8	3.2	3.1	6.1	25	3.8
4	2.0	3.3	2.1	4.9	27	4.5

NHP, non-human primates *M. Nemestrina* were given a single subcutaneous injection of *TLD-in-DcNP* dosage form as described in the materials and methods. The peripheral blood mononuclear cells (PBMC) were immediately isolated from blood samples and analyzed for drug concentrations. Data were expressed as PBMC-to-plasma drug ratio as mean of two set of 2 NHP.

The 3-HIV drugs (TLD) formulated in DcNP Long-acting dosage form provide HIV-host lymphocytes with higher plasma drug level (>1); it may provide higher degree of viral suppression

Ref: current oral pills in PLWHIV achieve cell-to-plasma ratio typically less than 1

The TLC-ART Team has successfully developed a DcNP process that transforms Short-acting to Long-acting TLD; increases AUC/dose
All 3 drugs, together in this one dosage form may provide a Long-acting HIV treatment to overcome pill fatigue and remain undetectable.

*DcNP: Drug-combination Nano-Particle Platform Technology

**Targeted, Long-acting, Combination Antiretroviral Therapy (TLC-ART) program, University of Washington, Seattle, USA

Supported by Unitaid 2020-39-GLAD and NIH grants #AI-120176; AI-148005; AI-149665
Presented at IAS 2023, the 12th IAS Conference on HIV Science

IAS 2023 23–26 July