Poster # 487

# Long-acting 3 HIV-Drugs-in-One Nanoparticle Formulation Intended for Adolescents

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## Introduction

An estimated 2.1 million children worldwide are living in HIV. However, the development of therapeutics aimed at children and adolescents has been limited with limited oral combination antiretroviral therapies (cART). Also, data indicates that only about 30% of adolescents experiences durable viral suppression. Even in cases with plasma viral suppression, residual virus can be isolated from tissues, particularly lymph nodes. Therefore, we have developed a drug combination nanoparticle (DcNP) containing three drugs with will-established antiviral potency and safety in pediatrics, targeting three different stages in the viral replication; protease inhibitor lopinavir (LPV), nonnucleoside reverse transcriptase inhibitor efavirenz (EFV), and nucleoside inhibitor tenofovir (TFV).

## Purpose

The objective of this study was to characterize targeted and long-acting effects of our validated 3-drug single DcNP formulation in HIV host cells and plasma in non-human primates for two weeks.

## Methods

Macaques were given a single dose of the DcNP subcutaneously. The drug concentrations in plasma, peripheral blood, and lymph nodes mononuclear cells were analyzed for two weeks. The pharmacokinetic parameters and cell-to-plasma relationship of the three drugs were determined.

The 3 drugs with different hydrophobicities (LPV, EFV, TFV: logP 4.7, 4.46, -3.6) were stabilized in one DcNP nanosuspension. The formulation was well-tolerated in non-human primates and no local reactions were noted. We found that the protease inhibitor (LPV) and reverse transcriptase inhibitor (EFV, TFV) levels persisted in plasma for the two week duration of the study (figure 1). Intracellular levels for all three drugs also persisted for two weeks and exhibited higher levels, especially for EFV and LPV, than those found in plasma. The pharmacokinetics of plasma and PBMC concentration-time profiles were analyzed and are shown in table 1. All three drugs had persisting lymph node drug concentrations at day 8 and by that time point the levels in the nodes were about equivalent to plasma for TFV and 65-222-fold higher for LPV and EFV (table 2).

## Results

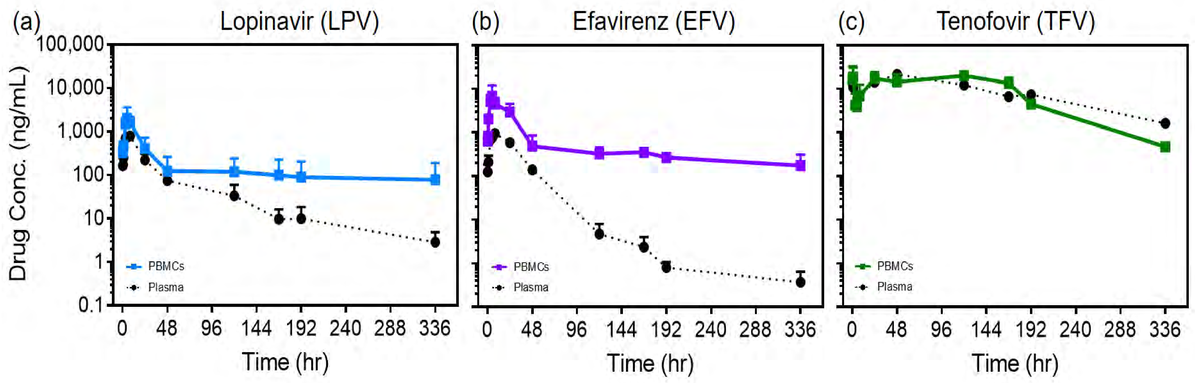



**Figure 1. Time-course of plasma and PBMC and LNMC intracellular concentrations of LPV, EFV, and TFV after a single SC dose of the drug combination nanoparticle (DcNP) suspension.** The squares (■) represent PBMC intracellular drug concentrations, and circles (●) represent plasma drug concentrations. Each time point represents arithmetic mean ± SD of plasma and PBMC intracellular drug concentrations from N=2 male pigtail macaques following a 25.0 mg/kg LPV, 16.7 mg/kg EFV, and 22.6 mg/kg TFV SC dose. PBMC and LNMC cell volume was assumed to be 0.2829 pL/cell.

**Table 1.** Plasma versus PBMC intracellular PK parameters for LPV, EFV, and TFV after a single SC dose of the drug combination nanoparticle (DcNP) suspension.

| | Lopinavir (LPV) | | Efavirenz (EFV) | | Tenofovir (TFV) | |
|---|---|---|---|---|---|---|
| | Plasma | PBMCs | Plasma | PBMCs | Plasma | PBMCs |
| $AUC_{0\text{-}336h}$ (hr•μg/mL) | **20.8** (19.9) | **59.0** (90.0) | **27.7** (11.0) | **211.2** (35.2) | **3,004.1** (3.3) | **3,146.3** (6.1) |
| $C_{max}$ (μg/mL) | **0.8** (22.5) | **2.2** (62.4) | **1.0** (0.7) | **7.1** (67.1) | **21.7** (1.7) | **25.4** (17.8) |
| $T_{max}$ (hr) | **8.0** (0.0) | **6.5** (32.6) | **8.0** (0.0) | **4.0** (35.4) | **48.0** (0.0) | **12.3** (135.6) |
| $t_{1/2}$ (hr) | **91.9** (7.3) | **308.9** (121.7) | **61.6** (4.1) | **418.0** (114.8) | **75.4** (9.1) | **38.8** (11.4) |

**Table 2**. LPV, EFV, and TFV intracellular concentrations in inguinal lymph nodes excised one and eight days after a single SC dose of DcNPs, and comparisons to drug levels at the same time points in PBMCs and plasma.

| | Lopinavir (LPV) | | Efavirenz (EFV) | | Tenofovir (TFV) | |
|---|---|---|---|---|---|---|
| SC Dose (mg/kg) | 25.0 | | 16.7 | | 22.6 | |
| **LNMCs** | | | | | | |
| $C_{24h}$ (μg/mL) | **0.76** | (3.9) | **17.91** | (0.13) | **17.23** | (43.9) |
| $C_{192h}$ (μg/mL) | **0.65** | (107.1) | **0.18** | (0.12) | **6.83** | (0.6) |
| **LNMCs/PBMCs** | | | | | | |
| $C_{24h}$ | **1.9** | (77.9) | **6.0** | (63.3) | **1.0** | (77.5) |
| $C_{192h}$ | **7.3** | (77.9) | **0.7** | (17.2) | **1.5** | (3.4) |
| **LNMCs/Plasma** | | | | | | |
| $C_{24h}$ | **3.5** | (40.7) | **30.5** | (30.7) | **1.2** | (36.6) |
| $C_{192h}$ | **65.0** | (39.5) | **221.7** | (21.6) | **0.9** | (5.2) |

## Conclusions

Collectively, this 3-in-1 DcNP formulation provided long-acting plasma drug concentrations and enhanced HIV host-cell localization in cells in blood and also lymph nodes.

This anti-HIV DcNP formulation should be considered for development intended for pediatrics. With a long-acting profile and higher penetration/persistence in cells, it has strong potential to enhance therapeutic efficacy of these well-studied HIV drugs due to co-localization of a combination of three drugs.

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