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First in Human Clinical Trial of a Next Generation, Long-Acting Injectable, Combination Antiretroviral Therapy Platform - Phase I Study

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Abstract

Phase I Study

Prospective, open-label, first-in-human study, with a pharmacologically-guided adaptive design for dose escalation, de-escalation and study duration.

The primary objectives are:

1. To characterize the plasma concentration-time course and pharmacokinetics (PK) of a single dose of the drug substances of TLC-ART 101 (LPV, RTV, TFV) administered by subcutaneous injection.
2. To characterize the safety and tolerability of a single subcutaneous injection of TLC-ART 101.
3. There are 4 exploratory mechanistic objectives (with related endpoints)

Guidelines

NIAID Clinical Trial Implementation Cooperative Agreement (U01) via PAR-18-633, Rachel Bender Ignacio, MD MPH (PI) (AI-148055)

Proposed IND Sponsor: Rodney Ho, PhD
IND Number: 133249
Protocol Chair: Rachel Bender Ignacio, MD, MPH
DAIDS Medical Officer/Medical Monitor: Pablo Belaunzaran Zamudio, MD, MSc
DAIDS Program Officer: Keith Crawford, RPh, PhD

Version Number: 9.0 (Date 14Mar2024)

The study will be conducted in accordance with the relevant, current protocol and will not make changes without permission of DAIDS, except when necessary to protect the safety, rights, or welfare of study participants. Informed consent and Ethics Committee or Institutional Review Board review and approval are required. Adverse experiences will be reported as per DAIDS policies and procedures.

LIST OF ABBREVIATIONS

	A	B
	Ab	antibody
	ACTG	AIDS Clinical Trials Group
	ACTU	AIDS Clinical Trials Unit
	AE	adverse event
	Ag	antigen
	AIDS	acquired immunodeficiency syndrome
	ALT	alanine aminotransferase
	API	active pharmaceutical ingredient
	ART	antiretroviral therapy
	ARV	antiretroviral
	asap	as soon as possible
	asses.	assessment
	AST	Aspartate aminotransferase
	ATV	atazanavir

	A	B
	AUC	area under the concentration-time curve
	BLQ	below the limit of quantification
	BP	blood pressure
	BUN	blood urea nitrogen
	CAP	College of American Pathology
	cART	combination antiretroviral therapy
	CBC	complete blood count
	CDER	Center for Drug Evaluation and Research (of the FDA)
	CFAR	Center for AIDS Research
	cGMP	Current Good Clinical Manufacturing Practice
	CMO	contract manufacturing organization
	Cmax	maximum concentration
	CRE	creatinine
	CFR	Code of Federal Regulations
	C-T	concentration-time
	CTSA	Clinical and Translational Science Award
	d	day
	d/c	discontinuation
	DAIDS	Division of AIDS
	DcNP	drug combination nanoparticle
	DMC	Data Monitoring Committee
	DMF	drug master file
	ECG	electrocardiogram
	EDTA	ethylenediaminetetracetic acid
	eGFR	estimated glomerular filtration rate
	EIA	enzyme immunoassay
	ETOH	ethanol (meaning alcohol to drink)

	A	B
	FDA	US Food and Drug Administration
	Fed Ex	Federal Express
	FIH	first-in-human
	ftn	function
	FSH	follicle stimulating hormone
	GCP	Good Clinical Practice
	GCLP	Good Clinical and Laboratory Practice
	GLP	Good Laboratory Practice
	GMP	Good Manufacturing Practice
	HBV	hepatitis B virus
	HCG	human chorionic gonadotropin
	HCV	hepatitis C virus
	Hg	mercury
	HIPAA	Health Insurance Portability and Accountability Act
	HIV-1 denoted as HIV	human immunodeficiency virus type one
	hr(s)	hour(s)
	Hx	history (as in medical or medication)
	IDRI	Infectious Diseases Research Institute
	IDS	Investigational Drug Service
	IMPAACT	International Maternal Adolescent AIDS Clinical Trials
	IND	investigational new drug (application)
	Inj.	injection
	INR	international normalized ratio
	IRB	institutional review board
	IU	international units
	IUD	intrauterine device
	ITHS	Institute of Translational Health Sciences

	A	B
	IV	intravenously
	K	clearance rate
	LA	long-acting
	LLoQ	Lower limit of quantification
	LN	lymph node
	LNMC	lymph node mononuclear cells
	LoQ	limit of quantification
	LPV	lopinavir
	MBPK	mechanism-based pharmacokinetic
	MC	metabolic correction
	med.	medical
	meds	medications
	mg	milligram
	min	minutes
	mL	milliliter
	MOPs	Manual of Procedural Operations (Manual of Operations)
	mos	months
	MS	mass spectometer
	NHP	non-human primate
	ng	nanogram
	NNRTI	non-nucleoside reverse transcriptase inhibitor
	NRTI	nucleos(t)ide reverse transcriptase inhibitor
	OA	Other Clinical Trial Related Attachments
	OTC	over the counter
	PBMCs	peripheral blood mononuclear cells
	PBPK	physiologically-based pharmacokinetic
	PE	physical exam

	A	B
	PeP	post-exposure prophylaxis (for HIV)
	pg	picogram
	PI	protease inhibitor
	PK	pharmacokinetics
	PrEP	pre-exposure prophylaxis (for HIV)
	Pt.	participant
	PT	prothrombin time
	PTT	partial thromboplastin time
	QA	quality assurance
	QC	quality control
	QD	daily
	RC	renal clearance
	RoS	review of systems (symptom review)
	RTV	ritonavir
	SAE	serious adverse event
	SC	subcutaneously
	SOE	Schedule of Events
	SOPs	standard operating procedures
	SST	serum separator tube
	T1/2	half-life
	Tmax	time of maximum concentration
	TAF	tenofovir alafenamide
	TDF	tenofovir disoproxil fumarate
	TLC-ART	targeted long-acting combination antiretroviral therapy
	TFV	tenofovir
	TFV-dp	tenofovir-diphosphate
	tox	toxicology

	A	B
	TRU	Translational Research Unit
	U/A	urinalysis
	UAB	University of Alabama
	UCol	University of Colorado
	UW	University of Washington
	UWMC	University of Washington Medical Center
	Wk	week
	x	fold (as in fold change)

INTRODUCTION

Background Information

Effective treatment for HIV has changed the course of the disease from progressive immune system deterioration with associated opportunistic diseases and premature death to a chronic manageable disease for individuals who are diagnosed with HIV, have access to antiretroviral therapy (ART), and adhere to treatment and care (1). Access to effective antiretroviral treatment continues to expand, with an estimated 21.7 million persons globally receiving ART as of the end of 2017 (2).

Modern antiretroviral regimens most often contain three active compounds taken orally once daily (3,4). The short-term goal of ART is to achieve suppression of plasma virus below the limit of detection with modern clinical HIV RNA assays (generally <50 copies/mL). While modern regimens are much simpler than in the past, subsets of individuals are still unable to successfully achieve virological suppression (5). Globally, it is estimated that at least 11 million persons prescribed ART have not achieved virologic suppression. Barriers to adequate ART adherence include lack of belief in ART, poor social support, active mental health issues and/or substance abuse (6-9). For children with HIV, the caregivers' role in administering antiretroviral therapy is key but can be challenging. Adolescents are particularly at risk for poor adherence due to emotional and mental immaturity; rates of adherence in adolescent populations are frequently lower than that observed in adults (10).

Multiple strategies have been proposed to help improve adherence (reviewed in 11) but few have been shown to be consistently effective. Directly observed therapy was shown in a pilot study to improve rates of adherence in injection drug users (12). However, other trials of modified forms of directly observed therapy in less specialized patient populations failed to show positive impact on either adherence or virologic suppression (13, 14). Problem solving has been shown in some settings to improve adherence and virologic outcomes, but the expertise needed may not be available in most clinical settings (15). Intermittent text messages to Kenyan adults improved adherence and rates of virologic suppression during initial antiretroviral therapy (16), but this result was not reproduced in a multinational study of persons living with HIV failing 2nd line ART (17). A pilot "High Needs Clinic" for HIV infected individuals who have been unable to stay engaged in care or unable to achieve virologic

suppression in standard care settings has improved engagement in care and virologic suppression rates using strategies including walk in appointments and conditional economic incentives (18).

There is high interest in long-acting, injectable regimens (reviewed in 19). For many persons living with HIV, intermittent ART administration would require less organizational skills and fortitude than taking daily oral medications. Shortly before U.S. FDA approval, a survey of 400 HIV-infected, ART-experienced patients underscored the interest in long-acting combination antiretroviral therapy, with 61% of respondents indicating they would probably or definitely be interested in weekly ART (20). Experience with other diseases, including diabetes mellitus and hypogonadism, have demonstrated that home administration of parenteral medication is feasible (21-23). Phase 3 studies of a long-acting, dual drug regimen provided as two intramuscular injections every month have been reported and this regimen was approved by the US FDA for treatment of HIV (24).

Parenteral combination formulations also have potential advantages in settings where ART cannot be given orally. Until recently, it was impossible to provide a standard recommended combination of antiretroviral drugs parenterally and is still challenging to combine parenteral antiretrovirals. Clinical settings, other than poor adherence or providing patients with options, where combination parenteral formulations would be useful include:

• critically ill patients in intensive care settings,
• settings where oral therapy is prohibited, such as perioperative periods, and
• persons with persistent, uncontrolled nausea or vomiting (e.g. gastroenteritis, chemotherapy) who are unable to take oral ART.

Parenteral formulations of drugs engineered to provide a slow, more sustained pharmacokinetic profile may also have potential advantages over oral administration of the same drugs if toxicities are related to peak concentrations, such as the central nervous system side effects of efavirenz (25). In addition, by avoiding the first pass metabolism that occurs in the gastrointestinal tract with orally administered drugs, it is possible that a lower total dose of parenteral medication might be as effective as a higher oral dose.

TLC-ART Platform Background

The University of Washington's Targeted Long-Acting Combination Antiretroviral Therapy (TLC-ART) program supports research that has a long-term goal of developing one or more safe, scalable, and well tolerated long-acting injectable combination treatments for HIV/AIDS. The TLC-ART program discovered, and validated in animal studies, a novel way to combine drugs (a platform) which is capable of stabilizing insoluble and soluble antiretroviral drugs together in a nano-drug combination suspension (26). This drug-combination platform is suitable for scale up and manufacture as an injectable pharmaceutical dosage form (reviewed in 27). This novel drug combination nanoparticle exists as a stable drug combination (DcNP) suspension. When existing short-acting antivirals are combined into these DcNPs, the drug molecules are stabilized by lipid excipients at concentrations that have been shown to be safe (at higher doses) in humans. A lead formulation (called TLC-ART 101) combines three FDA-approved drugs available generically – the protease inhibitors lopinavir (LPV) and ritonavir (RTV) and the nucleotide reverse transcriptase inhibitor tenofovir (TFV).

These three FDA-approved active drug substances have been in clinical use for approximately 20 years as Kaletra® (800 mg LPV and 200 mg RTV, PO) and Viread® (300 mg TFV PO as tenofovir disoproxil fumarate [TDF]) (28, 29). The 4:1 ratio of LPV to RTV is used so that RTV enhances (boosts) the exposure of LPV due to a drug-drug interaction (30). This is also the reason that RTV was included in the TLC-ART 101 DcNP formulation. The development of the TLC-ART formulations began when protease inhibitors were part of first-line ART, explaining the rationale for these drugs to be part of the first TLC-ART formulation to be tested. Subcutaneous injection of TLC-ART 101 in pre-clinical animal studies has demonstrated significant and controlled extension of the drug substances' concentrations in plasma out to 2 weeks for all 3 drugs (26, 31). This is the justification for a human study.

Substantial safety and efficacy data have been collected for these drug substances and lipid excipients from (1) pre-clinical animal studies, (2) clinical studies, and (3) long-standing clinical use in humans (26, 31-34). Most data are included in the regulatory filings and other published manuscripts for these FDA approved, commercially available drug products (35,36). Additionally, the plasma drug concentration ranges associated with effective HIV suppression are known for these drug substances(28,29), allowing for adjustment of the TLC-ART 101 formulation or other TLC-ART formulations once human pharmacokinetic scaling factors are characterized.

Available pharmacokinetic data for injectable TFV formulations both in human and non-human primates (NHPs) support scaling of the data and the proposed dose (providing an estimated 2%, 2%, and 3% of the oral FDA-approved doses (37). These data align closely with the general scaling factor information included in the FDA Center for Drug Evaluation and Research guidelines "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers".

However, there is currently no injectable LPV formulation for humans to inform dose selection and PK predictions for TLC-ART 101. In the absence of existing IV LPV human data, it is not possible to predict with confidence the dose-response plasma concentration-time course for LPV.

TLC-ART 101 has been studied in more than 20 NHP and produces LA plasma drug concentrations for at least 14 days, transforming the human plasma half-lives of oral LPV, RTV and TFV from 6, 5, and 7 hours, respectively, to approximately 150-250 hours (26, 28, 29, 31). There are a number of variables in scaling doses between NHP and man with respect to metabolic and elimination clearance capacities. The proposed study will provide the necessary first-in-human PK data for the plasma concentration-time course of the three active drug substances in the TLC-ART 101 formulation, and thus allow better inter species scaling to more accurately predict dosing frequency for humans. (See the Investigator's Brochure and Rationale for Initial Dose and TLC-ART Formulation sections below for summaries of the preclinical studies.)

Prior to the inception of the TLC-ART program, Dr. Ho and his colleagues demonstrated pharmacologic drug-insufficiency in cells isolated from lymph nodes (38) which led to the development of the TLC-ART DcNP technology to enable first-pass drug exposure in lymph node cells/tissue (26, 34). While the concept of pharmacologic drug insufficiency in lymph nodes is less well accepted than immunologic insufficiency (39, 40), the TLC-ART Program intentionally focused platform technology with three characteristics:

• LA PK,
• combination of ARVs, and
• enabling cell targeting
with a long-term plan to facilitate sustained viral suppression using a LA injectable dosage form for HIV treatment.

The first DcNP developed by the TLC-ART program is TLC-ART 101 and combines lopinavir (LPV), ritonavir (RTV, as a booster) and tenofovir (TFV) in the presence of lipid excipients.

As described above, based on NHP study data as well as mouse DcNP injection site disposition data (26, 31, 41), the TLC-ART program developed a preliminary quantitative physiologically driven mechanism based PK model (42) suggesting that DcNP leave the site of injection, target cells in lymph nodes, followed by PBMCs and plasma. In mice and NHPs, almost all DcNPs are cleared from the SC site of injection; about 64-70% of a single SC dose of LPV, RTV and TFV is distributed and retained in lymph nodes (presumably trapped within the sinuses) and 30% of the DcNP-formulated drugs are found in blood plasma (42). It is appropriate to validate these preclinical data with human data.

Antiretroviral Drugs (Active Pharmaceutical Ingredients) in TLC-ART 101

Lopinavir and ritonavir are protease inhibitors (PIs) and were approved by the FDA in 2000 as a combined formulation (Kaletra®) for treatment of HIV in combination with other antiretrovirals. Kaletra® was in widespread use in adults for over 10 years as part of initial and second-line antiretroviral regimens until other PIs and integrase inhibitors were demonstrated to be as or more effective and better tolerated. PIs are still in use globally. A reliable estimate of the number of persons who have been treated with lopinavir-containing regimens is not available in the public domain, although in 2011, it was estimated that 180,000 persons globally were receiving second-line ART, with the vast majority taking lopinavir-containing regimens (43).

Multiple side effects have been described when the oral formulation of Kaletra® (800 mg LPV and 200 mg RTV) is taken chronically daily in persons living with HIV, although it is not anticipated that such signs, symptoms, or laboratory abnormalities will be likely to occur after the single low dose of TLC-ART 101 administered in this study. The most common adverse events occurring in the 2,600 adults living with HIV participating in the Phase II-IV clinical trials of Kaletra® were diarrhea, nausea, vomiting and elevations of triglycerides and total cholesterol (28). One of the most notable issues with the use of oral ritonavir is its inhibition of CYP3A4 and the resulting potential for impacting the metabolism of many other drugs (adverse drug-drug interactions).

Tenofovir disoproxil fumarate (Viread®, commonly known as TDF) was the first formulation containing a prodrug of TFV to be approved by the FDA for treatment of HIV (in combination with other antiretrovirals); this occurred in 2001 (29). TDF remains part of initial recommended ART regimens globally as well as in the U.S. and has thus been used by millions of people for prolonged periods of time (years). In addition, this agent is FDA-approved for use for treatment of hepatitis B virus infection and in a combination formulation with another drug for HIV pre-exposure prophylaxis in persons without but at risk for HIV. More recently, in 2015, a newer prodrug formulation of TFV, tenofovir alafenamide (TAF), was approved for treatment of HIV as part of several combinations and has been used extensively by PLWH in the U.S. and selected other countries. As stated above for lopinavir and

ritonavir, most available human data about tolerability and side effects of TDF and TAF are from chronic oral daily dosing and may not be applicable to the single low dose of TFV that will be administered in this study as TLC-ART 101. The most common side effects described for TDF from over 12,000 adults in clinical trials or expanded access programs are rash, diarrhea, headache, pain, depression, asthenia and nausea (29). The most notable potential toxicity of TFV is renal toxicity, which is most common in individuals who have pre-existing renal disease, co-morbidities that affect the kidneys or are treated with concurrent nephrotoxins (29) In addition, in persons with HIV, TDF treatment is associated with higher rates of bone mineral density loss than other antiretroviral agents (44). The clinical profile of TAF suggests less impact on markers of kidney function and bone turnover, and bone mineral density than TDF (45,46) although some concerns about weight gain with this formulation have emerged

Inactive Ingredients

The TLC-ART 101 formulation contains two lipids that are included on the FDA's inactive ingredients list:

• 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and
• polyethylene glycol -lipid [N-(carbonyl- methoxypolyethyleneglycol-2000)-1,2-distearoyl-sn glycero-3-phosphoethanolamine (mPEG2000-DSPE).

The FDA considers inactive ingredients to be a component of a drug product other than the active ingredients (47). These are substances intentionally added to products which are not intended to exert therapeutic effects at the intended dosage; they may act to improve product delivery (e.g., enhance absorption or control release of the drug substance).

The two lipid excipients in TLC-ART 101 are used in several different FDA-approved intravenous medications including the following two liposomal preparations. DSP**C** is contained in DaunoXome (daunorubicin liposome injection) and mPEG2000-DSPE is contained in Doxil® (doxorubicin hydrochloride liposome injection). At the FDA-approved doses of these medications for adults treated for certain malignancies, the two lipid excipients are considered safe according to current data as well as data in the drug master files (DMF) #25436 and #20221 for these formulations, filed with the FDA, and which Corden has provided to the TLC-ART Program investigators. A different form of PEG-2000 is used in the COVID-19 mRNA vaccines, for which more than a billion global doses have been given.

DSPC (1,2-distearoyl-sn-glycero-3-phosphocholine; CAS No. 816-94-4)
DaunoXome was administered by intravenous infusion; the liposomal formulation contained 2mg/mL daunorubicin and 28.16 mg/mL DSPC (and cholesterol) (48). FDA-approved dosing recommendations for treatment of Kaposi's sarcoma with this formulation were 40 mg/m2 to be infused over one hour (every two weeks). The dose for an average adult (1.9 mg/m2) (49) corresponds to 76 mg of daunorubicin and 1070 mg of DSPC. The initial TLC-ART 101 dose proposed in our first-in-human study will contain 150 mg of DSPC (in a subcutaneous injection), approximately 14% of the dose of this excipient in a dose of DaunoXome. (If the initial PK results in this adaptive design study require us to increase the dose of TLC ART 101, we propose to increase the dose by 2-fold, which would contain 300 mg of the DSPC excipient or approximately 28% of the excipient in one dose of DaunoXome.)

mPEG2000-DSPE (polyethylene glycol-lipid [N-(Carbonyl-methoxypolyethyleneglycol-2000)-1,2- distearoyl-sn-glycero-3-phosphoethanolamine]) (CAS No. 147867-65-0)
Doxil® is administered by intravenous infusion over 1 hour; the liposomal formulation contains 2 mg/mL doxorubicin and 3.19 mg/mL of the MPEG2000-DSPE excipient (50). The FDA-approved dose of the liposomal form of doxorubicin for treatment of ovarian cancer is 50 mg/m2 every 4 weeks. This dose of liposomal Doxil® for the average adult (1.9 mg/m2)(49) corresponds to 95 mg of doxorubicin and 151.5 mg MPEG2000-DSPE. The TLC-ART 101 dose proposed in the first-in-human study proposal will include up to 60 mg of the MPEG2000-DSPE excipient in a single subcutaneous injection, or approximately 40% of the amount of this excipient in a dose of Doxil®. If the initial PK results in this adaptive design study require us to increase the dose of TLC-ART 101, the 2-fold higher dose of TLC-ART 101 would contain 120 mg of the MPEG2000-DSPE excipient, about 80% of the amount contained in a dose of Doxil®. Thus, the TLC-ART 101 doses will contain lower amounts of these excipients than are used currently in products that have been approved by the FDA.

The TLC-ART 101 formulation is a nanosuspension, not a liposomal preparation and will be administered by subcutaneous injection, not by intravenous infusion. Over 144 subcutaneous injections of TLC-ART 101 have been given to non-human primates in single dose and multiple dose studies and very limited injection site reactions or adverse events have been noted only after multiple injections (see below).

Following a single subcutaneous injection in rats at doses up to 60 mg/kg, there were no adverse events and, similarly, after single injections in dogs, there were no adverse events at 16 mg/kg.

In multiple dosing studies in rats (5 injections, once a week) done under Good Laboratory Practices (GLP), a maximum tolerated dose (MTD) could not be established but was considered to be higher than 30 mg/kg. This was due to the lack of clinically relevant dose-related findings in any dose group including the excipient (inactive ingredients) control group. In GLP multiple dosing studies in beagle dogs (5 subcutaneous injections, once a week), the MTD was determined to be 3.64 mg/kg as the dogs exhibited reactions following multiple injections although there were none noted after the 1st injection of TLC ART 101.

The no adverse effects levels of TLC-ART 101 in the above mentioned GLP weekly dosing studies were 1.5 mg/kg in rats and 0.4 mg/kg in dogs. These levels were largely based upon injection site reactions that occurred in both species after multiple injections and largely resolved by day 72, 6 weeks after the last of the five injections.

Injection site reactions in excipient (inactive ingredient) controls in multi-dose studies (weekly dosing) in rats and dogs were seen in both species, with the following caveat “suggesting effects of the formulation excipients and/or injection procedures” (51, 52). The injection site findings in these multi dose studies decreased in severity and incidence in the animals observed for six weeks after the last dose of TLC-ART 101, demonstrating recovery from the effects. Modeling done based upon preclinical studies done in non-human primates suggest that the TLC-ART 101 formulation will move from the site of injection to the lymphatic system and achieve lower peak concentrations in the blood than medications administered intravenously (42). No data are available about the PK of these excipients after TLC-ART 101 administration.

TLC-ART 101 Rationale for Initial Dose

The initial dose of TLC-ART 101 was chosen for scientific and pragmatic reasons. In pre-IND discussions with the FDA, they indicated that doses 5-8% of the approved oral doses of the three drug substances, LPV, RTV, and TFV, would be acceptable for a first-in-human study of a TLC-ART formulation. The table below shows the relationship of the oral daily dose of these drug substances to the proposed initial dose of TLC-ART 101 and show that they are within the dose range the FDA suggested would be acceptable.

	Oral adult daily dose	Proposed initial SC dose in TLC –ART 101	% of oral daily dose
LPV	800 mg	15.59 mg	1.9%
RTV	200 mg	4.12 mg	2.1%
TFV	300 mg as TDF	9.17 mg	~3.1%

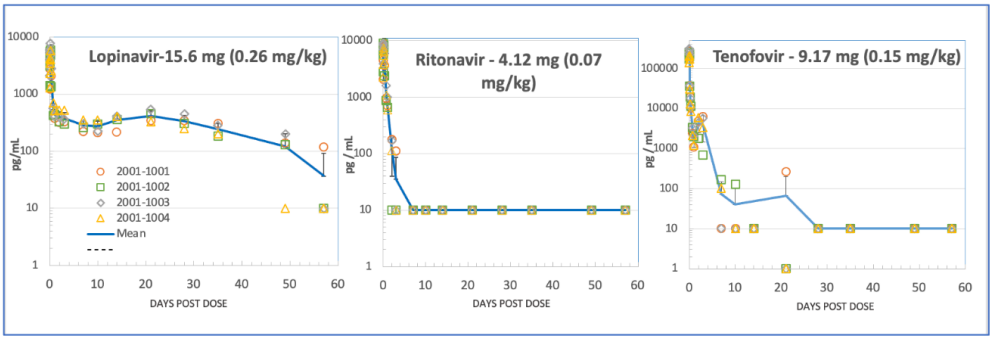
Since one of the primary objectives of this study is to characterize the pharmacokinetics of the active agents in TLC-ART 101, it is important to be confident that we be able to quantify the drug substances in this study. Ed Acosta, PharmD, of University of Alabama, Birmingham, has established GLP assays for the three drug substances with lower limits of quantification of 100 pg/mL (53,54). Dr Acosta's group has a ABSCIEX 6500+ QTrap LC-MS/MS system which makes drug quantitation 10 times more sensitive.

Modeling and simulation work done by our group, based upon multiple non-human primate studies, with allometric scaling adjusting for inter-species metabolic clearance difference, suggests that the plasma concentrations of the drug substances should be quantifiable for 2-4 weeks (Perazzolo S, Shireman L, McConnachie L, Koehn J, Kinman L, Lee W, Lane S, Collier A, Shen D, Ho RJY, "Integration of Computational and Experimental Approaches to Elucidate Mechanisms of First-Pass Lymphatic Drug Sequestration and Long-Acting Pharmacokinetics of the Injectable Triple-HIV Drug Combination TLC-ART 101." J Pharm Sci. 2020, 109(5):1789-1801. DOI: https://doi.org/10.1016/j.xphs.2020.01.016).

In addition, we have successfully formulated TLC-ART 101 in a formulation and concentration that would allow administration of the above listed doses in 1.7 mL, making it feasible for subcutaneous injection.

TLC-ART 101 Rationale for the Cohort 2 Dose

The initial dose resulted in detectable levels of LPV for the duration of the study (57 days) but no RTV was detected by Day 5 and only 1 participant had TFV detectable up to 20 days, the others had detectable levels for 14 or less days. All 3 peak (C_{max}) concentrations were within the safe limits as previously studied with oral formulations.

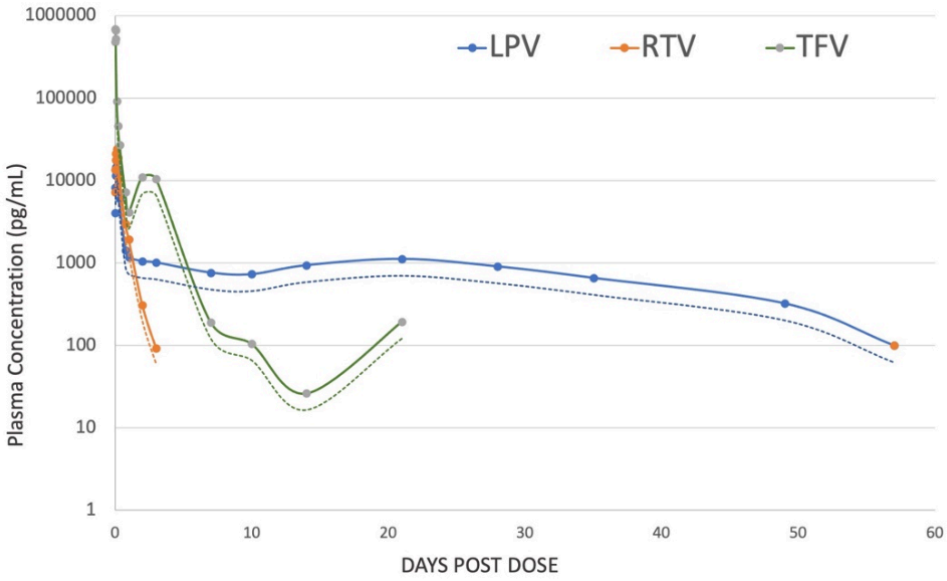


We hope that by administering the maximum volume that we had previously proposed as fitting well within the acceptable volume of fluid injected into the subcutaneous abdominal tissue (2 × 2mL injections), we will be able to keep the Cmax of each drug within what has been demonstrated for either the FDA-approved oral formulations of these drugs (LPV and RTV) or within what was shown to be safe in Phase I-II studies of higher oral or intravenous doses of tenofovir products[28,29,37]. We hope to further define the PK tail of each of the drugs, understand whether the concentrations scale linearly or otherwise with dose increase, and develop an improved understanding of safety of the product administered subcutaneously.

Therefore, we propose a 2.67x dose increase to the maximum suggested 2 injections of 2ml of TLC-101. This dose would contain:

LPV = 2 ml x 2 injections x (10.4 mg/ml) = 41.6 mg
RTV = 2ml x 2 x (2.8 mg/ml) = 11.2 mg
TFV = 2ml x 2 x (6.1 mg/ml) = 24.4 mg

Using non-compartmental modeling based on the Cohort 1 dose, we expect to see the following pharmacokinetics with a 2.67-fold dose increase. Because the kinetics after the drug reached below the limit of quantification (100pg/mL) are not known, increasing the dose would help us understand the subsequent kinetics better. Having two distinct dosing regimens will further allow modeling to understand future development of DcNP ART.



Projected LPV/RTV/TFV concentrations after a 2.67x dose increase to 4mL of total TLC-101 administered (solid lines) or a 1.67x dose increase to 2.5mL (dashed lines).

Risks of the interventions (LPV, RTV and TFV as well as the lipid matrix)

The risks of the interventions for the single TLC-ART 101 dose are minimal based on accumulated preclinical toxicology data and clinical experience using oral LPV and RTV as prescribed in Kaletra®, TFV in the oral prodrug of TDF as prescribed in Viread®, and the excipients in other FDA-approved drugs. Antiretroviral regimens are dosed lifelong, so the clinical experience is with regimens taken daily for months or years. As noted above, daily doses of Kaletra® contain 800mg LPV and 200 mg RTV and a daily dose of Viread® contains 300 mg of TFV. The Cohort 2 dose of TLC-ART 101 will contain 41.6 mg LPV, 11.2 mg RTV and 24.4 mg TFV in addition to the excipients. Thus, the initial first-in-human TLC-ART 101 single dose contains 2, 2 and 3% of the above oral daily dose of the three drug substances; the subsequent proposed single-dose is still no more than 8% of the oral daily dose of any of the three drugs. With no adverse effects noted with single doses of TLC-ART 101 in rats, dogs and non-human primates, including animals who received doses proportionately much higher than the dose to be given in this study (either the initial or subsequent dose, if relevant), and when used in FDA-approved products, the risks of the proposed medication is anticipated to be low.

Risk of the Subcutaneous Administration

The TLC-ART 101 dose will be administered subcutaneously in approximately 2 ×2 mL of osmotically balanced, bicarbonate-buffered saline at a physiologically compatible pH of 7-8. Having the TLC-ART 101 in an iso-osmotic suspension is designed to minimize pain at injection site which may occur with injections of acidic materials. Among the first 4 participants administered TLC-101 in the first cohort, each experienced a Grade 1 injection site reaction including expected symptoms such as redness, edema, tenderness, and/or local pruritis; injection site reactions lasted at most 7 days, but on average 2 days of erythema and 4 days of tenderness or pain among those experiencing each symptom. No concerning safety signals were noted in clinical or laboratory analyses.

Study Rationale

Rationale for a First-in-Human Study of the TLC-ART Platform Technology
While preclinical studies in three animal species demonstrate long-acting PK characteristics for several TLC-ART formulations, NO humans have been treated with any TLC-ART formulation. In addition, while the proposed TLC-ART formulation to be studied is composed of well characterized, FDA-approved antiretrovirals (and lipid excipients), safety data with this novel formulation's (drug combination nanoparticles) route of administration are needed. Human PK and safety data are essential to advance the development of this novel platform.

Many additional future studies will be necessary to fully characterize the TLC-ART formulations, including studies that explore the therapeutic dosing range, fully investigate short and long-term safety profiles, drug-drug interactions, as well as efficacy in the target populations with other drug combinations. This exploratory study is focused on developing data to verify inter-species scaling parameters in order to build a predictive PK model that will facilitate further development of the TLC ART technology.

Rationale for the TLC-ART Platform Formulation
Rapid advances have occurred in the ART field; the FDA has approved more than two dozen antiretroviral agents (3). Given the development time for novel formulations, it was not possible for the first TLC-ART formulation (TLC-ART 101) to include the latest antiretrovirals (ARVs). Thus, TLC-ART 101 is not intended as a commercial product but is a platform to verify the novel DcNP technology's characteristics in humans. It is composed of drug substances with both water-soluble and water insoluble PK characteristics that are relatively short-acting when taken orally. In addition, despite the Hatch-Waxman Amendments, which permit preliminary research on drugs under patent, it is easier and less expensive to investigate antiretroviral drugs that are not protected by U.S. patents (i.e. generic compounds).

The lack of PK knowledge for TLC-ART 101 is a critical barrier to further development of this novel platform. Conducting the first-in-human study of this novel platform technology and obtaining human PK data would substantially advance the development of this platform technology and increase the likelihood of garnering additional resources for additional research, potentially with current, modern antiretrovirals as drug substances. In non-human primates, after subcutaneous injection, the three drug substances were readily absorbed out of the injection site and distributed preferentially into lymphatic system before appearing in blood. The PK of weekly dosing of TLC-ART 101 in rats and dogs revealed differences between species in the PK characteristics, the relationships of the plasma concentrations of the three drug substances, and the maximal tolerated doses; emphasizing the need for data in humans in order to advance the development of the TLC-ART formulation process. The study is not designed to develop data about dose-proportionality or the excipients. It is anticipated that the once TFV appears in the blood, its distribution, metabolism, and elimination would be similar to that described for TFV derived from the FDA-approved prodrugs.

Given the investments that have been made in pre-clinical studies of TLC-ART 101, it seems prudent to proceed expeditiously to perform a first-in-human study in the near future, rather than wait the anticipated one or two years for a TLC-ART formulation with more recently approved antiretroviral drugs that would have to be studied outside the U.S. given patent issues.

There are other long-acting ARV formulations that were recently approved by the U.S. FDA as well as others in development (reviewed in 19). However, they have limitations. The TLC-ART DcNP platform's attributes are in contrast to those of the long-acting ARV treatment regimen that was recently approved for HIV treatment (a 2-drug regimen that combines the single agents of cabotegravir LA and rilpivirine LA). This 2-drug regimen requires 2 separate injections and is administered intramuscularly. As the drug depots for these two drugs remain at the intramuscular site of the injections, it takes days to achieve therapeutic levels. Thus, an oral induction or injectable loading doses or both have been previously used prior to administration of these two injectable drugs (24). Having a complete 3-drug ART formulation in one injection would be a significant therapeutic advance. Such a regimen currently does not exist. Being able to administer a complete regimen by one subcutaneous injection would be simpler than two intramuscular injections. Additionally, the TLC-ART formulations are administered subcutaneously (SC) (like insulin), raising the possibility of home administration if they are demonstrated to be effective and safe.

Rationale for Proposed Study Population

Persons without HIV

While the ultimate target population for the TLC-ART platform is persons living with HIV, this study proposes to study adults without HIV. Reasons for this decision include that effective combination ART is recommended for all persons with HIV and we have insufficient data to determine what the PK characteristics and safety of TLC-ART 101 would be. Thus, we cannot deem this combination safe and effective for the suppression of HIV AT THIS TIME and are not targeting doses that will result in therapeutic drug concentrations. Also, tenofovir-containing regimens are among the most commonly used to treat HIV infection (55). In order to characterize the PK parameters of TLC-ART 101 (which includes tenofovir, individuals cannot be concurrently taking regimens that include tenofovir (in a different formulation). Lastly, it in the absence of PK data about the formulation, it would be inappropriate to combine it with other drugs.

Persons with advanced HIV/AIDS may have substantial lymphoid fibrosis and loss of lymphoid immune cells, suggesting that tissue penetration of drugs may differ with advanced disease from earlier stages of HIV and from individuals without HIV (56). However, the exclusions for safety reasons, appropriate for this first-in-human study, would exclude persons with advanced HIV. Given the complexities of the pharmacologically-guided adaptive design, safety considerations, including the issues described above regarding the enrollment of persons living with HIV, it seemed preferable to propose a study with only participants who do not have HIV.

Rationale for Inclusion of Persons of Reproductive Potential Capable of Becoming Pregnant and Exploring Sex Differences

It is widely recognized that persons capable of becoming pregnant, many of whom identify as women, are under-represented in research in all fields of medicine (57, 58). Globally, women comprise close to 50% of persons living with HIV (59). To ensure that ART is safe and effective in female people, it is important to include people of pregnancy potential in research studies from the earliest possible timepoint, if this can be accomplished safely.

Safety issues for adults of pregnancy potential participating in clinical trials include personal health considerations. Thus, to avoid potential fetal exposure to the drug substances with possible long-acting PK characteristics, considerations regarding protection from pregnancy are relevant. Pregnancy tests done at

screening and before administration of study product can prevent exposure early in the study; however, without knowledge of the duration of the TLC-ART platform drug substances in humans, it is possible that drug substance exposure could occur well after the administration of study product.

Orally administered PIs at therapeutic doses may decrease the effectiveness of estrogen-based hormonal contraceptives (3), which are widely used to prevent pregnancy. Restrictions to avoid exposing potential offspring are thus appropriate for this study.. As the mechanism of action of levonogestrel (LNG) in hormonal intrauterine devices [(UDs) is local, with expected serum levels below 150pg/mL for an LNG-20 IUD and <100 for the lower-dose IUDs; the CYP2D6 interaction has potential to raise levels of LNG without any reverse impact on the PI metabolism, making the clinical use of LNG-IUDs with oral PIs clinically acceptable and a favored contraceptive mechanism on PI-ART. Therefore, LNG-IUDs will be the sole form of hormonal contraception allowed during this study. Also allowing enrollment of women who do not have sex with men may encourage younger women to enroll and result in a smaller age discrepancy between male and female participants in this study.

While this study is too small to rigorously compare male and female people, especially since they may be of different ages, exploring potential differences is appropriate. While this study will not have adequate power to do a definitive comparison of the PK parameters in male and female people, PK parameters of ritonavir differ in male and female people (60) and it would be useful to determine if this type of trend is seen with this and the other drugs in the TLC-ART platform. Body fat content is generally greater in female people than male people (61); this may impact absorption from the subcutaneous fat, where the study injections will be administered.

Study Hypothesis
The TLC-ART drug-combination nanoparticle (DcNP) platform is safe and able to transform the pharmacokinetics of three short-acting generic and physically diverse antiretroviral drugs to create a long-acting concentration-time course in human plasma (primary) and cells (exploratory).

Materials

TLC-ART 101 drug combination nanoparticle suspension includes lopinavir, ritonavir, and tenofovir stabilized with lipid excipients. The formulation is packaged in a 5 mL glass vial for single use containing a 5 mL fill volume.

Signature Page

1 Please see the attached PDF for the Principal Investigator signature page

Key Roles

2 Please see the attached PDF for study's Key Roles and their contact information

List of Abbreviations

3 Please see the Guidelines for the List of Abbreviations

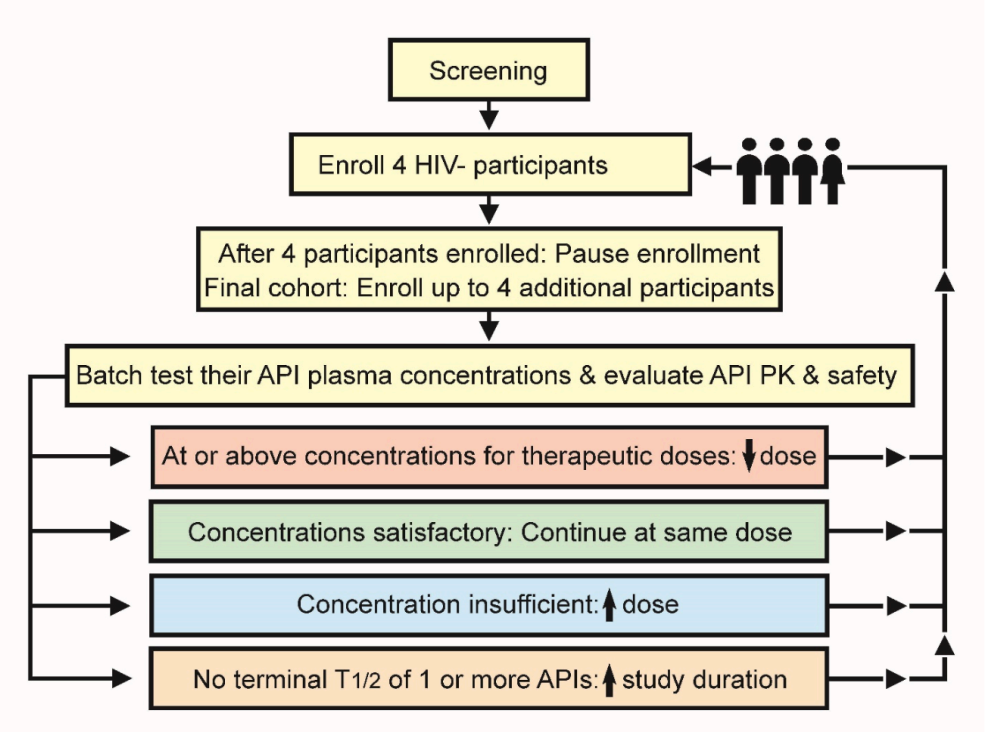
Protocol Summary

4

	A	B
	Full Title	First in human clinical trial of a next generation, long-acting injectable, combination antiretroviral therapy platform
	Short Title	First in human study of TLC-ART 101
	Sample Size	12-16
	Study Population	Healthy adults without HIV
	Participating Sites	University of Washington Positive Research (formerly the AIDS Clinical Trials Unit) and Translational Research Unit
	Study Design	Prospective, open-label, first-in-human study, with a pharmacologically-guided adaptive design for dose escalation, de-escalation and study duration
	Study Duration	57 days per participant with possible extension up to 70 days
	Study Regimen/Intervention	One subcutaneous dose of TLC-ART 101 (drug combination nanoparticle suspension of lopinavir, ritonavir, tenofovir)
	Primary Objectives	1) To characterize the plasma concentration-time course and pharmacokinetics (PK) of a single dose of

	A	B
		the drug substances of TLC-ART 101 (LPV, RTV, TFV) administered by subcutaneous injection. 2) To characterize the safety and tolerability of a single subcutaneous injection of TLC-ART 101. 3) There are 4 exploratory mechanistic objectives (with related endpoints)
	Primary Endpoints	1. Drug substance plasma pharmacokinetic parameters following single dose TLC-ART 101 (including Cmax; Tmax; AUC, terminal T1/2 of LPV, RTV, and TFV) 2. Clinical and laboratory toxicities related to TLC-ART 101 as graded by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1 – July 2017)

4.1 STUDY SCHEMA: Overview



API=active pharmaceutical ingredients (drug substances), BLQ=below limit of quantification,
HIV-=human immunodeficiency virus negative, PK=pharmacokinetics,

4.2 Study Stopping Rules

- The DMC may decide at any time to stop the study early if it is felt that participant safety

is at risk.

- The study team may also suggest early stopping if one or more participants have a confirmed Grade 4 AE (defined per DAIDS as “not definitely unrelated”) to study product, or

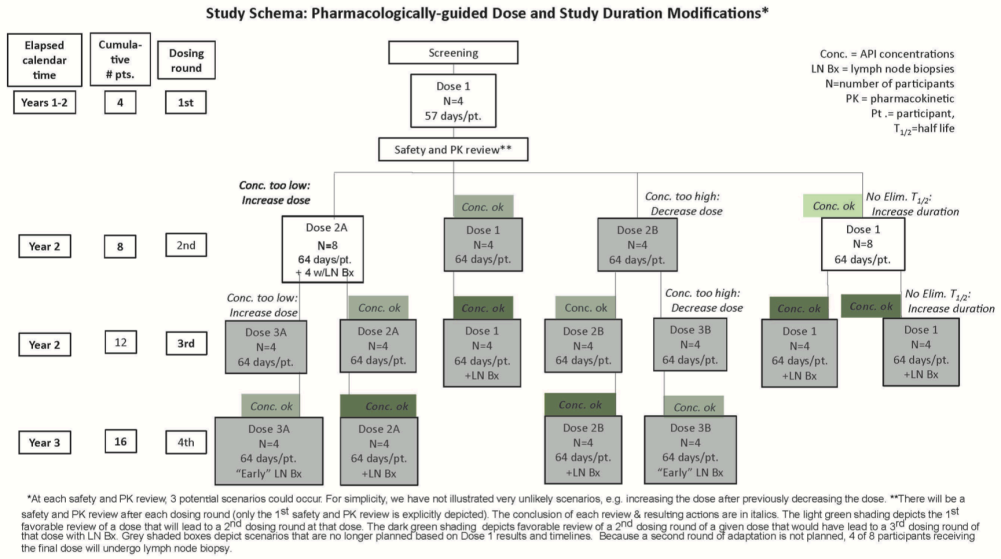
if two or more Grade 3 AEs related to the study product occur (regardless of the number of

participants with these AEs).

- The study will be stopped if there are any Grade 5 AEs (deaths) related to study product

administered according to the study protocol.

4.3 STUDY SCHEMA: Pharmacologically-guided Dose and Study Duration Modifications



Introduction

5 Please see the Guidelines

Objectives

6 **Primary Objectives**

6.1 To characterize the plasma concentration-time course and pharmacokinetics (PK) of a single dose of
the three drug substances of TLC-ART 101 (LPV, RTV, and TFV) administered by subcutaneous injection.

6.2 To characterize the safety and tolerability of a single subcutaneous injection of TLC-ART 101

7 **Exploratory Objectives**

7.1 To characterize the PK of the drug substances in human peripheral blood mononuclear cells (PBMCs)

7.2 To characterize the concentrations of intracellular TFV-diphosphate (the active moiety of TFV) in
PBMCs

7.3 To explore whether the PK parameters of the 3 drug substances differ between men and persons
able to bear children following a single dose

7.4 To compare lymphoid tissue mononuclear cell versus PBMC concentrations of the drug substances
in TLC-ART 101.

Study Design

8 Prospective, open-label, single site, first-in-human study of a long-acting, injectable combination antiretroviral therapy platform, with a pharmacologically-guided adaptive design for dose escalation, de escalation, and study duration. Up to 16 healthy HIV-uninfected adults will be enrolled. One dose of TLC ART 101 (drug combination nano-particle suspension of lopinavir, ritonavir, and tenofovir) will be given subcutaneously to each participant. The initial dose of TLC-ART 101 will contain LPV 15.59 mg, RTV 4.12 mg, and TFV 9.17 mg in approximately 2mL or less of the formulation. Each participant will undergo standardized pharmacokinetic (PK) sampling and safety assessments. The planned study duration will be 57 days per participant. Starting with the dosing of the first participant, the study duration will be about 28 months. There will be at least a week's lag between the dosing of each of the initial 4 participants at and after the first

participant in any increase in dose level, to allow for observation of any potential unanticipated side effects. The goal of the dosing for this study is to identify a dose of the study product that will permit the quantification of the drug substances in plasma and cells and a study duration that allows at least one terminal time-point for each drug substance to fall below the limit of quantification to permit full PK characterization of the drug substances. Assuming appropriate safety, this study will continue until at least 8 participants have received a dose that provides measurable plasma and cell concentrations for all three drug substances and have been followed for a duration that includes a final concentration below the limit of quantification for each drug substance. Once a safe and analyzable dose has been identified, four participants will undergo an inguinal lymph node biopsy (and concurrent blood sampling) about 24 hours after receiving that dose of TLC-ART to compare concentrations of the drug substances in the lymph node mononuclear cells versus those in PBMCs and plasma.

8.1 Pharmacologically-Guided Adaptive Design Overview

- The dosing of each of the initial 4 participants will be spaced by one week and the initial study duration will be 57 days for each participant.
- After the first 4 participants have enrolled, enrollment will be paused while these participants complete the study and the plasma drug concentrations of the drug substances for their specimens will be batch-tested. These plasma concentration-time data will be analyzed and reviewed by the study team to determine if the dose of TLC-ART should be increased or decreased or the blood sampling protocol (duration of the study) should be lengthened for additional participants. See **Study Schema, Part 2** for an overview and section 8.2 below for details.
- The available safety and PK data and team's recommendation will be reviewed by the independent study Data Monitoring Committee prior to any final decision regarding study modification.
- Twelve to 16 unique participants will complete the study. One to five different single doses may be administered, up to two dose adjustments, and three to four Dosing Rounds of study product administration will occur, depending upon the PK results. (**See Schema Part 2**)

8.2 Pharmacologically-Guided Adaptive Dosing

After analysis of the data from the initial 4 participants:

- If the plasma drug concentrations are below the limit of quantification (BLQ) such that the terminal phase of decline is not definable in one or more participants, a single

dose 2.67-fold higher than the initial dose (about 41.6 mg LPV, 11.2 mg RTV, and 24.4 mg TFV) will be administered to 4-8 additional participants. The available data from participants with quantifiable drug concentrations will be used to inform this decision.

- If the plasma drug concentrations after the first single dose are at or above the therapeutic plasma trough concentrations reported for LPV of 4-7 ug/mL or for TFV of 50 ng/mL (for persons with HIV) or the intracellular concentration ranges of TFV-diphosphate for daily treatment with TFV containing oral formulations (71 fmol/106 cells for TDF and 685 fmol/106 cells for TAF) (for persons without HIV) (6**2**-6**4**), the dose of TLC-ART 101 for the next 4 participants will be adjusted downward by 2-5 fold with anticipated doses of about 3.1 to 7 mg LPV, 0.82 to 2.06 mg RTV, and 1.83 to 4.5 mg TFV. The downward adjustment will be informed by the available data from the first 4 participants.

- Since the GMP formulation will have a fixed ratio of drug substances, if dose adjustments are made, the volume of TLC-ART 101 to be administered will change. If a dose increase is required, the number of injections for each participant may be increased to 2 so that there is a maximum volume per injection of 2 mL.

- If the plasma drug concentration of one or more drug substances is quantifiable at the final time point after the first single dose and a terminal T1/2 cannot be calculated, one or more additional time points after 57 days will be added, likely at 64 days, for the next 4 participants and potentially at about 70 days for later dosing groups. The evaluations to be done at any additional visits will be the same as those at the day 57 visit with the last study visit including testing for HIV, active hepatitis B and active hepatitis C viruses.

- If no changes in the study dosing or duration are warranted based upon analysis of the first 4 participants, an additional 4 participants will be enrolled and receive a single injection at the initial dose following the same SOEs.

- After each subsequent cohort has enrolled into the study, study enrollment will be paused, the plasma drug concentrations will be determined, and the analyses and data review will proceed as described above for the first 4 participants. Because Cohort 2 is proposed to enroll up to 8 participants, a brief safety pause will be performed when the 4th participant has completed their Day 7 study visit and the Day 7 lab results are available. The DMC will review only the clinical and laboratory safety data prior to enrolling the rest of Cohort 2; PK parameters will not be calculated at this time, but rather held to be batched longitudinally at the completion of the entire cohort, and therefore not reviewed by this interim DMC meeting.

- Dose modification will occur up to two times following the plan listed above with any additional dose increases made via a protocol amendment and serial decreases of 2-

5-fold from the previously administered dose.

- If time and resources allow, four additional participants will be dosed in Cohort 2, with four of the eight undergoing inguinal lymph node biopsy.

8.3 Safety Aspects for the Pharmacologically-Guided Adaptive Design

The plan for addressing safety, given the anticipated increase in half lives of the drugs in TLC-ART 101, is to be cautious in the doses administered, monitor very closely for potential adverse effects so they can be appropriately managed, and be intentional in the size of dose cohorts and selection of the study participants. Any toxicities will be handled by the study team or if expertise is needed that the study team doesn't have, the participant would be referred for the relevant care.

- The initial dose of TLC-ART will contain about 2%, 2%, and 3% of a daily oral dose of LPV, RTV, and TFV, so that even with prolonged half-lives, we anticipate minimal side-effects since the doses and anticipated drug concentrations will be low in comparison to the therapeutically active concentrations of three drugs when given orally.

- We propose in-patient administration of TLC-ART to the first four participants at the initial dose level, so that continuous observation will be possible, and the services of a major medical center will be available, should a need for intervention arise. Additionally, the first participant of any dose level increase will be observed for 24hrs after dosing. Because each of the 3 active drugs and the inactive components of the nanoformulation have been given to many thousands (lipid components) or millions of people (active ART components), we propose a shorter in-patient observation than recommended for truly novel first-in-human drug trials. Additionally, a similar mPEG component has now been administered in >1 billion doses of mRNA vaccines. Anaphylactic reactions presumptively due to mPEG in mRNA vaccines administered intramuscularly occur generally within 30 minutes of administration and non-anaphylactic immediate hypersensitivity reactions are generally observed within 4 hours(65). This shorter duration of the enrollment visit will also facilitate more rapid enrollment of early cohorts and decrease delays between each analysis pause. After the first participant of Cohort 2 is enrolled, the subsequent participants will not be enrolled until 7 days after to ensure tolerance of an increased dose. Subsequently, more than one participant per week may be enrolled through completion of the study.

- This protocol proposes clinical evaluations at specified intervals, to maximize the opportunity to capture even subtle effects of TLC-ART 101.

- The dose cohort size of four was chosen to balance the desire for safety (in favor of a small size cohort) and a larger size (to account for inter-patient variability in PK parameters). The final cohort size of 8 was selected to obtain additional information about safety and PK of the final dose rather than pausing between two groups of 4 persons who, because of funding and time constraints, would be receiving the same final dosage without possibility of a subsequent dose change. Therefore, a pause in enrollment after the 4^{th} participant will serve as the safety assessment that would otherwise be performed between cohorts

- The participants will be healthy, without chronic medical issues, and not taking chronic systemic medications, to minimize the likelihood that any potential adverse effect would results in clinically relevant toxicity and to minimize the potential for adverse drug-drug interactions.

Study Population

9 **Inclusion/Exclusion Criteria**

9.1 **Participant Inclusion Criteria (at time of screening visit)**

- Age 18-65 years
- A BMI between 18.5 to 31.9 kg/m2
- Non-smoker or former smoker (defined as no smoking or no vaping or no use of tobacco cessation products for greater than 1 year)
- Persons of any gender are eligible if they otherwise meet all other entry criteria.
- Assessed by the study staff as being at low risk for HIV acquisition and committed to maintaining behavior consistent with low risk of HIV exposure without PrEP until after the participant has completed the study.
- Willing and able to give informed consent.

Note

Note: Select participants will have a 25-hour in-patient stay at UW Medical Center or UW Positive Research at Harborview Medical Center.

Note: Select participants will undergo an inguinal lymph node biopsy.

- For individuals who can become pregnant, a negative serum or urine pregnancy test (the test must have a sensitivity of <25mIU) by any US clinic or laboratory that has a CLIA certification or its equivalent, or is using a point of care/CLIA-waived test

Note

NOTE A: Individuals who can become pregnant are defined as those who have reached menarche and who have not been post-menopausal for at least 12 consecutive months (i.e., have had menses within the previous 12 months) and have not undergone surgical sterilization such as hysterectomy, or bilateral tubal ligation, oophorectomy, or salpingectomy.

Note

NOTE B: Menopausal status is defined as age >40 years, with a history of amenorrhea >12 months, FSH> 40 mIU/mL, and no history of oral or injectable hormone use within 12 months prior to study screening.

- If participating in sexual activity that could lead to pregnancy, individuals who can become pregnant must agree to use specific forms of contraception throughout the study. At least two of the following must be used throughout the study:
  - Condom (male or female)
  - Diaphragm or cervical cap
  - Copper-based intrauterine device
  - Levonogestrel-based intrauterine device
  - Vasectomy in the male partner

9.2 Participant Exclusion Criteria

Note

The following criteria refer to values from the screening visit.

- Positive HIV-1 fourth generation antigen/antibody test
- Positive hepatitis B surface antigen test
- Active HCV infection

Note

Participants that are positive for HCV antibody must have a negative HCV RNA

- Any chronic medical condition deemed significant by the investigator (e.g., asthma, severe allergies, hypertension, heart disease, diabetes mellitus, hyperlipidemia)
- Taking any chronic oral or other systemic prescription medications (including indwelling hormonal implants other than LNG- intrauterine devices) within 30 days before the Entry visit
- Taking any chronic oral or systemic non-prescription (over the counter, OTC) medications that cannot be safely stopped
- Any clinically significant abnormal value of CBC, creatinine, AST, ALT, alkaline phosphatase, total bilirubin
- PT/INR, PTT above the upper limit of normal
- U/A with any clinically significant abnormality
- Any clinically significant finding on ECG per physician review
- Urine toxicology screen positive for any illicit drug (other than cannabis if the participant agrees to stop use of cannabis for 14 days prior to entering the study and for the duration of the study, and is believed to be credible in this promise in the opinion of the investigator)
- BP > 150 systolic or > 100 diastolic mmHg
- Known allergy/sensitivity or any hypersensitivity to LPV, RTV, TFV or either of the lipids in TLC ART 101 (including anaphylaxis to a COVID-19 mRNA vaccine)
- Active drug or alcohol use or dependence or psychiatric illness that, in the opinion of the site investigator, would interfere with adherence to study requirements
- Acute or serious illness requiring systemic treatment, antibiotics, and/or hospitalization within 90 days prior to study entry
- Scars or tattoos on the central abdomen that would interfere with administration of a subcutaneous injection or assessment of the location where the study medication is planned to be administered (within 1 inch of the umbilicus)
- Diagnosis of syphilis, gonorrhea, or chlamydia in the past year
- People who are pregnant, intend to become pregnant, or are breastfeeding

9.3 Additional Exclusion Criteria for Participants who will Undergo Lymph Node Biopsy

- Allergy to lidocaine or any related “-caine” drug
- Chronic scars or tattoos in both inguinal areas that might interfere with performance of a lymph node biopsy or increase the likelihood of a poor cosmetic result
- Chronic anxiety or any other condition that has a high likelihood of interfering with the successful performance of a lymph node biopsy done under local anesthesia
- Any coagulopathy or condition that would increase the potential for bleeding

9.4 Co-enrollment Criteria

- Participants should not be concurrently enrolled in any research study that collects blood or will interfere with the completion of this study.

10 **Recruitment Process**

Study participants will be recruited following the IRB-approved, standard recruitment policies and procedures in place at the DAIDS-approved UW Positive Research CRS Site 1401. These include posting IRB-approved flyers or posters in locations likely to be seen by healthy adults; using social media to communicate information about the study; posting information about the study on the UW ITHS research volunteers web site (Research Match), ParticipateinResearch.org, and UW Positive Research's web site; publicizing the study to local physicians, clinics, and community-based organizations with links to healthy adults without HIV who might be interested in HIV-related research; providing information to our mailing list of participants without HIV who have either participated in past research studies done at UW Positive Research or expressed interest in hearing about research studies; encouraging current UW Positive Research study participants to inform friends about the study, if they are willing; and potentially advertising in selective local print and on-line media likely to be accessed by the target population.

11 **Participant Retention**

Measures to encourage participant retention in the study include careful informed consent (which includes assessment of each potential participant's understanding of study procedures/visits and expectations for participants), encouraging potential participants to discuss their participation with friends or family in advance of agreeing to study participation, having our friendly, experienced clinical staff members build rapport with participants, helping participants develop a realistic transportation plan for study visits, providing reminder calls/messages in advance of visits, clearly explaining the study rationale and potential impact of the results, reminding participants about the importance of their participation, providing snacks/meal vouchers for fasting visits and visits that occur during mealtimes, and providing appropriate, IRB-approved level of compensation for participants that includes a bonus for study completion.

12 **Study Enrollment Plan**

All necessary regulatory approvals must have been received and all study start up procedures must have been completed prior to the enrollment of any study participant.

Dosing of the initial 4 participants at the initial dose will occur at the UW Medical Center's in-patient Translational Research Unit (TRU), formerly called the General Clinical Research Center (a component of the UW's Clinical and Translational Science Award). These participants will each be observed for 24 hours post-dosing as in-patients at this unit and then remain under daily follow up at 48 and 72 hours after dosing prior to initiating subsequent interval follow up. The first participant of any higher dose will be observed for 24hrs post-dosing at UW Positive Research. Dosing for the initial 4

participants of the initial dose and between the first and second participant at any higher doses will be staggered by one week each to allow for a period of observation between these participants; subsequent to this, multiple participants may be dosed within one week. Participant screening visits and outpatient follow-up visits will occur at UW Positive Research; visits after Day 1 may occur off-site at a location mutually agreeable to the participant and study team (eg participant's home or the TRU for convenience and as long as all study procedures can be accomplished). Dosing of participants after the initial 4 participants may occur at UW Positive Research.

Informed consent to undergo lymph node biopsies will be discussed in an opt-out fashion until 4 participants in Cohort 2 have agreed to and undergone lymph node biopsies; once four participants have undergone lymph node biopsy, potential participants will no longer be requested to consent to this procedure as part of screening.

Interventions

13 **Biomedical Interventions**

13.1 **Regimen: One subcutaneous dose of TLC-ART 101 (drug combination nano-particle suspension of LPV, RTV, and TFV) administered into the abdomen**

The dose of TLC-ART 101 for the first four participants will contain LPV 15.6mg, RTV 4.2 mg, and TFV 9.15
mg in 1.5mL of the formulation. See sections the **Study Design section** (8.1 and 8.2) for explanation about subsequent doses. Each participant will receive a single dose of TLC-ART 101.

13.2 **Study Product Formulation, Storage and Preparation**

TLC-ART 101 will be manufactured under Good Clinical Manufacturing at Access to Advanced Health Institute (AAHI) (formerly Infectious Disease Research Institute [IDRI]) and not released for this study until it has passed all lot-release criteria. TLC-ART 101 drug combination nano-particle suspension includes all 3 drug substances – LPV, RTV and TFV stabilized with lipid excipients that meet the product specification and USP standard of a sterile injectable dosage form of TLC-ART 101 for subcutaneous injection. Packaged in a 5 mL glass vial for single use containing a 5 mL fill volume. Formulated as a sterile white to off-white opaque suspension free of particulates with the following drug combination concentrations: LPV: 10.4 mg/mL RTV: 2.8 mg/mL TFV: 6.1 mg/mL Excipients DSPC: 115.5 mg/mL mPEG2000-DSPE: 45.0 mg/mL per vial.

The drug for this study will be stored and managed at UW Positive Research Pharmacy at Harborview Medical Center and the University of Washington Medical Center. Investigational Drug Service Pharmacy. Back up storage of study product may occur at HMC or UWMC's Investigational Drug Service and/or the Vaccine Trials Unit's pharmacy. Study product will be stored in a continuously monitored, temperature-controlled refrigerator at 2-8°C and protected from light, in a limited access area within each pharmacy. Study product will be transported at 2-8 °C protected from light and stored until needed for the participants. The single use study vial can be stored at room temperature for up to 24 hours prior to study product preparation. The chain of custody (and appropriate storage conditions) for TLC-ART 101 will be documented from the time the study product leaves either pharmacy until it is administered.

The single dose vial of study product will be drawn into a sterile plastic syringe by a licensed health care provider at the bedside/in the clinic room and administered immediately or no later than 1 hour following the start of the study product preparation. Just prior to drawing TLC-ART 101 into a sterile syringe, mix very gently by inverting the vial using caution to avoid foaming. Immediately prior to administration warm the syringe between hand(s) to reach approximate body temperature.

13.3 **Study Product Supply and Accountability**

The study product will be provided by AAHI as described in the above step. The study product will be shipped to the pharmacies named above during the study preparation phase. The site pharmacist will maintain complete records of all study product received, dispensed, or destroyed for this study. All vials that contained study product, including vials containing unused study product, will be returned to the UW Positive Research pharmacy for return to the IND holder. Study product will only be dispensed and administered upon a written order of one of the appropriate study staff or faculty members with prescriptive authority (e.g., physician, physician's assistant, or nurse practitioner.)

13.4 **Concomitant Medications**

Participants will be receiving no concomitant medications between screening and study entry through the completion of the study with the exception of medications associated with the lymph node biopsy or for management of adverse events that occur between screening and the end of the study.

Note

An oral anxiolytic medication prior to the inguinal lymph node biopsy is allowed. The medications used for local anesthesia for the lymph node biopsy and management of post-biopsy pain are allowed.

- Any non-study antiretroviral medications are prohibited, including antiretroviral medications prescribed for pre- or post-exposure HIV prophylaxis.
- If a participant develops signs or symptoms between the screening and entry visit or during the study that require medical intervention, appropriate medical therapy can be provided as long as it is not contraindicated with ritonavir. The medication, dose, and date(s) and time(s) it is used should be documented. These participants will not be enrolled in the study.

Of note, the list of medications contraindicated with ritonavir should be reviewed prior to any study medication being administered and after the dose of the study product has been given. (This list will be included in the study Manual of Procedural Operations).

Note

Participants can still have the entry visit if the event is mild and has resolved before the entry visit, if the participant is otherwise still eligible to participate. The participant can be rescreened if the screening period has ended by event resolution and the participant otherwise
remains eligible and interested in participating.

For example:
If a participant develops a headache, they may take acetaminophen or an over-the-counter non-
steroidal anti-inflammatory agent at the recommended dose.

If a participant develops a severe injection site reaction, topical hydrocortisone, or oral acetaminophen (500-1000 mg/dose every 6 hrs) can be used.

If a participant develops an allergic reaction to the study product, diphenhydramine (25-50 mg/dose given orally or IV and repeated prn as appropriate) or cetirizine (10-20mg/dose given
orally and repeated prn as appropriate) may be used.

Full medication recommendations to manage minor through serious adverse events are detailed
in the Manual of Procedures.

Study Procedures/Evaluations

14 Clinical Evaluations and Procedures

14.1 Schedule of Events (SOE)

See Appendix A of the protocol for the SOE.

Instructions for the evaluations follow.

14.2 Physical Exam

The physical exam should include examination of the skin, head, neck, mouth, auscultation of the chest
and heart, inspection of the abdomen, an abdominal exam, examination of the extremities and an
overall assessment of the potential participant's mental status. It does not need to include a genital or
rectal exam or a comprehensive neurologic exam.

Note

The physical exam for participants who will undergo a lymph node biopsy will include inspection
and examination, including palpation, of bilateral inguinal areas.

14.3 Medical History, Systems Review, Medications, and Symptom-directed Physical Exam

- At Screening, the medical history should focus on serious and chronic conditions and allergies. The medication history should focus on both prescription and non-prescription medications taken within the past 3 months and any prescription medication taken for 4 weeks or longer within the past 3 years. Exact dates should only be recorded or estimated for medications (including cannabis) taken within the previous 30 days of screening (that will be stopped prior to study entry). If the potential participant is sexually active, specific questions about use of antiretroviral medications for HIV pre- and post-exposure prophylaxis should be asked.
- Starting at the Entry Visit and for all subsequent visits, the medical history, systems review, and medication review should collect interim information (since the last visit or collection of this information)
- At each study visit after a lymph node biopsy, the evaluations will include inspection and examination (including palpation) of the inguinal area where the biopsy was taken until the incision is completely epithelialized and no abnormal signs or symptoms from the biopsy remain.

14.4 Vital Signs

- Vital signs at Screening should include temperature, blood pressure, heart rate, respiratory rate, weight, and height.
- Vital signs at other visits do not need to collect height.

14.5 **Injection Site Assessment**

- The periumbilical area will be inspected and palpated prior to the administration of the study medication.
- The location of the study injection will be documented and subsequently assessed as per the Schedule of Evaluations (Protocol Appendix A).
- Participants will also be asked to complete a visual analog scale to rate any pain they note peri umbilically (prior to the injection) and at the site of the injection (after the injection of study medication) (0=no pain, 100=most severe pain possible).

14.6 **Drug and Alcohol History**

This history should be in sufficient detail to determine if the participant meets the exclusion criterion for active or recent substance abuse that would likely interfere with completion of the protocol.

14.7 **ECG**

A resting ECG will be done and the results (including the heart rate and rhythm, PR and QTc intervals) must not show any clinically significant abnormality in order for the participant to be eligible for the study.

Instructions for invasive procedures follow.

14.8 **Lymph Node Biopsy**

Once a detectable dose and appropriate study duration has been identified using the adaptive design (Sections STUDY DESIGN, "Pharmacologically-Guided Adaptive Design Overview" and "Pharmacologically-Guided Adaptive Dosing" steps), 4 participants will undergo an inguinal lymph node (LN) biopsy on Day 1 after receiving study product at this dose. Immediately after the LN is removed, blood will be collected from the participants for plasma and PBMC drug concentration assays.

The lymph node biopsy will be performed by study Co-Investigator Dr. Jeffrey Schouten, an experienced surgeon who has completed a general surgery fellowship and is a member of the UW Medicine Department of Surgery. In case of unavailability of Dr. Schouten, other qualified general surgeons may perform the procedure if office-based lymph node excision is within their scope of clinical practice and they are credentialed at

UW Medicine. The biopsy will be done under local anesthesia. The procedures will be done according to standard surgical techniques using sterile technique.

The local anesthetic to be used for the biopsies is 1% lidocaine with epinephrine buffered 1:10 with sodium bicarbonate. One incision (approximately 2-3 cm) will be made just below the inguinal fold superficial to a palpable lymph node. One lymph node will be removed. If a superficial lymph node
cannot be identified, the procedure will be terminated, and no deeper dissection will be done. Either dissolvable sutures or glue (with electrocautery if needed) will be used to close the incision depending upon the surgeon's preference. Amendments to the biopsy may be performed if medically necessary during the procedure, including to manage bleeding or other emerging situations. At the end of the procedure, bupivacaine may be used to lessen discomfort.

Participants will be provided acetaminophen (650 mg orally q 6h prn) to be used for post-biopsy pain if they do not already have ready access to this medication. We will follow standard of care procedures if additional situations occur that require additional interventions or medication.

15 **Laboratory Evaluations**

15.1 **Total Blood Volume**

The blood volume to be collected for each visit and the cumulative blood volume to be drawn for study evaluations as of the end of each visit is shown on the Schedule of Evaluations. The blood volume to be collected for each type of test is indicated below. Please note that several of the blood tests are done as panels so that the total blood volume may be less than the sum of the individual components if the tests are done on the same tube of blood.

15.2 **Safety Laboratory Assessments**

- Complete blood count with platelet count: 3 mL
- Renal function, liver panel, phosphate, and glucose: 5 mL

The renal panel will include creatinine, blood urea nitrogen and estimated glomerular filtration rate (eGFR). eGFR will be calculated by the Cockcroft-Gault equation. The liver panel will include aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin.

- Lipid panel: added to 5mL for renal function

The lipid panel will include total cholesterol, low density lipoprotein-cholesterol, high density lipoprotein-cholesterol, and triglycerides

- Coagulation studies (PT/INR/PTT): 2.7 mL
- Pregnancy testing may be done on blood or urine. If done on blood, no additional blood is required because of testing described in the step below.

15.3 **Virology Studies**

- HIV 4th generation EIA/Ag: 6 mL
- Hepatitis B surface antigen: 5mL
- Hepatitis C testing: HCV Ab test will be done. If it is positive, a reflex HCV RNA test will be performed on the same blood specimen by the testing lab. 5mL
- Follicle Stimulating Hormone: no additional blood when collected with blood described in 15.2, Renal Function.

15.4 **Pharmacokinetic Blood Samples**

- For plasma, PBMCs, and storage: 21 mL

16 **Schedule of Procedures/Evaluations: Timing and Definitions**

16.1 **Screening**

Screening refers to an in-person visit whose procedures occur after a potential participant has signed a study consent form. Screening may occur at one visit or over multiple visits, depending upon the potential participant's preferences and scheduling logistics. All screening procedures must occur within 30 days prior to the Entry visit. If any screening evaluation documents a clinically significant abnormality or abnormalities, the potential participant will be excluded, counseled about the result and referred for appropriate follow-up.

16.2 **Entry Visit (Enrollment)**

- The Entry Visit is considered Day 0 of the study.

- The Entry visit must occur within 30 days after the Screening Visit (1st part of screening visit if it involves multiple visits).
- People of reproductive potential must have a negative pregnancy test within 72 hours before or at the entry visit prior to the administration of study product. The results of the pregnancy test must be documented to be negative prior to administration of study product.
- At the Entry Visit, a Systems Review and Symptom-directed Physical Exam (and examination of the peri-umbilical area) should be done prior to the study injection.
- Vital signs on the Entry Day should be taken before the study injection, and at approximately 45 minutes, 2-, 4-, and 6-hours post-dose, and as needed.
- The injection site assessment/exam will be done during the Entry visit prior to the injection and at approximately 45 minutes, 2-, 4-, and 6-hours post-dosing, and as needed.
- At approximately 45 minutes, 2-, 4-, and 6-hours post-dosing, and as needed), participants should complete the visual analog scale to rate any pain they note

16.3 **Days 1 and 2**

If the participant is an in-patient, vital signs should be taken twice, at least 6 hours apart. If the participant is an out-patient, vital signs only have to be taken once on these days.

16.4 **HIV Counseling and Testing**

Informed consent for HIV testing will be obtained anytime a HIV test is performed and appropriate pre and post-test counseling will be done.

16.5 **Follow-Up Visit Windows**

- The preferred visit windows for the blood draw(s) on Days 1, 2, and 3 are timed from the injection and are +/- 2 hours

Note

See SOE for the timepoints.

- The preferred visit windows for the visits on Days 7, 10, 14, 21, 28, 35, 49, and 64 are +/- 2 days
- The preferred visit window for the visit on Day 57 is +1 day

16.6 **Early Termination Visit**

If a participant terminates their participation before the end of the study or is terminated for cause before the end of the study, they will be asked to have the evaluations indicated in the Schedule of Evaluations (Protocol Appendix A) within 2 weeks of their discontinuation. If they have received a dose of study medication, they will be encouraged to continue in the study and receive all study evaluations.

16.7 **Pregnancy Visit**

If a participant of reproductive potential on the study informs a staff member that they are pregnant other than at a visit, they will be asked to come to the clinic as soon is feasible for a visit to discuss the situation and appropriate evaluations. See section "Clinical Management, Pregnancy" below.

16.8 **Other Visits**

If participants develop signs, symptoms, or concerns related to the study, they will be asked to come for an in-person evaluation as soon as convenient. The events of such a visit would be individualized according to the type of issue. If participants have signs or symptoms that might be related to study participation, they will undergo an interim history, systems review, interim medication history, a symptom directed PE and vital signs. Lab testing relevant to the issue would be performed.
If the evaluation identified an abnormality of signs, symptoms or laboratory results that are related to study participation, the participant would be asked to have periodic visits to monitor the issue, hopefully to resolution. The frequency and content of these visits would be individualized depending upon the type and severity of the issue (see Section "Clinical Management"). If the concern could be adequately followed over the phone, a participant might be asked to have follow-up by telephone rather than in-person follow-up.

16.9 **Final Study Visit**

Day 64 will be the final study visit (unless the participant is being followed for a safety concern or the study duration is extended as part of the Pharmacologically-Guided Adaptive Design [see Section "Study Design"]). If additional visits beyond Day 57 are added, only samples for PK testing will be performed; the safety labs including fasting lipids will remain at Day 57 in order to be comparable between cohorts.

Note

The blood tests to be done across the entire study may need to be modified by eliminating one or more drug concentration timepoints if the study duration is extended, in order to remain within safe phlebotomy limits of 450-550 mL in 56 days.

Assessment of Safety

17 **Safety Assessment Overview**

Since one of the objectives of the study is to assess the safety of the study medication, the study has been designed to maximize the safety of participants. The inclusion and exclusion criteria are designed to maximize the likelihood that the participants will be healthy individuals not taking medications that could potentially have adverse drug-drug interactions with the drugs in the study formulation. This will minimize any potential clinical adverse events or interactions that could impact on the PKs of the study medications.

The SOE (Appendix A) describes the standardized clinical and laboratory assessments that will be completed during the protocol. These assessments will be performed by highly experienced research personnel. All signs, symptoms, exam findings, laboratory results and toxicities will be recorded and graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1 – July 2017) which is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables and attached to this protocol as Appendix B. They will be assessed for severity and the potential relationship to the study product and study procedures.

18 **SERIOUS ADVERSE EVENT (SAE) REPORTING**

18.1 **SAE Reporting to the FDA**

Reporting of serious adverse events will follow federal regulations (21 CFR 312.32 [d]). Dr. Ho, as the IND holder, has the responsibility for reporting to the FDA. Unexpected fatal or life-threatening events will be reported to the FDA within 7 days, and other reportable events will be reported to the FDA within 15 days.

The reporting plan will be included in the study Manual of Procedural Operations (MOPs). All SAEs will be reported to the FDA, the Data Monitoring Committee, the IRB, the DAIDS Medical Monitor and DAIDS Medical Officer. Expedited Adverse Events (EAEs) will be reported to the DAIDS Medical Officer within 72 hours of site awareness.

18.2 **SAE Reporting Requirements for the Study**

The Serious Adverse Events (SAE) Reporting Categories for this study are as follows:

A Serious Adverse Event (SAE) is any untoward medical occurrence (i.e., an adverse event) that meets one or more of the following the criteria for seriousness as defined by the International Conference on Harmonisation (ICH):

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect OR
- Is an important medical event that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed above.

In addition, for this study, grade 3 or higher complications related to a lymph node biopsy will also be considered a SAE.

Note that an SAE is different than an Adverse Event (AE), which is any untoward medical occurrence in a study participant administered a study product and which does not necessarily have a causal relationship with study treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study product, whether or not related to the study product.

The study products for which SAE reporting are required are lopinavir, ritonavir, tenofovir and the lipid excipients.

In addition to the SAE Reporting Categories identified above, other adverse events that must be reported to the Medical Officer as an EAE are:

- Any AEs thought to be acute systemic allergic reactions or hypersensitivity to the study product and any injection site reactions grade 3 or higher.

18.3 Grading Severity of SAEs

As noted above, the most current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table) will be used for this protocol (currently this is Corrected Version 2.1, dated July 2017). It is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical research-sites/safety-reporting/daids-grading-tables.] and attached to this protocol as Appendix 2.

18.4 **SAE Reporting Period**

The SAE reporting period for this study is from study enrollment to each participant's last study visit.

After the protocol-defined SAE reporting period, unless otherwise noted, only Suspected and Unexpected Serious Adverse Reactions as defined below, will be reported, if the study staff become aware of such an event.

The definition of a Suspected Unexpected Serious Adverse Reaction is as follows: An AE that is

• Serious (i.e., an SAE)
• Related (i.e., there is a reasonable possibility that the AE may be related to the study product or the research procedures) AND
• Unexpected (i.e., an AE whose nature or severity [intensity] is not consistent with the research procedures that are described in the protocol-related documents, including the protocol, informed consent document, and the TLC-ART 101 Investigator's Brochure.

19 **Reporting to the IRB**

This protocol will also follow the reporting requirements of the UW Human Subjects Division (Review Committee). This includes following the policies and procedures for the reporting of new information. For example, new information related to confidentiality issues must be reported within 24 hours of awareness, new information about incarceration must be reported within 3 days of awareness, and all other relevant new information must be reported within 10 working days.

Clinical Management

20 **Clinical Management of Adverse Events**

For the purposes of this protocol, the management section will focus on the management of events related to the study product or study procedures. Per the DAIDS Expedited Adverse Event reporting guidelines, "Related" AEs includes AEs for which there is a reasonable possibility that the AE is related to the study product.

If a sign, symptom, or laboratory abnormality is assessed as not related to the study product or participation in the study, participants will be referred to their primary care provider (or a community provider if they do not have a primary care provider) for management of the condition. Not related means there is not a reasonable possibility that the AE is caused by the study product and there is an alternative etiology or explanation for the event.

All signs, symptoms, exam findings, laboratory results and toxicities will be recorded and graded according to the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1 – July 2017) which is available on the DAIDS RSC website at http://rsc.tech-res.com/clinical-research-sites/safety-reporting/daids-grading-tables and attached to this protocol as Appendix B.

20.1 Management of Issues other than Injection Site Reactions

Grades 1-2:
Grades 1-2 symptoms may be handled with appropriate supportive and symptomatic therapy at the clinical investigator's discretion. Grade 1 signs/symptoms may be evaluated and managed over the telephone at the discretion of the study physician. Any possible grade 2 sign or symptom should be
evaluated in person. Grade 1-2 laboratory abnormalities will be followed/repeated at the participant's next scheduled protocol visit (with repeat testing done at a shorter interval if necessary per clinical discretion). If repeat testing is done at a visit other than the next scheduled protocol visit, a blood specimen for study drug concentrations should also be collected.

Grade 3:
Grade 3 signs/symptoms should be closely monitored at frequent intervals. Grade 3 laboratory abnormalities that are not associated with any clinical symptoms should be repeated within 3 days of receipt of results. A blood specimen for study drug plasma concentrations should be drawn whenever repeat laboratory testing is done. The participant should be followed >2 times a week until the toxicity grade decreases to grade 2 or less. The participant should be followed until resolution of the toxicity.

Grade 4:
Grade 4 signs/symptoms should be evaluated daily until they decrease in grade. Grade 4 laboratory abnormalities should be repeated as soon as is practical after receipt of results. A blood specimen for study drug plasma concentrations should be drawn whenever repeat laboratory testing is done. The participant should be followed daily until the toxicity grade decreases to Grade 3. The participant should be followed until the resolution of the toxicity.

20.2 Management of Injection Site Reactions

For Grade 1 or 2 reactions, appropriate medical therapy including cold compresses and topical corticosteroids will be advised. For Grade 3 and higher reactions, appropriate care will be provided, and a dermatologist will be consulted if needed to optimize management.

20.3 **Follow-up of Adverse Events and Serious Adverse Events**

All participants experiencing any AEs of any grade related to the study medication and all SAEs will be followed until resolution of the toxicity even if it is longer than 28 days post-injection.

20.4 **Other Adverse Events**

No specific other events related to the study medication are anticipated, although all toxicities will be captured and managed.

21 **Pregnancy**

If a potential participant or a participant becomes pregnant on the study, they will be informed about the result of their pregnancy test and referred for appropriate prenatal care.

If a pregnancy is discovered at the Screening visit, the participant would not be eligible for the study. If a pregnancy is discovered at the Entry visit, the participant will not receive a dose of study medication and will be discontinued from the study. If a pregnancy becomes known other than during a study visit, the participant would be asked to have an additional visit to discuss the potential impact of study medication and participation on the pregnancy and pregnancy outcome. If a pregnancy is discovered after a participant has received the study medication, they will be encouraged to continue in the study although they would not be eligible to undergo a lymph node biopsy.

The site staff would report information about the pregnancy prospectively to the "Antiretroviral Pregnancy Registry" (In US and Canada: 1-800-258-4263). If a participant has completed the study or stopped study participation before the end of their pregnancy, the staff will try and contact them or their physician to learn about the outcome of the pregnancy so it can be included in the information reported to the Antiretroviral Pregnancy Registry.

22 **Breastfeeding/Replacement Feeding**

Breastfeeding persons are not eligible for the study.

23 **HIV Infection**

If HIV infection were to inadvertently occur during study participation, the participant would be referred asap for expert HIV management and initiation of an antiretroviral regimen that did not include any of the drug substances or related drugs.

24 **Criteria for Discontinuation**

24.1 **Criteria for Permanent Study Treatment Discontinuation for an Individual Participant**

The criteria to not administer the study product at the Entry visit to a participant are:
• Use of a prohibited concomitant medication
• Pregnancy or breastfeeding recognized prior to the administration of the study injection. • Request by participant to terminate their participation in the study
• Clinical conditions, which in the best judgment of the investigator are believed to be harmful or potentially life-threatening to the participant, even if not addressed in the AE Management section of the protocol
• Recommendation by the Institutional Review Board, Data Monitoring Committee, Office of Human Research Protections, Food and Drug Administration or any other relevant regulatory entity

24.2 **Criteria for Premature Study Discontinuation for an Individual Participant**

The criteria for premature discontinuation from the study for an individual participant are:
• Participant unable or unwilling to receive the study product injection
• Participant repeatedly non-compliant with study specimen collection, at the discretion of the site investigator
• Failure of the participant to attend 3 consecutive clinic visits for unexcused reasons, at the discretion of the site investigator
• Incarceration
• Request by participant to withdraw
• Request of the primary care provider if s/he thinks the study is no longer in the best interest of the participant
• Participant judged by the investigator to be at significant risk of failing to comply with the provisions of the protocol or at significant risk of causing harm to self or seriously interfering with the validity of study results

Statistical Considerations

25 **Overview and General Design Issues**

This first-in-human study is designed to assess acute toxicity, safety, and tolerability in a small number of
healthy participants. Small sample sizes are chosen to assure that important safety events are not
observed prior to exposing additional participants to the new product. This study is also designed to

provide a preliminary description of PK characteristics for the three drug substances contained in the
platform's lead formulation. Four participants at each dose level are targeted for evaluation during the
initial adaptive phase, and, if possible, eight additional participants will be enrolled once an appropriate
dose has been identified, for a total of 12-16 participants.

The ability of the study to detect serious adverse experiences can be expressed as the true event rate
above which at least one event would likely be observed, and the true event rate below which no events
would likely be observed. For each dose group of size n=4, there will be a 90% chance of observing at
least one event if the true rate of such an event is 43.8% or more; and there will be a 90% chance or
more of observing no events if the true rate is 2.5% or less.

For the combined sample of n=12, there will be a 90% chance of observing at least one event if the true
rate of such an event is 17.5% or more; and there will be a 90% chance or more of observing no events if
the true rate is 0.9% or less. For a combined sample of n=16, there will be a 90% chance of observing at
least one event if the true rate of such an event is 13.5% or more; and there will be a 90% chance or
more of observing no events if the true rate is 0.65% or less. All participants receiving study product will
be observed for at least some amount of time, contributing at least some safety data. Hence, no
missingness is assumed for this calculation.

26 **Primary Endpoints**

26.1 Drug substance plasma pharmacokinetic parameters following single dose TLC-ART 101 (including
C_{max}; T_{max}; AUC, and terminal Kel and $T_{1/2}$ of LPV, RTV, and TFV)

Note

Drug concentrations of the three drug substances will be measured by a highly sensitive, validated assay with a lower limit of quantification of 100 pg/mL (or less) for LPV, 100 pg/mL (or
less) for RTV, and 1 ng/mL (or less) for TFV.

26.2 Clinical and laboratory toxicities related to TLC-ART 101 as graded by the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1 –
July 2017)(DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events (Corrected Version 2.1 –July 2017)

27 Exploratory Endpoint(s)

27.1 Pharmacokinetic parameters of intracellular LPV, RTV and TFV in peripheral blood mononuclear
cells (PBMC) (Cmax, Tmax, AUC, terminal Kel and $T_{1/2}$ of LPV, RTV, and TFV)

27.2 $T_{1/2}$ of intracellular PBMC TFV-diphosphate PBMCs

27.3 Differences of plasma and PBMC drug substance pharmacokinetic parameters between women
and men

27.4 Lymph node mononuclear cell concentrations and PBMC concentrations of LPV, RTV, and TFV

28 Study Hypothesis and Objectives

28.1 Study Hypothesis

The TLC-ART drug-combination nanoparticle (DcNP) platform is safe and able to transform the
pharmacokinetics of three short-acting generic and physically diverse antiretroviral drugs to create a
long-acting concentration-time course in human plasma (primary) and cells (exploratory).

28.2 Primary Objective(s)

- To characterize the plasma concentration-time course and pharmacokinetics of a single dose of the three drug substances of TLC-ART 101 (LPV, RTV, and TFV) administered by subcutaneous injection.
- To characterize the safety and tolerability of a single subcutaneous injection of TLC-ART 101.

Note

There are 4 exploratory mechanistic objectives (with related endpoints).

28.3 **Exploratory Objective(s)**

- To characterize the PK of the drug substances in human peripheral blood mononuclear cells (PBMCs).
- To characterize the concentrations of intracellular TFV-diphosphate (the active moiety of TFV) in PBMCs.
- To explore the PK parameters of the 3 drug substances differs between men and women following a single dose.
- To compare lymphoid tissue mononuclear cell versus PBMC concentrations of the drug substances in TLC-ART 101.

29 **Sample Size Considerations**

See "Overview and General Design Issues" in this section above.

30 **Enrollment Procedures**

A total of 12-16 healthy participants will be enrolled in sequential groups of four. Given the planned
pharmacologically-guided adaptive design, enrollment pauses and interim drug concentration and safety
reviews, enrollment is expected to occur over approximately 28 months. See the "Study Design" section for details.

31 **Participant Enrollment and Follow-up**

Each participant in the initial enrollment group (n=4) (Dose 1, Round 1) will be followed for 60 days and
evaluated for safety and PK parameters prior to enrollment of subsequent groups. Follow-up durations
for individual participants in subsequent groups may be extended by 7-14 days (with the approval of the

DMC), if warranted by PK results.

32 Data and Safety Monitoring Plan

32.1 Overview

Routine study conduct, including enrollment, eligibility, visit and data completion and safety reviews will
occur **quarterly** throughout the study. Reviews will use protocol-specific reports. The reports will be
reviewed by the protocol chair, and if desired, by the protocol's Medical Officer.

The protocol chair and the DAIDS Medical Officer will conduct an immediate safety review of all related
Grade >3 events (sign, symptom, laboratory abnormality or diagnosis) and all grade 4 or 5 events.

During the monthly review of clinical events, the PI will assess the relationship between events < Grade
3 and the study product or procedures. Any event related to the study product or study will be added to
the cumulative Adverse Reactions Database for the study and will be forwarded to the Program Officer
and the protocol statistician.

In addition to these routine reviews, the study will be overseen by a Data Monitoring Committee (DMC).

32.2 Data Monitoring Committee

The UW ITHS will assist the study team in developing a Charter for the Data Monitoring Committee
(DMC), identifying independent members (to include at a minimum an investigator with HIV clinical
research expertise, a biostatistician, and a community member (potentially drawn from one of the
recently active HIV research Community Advisory Boards in Seattle). The chair of the DMC will be
Benjamin S. Wilfond, MD, who is the former director of the Center for Pediatric Bioethics at the Seattle
Children's Research Institute and is an Emeritus Professor of Bioethics and Pulmonary Medicine at the

Seattle Children's Hospital and Medical Center. The first meeting of the DMC will be an organizational
meeting to review the group's Charter and the study protocol prior to enrollment of the first participant.
The subsequent meetings will be held as described below in this section under "Planned Interim Analyses for the Adaptive Design" and "Safety Reviews" steps.

32.3 **Role of the DMC**

The role of the Data Monitoring Committee is to monitor study quality, participant safety, and oversee
changes in the dosing or study duration per the adaptive design and the study stopping rules.

32.4 **Communication with DAIDS**

The DAIDS Program Officer and Medical Officer will be provided copies of all minutes from Data
Monitoring Committee meetings.

32.5 **Study Stopping Rules**

- The DMC may decide at any time to stop the study early if it is felt that participant safety is at risk.
- The study team may also suggest early stopping if one or more participants have a confirmed Grade 4 AE related (defined per DAIDS as "not definitely unrelated") to study product, or if two or more Grade 3 AEs related to the study product (regardless of the number of participants with these AEs).
- The study will be stopped if there are any Grade 5 AEs (deaths) related to study product administered according to the study protocol.

32.6 **Planned Interim Analyses for the Adaptive Design**

The first planned interim analysis will be done after the first 4 participants have completed the study.
Safety and plasma PK data will be reviewed, along with the Core Study team's recommendation for the
dose and study duration for the next 4 participants.

The next planned interim analysis will be done after the next 4 participants (#5-8) have completed at
least Day 7 of the study. Safety, including clinical and laboratory AEsthrough Day 7 will be assessed by
the study team and presented to the DMC. Ongoing study enrollment will be paused until the DMC
agrees that safety merits proceeding with ongoing dosing of subsequent participants. No PK analysis will
be performed or reviewed until the 12th or final participant has completed the study.

The 3rd planned interim analysis will be done after the next 4 participants (#9-12) from Cohort 2 have
completed the study. Safety and plasma PK data will be reviewed.

Prior to each meeting of the DMC after the initial meeting, the study statistician and Protocol Chair will
provide a report of safety (interval and cumulative) and PK data, with the exception of the 2nd interim
DMC meeting, which will include only safety data.

32.7 **Safety Reviews**

It is anticipated that the interim reviews described above in the step above will include safety as well as PK
(except for reviews of participants 5-8 in real time; PK for participants 5+ will be evaluated following
study completion as no further doses will be selected). If more than 1 year were to elapse between
interim reviews for the adaptive design, an interim safety review will be conducted a year after the most
recent interim data review. (Note: The DMC may elect to waive such a review in the final year of the
protocol if prior reviews of the safety data warrant).

33 **Analysis Plan**

Descriptive statistics for various PK parameters (e.g., C_{max}, T_{max}, and $T_{1/2}$) for each drug substance will
include the mean, median, min, max, and standard deviation. The precision with which these quantities
can be estimated depends on both the sample size and the true standard deviation (including both
population variability and measurement error). For the sake of brevity, the estimation characteristics for
only the sample mean are presented here. It is assumed that if any of the first n=4 enrolled participants
do not complete the full course of planned follow-up, they will be replaced, and hence the sample size
for the first analysis will be n=4. (Note: Any participant who is replaced for this analysis will still be
included in the safety analysis.) For later enrollees at later follow-up time points, missing data will be
possible, and hence we assume n=11, representing a loss-to-follow-up rate of 8.3%. If dose adaptation

occurs at both interim-analysis points, there will be at most n=4 participants in each dose group.

Table 3 contains 95% confidence intervals for various possible observed levels of (time-point specific)
mean plasma drug substance concentration, assuming a log-normal distribution for concentration, a log-
scale standard deviation of 0.75, and using t-distribution to account for small sample sizes.

Partial data may be used in the estimation of PK parameters; for example, if a participant has data for
the first several evaluations but not the final evaluations, early data from that participant may be used
to compute time-point specific statistics but may be excluded from the estimation of PK parameters
requiring the entire PK profile. Participants who for any reason receive an incomplete dose will be
excluded from the descriptive analyses of PK parameters. Participants receiving any amount of study
product will be included in the safety assessment. Any transgender enrollees will be analyzed based
upon sex assigned at birth. Statistical analysis will be performed using SAS and R.

Observed average drug substance concentration (µg/mL)	SD of $\log_e$-drug substance concentration ($\log_e$ µg/mL)	95% confidence interval (µg/mL)	
		n = 4	n = 11
0.5	0.75	(0.2, 1.6)	(0.3, 0.8)
1		(0.3, 3.3)	(0.6, 1.7)
3		(0.9, 9.9)	(1.8, 5)
5		(1.5, 16.5)	(3, 8.3)
10		(3, 33)	(6, 16.6)
20		(6.1, 66)	(12.1, 33.1)
30		(9.1, 99)	(18.1, 49.7)
40		(12.1, 131.9)	(24.2, 66.2)
50		(15.2, 164.9)	(30.2, 82.8)
100		(30.3, 329.8)	(60.4, 165.5)
250		(75.8, 824.6)	(151, 413.8)

Table 3. Two-sided 95% confidence intervals based on observing a particular average loge drug
substance concentration in participants, accounting for 8.3% attrition in the overall analysis.

Data Handling and Recordkeeping

34 All participants who sign a consent form for the study will be assigned a confidential unique patient identification number. All data and specimens collected for the study will be identified by this number so that only the clinical investigators and clinical staff or faculty members will be aware of the identity of participants. Any data with identifying information, including signed consent forms, will be stored in locked cabinets with access limited to the study staff with a need to know. As is standard for the clinical trials conducted at the UW Positive Research, the primary clinical data will be collected on paper on a document called a “visit record”, which is a record to facilitate collection of correct and complete data and specimens at each visit. This document is organized in a logical fashion to facilitate completion during study visits; a visit record is created for each study visit. The visit records are stored in each participant’s research chart, which also contains the signed consent form, contact information, documentation of reimbursement, copies of medical record releases, laboratory results, and flow sheets for medications, diagnoses, and symptoms, and outside medical records in organized sections, in reverse chronological order.

The study data will be directly data entered from the visit record into an electronic data capture (EDC) system study database via double data entry conducted by the UW Positive Research personnel. Data quality assurance procedures will follow the

procedures outlined in the UW Positive Research's Clinical Quality Control Management Plan that will be included in the MOPs.

All data, the entry criteria for all subjects, any grade 3, 4 or 5 toxicities, any events leading to premature study discontinuation, all participant's charts and case report forms will undergo quality assurance review by an individual not involved with collection of the primary data.

34.1 **Data Management Responsibilities**

The data will be managed by the UW Positive Research's highly experienced Study/Data Manager (Study
Coordinator) (who has 20 years of data management experience). Data will be entered by UW Positive
Research personnel, with the Study/Data Manager performing quality control checks. The Study/Data
Manager will be responsible for the oversight of paper CRFs and lab data aggregation. Aggregation of all
clinical data will be performed twice a month and a written report provided to the Clinical Research
Team and the protocol statisticians monthly.

34.2 **Essential/Source Documents and Access to Source Data/Documents**

We will follow the DAIDS Essential Documents Recordkeeping Requirements policies and procedures
(DAIDS Policy Essential Documents). The UW Positive Research follows these for its ACTG protocols, and
we propose to use our standard operating procedures for the proposed clinical trial. The recordkeeping
requirements describe the name of each document, its purpose, and a suggested file location (e.g., an
institutional business office file, central site file, a protocol-specific file, pharmacy file, laboratory file, or
participants' research record/research chart, or other locally mandated location).

34.3 **Quality Control and Quality Assurance**

Missing data and outliers will be investigated on a case-by-case basis to confirm accuracy and achieve a
dataset that is as complete as possible. A number of data checks will be pre-specified, and additional
data checks will be identified and coded as needed during interim QC, analysis, and review.

Clinical Site Monitoring

35 Site monitors from the UW Clinical Trials Office will visit the sites conducting this study to review participants records, including consent forms, case report forms, medical records (both paper and electronic, including progress notes, nurses' notes, and laboratory reports and records) to ensure protection of study participants, compliance with the IRB approved protocol/amendments, and accuracy and completeness of records. The monitors may inspect sites' regulatory files to ensure that local regulatory requirements, in addition to U.S. Federal regulations, are being followed. They may also inspect sites' pharmacies to review product storage and management.

Human Subjects Protections

36 **Institutional Review Board/Ethics Committee**
The protocol, informed consent documents and any subsequent modifications will be reviewed and approved by the institutional review board of the University of Washington FWA00006878. Written informed consent will be obtained from each participant. A copy of the consent form will be given to each participant.

All laboratory specimens, case report forms, visit records, study summaries and reports will be identified only by a coded number to maintain confidentiality. Study information will not be released without written permission of the participant, except as necessary for monitoring by the DAIDS, FDA, OHRP, the IRB, and any other relevant domestic or international regulatory entities.

37 **Vulnerable Participants**

37.1 **Pregnant persons and fetuses**
If a person of reproductive potential accidently becomes pregnant while participating in this study, they and their fetus would be followed for the outcome of the pregnancy and the condition of the neonate at birth.

37.2 **Prisoners**

No prisoners will be enrolled.

37.3 **Children**

Children under 18 years will be excluded from this early trial for reasons of safety.

37.4 **Illiterate participants**

With IRB approval, if a potential participant had difficulty reading the consent form, we would ask them
whether they wanted a staff or faculty member to read it to them or whether they wanted to take the
consent form home with them and ask a trusted family member or friend to read them the document
and reschedule another screening visit after this had occurred. Regardless of the answer to this
question, after the potential participant has been read the consent form, the study staff or faculty
member would review the content of the consent form and assess the potential participant's
understanding of the study prior to asking them to sign the form.

We would describe the consent process in the participant's source document, ask the participant to
make "their mark" on the consent form, and ask an unbiased witness to write a brief statement verifying
that they observed the participant make their mark to represent their consent for this study. The
witness will be asked to print his/her/their name, sign, and date the statement.

38 Informed Consent

38.1 **Informed Consent Process**

Potential participants will meet with one of the UW Positive Research staff or faculty members or
physician investigators to determine their potential eligibility for the study. If interested in this study,
they will be provided informed consent for this study. Potential participants will be shown the study Fact
Sheet (a summary of the key elements of the study written in lay language) to provide a sense of what

this study involves before reviewing the consent form. The potential participant will be asked to read
the consent form. The informed consent process includes discussion of the study, ensuring that the
participant has had an opportunity to read the document, review of the sections of the informed
consent document by the staff or faculty member with the potential participant, and time for the
potential participant to have any questions about the study they have answered. The process also
includes the UW Positive Research personnel asking questions of the potential participant to verify that
they understand key aspects of the study. The staff or faculty member uses their professional
judgement as to the wording of such questions. This process can occur at their first visit with a UW
Positive Research staff or faculty member or at a subsequent visit. All potential participants will be
encouraged to discuss their study participation with their primary care provider (if applicable) and/or
family/close friends before signing the informed consent document. When the informed consent
process has been completed and the patient/participant indicates that they are ready to sign, the
participant is asked to sign the consent form. (If the screening for a study is spread over more than one
visit, no study-specific procedures are done until a participant signs this study's consent form.)

At follow-up visits, the procedures for that visit and the next visit will be reviewed, the participant's
understanding of the key aspects will be assessed, and their verbal consent will be obtained. We will
also make certain that the participants understand that they should contact the study staff (or relevant
faculty member) between visits if they have any questions or concerns.

38.2 **Assent Process (in Case of a Minor)**
No minors will be enrolled (other than a neonate of a participant who inadvertently became pregnant).

38.3 **Documentation of Informed Consent**
All consent will be documented in writing.

38.4 **Waiver of Informed Consent**
Not applicable.

38.5 **Waiver of Documentation of Informed Consent**
Not applicable.

38.6 **Stored Samples and Associated Data Considerations**
All specimens and data will be coded. The laboratories that receive the samples for this study and the
Data Monitoring Committee will not have access to any other identifying information. See section "Participant Privacy and Confidentiality" below.

39 **Risks**

39.1 **Risks of Antiretroviral Therapy**
Although we do not anticipate that the concentrations of the three drug substances will approach the
concentrations that are achieved with oral dosing of these medications, it is possible that this may
occur, in which case, the potential risks might include those which occur with oral administration. These
are as follows:

Protease inhibitors have been associated with increased bleeding, the development of diabetes mellitus
and worsening lipids.

Tenofovir has been associated with renal toxicity, mostly in the setting of concurrent nephrotoxins or
renal impairment from concurrent illness. Tenofovir has also been associated with bone toxicity and
bone mineral density loss, most commonly when administered over prolonged time periods.

A variety of other side effects have been associated with the three drug substances when taken orally,
most commonly gastrointestinal symptoms, rash, abnormal liver function tests, and fatigue. We will use
the DAIDS-approved risk lists for the oral versions of the three drug substances in the consent form.

It is possible that there may be unanticipated toxicities from this new formulation.

39.2 **Injection Site Reactions**
Pain or redness, swelling, itching, bruising, lumps, and irritation

39.3 **Risk of hypersensitivity reactions**
Systemic hypersensitivity reactions, including severe reactions such as anaphylaxis, angioedema, or
generalized rashes could occur due to any of the antiretroviral drugs or the two lipid excipient
components. For this reason, TLC-ART 101 will be administered in a monitored medical setting with
appropriate protocols and equipment to respond to mild through life-threatening reactions, with
procedures for varying degrees of systemic hypersensitivity laid out in the MOP and/or UWPR SOPs.

39.4 **Risk of Anxiety**
Some people may feel embarrassed when discussing their medical history or during a physical exam.

39.5 **Risks of Fasting**
Anxiety, irritability, hunger

39.6 **Risks of Drawing Blood**
Mild pain or discomfort, bruising and infection or fainting (rare)

39.7 **Risks of Lymph Node Biopsy**
Participants who undergo lymph node biopsy will have a small permanent scar in their inguinal area at
the site of the biopsy. There is a risk of pain, bleeding and/or infection at the site of the biopsy. The
administration of the local anesthetic may cause brief discomfort. There is a risk of an allergic reaction
to the anesthetic or the pain medication.

If a major complication developed from a lymph node biopsy, there is a risk that antibiotics might be
required, or an additional surgical procedure might be needed or that hospitalization might be required.

39.8 **Risks of Unexpected Diagnoses**
It is possible that participation in this study could uncover a previously unknown medical condition.

40 **Social Impact Events**

Individuals enrolled in this study may experience personal problems resulting from the study participation. Although study staff and investigators will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that participants may experience stigmatization or discrimination as a result of being perceived as being a person living with HIV or at risk for HIV infection. Problems may also occur in circumstances in which study participation is not disclosed, such as impact on employment related to time taken for study visits.

In the event that a participant reports this type of issue, every effort will be made by study staff or faculty to provide appropriate assistance, and/or referrals to appropriate resources. Such events would be reviewed as part of the monthly safety review of the Clinical Study team and reported to the DMC Head (and DAIDS Medical Officer, if desired).

41 **Benefits**

41.1 **Participants**

The potential benefits of this study for participants are the feeling of satisfaction that sometimes comes when individuals contribute to society. Otherwise, there are no benefits to the participants.

41.2 **Society**

The benefits of this study are the advancement of scientific knowledge about a novel new combination drug platform that may allow short-acting agents to be converted to a form that allows for long-acting characteristics. This platform has the potential to contribute to the development of a novel ART that may help improve adherence in persons living with HIV who have been unsuccessful with oral ART or improve treatment options for persons living with HIV or permit persons who can't take oral ART to be treated.

42 **Compensation**

Participants will receive an Institutional Review Board-approved amount of compensation for their time
and effort with a retention bonus if they complete all procedures.

43 **Participant Privacy and Confidentiality**

All participant-related information, including case report forms, laboratory specimens, evaluation forms,
reports, etc. will be kept strictly confidential. All records will be kept in a secure, double locked location
and only UW Positive Research staff will have access to the records.

Research charts will contain direct participant identifiers because they are the source documentation for
the study data. Each research chart is identified by a local unique participant identification number with
no other identifiers on the outside of the chart. The research charts and the list which links this unique
identification number to each participant's name are kept in locked cabinets at UW Positive Research
unless they are actively being used. Access to the cabinets and the charts is limited to UW Positive
Research staff with a need to access the research chart or the coding list. Upon request, representatives
of the study sponsor or its representatives or monitors, the ITHS monitors, and appropriate regulatory
authorities would also be provided access to the research charts. The computer with the coding
electronic list is double password protected and accessible only to the relevant UW Positive Research
staff. This computer is a UW computer maintained by UW technology staff.

44 **Certificate of Confidentiality**

In accordance with current NIH policies for funded clinical trials, this clinical trial will be covered under a
Federal Certificate of Confidentiality.

45 **Communicable Disease Reporting**

If a diagnosis of active hepatitis B or any other communicable disease reportable in the State of
Washington is made by participation in this study, the condition will be reported to the local public
health authority. In the State of Washington, researchers are not required to report HIV infection to the

local public health authority but are required to remind the personal physician of any participant that
HIV is a reportable disease, if a study performs a HIV test that is positive.

46 **Incidental Findings**

Some of the study evaluations may reveal a previously unknown health condition that has clinical
significance and would be actionable. All the clinically relevant testing that we would provide to a
participant will be done in College of American Pathology (CAP)-certified laboratories except for CLIA-
exempt tests. Results meeting the characteristics above will be shared with the participant. Such
findings include anemia, abnormal kidney function, abnormalities of liver function or coagulation tests,
high fasting glucose, abnormal phosphate, abnormal U/A parameters, pregnancy, and abnormalities on
an ECG. If there was an unexpected result, a laboratory test might be repeated in order to determine if it
was a spurious finding. We will counsel the participant about the test results and refer him/her/them to
their primary care provider (if applicable) or to a source of medical care in the community as
appropriate. With their permission, we would provide the participant's health care provider the test
results.

Note that the PK parameters for this protocol do not have clinical significance and will not be provided
to the study participants.

47 **New Findings**

The purpose of the study is to produce new findings. All findings will be made publicly available
according to the Resource and Data Sharing Plan submitted as part of the application for funding for this
protocol and in accordance with current NIH policies.

48 **Study Discontinuation**

The study may be discontinued at any time by the Institutional Review Board, National Institute of
Allergy and Infectious Diseases, the Food and Drug Administration or other government entities as part
of their duties to ensure that research participants are protected.

49 **Post-Trial Access**
This experimental platform medication will not be available after the study has been completed.

50 **Ancillary Benefits**
At least one postdoctoral fellow will further his/her scientific career by working on this clinical trial.

51 **Community Advisory Board and Other Relevant Stakeholders**
Information about this study will be presented to the UW Positive Research Community Advisory Board.

Administrative Procedures

52 **Protocol Registration**
Enrollment of the first participant will not occur until the protocol site has been activated by the DAIDS
Program Officer.

53 **Regulatory Oversight**
Protocol conduct will be overseen by the UW IRB, the NIAID/DAIDS, the Food and Drug Administration,
and relevant regulatory oversight entities at the UW.

54 **Study Implementation**
The study will not be implemented until all relevant approvals have been received, including from the
UW Institutional Review Board, NIAID/DAIDS, the Food and Drug Administration, the UW ITHS TRU, and
UW Clinical Research Budget and Billing Office; the study visit records and case report forms have been
finalized; and study product has been received at the study pharmacies.

55 **ClinicalTrials.gov**
This protocol is subject to the Food and Drug Administration Amendments Act of 2007 (FDAAA) and, if
appropriate, will be registered in ClinicalTrials.gov within the currently approved timeframe. (Please
note that Phase 1 studies are not to be registered.)

Publication Policy

56 The results of this clinical trial will be published in the medical literature according to current NIH

policies. Journals will be chosen for their suitability based upon the purpose of the manuscript and
likelihood of acceptance. Authorship will be determined by the contribution of the individual to the
conduct of the study and their expertise. The senior author will have the final say in the identity of the
masthead authors and author order.

Biohazard Containments

57 Transmission of HIV and other blood borne pathogens can occur through contact with contaminated
needles, blood, and blood products. Respiratory pathogens such Mycobacterium tuberculosis are
transmitted by inhalation of droplet nuclei. Appropriate blood, secretion, and respiratory precautions
will be employed by all personnel for the collection of clinical samples and the shipping and handling of
all clinical samples and isolates for this study, as currently recommended by the Centers for Disease
Control and Prevention in the United States, the World Health Organization internationally, and the
National Institutes of Health.

All protocol specimens will be shipped using packaging that meets requirements specified by the
International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance,
Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as
specified for UN 2814 Category A Infectious Substances.

Appendix A

58 Please see the attached PDF for Apppendix A.

Appendix B

59 Please see the attached PDF for Apppendix B.

Protocol references

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