MOVE-LA Protocol

Mobile Vehicle-Based Delivery of Lenacapavir PrEP in Los Angeles County

Funded by:
Gilead Sciences

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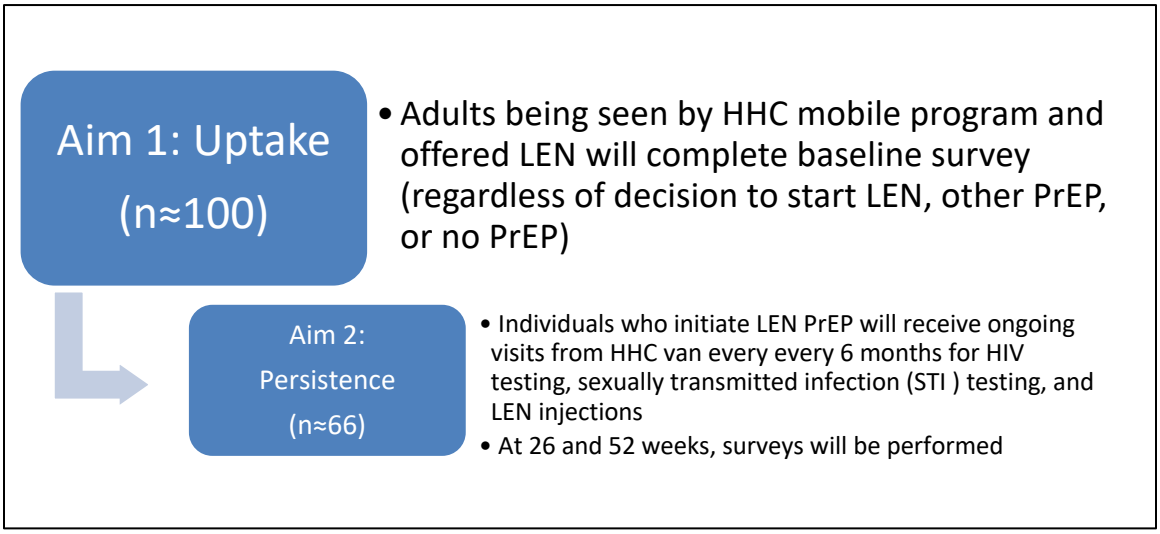
SCHEMA

MObile VEhicle-Based Delivery of Lenacapavir Pre-Exposure Prophylaxis in Los Angeles County (MOVE-LA)

DESIGN	This study is a prospective cohort study of lenacapavir pre-exposure prophylaxis (LEN PrEP) in unstably housed people receiving health services from the Homeless Healthcare Collaborative's (HHC) mobile program. Adults (≥18 years) being seen by the HHC team for routine health services will be screened for human immunodeficiency virus (HIV) risk and LEN eligibility. All individuals offered PrEP (regardless of decision to start LEN, other PrEP, or no PrEP) will be referred to research staff for survey completion, with those starting LEN also receiving assistance from staff for LEN initiation and continuation.
DURATION	All participants starting LEN will be followed for 52 weeks.
SAMPLE SIZE	100 adults receiving services from the HHC mobile program
POPULATION	For Aim 1 (Survey) Individuals being reached for mobile health services by the HHC mobile program that are at least 18 years old, able to provide informed consent, English- or Spanish-speaking, willing and able to comply with study procedures. For LEN, must be at-risk for HIV based on clinician assessment (based on CDC guidelines; includes any individual requesting PrEP, regardless of reported risk factors for HIV) and negative by both 4th generation HIV Ab/Ag testing and viral load prior within 14 days prior to LEN injection.
REGIMEN	Lenacapavir (LEN PrEP) subcutaneous (927 mg, in two 1.5-ml injections) every 26 weeks (within a window of ±14 days). Participants will receive loading doses of two 300-mg tablets (600mg) of LEN on day 1 and two 300-mg tablets (600mg) of LEN on day 2.

SCHEMA (Cont'd)



1.0 OBJECTIVES, OUTCOME VARIABLES, and ESTIMANDS

1.1 Hypotheses

Primary Hypotheses:
For the primary outcome of LEN PrEP uptake, the study will enroll ~100 individuals and hypothesize, based on preliminary data in a similar population, that approximately two-thirds of those offered LEN PrEP will receive a first dose (n~66) within two weeks of baseline assessment and offer (uptake).

Secondary Hypotheses:

1) Factors associated with LEN PrEP uptake will include perceived HIV risk (higher vs lower), self-efficacy for health care (higher vs lower on a validated tool), education level (high school or more vs less than high school), transitional or encampment housing (vs unsheltered), and comorbidities (absence vs presence of substance use disorders and mental health conditions).

2) Persistence at 52 weeks will be in the range of 50%-60%. Factors associated with persistence will be similar to uptake, with the strongest associations for degree of housing instability and comorbidities, such as substance use disorders.

3) Mobile delivery of LEN PrEP will have high acceptability to clients.

4) Common participant-reported barriers to use of mobile LEN PrEP will include competing life priorities (need for food, employment, shelter) and high level of mobility among the population within and outside of Los Angeles County (LAC); relationships between participants and community-based organizations working with HHC will help alleviate but not overcome barriers.

5) The cost of adding LEN PrEP health services to the existing HHC mobile van program will be low and will result in a favorable cost per participant initiated on LEN PrEP and cost per participant persisting on LEN PrEP.

6) LEN PrEP will be well-tolerated, with rare discontinuations due to side effects.

7) The mobile van LEN PrEP delivery model will be feasible for HHC to implement and highly acceptable to staff, health system and public health leaders, and community organizations (as explored via the Theoretical Framework for Acceptability); relevant determinants of scalability and sustainability will include cost, perceived effectiveness, complexity of service delivery, and factors related to leadership and organizational capacity.

8) AirTag uptake and acceptability with be high among participants; however, over time, AirTags are likely to be lost or discarded and become less useful for tracing beyond 26 weeks of follow-up.

1.2 Primary Objectives and Outcome Measures

The primary objective is to characterize uptake of LEN PrEP among unstably housed people receiving health services via HHC's mobile program. The primary outcome will be defined as receiving a first injection of LEN (along with both oral doses on days 1 and 2). All participants will have the option of directly observed therapy (DOT) for the second oral LEN dose. Those not receiving DOT will receive a phone call on the second day to confirm they have taken the dose and remind/prompt them to take it, if they have not.

1.3 Secondary Objectives and Outcome Measures

1) Characterize predictors of uptake. Surveys will be performed at baseline to measure sociodemographic factors, HIV risk perception, PrEP knowledge, PrEP self-efficacy, and clinical factors.

2) Describe LEN PrEP persistence at 26 weeks (defined as receiving a second injection of LEN on-time [+/- 14 days]).

3) Evaluate LEN PrEP persistence at 52 weeks (defined as receiving a third injection of LEN on-time [+/- 14 days]).

4) Understand acceptability of mobile LEN PrEP delivery.

5) Characterize predictors of persistence at 26-and 52-weeks utilizing baseline survey data.

6) Characterize barriers to LEN PrEP via a mobile delivery model of care.

7) Describe satisfaction with LEN PrEP via a mobile delivery model of care.

8) Describe costs and cost-outcome of mobile delivery of LEN PrEP. Costs will be collected from the health system perspective. The study will calculate the cost per person who initiates LEN and cost per person persisting on LEN PrEP over 52 weeks, in a cost-outcome analysis.

9) Characterize feasibility, acceptability, scalability, and sustainability of the mobile LEN PrEP delivery model using qualitative methods. The study will perform in-depth interviews with stakeholders including HHC leadership, field-based HHC staff, LAC public health leaders, and community leaders (n~25) to understand feasibility, acceptability, and service- and system-level factors hypothesized to be associated with scalability and sustainability of the program.

10) Explore uptake and acceptability of AirTags for geolocation among participants enrolled in the study. This will be measured as proportion of individuals accepting an AirTag at enrollment, proportion keeping the AirTag through 26 and 52 weeks, and acceptability questions on surveys at baseline and at week 26 and 52.

11) To describe tolerability of LEN PrEP, including frequency and severity of injection site reactions. This will be measured by phone calls with participants 48 hours after each injection as well as field-based clinical assessments for those who report moderate to severe reactions. The study will also describe the proportion of participants who discontinue LEN PrEP due to side effects.

12) To describe real-world effectiveness of LEN PrEP for HIV prevention as measured by both rapid and lab-based 4th generation Ag/Ab testing done at 6 and 12 months.

13) Describe whether providing an oral bridge of tenofovir-based PrEP is associated with improved uptake of LEN PrEP (relative to those not receiving oral PrEP as a bridge).

2.0 INTRODUCTION

2.1 Background

HIV is a public health priority in LAC due to high incidence of infections (~1,600 annually) (1). New infections are most common in people of Black and Latinx backgrounds, with significant "hot spots" in areas which also have a high prevalence of unstably housed people. In 2022, approximately 13% of newly diagnosed HIV cases in Los Angeles County were experiencing homelessness, a 36% increase over the prior period (2).

Access to HIV prevention services for unstably housed people in LAC has been limited due to barriers in seeking care at health facilities. Unstably housed people face barriers including competing life priorities (such as seeking food, shelter, and employment), low health literacy, particularly around HIV prevention, and comorbidities such as substance use and mental health disorders. **A mobile healthcare service that offers LEN PrEP is ideal to help overcome these barriers** by providing a low-complexity biomedical PrEP option in locations where unstably housed people congregate (i.e., shelters, encampments, community centers, and transitional housing facilities). The University of California, Los Angeles (UCLA) Health Homeless Healthcare Collaborative (HHC) was founded in January 2022 and currently operates six mobile vans, which deliver urgent care, primary care, behavioral health services, and medication-assisted treatment for substance use disorders. At least one mobile van is in the field offering services every day of the week, including weekends. The van is staffed by clinicians and community health workers, who link clients to social services. HHC recently began providing point-of-care HIV and STI testing and is well-positioned to integrate LEN PrEP into their program.

Based on Andersen's behavioral model (3) and using Proctor et al's implementation outcomes (4), the investigators propose the following:
Aim 1. Characterize uptake of LEN PrEP among unstably housed people in Los Angeles County receiving health services via HHC's mobile program. People without HIV receiving health services via the HHC mobile unit (n~100) will be offered LEN PrEP. A baseline survey will be performed (sociodemographics, clinical information, HIV risk, PrEP knowledge, self-efficacy for health care, and acceptability of mobile PrEP offer). The primary outcome will be uptake, defined as receiving a first injection of LEN

PrEP and both oral doses on days 1 and 2. All participants will have the option to receive an Apple AirTag to enable directly observed therapy (DOT) for the second oral LEN dose and for follow-up LEN PrEP injections.

Aim 2. Evaluate LEN PrEP persistence through 52 weeks. Participants who initiate LEN PrEP (estimated n~66) will receive ongoing visits from the HHC mobile unit for STI testing every 3 months and HIV testing and LEN injections every 6 months. The study will estimate the share of initiators who receive LEN PrEP through week 52 ("persistence" defined as completing the third dose on-time [+/-14 days]). Surveys will be performed with all individuals who can be reached at 52 weeks (both persisters and non-persisters), to understand acceptability of mobile LEN PrEP, barriers to this care, and satisfaction with care.

Aim 3. Understand costs, acceptability, feasibility, scalability, and sustainability of the mobile LEN PrEP delivery model. Costs will be collected from the health system perspective. The study will calculate the cost per person who initiates LEN PrEP, and cost per person persisting over 52 weeks. The investigators will additionally perform in-depth interviews with stakeholders, including HHC leadership and van staff, public health leaders, and community leaders (n~25) to understand acceptability and feasibility of this model, and service- and system-level factors hypothesized to be associated with scalability and sustainability of the program.

The study will collaborate with existing HHC community partners (Casa Milagrosa and the Santa Monica Salvation Army), which provide social services to HHC clients. This supportive scaffolding will increase success of the project and long-term sustainability of mobile LEN PrEP delivery. For feasibility, the study will focus on individuals with Medi-Cal or other insurance at the time of screening (anticipated to be ~70% of the HHC population served); however, HHC provides referrals and navigation for obtaining insurance, and individuals without insurance will be linked to certified Medi-Cal enrollment counselors – and once insured, can be referred back to the study for LEN PrEP initiation.

This project brings together experts in biomedical HIV prevention (Hoffman, Landovitz) and implementation science (Hoffman, Moucheraud), experts in the delivery of street medicine using a mobile van model (Weaver, Zunner-Keating), and a costing expert (Wagner). Dr. Hoffman is currently leading a project in collaboration with the LAC Department of HIV and STD Programs on mobile delivery of cabotegravir PrEP to unstably housed women in Los Angeles County. She has leveraged important lessons learned from this ongoing study for the design of this proposed work on LEN PrEP implementation in a similar context. Table 1 (Timeline in supplementary file) demonstrates how the project can be completed in 18 months. Table 2 (supplementary file) summarizes the key implementation science elements of the proposed project. The investigators anticipate 2 manuscripts from this project (see Timeline in supplementary materials) and will submit abstracts to national and international meetings (e.g., CROI, IAS, etc.).

1- http://www.publichealth.lacounty.gov/dhsp/Dashboard.htm
2- http://publichealth.lacounty.gov/dhsp/Reports/HIV/PEH%20Fact%20Sheet%20FINAL.pdf

3- https://pubmed.ncbi.nlm.nih.gov/18580382/
4- https://pmc.ncbi.nlm.nih.gov/articles/PMC3068522

3.0 STUDY DESIGN AND AIMS

The investigators will perform a prospective cohort study of unstably housed individuals with an elevated likelihood of acquiring HIV (see inclusion criteria) being offered LEN PrEP via HHC. Findings from this study will be generalizable to similar urban settings with a high HIV incidence and high prevalence of unstably housed individuals.

Aim 1 (Uptake): Adults (≥18 years) being seen by the HHC team for routine health services will be screened for HIV risk and LEN eligibility (see inclusion/exclusion criteria). Those eligible will be offered a rapid HIV test (4th generation Ag/Ab), provided with counseling about HIV prevention, and offered LEN or referred to a facility for cabotegravir or oral PrEP. Those who select LEN will have blood drawn for lab-based 4th generation and quantitative viral load testing.

All individuals offered PrEP (regardless of decision to start LEN, other PrEP, or no PrEP) will be referred to research staff for information about the study, eligibility determination, and informed consent. A baseline survey will be interview-administered in English or Spanish with a focus on sociodemographic characteristics, PrEP knowledge, HIV risk perception, self-efficacy for health care, and acceptability of the offer of LEN via the mobile van. Participants will be compensated for their time with a Visa gift card ($50). Those who accept LEN PrEP will be offered an Apple AirTag for geolocation for follow-up. An appointment will be scheduled for one week later to initiate LEN PrEP, which allows time for the medication to be delivered to the HHC dispensary and loaded on the van. For those with normal renal function (based on point-of-care creatinine testing or pre-existing labs available in the medical record), oral tenofovir-based PrEP will be offered as a bridge to LEN PrEP.

Directly observed therapy (DOT) will be offered for the second dose of oral LEN if requested by the participant or at the discretion of the clinician (using a private vehicle and nurse/community health worker (CHW) team). In addition, all participants will be called 48 hours after the injection to ask about injection site reactions (ISRs). For those reporting moderate to severe reactions, an HHC team will do a field-based assessment and refer for higher level care, if needed.

Aim 2 (Persistence): Individuals who initiate LEN PrEP (n~66) will receive ongoing visits from the HHC mobile health van every 6 months for HIV testing and LEN injections. Prior to each follow-up injection, a negative rapid 4th generation HIV Ag/Ab test will be required. STI screening will be offered at 3-month intervals either through the van or at brick-and-mortar health clinics (a list of clinics will be provided to all study participants initiating LEN).

Persistence on LEN PrEP will be defined by receiving two additional on-time injections by 52 weeks (+/- 14 days, or as indicated in the package insert). Baseline survey data will be used to understand predictors of LEN PrEP persistence. At 26 and 52 weeks, surveys will be performed for all participants (including non-persisters, if traceable) to understand acceptability, barriers to LEN PrEP, and satisfaction with care. The study will also characterize the proportion who transition to facility-based PrEP (LEN or other PrEP). Participants will be compensated with a Visa gift card ($50) for each survey.

Aim 3 (Costs, Acceptability, Feasibility, Scalability, and Sustainability): Costs of the HHC mobile LEN PrEP delivery program will be collected during study implementation. The study will allocate the share of costs to LEN PrEP based on the proportion of time spent on this

component of care, quantified using time logs and time-and-motion techniques. The investigators will also perform in-depth LAC public health leaders, and community leaders to understand feasibility and acceptability of the mobile program as well as service-level and system-level barriers and facilitators to scalability and sustainability of the program. The study will use Moucheraud *et al's* framework for determinants of sustainability.

4.0 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

4.1.1 Being reached for mobile health services by a UCLA HHC mobile van

4.1.2 ≥18 years of age

4.1.3 Able to provide informed consent

4.1.4 English or Spanish-speaking

4.1.5 Willing and able to comply with study procedures

4.1.6 HIV unknown or negative status and HIV negative based on rapid 4th generation Ag/Ab test on the day of enrollment

4.1.7 At-risk for HIV, based on clinician assessment (based on CDC guidelines; includes any individual requesting PrEP, regardless of reported risk factors for HIV)

4.1.8 Pregnant and breastfeeding women/people can be offered LEN with counseling about benefits and risks.

4.2 Exclusion Criteria

4.2.1 Any clinical or psychosocial condition or prior therapy that, in the opinion of the investigator, would make the participant unsuitable for the study or unable to comply with LEN PrEP

4.2.2 On a strong CYP3A4 inducer at time of screening (given lack of dosing guidance in package insert).

4.2.3 History or clinical evidence of cirrhosis or severe liver disease (jaundice, ascites, encephalopathy, etc.).

4.2.4 End stage renal disease on dialysis (CrCl <15ml/min)

4.2.5 Known hypersensitivity to the study drug, the metabolites, or formulation excipient

4.2.6 BMI <35 kg/m2 (77 pounds)

4.2.7 On oral or other long-acting PrEP and unwilling to discontinue

4.2.8 Already taking LEN for HIV prevention

4.2.9 Known HIV diagnosis or positive 4th generation HIV Ab/Ag test (on day of enrollment) or subsequent lab-based confirmatory testing. Note: those who have a negative rapid HIV test on the day of the study and a subsequent positive lab-based HIV test [which will be performed on all participants prior to the first dose of LEN] will be discontinued from the study and linked to care for antiretroviral therapy

4.2.10 Do not have any active insurance, including Medi-Cal (those without insurance will be referred to an enrollment counselor and may be re-screened for the study once insurance is active)

5.0 CLINICAL AND LABORATORY EVALUATIONS

5.1 Schedule of Evaluations

	Screening /Enrollment	LEN Initiation (+14 days after enrollment)	LEN Oral load Follow-up (LEN injection + 1day)	Week 26 (after LEN dose #1 +/- 14 days)	Week 52 (after LEN dose #2 +/-14 days)	Notes
Brief medical history	X					
Medication history	X			X	X	
Targeted physical exam	X			X	X	
Pregnancy Test (if indicated)	X	X		X	X	Pregnant clients may be offered LEN with discussion of risks and benefits
Hepatitis B Surface Ag, surface Ab, core Ab	*X**					*Recommended, if starting oral PrEP as bridge to LEN
Comprehensive metabolic panel	*X**					*Consider if comorbidities or clinical concern based on medical history or exam

Rapid 4th generation HIV test	X	X		X	X	
Confirmatory 4th generation HIV test (laboratory)	X			X	X	
HIV viral load (laboratory)	X					Repeat viral load testing if concern for acute HIV or if late for injection, prior to re-starting
STI testing (RPR, GC/chlamydia all sites where sexually active, HCV as indicated)	X			X	X	STI testing will be offered every 12 weeks with option of mobile testing by HHC or referral to facility-based services
Phone for oral load dose #2			X			
ISR Assessment			X	X	X	Will occur by phone 1-2 days after each injection
Air Tag Distribution		X				Optional for those who opt-in for use at time of first injection
Baseline Survey*	X					
Follow-up Survey*				X		
Endline Survey*					X	

*Includes questions about HIV risk, substance use, and LEN acceptability, tolerability, satisfaction, and barriers to ongoing LEN PrEP

5.2 Instructions for Evaluations

Brief Medical History: At clinician discretion, with focus on conditions like latent or active tuberculosis, seizure disorder requiring medication, chronic kidney disease/end stage renal disease requiring dialysis, liver disease/cirrhosis, history of STIs, and recent risk for HIV exposure. At weeks 26 and 52 this will include recall related to any ISR experienced during the prior injection.

Medication History: With focus on active prescriptions for medications that may have interactions with lenacapavir (CYP3A inducers).

Drug class	Interaction and management
Antibiotics for treatment of tuberculosis (TB) Rifabutin	**Potential interaction, which requires dose adjustment** Induction of CYP3A4 can substantially reduce LEN

Rifampicin Rifapentine	concentrations which may result in loss of its prevention efficacy.
Anticonvulsants Carbamazepine Phenobarbital Phenytoin	**Potential interaction, which requires dose adjustment** Induction of CYP3A4 can substantially reduce LEN concentrations, which may result in loss of its prevention efficacy.
Illicit/recreational Ketamine	**Potential interaction, which may persist after discontinuation of lenacapavir** Ketamine concentrations may increase due to inhibition of CYP3A4 by LEN and may increase side-effects associated with ketamine, such as respiratory depression and hallucinations.
Erectile dysfunction Avanafil Sildenafil Tadalafil Vardenafil	**Potential interaction, which may persist after discontinuation of lenacapavir** Sildenafil, tadalafil and vardenafil concentrations may increase due to inhibition of CYP3A4 by LEN.
Gender-affirming hormones Estradiol Conjugated estrogens Ethinylestradiol Medroxyprogesterone Micronized progesterone Testosterone	**No dose adjustment required.** LEN is a moderate inhibitor of CYP3A4 and could potentially increase exposure of the gender-affirming hormone, although to an extent that does not require dose adjustment.
Hormonal contraceptives Ethinylestradiol Etonogestrel Levonorgestrel Medroxyprogesterone Norethisterone Norgestrel	**No dose adjustment required.** LEN is a moderate inhibitor of CYP3A4 and could potentially increase exposure of the contraceptive hormone, although to an extent that does not require dose adjustment.
*Ref: WHO LEN Guidelines: https://www.who.int/publications/i/item/9789240111608	

Additional medications listed here:

Strong inducers	Moderate inducers
▪ Apalutamide ▪ Carbamazepine ▪ Encorafenib ▪ Enzalutamide ▪ Fosphenytoin ▪ Lumacaftor ▪ Lumacaftor-ivacaftor ▪ Mitotane ▪ Phenytoin ▪ Rifampin (rifampicin)	▪ Bexarotene ▪ Bosentan ▪ Cenobamate ▪ Dabrafenib ▪ Dexamethasone[Δ] ▪ Dipyrone ▪ Efavirenz ▪ Elagolix, estradiol, and norethindrone therapy pack[◇] ▪ Eslicarbazepine ▪ Etravirine ▪ Fexinidazole ▪ Lorlatinib ▪ Mitapivat ▪ Modafinil ▪ Nafcillin ▪ Pacritinib ▪ Pexidartinib ▪ Phenobarbital ▪ Primidone ▪ Repotrectinib ▪ Rifabutin ▪ Rifapentine ▪ Sotorasib ▪ St. John's wort

Targeted Physical Exam: Focused on stigmata of end stage liver disease/cirrhosis and skin lesions that would pose an issue for LEN injection. At week 26 and 52, exam of prior injections sites for any evidence of nodule or abnormalities from ISR due to last injection

Pregnancy Test: If indicated based on sex at birth and report of last menstrual period. Any participant who becomes pregnant while on LEN will be counseled on risks and benefits of continuation by a clinician and reported prospectively to the Antiretroviral Pregnancy Registry: https://www.apregistry.com/ (1-800-258-4263).

Support for completion of oral load: The day after the first injection, each participant will receive a phone call to confirm they have taken the second dose of the oral load and support completion of the dose, if it has not yet been taken. If the participant does not have a phone, outreach will be undertaken by the community partner to assist with confirmation that load was completed. For clients who request in-person DOT of the second dose, a nurse/community health worker team will deliver this dose in a location agreed upon on the day of the injection.

ISR Assessment: 24-48 hours after each injection, participants will receive a phone call to assess for ISRs. For the first injection, this will be done at the same time as the phone call to support completion of the oral load. The assessment will used a standardized format for recording the type and extent of reaction (Table below). If the participant does not have a phone, the client will be given clear parameters for when to seek evaluation and the ISR type and extent will be assessed retrospectively at weeks 26 and 52. See below (section 6.0) for clinical management of ISRs.

Standardized Data Collection for ISRs (Assessed by phone or in person 24-48 hours after injection at baseline, week 26, and week 48)
Since the injection did you/are you experiencing any of the following (check all that apply
Pain
Swelling
Redness
Nodule/lump/bump
Itching
Bruising
Other (Describe)
Which best describes the how this/these symptoms affected you:
No symptoms
No or minimal problems with usual daily activities (equivalent to grade 1)
Some or moderate problems with usual daily activities (equivalent to grade 2)
Unable to perform usual daily activities (equivalent to grade 3)
Unable to perform basic self-care, or hospitalized due to injection site reaction (equivalent to grade 4)

Baseline laboratories (at time of prescription)

a. Rapid 4th generation HIV Ag/Ab test negative result (***Note****: this is the only result required to prescribe LEN*)
b. 4th generation HIV Ag/Ab (lab-based) drawn (***Note****: this should be negative within 14 days before the first dose of LEN is given*)
c. HIV viral load (lab-based) drawn (***Note****: this should be negative within 14 days of the first dose of LEN. If not available and 4th gen testing is negative, LEN can be given and viral load drawn that day based on discretion of clinician.)*
d. RPR with reflex to FTA confirmation and titer
e. Chlamydia and gonorrhea from all sites where sexually active (urine, rectal, oral); do not withhold offer of LEN to clients who decline but continue to encourage testing at follow-up interactions. If asymptomatic, send samples to lab; if

symptoms, perform point-of-care, if available (can be done with Roche test only with male urine and female vaginal swabs)

f. Hepatitis C antibody with reflex (*not required*, recommended to screen and offer treatment)
g. Comprehensive metabolic panel (*not required*, recommended particularly for people with comorbidities if indicated for other reasons)
h. Pregnancy test, as indicated

Can also consider if feasible and relevant for clinical context

- CBC/diff
- Hepatitis B surface antigen, (also hep B core antibody and hep B surface antibody to assess if vaccination needed, if feasible)

Follow-up Laboratory monitoring at injection visits

i. Every injection visit (assuming on-time injections +/-14 days)
    i. Rapid 4th generation HIV test (If negative, provide dose)
    ii. 4th generation HIV Ag/Ab test (lab-based)
j. Every 3 months (strongly recommended, not required)
    i. STI testing (d and e above)
    ii. Pregnancy testing, as indicated
    iii. Assess for HCV risk factors and symptoms, optional testing if concern
k. For late injections (>14 days late or >28 weeks since last injection), the decision to give LEN should be based on duration of lapse and risk of having acquired HIV in this period. If concern for HIV acquisition, confirmation of a lab-based HIV test should be received before re-starting injections using HIV 4th gen and HIV viral load. See below LEN dosing for late injections.
    i. Note - Viral load should be repeated if more than 14 days late for injection (more than 28 weeks since last injection) or if signs/symptoms of an HIV seroconversion event; or if recent high-risk exposure.

Surveys (see Manual of Procedures for detailed procedures of surveys)
Among all participants at baseline and among those who start LEN, additional timepoints of week 26 and week 52, brief surveys will be administered to record sociodemographics, HIV risk factors, medical conditions (including mental health and substance use disorders, detailed housing information, HIV and PrEP knowledge, HIV and LEN acceptability, barriers to HIV prevention/LEN care, and satisfaction with LEN and mobile delivery. At endline, surveys will be obtained for all participants who initiated LEN and can be reached at endline regardless of whether they have continued on LEN through 52 weeks. Participants will receive a $50 gift card for completion of each survey completed.

5.3 LEN DOSING

Dosing is based on the package insert as follows:

Table 1. Dosing Schedule for YEZTUGO Initiation and Continuation in Adults and Adolescents Weighing at Least 35 kg

Time	
	Dosage of YEZTUGO: Initiation[a]
Day 1	927 mg by subcutaneous injection (2 x 1.5 mL injections) and 600 mg orally (2 x 300 mg tablets)
Day 2	600 mg orally (2 x 300 mg tablets)
	Dosage of YEZTUGO: Continuation
Every 6-months (26 weeks)[b] +/-2 weeks	927 mg by subcutaneous injection (2 x 1.5 mL injections)

a. The complete initiation dosing schedule, consisting of subcutaneous injections and oral tablets, is required; the efficacy of YEZTUGO has only been established with this dosing schedule.
b. From the date of the last injection.

Oral bridging for planned missed LEN doses: Clients should be given oral PrEP and counseling about adherence. Baseline renal function and hepatitis B status are recommended as baseline for use or oral tenofovir-based PrEP. An adequate supply should be given until LEN can be resumed.

Missed Day 2 oral load: If the day 2 loading dose of oral LEN is missed, it should be taken as soon as possible, and clients should be counseled on using barrier protection to reduce risk of HIV acquisition.

Late or missed LEN injections: If more than 28 weeks have elapsed since last dose, the oral load of LEN should be resumed along with the injection, as in the Table above.

Discontinuation of LEN: At time of planned discontinuation, clients should be counseled on use of condoms to prevent HIV transmission (to reduce the risk of HIV acquisition and LEN resistant virus) and STIs and encouraged to receive regular HIV and STI testing. Alternative types of PrEP should be discussed/offered, if appropriate.

5.4 Counseling prior to LEN initiation

- Discuss importance of keeping next injection appointment
- Counsel on the possibility of pain, swelling, redness, or a small bump at the site of injection. This typically lasts 1-2 days. Symptoms can be self-managed with warm compresses or ice (10-20 minutes at a time) or Tylenol. Seek medical care for a more severe reaction.
- Seek medical care for any unusual symptoms after injection (fever, nausea, vomiting, rash)
- While there are no medications that cannot be taken while on LEN, there are some interactions that may result in higher or lower drug levels, particularly medications that are used to prevent and treat tuberculosis (TB) and seizures medications. Counseling should be provided to report use of LEN to other clinicians, emergency room/urgent care providers. All clients should be provided with a “prescription card” that can be presented

to any health care providers that includes name of the medication “Yeztugo or lenacapavir”, the date the last dose was due, and the date the next dose is due. Clients should be counseled to present this card at routine primary care, urgent care, emergency care, and/or specialty appointments.

6.0 CLINICAL MANAGEMENT

6.1 Precautionary Medications

There are no contraindicated medications, but drug interactions for strong CYP3A4 inducers (rifampin and related and various seizure medications except for Keppra) require dose adjustment; if medication list not available, ask if client takes anything for seizures or treatment or prevention of tuberculosis. If patient has a pharmacy, call pharmacy to verify medications. If cannot confirm, defer LEN prescription until medication list can be obtained.

Table 4. Dosing Recommendations for Individuals Receiving YEZTUGO and Initiating Therapy with Strong CYP3A Inducers[a]

Maintain Scheduled Continuation Injection Dosing	Schedule for Supplemental Doses of YEZTUGO	
	Time	**Dosage**
Continue to administer once every 6-months scheduled continuation dosing of YEZTUGO 927 mg subcutaneously (2 x 1.5 mL injections) *(see Table 1)*, plus administer supplemental doses of YEZTUGO as shown in this table	On day strong CYP3A inducer is initiated (which should be at least 2 days after YEZTUGO is first initiated)	**Supplemental dosage: Step 1** 927 mg subcutaneously (2 x 1.5 mL injections) and 600 mg orally (2 x 300 mg tablets)
	On day after strong CYP3A inducer is initiated	**Supplemental dosage: Step 2** 600 mg orally (2 x 300 mg tablets)
	If strong CYP3A inducer is co-administered for longer than 6 months	**Subsequent supplemental dosage** Every 6-months[b] from initiation of strong CYP3A inducer, continue to administer supplemental doses of YEZTUGO as described above in Steps 1 and 2.
	After stopping the strong CYP3A inducer, continue the once every 6-months scheduled continuation injection dosing of YEZTUGO *(see Table 1)*.	

a. Dosing recommendations are not available for the initiation of YEZTUGO in individuals already receiving strong CYP3A inducers, nor in individuals receiving the weekly oral dosage of YEZTUGO *(see Table 2)*.

b. 26 weeks +/-2 weeks.

1. If on a CYP3A4 inducer would defer LEN and offer oral PrEP due to limited data
2. If on LEN and needs to start a CYP3A4 inducer, LEN dose adjustment will be required as per Tables 4 (strong inducer) and 5 (moderate inducer) from Package Insert below

Table 5. Dosing Recommendations for Individuals Receiving YEZTUGO and Initiating Therapy with Moderate CYP3A Inducers[a]

Maintain Scheduled Continuation Injection Dosing	Schedule for Supplemental Doses of YEZTUGO	
	Time	**Dosage**
Continue to administer once every 6-months scheduled continuation dosing of YEZTUGO 927 mg subcutaneously (2 x 1.5 mL injections) *(see Table 1)*, plus administer supplemental doses of YEZTUGO as shown in this table	On day moderate CYP3A inducer is initiated	**Supplemental dosage** 463.5 mg subcutaneously (1 x 1.5 mL injection)
	If moderate CYP3A inducer is co-administered for longer than 6 months	**Subsequent supplemental dosage** Every 6-months[b] from initiation of moderate CYP3A inducer, continue to administer a supplemental dose of YEZTUGO as described above.
	After stopping the moderate CYP3A inducer, continue the once every 6-months scheduled continuation injection dosing of YEZTUGO *(see Table 1)*.	

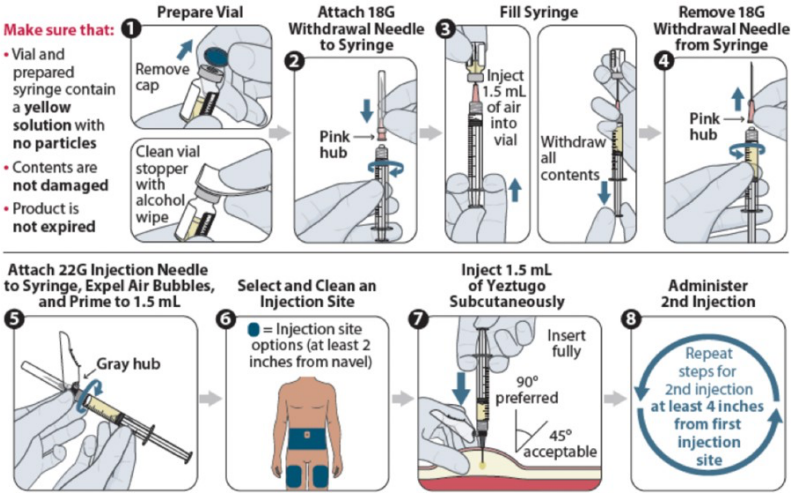
a. Dosing recommendations are not available for the initiation of YEZTUGO in individuals already receiving moderate CYP3A inducers, nor in individuals receiving the weekly oral dosage of YEZTUGO *(see Table 2)*.

b. 26 weeks +/-2 weeks.

6.2 Injection Technique: All clinicians administering LEN will be trained in administration of injections as outlined in the Package Insert (see figures 1 and 2 below from the insert). An initial training by a Gilead nurse will be provided to all HHC staff and subsequent training done after study launch will be done by an experienced staff person who was previously trained by Gilead and has experience with injections.

Figure 1 YEZTUGO Withdrawal Needle Injection Kit Components

Figure 2 YEZTUGO Injection Steps for Withdrawal Needle Injection Kit



LEN is a subcutaneous injection. Note serious reactions have occurred with subdermal injections. Injections should be given in the abdomen but may be given in the thigh as an alternative.

6.3 Support for second oral dose of load:
A member of the HHC clinical team or study team will call each participant who receives a first LEN oral dose and injection on day 1 to support completion of the second oral dose. If participants do not have a phone or have preference for receiving in-person directly observed therapy (DOT) for the oral dose, a member of the clinical team will perform in person DOT on day 2.

6.4 Side effect/adverse reactions
The most common adverse reactions to LEN include injection site reactions (ISRs), headache, and nausea. As per standard of care, all clients will receive counseling prior to LEN administration on the possible side effects as well as instructions on managing the most common types of ISRs. All participants will be called on day 2 after the subcutaneous injection for DOT of the second oral dose and to assess for any side effects from the injection or other potential medication side effects. Individuals with minor ISRs will be counseled on symptomatic management. For any ISR that is described as severe, the participant will have the choice of seeking care at a brick-and-mortar health clinic nearby or a visit from HHC to their location for an assessment and clinical care, if feasible within a reasonable timeframe. Individuals with adverse reactions will receive frequent follow-up phone calls and/or mobile visits until the issue(s) are deemed sufficiently resolved by the treating clinician. The decision to discontinue LEN due to a reaction will be determined by the clinician and client based on shared decision making about risks and benefits.

All side effects and adverse reactions such as ISRs will be recorded in an electronic case report phone created for this purpose.

6.5 Follow-up

Support for continued clinical follow-up will be provided with reminder text messages and phone calls or via trusted contacts in community organizations. Participants will only be contacted via routes they consent to as part of the informed consent process. Apple AirTags will be offered to all participants who start LEN (at time of first injection) for geolocation for follow-up injections. AirTags will be labeled with unique IDs and data will only be visible to a limited number of highly trained study staff.

7.0 STATISTICAL CONSIDERATIONS

7.1 Sample Size

The sample size is determined by the feasibility of enrollment over a 6-8-month period to allow for follow-up to evaluate persistence at 52 weeks. For the primary outcome of uptake, with a sample of ~100 offered LEN PrEP and an anticipated LEN PrEP uptake rate of approximately two-thirds (n~66), the study will achieve a margin of error of 9.2% in estimating the uptake rate. For the secondary outcome of persistence at 52 weeks, with an expected rate of 50-60%, this sample size will provide a margin of error of 11-12% in estimating the persistence rate.

7.2 Endpoints

Primary Endpoint

The primary endpoint is uptake of LEN PrEP among unstably housed people receiving health services via HHC's mobile program. The primary endpoint will be defined as receiving a first injection of LEN and the oral load on days 1 and 2. This will be measured through records of LEN administration, which will include telephone confirmation (or DOT) of the second oral dose. The investigators will perform a sensitivity analysis that defines uptake based on the injection and day one oral dose only. The investigators will also use study records to describe the proportion of those offered LEN who declined all PrEP versus selected cabotegravir or oral PrEP and were referred to a facility for this care (as these will not be provided long-term by the HHC mobile van during the time of the study).

Secondary Endpoints

1) LEN PrEP persistence at 26 weeks defined as completing the second dose of LEN on-time (+/- 14 days or as defined in the package insert) based on records of drug administration.
2) LEN PrEP persistence up to 52 weeks defined as receiving a third injection of LEN on-time (+/- 14 days or as defined in the package insert) based on records of drug administration.
3) Acceptability of mobile LEN using survey questions based on the Theoretical Framework of Acceptability.
4) Predictors of uptake based on surveys at baseline including sociodemographic factors, HIV risk perception, PrEP knowledge, self-efficacy, and clinical factors.

5) Predictors of persistence at 52 weeks based on surveys at baseline including sociodemographic factors, HIV risk perception, PrEP knowledge, self-efficacy, and clinical factors.
6) Barriers to LEN PrEP via mobile delivery based on surveys at baseline, 26, and 52 weeks (including non-persisters, if they can be reached).
7) Satisfaction with LEN PrEP via mobile delivery based on surveys at 26, and 52 weeks (including non-persisters, if they can be reached).
8) Cost per person who initiates LEN PrEP and cost per person persisting over 52 weeks.
9) Qualitative data on feasibility, acceptability, scalability, and sustainability of the mobile LEN PrEP delivery model.
10) Uptake and acceptability of AirTags for geolocation among participants enrolled in the study. Acceptability will be determined using survey questions based on the Theoretical Framework of Acceptability
11) Tolerability of LEN PrEP, including frequency and severity of injection site reactions as measured by phone calls with participants 48 hours after each injection as well as field-based clinical assessments done for those who report moderate to severe reactions; proportion of participants who discontinue LEN PrEP due to side effects.
12) Number of HIV infections that occur among participants while covered by LEN PrEP, as measured by both rapid and lab-based 4th generation Ag/Ab testing done at 6 and 12 months among those who remain in care.
13) LEN PrEP uptake by oral tenofovir-bridge status (those who accept versus those who do not, among those eligible for tenofovir-containing regimens)

7.3 Analyses

Statistical Analyses for Aim 1 (uptake):
Descriptive statistics (mean, standard deviation, median, inter-quarter range) will be generated for baseline sociodemographic factors and clinical information to characterize the study population. The percentage of LEN PrEP uptake will be calculated defining uptake as receiving the first injection and both oral doses as the primary outcome. A sensitivity analysis will be performed in which uptake is defined as receiving the first injection and day 1 oral dose only (i.e., including participants in the 'uptake' group who could not be reached to confirm they took the second oral dose). Data from baseline surveys regarding barriers to care, acceptability of mobile LEN PrEP offer, HIV risk and risk perception, and self-efficacy for health care will also be summarized, and associations with LEN PrEP uptake will be explored using logistic regression models.

Statistical Analyses for Aim 2 (persistence):
The rate of LEN PrEP persistence over 52 weeks among participants initiating LEN will be estimated. Data from baseline and 52-week surveys will be summarized using descriptive statistics. A logistic regression model will be employed to examine predictors of persistence at 52 weeks using baseline data.

Statistical Analyses for Aim 3 (cost and qualitative outcomes):
Cost-outcome: The study will conduct a cost-outcome analysis focusing on the average cost per person initiating LEN PrEP, and the average cost per person persisting through 52 weeks. The investigators will define the outcome of "persisted on LEN PrEP" by

including those with late doses and will perform a sensitivity analysis including only those who received injections on time (+/- 14 days). From the cost data collected, the study will estimate a total program cost. The study will report all cost data as means with 95% confidence intervals and medians with interquartile ranges. Finally, the investigators will use the latest available data on HIV incidence in the populations of interest (by sex and gender), the efficacy of LEN PrEP (based on clinical trial data for each population), and this study's cost data to estimate the number of HIV infections averted by this program and the cost per HIV infection averted.

In-depth interviews: The interview guide will be informed by Sekhon's Theoretical Framework of Acceptability and the Moucheraud *et al* framework for sustainability. Table 4 (supplementary file) shows how the sustainability framework will be applied to the interview guide. The investigators will also ask about system components that would facilitate scale-up, such as what type of scaling up will be appropriate; how it will be organized and how fast it will be pursued; and how various environmental challenges and opportunities will be addressed. Interviews will last no more than one hour, and a $50 electronic gift card will be provided to those who participate. Interview recordings will be transcribed, and transcripts will be analyzed using standard qualitative analysis methods: a codebook will be developed deductively, and emergent codes will be included as relevant. With ~25 stakeholders, the study should have sufficient sample to achieve saturation of themes. If the study does not achieve saturation with this sample, the investigators will add additional key informants until saturation is achieved.

8.0 DATA COLLECTION AND MONITORING

8.1 Records

Participants will be identified by the unique identification number (UID) created upon study enrollment and all personally identifiable information collected from participants will be stored under this UID. All personally identifiable information will be stored on UCLA encrypted computers or UCLA encrypted Box files and held separately from other data. Access to identifiers will be limited to key study personnel trained in management of these data.

8.2 Privacy

All study activities will be conducted in the privacy of the mobile van or in a private space at a brick-and-mortar building where the van is located on the day of service. Surveys will be conducted in the van or a private room, without other staff so that conversations cannot be heard by others. For study procedures conducted by telephone or text messages (i.e. appointment reminders, follow-up, etc.), participants will agree to their preferred modalities in the tracing form, which will be updated at each study visit, and only their preferred modalities will be used.

8.3 Confidentiality

All devices used by study personnel (phones, tablets, computers) will be encrypted, password protected and kept in locked offices when not in use. Any paper records will

be stored in locked cabinets in locked offices and will only be accessible by select members of the study team. Participants who have opted in to use an AirTag to support their ability to remain on LEN PrEP and be reached for on-time injections (in the case only that they are unable to be reached via other mechanisms on the tracing form) will be linked to the AirTag through a unique identification number (not the participant's name) that only key project staff will have access to geolocating via an encrypted study phone. Participants can decide at any time to return the AirTag or discard it.

8.4 Reporting Protocol Deviations

The principal investigator and personnel are responsible for identifying, and reporting deviations. Once protocol deviations are identified, corrective actions are to be developed by the site and implemented promptly. Protocol deviations will be sent to the UCLA IRB per their guidelines.