BMJ Open

Innovative administration of long-acting injectables for HIV treatment enhancement at home (INVITE-HOME): implementation science study protocol

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To cite: Bourdeau B, Rebchook G, Shade SB, *et al*. Innovative administration of long-acting injectables for HIV treatment enhancement at home (INVITE-HOME): implementation science study protocol. *BMJ Open* 2025;**15**:e097921. doi:10.1136/bmjopen-2024-097921

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-097921).

Received 13 December 2024
Accepted 06 July 2025

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ABSTRACT

Introduction There is high interest in long-acting injectable antiretroviral therapy (LAI-ART) among people with HIV (PWH), with many conveniences for uptake and persistence. However, both patients and clinicians have expressed important barriers to effective implementation, including concerns about frequent clinic visits and strain on clinic resources. Administration of LAI-ART by a trained layperson injector (such as family, friend or partner of the patient) can help mitigate some of these patient-identified and clinician-identified barriers. Alternative LAI-ART delivery methods have the potential to increase the PWH and layperson injector's confidence, empowerment, convenience, privacy and self-management skills and ultimately facilitate LAI-ART uptake and persistence.

Methods and analysis INVITE-Home (innovative administration of long-acting injectables for HIV treatment enhancement at home) will support the expansion of LAI-ART in non-clinical settings by developing, implementing and evaluating a comprehensive, theory-informed training to support the administration of LAI-ART by a trained layperson injector. First, INVITE-Home will design and develop an innovative, theory-based layperson injector training to improve acceptability and uptake of LAI-ART in home-based settings, grounded in qualitative evaluation of training barriers and needs of PWH, layperson injectors and clinicians to develop the training. In Aim 2, INVITE-Home will enhance understanding of home-based LAI-ART using the training, by examining implementation and effectiveness of home-based LAI-ART injections.

Ethics and dissemination This study and its protocols have been approved by the University of California, San Francisco (UCSF) Institutional Review Board and the scientific staff of HIV Research Branch, Division of HIV Prevention, National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, at the Centers for Disease Control and Prevention. Study staff will disseminate findings locally (eg, to partnering clinics, via the UCSF Center for AIDS Prevention Studies' Community Engagement Core), statewide (eg, the California Department of Public Health's Office of AIDS) and nationally at conferences related to HIV.

Trial registration number NCT06488846.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study leverages various methods to assess concepts of the implementation research logic model, providing a thorough assessment through multiple indicators.
⇒ The longitudinal approach will permit assessment of changes in implementation through multiple phases, including planning and implementation.
⇒ All of the clinical sites in this study were primary care clinics located in San Francisco, and the data from this study may not be generalisable to other non-primary care clinics and to primary care clinics outside of San Francisco.

INTRODUCTION

Background and rationale

In the USA, only approximately 60% of people with HIV (PWH) are virally suppressed.[1 2] Barriers to optimal HIV treatment and care are driven by multiple factors, including acceptability, dosing requirements, pill fatigue and care delivery.[3] Long-acting injectable antiretroviral therapy (LAI-ART) alleviates the burden of daily pill-taking and has the potential to close critical gaps in HIV care.[3 4] Long-acting cabotegravir (CAB) and rilpivirine (RPV) received regulatory approval in the USA as a monthly or bimonthly injection for HIV treatment,[5 6] and other LAI-ART formulations are currently being developed.[7]

There is high interest in LAI-ART among PWH, with many describing convenience as a key determinant of LAI-ART uptake and persistence.[8–10] However, patients and clinicians have identified important barriers that may hinder the effective implementation of LAI-ART. For example, patients have expressed concerns that monthly or bimonthly clinic visits for injections are inconvenient, can increase the risks associated with HIV-related stigma and unwanted disclosures

and lead to frequent disruptions in their lives.[4 8 11] The need to travel to a clinic for injection visits multiple times a year can also be financially and logistically prohibitive and can widen existing healthcare disparities, particularly among individuals who already face multiple structural barriers to accessing care.[3 4 8 12] Similarly, clinicians worry that additional visits outside of those required for routine HIV care may lead to frequent missed appointments, decreased care engagement and added strain on clinic resources.[3 4 13] Further, clinicians note that missed injections may increase the risk of drug resistance.[13–15] Thus, to ensure the optimal public health impact and equity of LAI-ART, there is an urgent need to evaluate effective and accessible alternatives to clinic-based delivery methods.[16]

While there are many benefits to LAI-ART, including 'freedom' from the logistical and psychosocial demands of daily oral ART, less risk of missing a dose, convenience and privacy,[9] many implementation barriers to the use of LAI-ART in clinics exist. These barriers include the need for: (1) more frequent clinic visits (ie, every 1–2 months) versus oral ART (every 6–12 months); (2) clinical personnel who are trained in administering intramuscular injections; (3) private space for buttock injections; (4) cold-chain storage (ie, RPV needs to remain at 2°C–8°C (35.6°F–46.4°F) and needs to be used within 6 hours of bringing to room temperature); (5) personnel to handle scheduling injection visits and the implications of missed injections; and (6) ensuring equitable access and distribution of LAI-ART in a cost-effective manner. Clinicians are also concerned about the capacity of clinics to handle the increased volume of visits.[3] These barriers can limit the public health impact of LAI-ART and exacerbate healthcare disparities.

Objectives

The innovative administration of long-acting injectables for HIV treatment enhancement at home (INVITE-Home) study has the potential to address critical barriers to progress in the field of HIV treatment by expanding the possible modes of LAI-ART delivery to include administration in the patient's home by trained, non-medical personnel. The overall study has two primary objectives:

1. Implementation study: assess the feasibility and acceptability of an innovative, theory-informed treatment buddy training for the administration of LAI-ART in home-based settings.
2. Effectiveness study: examine the effectiveness of home-based LAI-ART injections using the training developed relative to both clinic-based administration and oral ART.

Research design

To achieve the objectives focused on implementation and effectiveness, we will conduct a hybrid type 2 implementation-effectiveness study using a prospective cohort of 250 PWH and treatment buddies from partnering HIV clinics. This study phase will include two components: (1) implementation study: assessing the implementation barriers and facilitators and implementation outcomes (eg, acceptability, feasibility) associated with home-based LAI-ART. (2) Effectiveness study: comparing health outcomes among PWH receiving home-based LAI-ART over 12 months and 250 individuals who choose to receive clinic-administered LAI-ART. We will also compare 12-month outcomes among those who choose to receive LAI-ART with 500 individuals in the partner clinics who are virally suppressed on oral ART.

METHODS AND ANALYSIS

Participants, interventions and outcomes

Patient and public involvement statement

The study team solicited input from patients and individuals with HIV primarily through Community Advisory Boards. Within the first 7 months of the project funding, the study team presented the overall aims and methods for the implementation and effectiveness studies to a Community Advisory Board that serves the Center for AIDS Prevention Studies. Following discussion during a regularly scheduled meeting, Community Advisory Board members pilot tested the patient survey and provided feedback. At the conclusion of the formative interviews, interview participants were invited to participate in the INVITE-Home community advisory board. This group met for several hours during which time the study clinician gave a demonstration of the first visit training and shared the training materials. Attendees provided feedback on the initial visit training through discussion and survey responses. The INVITE-Home Community Advisory Board will be invited back for another session in order to provide feedback on the questionnaire developed to assist patients with selecting a treatment buddy.

Study setting

The study team has partnered with clinics in the San Francisco Bay Area to recruit participants and examine the implementation and effectiveness of the home-based LAI-ART injection training and include a Ryan White public health safety-net clinic, a national demonstration site for trauma-informed primary care which provides comprehensive medical and social services to cisgender and transgender women with HIV, one whose population is primarily underserved African American men with HIV and PWH aged 50 or older, and an adult outpatient HIV primary care county clinic. Details about participant eligibility for each of the research activities can be found in table 1.

Intervention

Intervention development

Initial interest in receipt of home-based LAI-ART administration will be assessed in the first months of the project. A one-page survey, including questions about potential interest and ability to identify a treatment buddy, will be offered to LAI-ART patients as they arrive for their monthly or bimonthly injections and will provide

Table 1 Eligibility criteria by aim

	People with HIV (PWH)	Treatment buddies	Clinicians
Obj 1: interest survey	1. ≥18 years of age 2. Receive HIV care at one of the partnering clinical sites 3. Prescribed monthly or bimonthly cabotegravir and rilpivirine combination injection (CAB/RPV) for HIV treatment as part of routine care 4. Have completed at least the loading dose of CAB/RPV (ie, 600 mg/900 mg intramuscular) and without serious adverse events	N/A	N/A
Obj 1: interview	5. Identify a treatment buddy (ie, family, friend or partner) who would be willing and eligible to participate and to whom the patient has disclosed their HIV status	1. Are ≥18 years of age 2. Has been identified by or can identify a PWH who meets the above eligibility criteria 3. Would *consider providing* injections to the PWH, who has also agreed to participate	1. Work at one of the three partnering clinics 2. Would consider referring patients to a support person (ie, treatment buddy) injection programme
Obj 2: intervention and surveys	6. Virologically suppressed (HIV RNA <50 copies/mL) 7. No history of treatment failure 8. No known or suspected resistance to either RPV or CAB 9. Interested in receiving home-based LAI ART injections 10. Approved by their clinical team as a candidate for home-based injections 11. Intention to use CAB/RPV for at least 12 months.	4. Willing and able to *provide* monthly or bimonthly LAI-ART injections at the PWH's place of residence	N/A
Obj 2: intervention interviews	Eligibility to be determined	Eligibility to be determined	N/A
Obj 2: implementation interviews and surveys	N/A	N/A	No additional criteria

LAI-ART, long-acting injectable antiretroviral therapy; Obj, objective; PWH, people with HIV.

the clinics with information on the level of interest in home-based administration. The formative work necessary to develop the INVITE-Home intervention includes conducting qualitative interviews with up to 30 clinicians from the partnering clinics who are involved in the administration of LAI-ART and up to 15 dyads of PWH who receive LAI-ART in the partnering clinics and their selected treatment buddy. The information gleaned from these interviews will inform the workflows and operating procedures for the referral, medication administration and documentation of home-based LAI-ART, as well as contributing to the development of the training intervention by the INVITE-Home curriculum team. Once the training curriculum is drafted, interview participants who had previously indicated an interest in being recontacted will be recruited to participate in the INVITE-Home advisory board, which will review the training curriculum and meet, at least once, for a group feedback session. This feedback will drive additional edits and refinements, and the curriculum, including additional resources and online supplemental materials, will be finalised.

INVITE-Home intervention

All referred PWH will be screened for eligibility and—if found to be eligible and interested—research staff will conduct informed consent and enrol PWH in the study (see below for recruitment details). Participants will be asked about any special considerations related to their home or other administration location for the safety of the participants (eg, discretion) and the study staff (eg, pets, locked gates). We anticipate that the PWH in the home-based administration arm and their treatment buddies will be sent previsit training materials to review prior to visit 1 with a licensed nurse practitioner (study clinician). Previsit training will deliver content-based learning through online videos that will provide overviews of the medications, potential side effects and side effects management, adherence, handling missed doses, discontinuing LAI-ART and an injection demonstration. Materials from the videos will also be provided in digital (PDF) or paper form, along with a reusable checklist for injection steps and a needlestick protocol. We anticipate that the PWH and the treatment buddy will

spend approximately 30–45 min reviewing the previsit materials.

The study coordinator will facilitate medication delivery to the patient's home, confirm receipt of the medication and that it was properly stored. This includes confirming that the medication is shipped in an insulated box with a temperature strip affixed to the outside and confirming that the patient was home when the packages were delivered, and that the medication was placed directly into the refrigerator on receipt. Individuals needing larger gauge needles will receive them in the package with the medication, as provided by the pharmacy.

Intervention visits will occur according to when the patient is expected to receive their injections (monthly or bimonthly ±7 day window), and personnel will be dressed in street clothes without any study identifiers to obscure the medical nature of their visit. The PWH and their treatment buddy will be followed over 12 months by the study clinician (ie, for 6 bimonthly or 12 monthly injections). The study clinician will bring supplies to facilitate the injection (eg,sharps disposal container, gloves, gauze pads, bandages), leaving a sufficient amount for the remaining injections to visit 1, which will take place in the location of the PWH's choosing (anticipated to be their home). At this visit, the study clinician will review key points of the training materials using problem- and experience-based learning strategies outlined in the training, including reviewing the injection checklist and the needlestick protocol (see online supplemental materials). The study clinician will demonstrate the preparation and administration of CAB/RPV using normal saline on a training manikin. The treatment buddy will then be asked to practise the injection on the manikin and then perform the injection on the PWH using the patient's medication under the supervision of the study clinician, who will provide prompts and cues. Per standard clinic protocol, the study clinician will monitor individuals for 15 min following all injection administrations to assess any side effects.

For subsequent visits, the study clinician will briefly reinforce key points, and the treatment buddy will prepare and administer CAB/RPV. During visits 3–12 (or visits 3–6 for bimonthly LAI-ART), the study clinician will work with the PWH and treatment buddy to determine when study clinician oversight during visits could transition from in-person to videoconferencing. The PWH and treatment buddy will be given a 24-hour study phone number to contact the study clinicians in case of questions.

Intervention retention and termination

We will use a multipronged approach to maintain patient and treatment buddy retention in the intervention, including obtaining multiple forms of contact information, updating a locator form at each visit and sending visit reminders. The study clinician will notify the clinics regarding all LAI-ART administered, as well as late or missed doses. We will also communicate any difficulty in the retention of the treatment buddies with the clinics to assess the appropriateness of continued home-based injections. Given current Food and Drug Administration guidelines, PWH who participate in the study will resume clinic-based care and treatment administration at the end of the 12 months. At their last visit, the study clinician will assist PWH in scheduling their next clinic visit to avoid lapses in medication coverage.

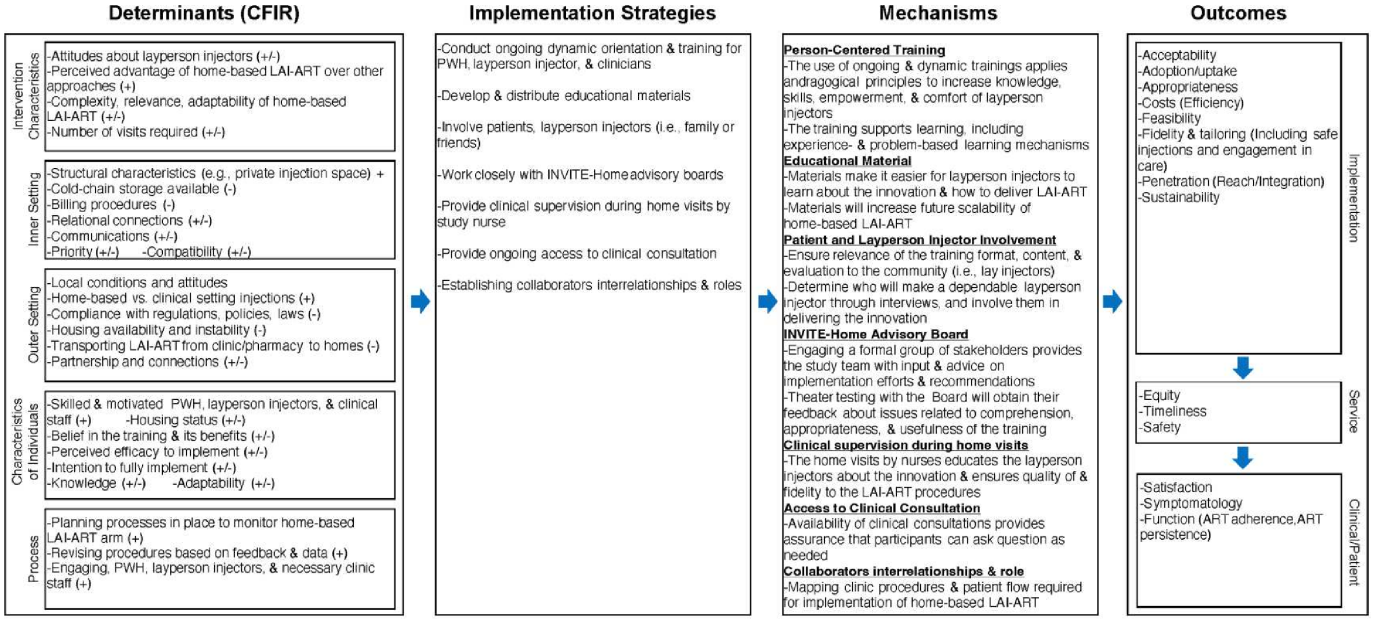
Both participants need to agree to participate in the intervention to be retained. If at some point during the intervention year, a treatment buddy decides they no longer want to provide injections, the patient will need to find another person to take on the treatment buddy role or return to clinic administration. Both patients and their treatment buddies can continue with research activities (surveys, interviews) even if the patient returns to clinic administration before the intervention year is complete. Both patients and their treatment buddies can also opt to cease participation in the study activities in addition to the intervention.

Participant intervention payment

Participation payment for the initial training will be US$20 per person (US$20 to the PWH and US$20 to the treatment buddy), US$15 per session per person for training/visits 2–6 and those who receive injections monthly will be eligible for payment for visits 7–12 at US$10 per visit per person. Incentives will be payable via a digital wallet option or gift card, whichever is preferred by the participants.

Outcomes

The implementation study will include an observational cohort design to longitudinally evaluate the implementation of the intervention using qualitative and quantitative research methods and guided by the implementation research logic model (IRLM)[17] domains (see figure 1). Primary *implementation outcomes* will focus on feasibility and acceptability as reported by PWH, treatment buddies and staff involved in the injectable programmes at partnering clinics. Data collection methods will include additional assessments of appropriateness, sustainability, reach, uptake, cost, barriers and facilitators. The focus of the effectiveness study will be the primary cohort of 250 individuals who are prescribed LAI-ART and choose to receive support via treatment buddy-administered ART at home. The primary outcome for the effectiveness study is HIV symptomatology, defined as viral suppression (<200 copies/mL) and durable viral suppression (two suppressed viral loads at least 3 months apart)). Additional outcomes will be guided by IRLM domains, including *service outcomes* (equity, defined through statistical comparison of other service and client outcomes by clinic, age, race/ethnicity and gender; timeliness, defined as elapsed days from injection due date to date administered and days from missed appointments to injection; and safety, defined by having moderate or severe side effects of injections) and *client outcomes* (satisfaction with home-based/treatment buddy-administered injections;



(+/-) indicates whether the factor acts as a facilitator (+), barrier (-), or potentially both

Figure 1 Implementation research logic model for INVITE-Home. INVITE-Home, innovative administration of long-acting injectables for HIV treatment enhancement at home; LAI-ART, long-acting injectable antiretroviral therapy; PWH, people with HIV; CFIR, Consolidated Framework for Implementation Research.

client function, measured as ART adherence (proportion of days during the 12-month follow-up period that patients are 'covered' by ART) and persistence (proportion of patients with no gap in injection or prescription of ART).

Sample size

Research staff aim to recruit 250 individuals for the home-based LAI-ART arm. Further, using EHR data, we will create a cohort of 250 patients who are receiving clinic-based LAI-ART. We will also create a cohort of 500 PWH who are eligible for LAI-ART but continue with oral ART; we will match them to those on LAI-ART (both home- and clinic-based) by clinic, age, race/ethnicity and gender via propensity score matching during modelling. A sample composed of these sizes will provide 90% power to allow us to detect non-inferiority in the maintenance of viral suppression at 12 months within 3% if the upper bound of the one-sided 95% CI is less than (a) 10.1% higher for the home-based LAI-ART compared with the clinic-based LAI-ART and (b) 7.6% higher for oral ART compared with LAI-ART. These estimates assume a true value of viral suppression at 12 months of 95% among patients on oral ART, 93.5% among patients on clinic-based LAI-ART and 90.5% among patients on home-based LAI-ART.

Recruitment

Participant clinicians will include physicians, nurses, physician assistants and clinical pharmacists who provide direct patient care to PWH at our three partnering clinics, as well as any administrative staff whose work responsibilities interface with LAI-ART services (eg, benefits and billing). Recruitment of clinicians will take place during project meetings or via email outreach. We will approach the clinicians who provided letters of support for the study first, and then any colleagues they refer.

To reach PWH/treatment buddy dyads, the research team will post participant recruitment flyers and postcards at the three clinical sites. The study telephone line and email account will be posted on flyer materials and shared with clinic providers. Patients who have been prescribed injectable CAB/RPV as part of their routine care may also be approached by clinic staff to participate and given recruitment materials. We will collaborate with clinicians at each clinic to provide study materials to PWH and their candidate treatment buddies (family, friends or partners).

For interested participants who reach out, research staff will explain the study and screen them for eligibility over the telephone. To protect the PWH's private medical data, if the treatment buddy is the first study contact, that person will be encouraged to talk with the PWH to assess interest in the study. If they have already spoken to and confirmed the interest of the PWH, the treatment buddy will be informed that the PWH must contact the study team directly so that disclosure of the PWH's status will be made by the PWH themselves. If the PWH initiates contact with the study team, they will be asked to provide the name and contact information of a person who would be their treatment buddy during their eligibility screening. Both individuals would need to agree to participate to be included. Research staff will also confirm eligibility with the clinic provider.

Participant timeline

PWH participants and their treatment buddy will both need to be confirmed eligible for participation and consented prior to enrolment, including obtaining approval from their clinician to participate in the study. Intervention contacts include the first home-based training visit and administration, followed by either monthly or bimonthly (depending on medication prescription) continued administration supervision. PWH and treatment buddies will complete study surveys at enrolment, 6 months and 12 months. Qualitative interviews with a subset of participant PWH and their treatment buddies will also take place at the same time points but be conducted separately from the clinician visits. See figure 2 for the schedule of participant contact. In addition, for the implementation study, clinical staff will be interviewed and administered surveys prior to intervention implementation, at a midpoint and after implementation.

Methods: data collection, management and analysis

Data collection methods

Implementation study data will be collected from the PWH, their treatment buddy, clinicians in partnering clinics and programme documents (eg, funder reports) (see table 2 for the list of data sources and timing by IRLM concept). Clinicians (n=20) will be surveyed and interviewed at three points: prior to implementation of the intervention, mid-implementation and post implementation. Clinical staff members involved in the administration of LAI-ART (eg, providers, administrators, finance) will be recruited to participate in surveys/interviews regardless of whether they have referred anyone at the time of the survey. Clinician interviews and surveys will assess the *outer* and *inner setting* domains, as well as characteristics and processes related to the intervention, *implementation strategies* and *implementation outcomes* (acceptability, feasibility, appropriateness, sustainability, barriers and facilitators).

All enrolled dyads will complete surveys which will assess the *individual characteristics*; components of the *inner setting*, such as attitudes and beliefs about injections, medical background and/or injection experience, knowledge of HIV/ART and efficacy for performing/receiving injections at home; and *implementation outcomes* (acceptability, feasibility and appropriateness of the intervention).

A subset of the intervention participants (n=20 dyads) will be recruited to participate in a set of three qualitative interviews, the first at enrolment, then at 6 months and at 12 months. The selection of potential participants in the interviews will be guided by several factors: the results of the interviews in the formative phase, feedback from the study clinician and/or interviews with clinicians in the implementation component of the study. These interviews will be focused primarily on *implementation outcomes*, specifically acceptability, feasibility, barriers and facilitators to home-based LAI-ART administration.

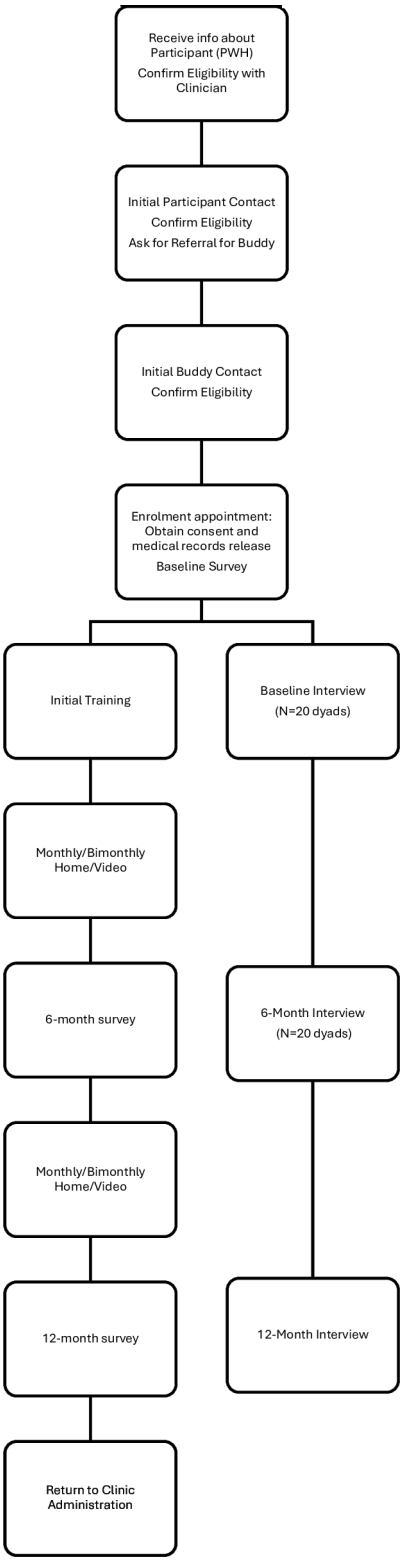


Figure 2 Intervention participant contact flow chart. PWH, people with HIV.

Additional documentation review will be conducted by the qualitative research experts on the study team, including[1] scanning public-facing reports to determine structural characteristics of each of the partnering clinics (funding sources, patients served per year, etc);[2] review of standard operating procedures for each clinic and

Table 2 IRLM domains, elements and methods to guide the implementation study

Method: quasiexperimental observational design using mixed methods			
Concepts	**Methods**	**Proposed measure(s)**	**Timing**
Outer setting domain: local conditions and attitudes, partnerships and connections, policies and laws			
Equity: patient mix, underlying socioeconomic conditions	Qualitative: document review	Annual public-facing reports Ryan White services report other funder-required reporting	Ongoing
Funding: sustained fiscal support, fit with existing service funds			
Inter-organisational relationships: contracting, information sharing	Qualitative: clinician interviews	Interview guide	Pre-implementation only
Inner setting domain: structural characteristics, relational connections, communications, priority and compatibility			
Organisational			
Organisational characteristics: leadership, structure, priorities/ goals, readiness for change, receptivity context, culture/climate Innovation-values fit staffing: staff selection criteria, validated selection procedures	Qualitative: clinician interviews	Interview guide	► Pre-implementation ► Mid-implementation ► Post implementation
	Quantitative: clinician surveys	Accelerated Healthcare Innovation Capacity Scale[18] Organisational Readiness for Implementing Change Scale[19]	► Pre-implementation ► Mid-implementation ► Post implementation
Individual			
Individual adopter characteristics: demographics, adaptability, knowledge, attitudes, beliefs	Quantitative: treatment buddy surveys	Modification of ART knowledge, attitudes, beliefs[20]	► Enrolment ► 6 months ► 12 months
	Quantitative: PWH surveys		
	Qualitative: treatment buddy interviews	Interview guide	► Enrolment ► 6 months ► 12 months
	Qualitative: PWH interviews		
Intervention characteristics and processes			
Characteristics: complexity, relevance, adaptability, perceived advantage	Qualitative: clinician interviews	Interview guide	► Pre-implementation ► Mid-implementation ► Post implementation
Processes: planning and evaluation systems, standard operating procedures	Qualitative: clinician interviews	Interview guide	► Pre-implementation ► Mid-implementation ► Post implementation
	Qualitative: document review	Review of revised SOPs developed in formative phase and any additional modifications	Quarterly
Implementation strategies: policy context, planning, educational, restructuring, quality management, financial			
Clinicians buy-in, workflow changes, engaging client advisory board, etc.	Qualitative: clinician interviews	Interview guide	► Pre-implementation ► Mid-implementation ► Post implementation
	Qualitative: document review	Study clinician process notes	Quarterly
Implementation Outcomes			
Reach	Quantitative: Electronic Health Record (EHR) enrolment	Proportion of eligible patients enrolled per clinic	Conclusion of patient enrolment

Continued

Table 2 Continued

Method: quasiexperimental observational design using mixed methods			
Concepts	**Methods**	**Proposed measure(s)**	**Timing**
Uptake	Quantitative: EHR referrals	Proportion of clinicians who make referrals per clinic	Conclusion of patient enrolment
Acceptability, appropriateness, feasibility	Quantitative: clinician surveys	Acceptability of Intervention Measure, Intervention Appropriateness Measure and Feasibility of Intervention Measure	► Pre-implementation ► Mid-implementation ► Post implementation
	Quantitative: treatment buddy surveys		► Baseline ► 6 months ► 12 months
	Quantitative: PWH surveys		
Fidelity and tailoring	Quantitative: EHR data	Number of rescheduled and missed injection visits and number of clinic visits	Conclusion of patient enrolment
	Qualitative: document review	Study clinician process notes	Quarterly
Cost	Quantitative: cost	Excel template	► Pre-implementation ► Mid-implementation ► Post implementation
Sustainability	Qualitative: clinician interviews	Interview guide	Post implementation only
Barriers and facilitators	Qualitative: clinician interviews	Interview guide	► Pre-implementation ► Mid-implementation ► Post implementation
	Qualitative: treatment buddy interviews	Interview guide	► Enrolment ► 6 months ► 12 months
	Qualitative: PWH interviews		

ART, antiretroviral therapy; IRLM, implementation research logic model; PWH, people with HIV; SOP, standard operating procedure.

their evolution over the course of implementation; and[3] template analysis of the study clinician's process notes taken during each home visit/administration supervision. Quantitative researchers on the study team will review documentation related to enrolment and referrals in the clinics' EHR to provide an assessment of *implementation outcomes* (reach and uptake). The quantitative team will also develop a data collection tool and work with clinic programme and finance staff to assess all activity-based *costs*. The tool will contain information on resource categories (personnel, recurring costs, capital investments and infrastructure), time period (pre-implementation or start-up, implementation) and personnel activity.

Data management

All participant surveys will be self-administered using REDCap (data collection tools comliant with the Health Insurance Portability and Accountability Act (HIPAA)). All clinics obtain medical releases of information from clients. They will only provide deidentified data related to the study. All project-related files, including data collection tools, institutional review board (IRB) documentation and data generated will be stored using HIPAA-compliant UCSF Box. Using both a server and cloud-based support model, users store files in a central location, accessible online via UCSF Box. UCSF Box offers unlimited storage and HIPAA-compliant folders. These files will be restricted to UCSF staff who are a part of this research project.

Statistical methods

For the implementation study, the total number of PWH and treatment buddies referred and enrolled per clinic will be tracked to monitor progress. The analysis will describe feasibility, acceptability and other quantitative implementation outcomes, using information from surveys with PWH, layperson injectors and clinicians, using descriptive statistics, including frequencies, proportions and measures of central tendency (means, SD). Differences in implementation outcomes by clinic, age, race/ethnicity, as well as changes in implementation outcomes over both study and calendar time, using generalised estimating equations (GEEs) to account for multiple observations on each participant. Clinic-level data will be used in conjunction with the referral and enrolment data to assess:[1] reach: by examining the proportion of those

eligible who enrol to receive home-based delivery of LAI-ART (ie, have received LAI-ART, have clinician approval for study participation, have identified a candidate treatment buddy who has also agreed to participate, etc);[2] uptake: by determining the number of clinicians at each site and assessing the proportion (and 95% CI) of those who provide referrals to the INVITE-Home study. We will use a benchmark of ≥80% to establish reach (ie, ≥80% of those eligible agree to participate) and uptake (ie, ≥80% of eligible clinicians provide referrals). We will estimate the cost per PWH (efficiency) associated with each study arm. We will compare cost per PWH across study arms to assess the incremental cost or savings per PWH associated with home-based LAI-ART compared with clinic-based LAI-ART and LAI-ART overall compared with oral ART. We will report the variability of these estimates across sites and over time.

The effectiveness study analysis will include descriptive statistics including proportions and measures of central tendency to characterise the study sample as well as service and client outcomes. Frequency tables will be created for all categorical variables and measures of central tendency and variability for continuous variables (eg, age, satisfaction). We will characterise the sample overall and stratified by study group to check for imbalances. If groups differ significantly at baseline on one or more covariates, we will use causal modelling methods (eg, propensity scores, targeted maximum likelihood estimation) to obtain the desired marginal effect estimates under the counterfactual assumption of balanced arms. We will use multiple imputations to handle missing covariate and outcome data, with missing imputations formed based on clinic, age, race/ethnicity, gender and other relevant baseline characteristics.

Primary analyses will focus on two comparisons:[1] the home-based LAI-ART group to the clinic-based LAI-ART group and[2] the combined LAI-ART group (ie, home+-clinic) to the oral ART group. We hypothesise that[1] client function (ART adherence and persistence) and HIV symptomology (viral suppression and durable viral suppression) will be non-inferior in the home-based LAI-ART group relative to the clinic-based LAI-ART group and[2] in the LAI-ART group relative to those in the oral ART group. We will conduct propensity score matching based on clinic, age, race/ethnicity and gender. We will use logistic GEE models to test each hypothesis. These analyses will account for repeated observations for each outcome and matching strata.

We will conduct an exploratory analysis of changes in service and client outcomes over time by including interaction terms for calendar time in our GEE models to compare home-based LAI-ART to clinic-based LAI-ART and combined LAI-ART to oral ART.

Data monitoring

The data management staff will periodically review data entered into the injection side effects form in REDCap and discuss findings in the research team meetings. When data are provided for PWH participating in the research study, the study team will cross-reference study IDs provided with the date of birth we have recorded for the participant to ensure that the study IDs have been correctly assigned. When data are submitted to the study's data management team, descriptive statistics will be used to visually assess the data and check for outliers or unexpected data (eg, categorical data where numeric data are expected or a large number of results that are higher or lower than expected). These types of observations will be followed up on and/or accounted for in the analysis.

Ethics and dissemination

All participants will be informed that their participation in the study is voluntary and that they may decline to participate for any reason without any negative consequences. Referrals for emotional support and mental health will be available. All participants will have the opportunity to retain a copy of the consent form, on paper or delivered via email. The study consent forms will inform participants of confidentiality guidelines. Strict confidentiality will be maintained. Records that have personal identifiers will be stored in a locked cabinet separate from the research record, which will contain only the participant's ID number. Only the research team and clinical staff assigned to the care of the participants will have access to non-anonymous records. Consent forms, which contain names, are stored separately. No presentation or publication of the study results will refer to participants by name. In addition, representatives from the Centers for Disease Control and Prevention (CDC) and the UCSF Institutional Review Board (IRB) will have limited access to the research records (ie, in the event of a serious adverse event, the IRB may request a review of the chart to assess the adequacy of care during the trial). Prior research participants have expressed great concerns about HIV-related stigma; therefore, the researchers want to respect their privacy concerns by limiting access to the data. In addition to informed consent, we will ensure to maximise privacy and confidentiality protections (eg, de-identification of data, certificates of confidentiality and other protective measures). Prior to any sharing of the research dataset, all personal identifiers will be removed. The formative work has been approved by the UCSF IRB (#23–40016) and the implementation study approved separately (#24-42341), also by the UCSF IRB.

We will present periodic data updates throughout the project period to the INVITE-Home advisory board and partner clinics to promote increased stakeholder engagement, share learning across clinical partners and inform decisions made in relation to the intervention. The capstone product of this research will be an intervention training and implementation manual. UCSF will work with CDC programme staff to conduct additional publication and dissemination activities, including conference presentations and writing manuscripts for submission to peer-reviewed journals.

DISCUSSION

This model of care has been used successfully in other contexts, such as hormone regulation, fertility treatments and contraception, but up to now it has not been evaluated for HIV treatment. Alternative LAI-ART delivery methods have the potential to increase the PWH and layperson injector's confidence, empowerment, convenience, privacy and self-management skills and ultimately facilitate LAI-ART uptake and persistence. This study will address a critical need to develop alternative and decentralised LAI-ART delivery methods that can mitigate barriers to ART uptake and persistence, enhance real-world LAI-ART effectiveness, reduce systemic and structural inequities, address clinical and policy challenges and close key gaps in HIV care. By combining behavioural and biomedical approaches, this study can lead to improved implementation of LAI-ART by expanding care delivery outside of clinical settings and medical providers and increasing rates of virologic suppression, thereby improving patient health and leading to reduced HIV transmission. INVITE-Home is aligned with the 2022–2025 HIV National Strategic Plan and the US Ending the HIV Epidemic initiative 'Treat' Pillar. We aim to tackle potential barriers associated with LAI-ART, discover solutions to optimise the health of PWH, address and advance equity by removing structural barriers and use rigorous methods to test our innovative strategy.

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Acknowledgements The authors wish to thank Josh Betts and Heather Tevendale for their contribution to the research protocol and programme support, as well as the leadership of partnering clinics, including Al Paschke, RN; Edward Machtinger, MD, Monica Gandhi, MD, MPH, and Sunny Lai, MD.

Contributors BB: project administration, supervision, funding acquisition, writing – original draft. GR: conceptualisation, methodology, funding acquisition, writing – review and editing. SBS: conceptualisation, methodology, writing – review and editing, funding acquisition. JO'S: supervision, writing – review and editing. KB: supervision, writing – review and editing. OH: conceptualisation, writing – review and editing. MOJ: conceptualisation, writing – review and editing. MP: software, investigation, writing – review and editing. ATB: methodology, investigation, writing – review and editing. JVN: resources, project administration, writing – review and editing. EM: resources, project administration, writing – review and editing. PS (guarantor): conceptualisation, funding acquisition, supervision, writing – original draft, writing – review and editing.

Funding This publication is supported by the Centers for Disease Control and Prevention (CDC) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (Grant Number U01-PS005259-01) totaling US$4 000 000 with 100 per cent funded by CDC/HHS. Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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