



Acceptability and feasibility of long-acting injectable antiretroviral therapy for HIV-infected persons who inject drugs in Vietnam: a qualitative study

Sarah E. Rutstein,^{a*} Adams L. Sibley,^b Hanna E. Huffstetler,^b Trang Thu Do Nguyen,^c Ha Viet Tran,^c Giang Le Minh,^e Teerada Sripaipan,^b Minh Nguyen,^b William C. Miller,^d Joseph J. Eron,^a Cynthia L. Gay,^a and Vivian F. Go^b

^aDivision of Infectious Diseases, University of North Carolina at Chapel Hill, 130 Mason Farm Rd, Chapel Hill, North Carolina 27599, USA

^bDepartment of Health Behavior, University of North Carolina at Chapel Hill, 135 Dauer Dr, Chapel Hill, North Carolina 27599, USA

^cUNC Project-Vietnam, Hanoi, Vietnam

^dDepartment of Epidemiology, The Ohio State University, 1841 Neil Ave, Columbus, Ohio 43210, USA

^eHanoi Medical University, Hanoi, Vietnam

Summary

Background In Vietnam, HIV prevalence among people who inject drugs (PWID) is several times higher than in the general population (15% versus 0.3%). PWID also experience higher rates of HIV-related mortality, driven by poor antiretroviral therapy (ART) adherence. Long-acting injectable ART (LAI) is a compelling opportunity to improve treatment outcomes, but acceptability and feasibility among HIV-infected PWID remains unexplored.

Methods We conducted key informant in-depth interviews in Hanoi, Vietnam (February–November 2021). Participants were purposively sampled and included policymakers, ART clinic staff, and HIV-infected PWID. We applied the Consolidated Framework for Implementation Research to guide study design and analysis, using thematic coding to develop and iteratively refine a codebook and characterize barriers and facilitators to LAI implementation.

Findings We interviewed 38 key stakeholders: 19 PWID, 14 ART clinic staff, and five policymakers. Participants were enthusiastic about LAI convenience, highlighting less frequent and more discreet dosing. However, contrasting providers, several policymakers suggested LAI was not needed given perceived exceptional oral ART outcomes and rare viral failure among PWID. Policymakers also criticized strategies prioritizing PWID for LAI, emphasizing equity, whereas providers identified PWID as an ideal population for LAI given adherence challenges. LAI complexity, including storage and administration logistics, were deemed surmountable with training and resources. Finally, providers and policymakers acknowledged that adding LAI to drug formularies was key, but an onerous process.

Interpretation Although anticipated to be resource-intensive, LAI was a welcome addition for interviewed stakeholders and likely an acceptable alternative to oral ART among PWID living with HIV in Vietnam. Despite enthusiasm among PWID and providers that LAI could improve viral outcomes, some policymakers—whose buy-in is critical to LAI implementation—opposed strategies that preferentially distributed LAI to PWID, highlighting values of equity and revealing differences in perceived HIV outcomes among PWID. Results provide a vital foundation for developing LAI implementation strategies.

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*Corresponding author at: 130 Mason Farm Rd (Bioinformatics), CB#7030, Chapel Hill, NC 27599-7030, USA.
E-mail address: srutstein@unc.edu (S.E. Rutstein).

Research in context

Evidence before this study

Phase three randomized clinical trials have demonstrated efficacy of long-acting injectable antiretroviral therapy (LAI) as non-inferior to daily oral antiretroviral therapy (ART). Open label extension trials suggest LAI is highly acceptable, with 97% opting to remain on injections. LAI acceptability among persons who inject drugs (PWID) is not known, and this group was excluded from phase three trials. In much of Southeastern Asia, including Vietnam, PWID have worse viral suppression and have higher rates HIV-related morbidity and mortality compared to persons who do not inject drugs. Economic models suggest LAI will only be cost-effective in low- and middle-income countries if deployed among persons with HIV who are most likely to fail therapy. Furthermore, despite the unique challenges of LAI implementation in low- and middle-income countries, qualitative studies examining LAI acceptability and feasibility are largely limited to stakeholders in resource-wealthy settings and have not included policymakers. Our assessment of the evidence is based on PubMed and Google Scholar searches from database inception to June 25, 2022, using combinations of search terms that focused on acceptability, feasibility, injection drug use, and long-acting injectable HIV therapy. No language restrictions were applied to these searches.

Added value of this study

This study fills a critical gap in evidence around the determinants of LAI implementation among PWID in a more resource-limited setting. Drawing on in-depth qualitative methods and applying a robust analysis framework (Consolidated Framework for Implementation Research [CFIR]), this study identifies critical barriers and facilitators to LAI use in this patient population that experiences some of the worst HIV treatment outcomes globally. PWID were excited by the prospect of LAI, citing improved convenience and discreet dosing as promising for improved viral suppression. We gained unique insights into areas of discord between national policymakers and HIV providers responsible for implementing HIV treatment. Discrepancies in perceived need for and appropriateness of PWID-targeted LAI interventions exposed salient themes of stigma and equity as key considerations for LAI implementation. Enthusiasm for LAI among all interviewed stakeholders was tempered by logistical and operational concerns and diverging perspectives regarding patient eligibility or selection.

Implications of all the available evidence

Strategies to improve viral suppression and reduce HIV-related morbidity and mortality among HIV-infected PWID are urgently needed. LAI is a tantalizing opportunity to improve viral suppression among PWID. Effective implementation of LAI requires attention to the perceptions of this evidence-based intervention among

patients, providers, and policymakers. The CFIR constructs, including *tension for change*, *relative advantage*, and *external policies*, may be a helpful guide to developing acceptable, feasible, and efficient LAI implementation strategies, particularly in low- and middle-income countries where careful patient selection is critical to optimize this novel therapy.

Introduction

Injection drug use is the primary driver of the HIV epidemic in Southeast Asia.¹ Parenteral exposure to infected blood is one of the most efficient means of HIV transmission, which has resulted in rapid and uncontrolled HIV epidemics among people who inject drugs (PWID).^{2–4} As a result, HIV prevalence among PWID in Southeast Asia (15%) is markedly higher than that of the general population (0.3%).^{4–6} Reflecting these regional trends, Vietnam's HIV epidemic is heavily concentrated among PWID, and the country has been identified as one of six that accounts for half of the global population of PWID, with HIV prevalence in PWID estimated from 15–30%.^{1,7,8}

Compared to other groups of persons with HIV (PWH), PWID with HIV have low rates of antiretroviral therapy (ART) initiation, retention in care, and viral suppression.^{9–11} These outcomes reflect the social and structural challenges PWID often face in accessing adequate HIV testing and treatment, including stigma and discrimination, criminalization, and economic precarity.^{12,13} PWID subsequently experience high rates of HIV-related and all-cause mortality at all stages of the HIV care continuum.^{14,15} As a result, PWID urgently need more effective HIV treatment programs.^{1,5,12}

Within the HIV treatment cascade, ART adherence is an important step to intervene to support PWID with HIV. In a randomized controlled trial (HIV Prevention and Trials Network 074), an integrated intervention that combined systems navigation and brief psychosocial counseling for PWID increased ART use and increased rates of viral suppression.¹⁶ Despite favorable ART uptake and suppression outcomes in the intervention arm, only 50% of intervention participants from Vietnam were alive and virally suppressed at 52 weeks. In the standard of care arm, 56% reported being on ART but only 30% of participants were virally suppressed one year into follow-up. The discrepancy between reported ART uptake and viral suppression suggests a critical gap in ART adherence to target for additional innovation and support.

Monthly and every other month intramuscular injections of long-acting cabotegravir (an integrase strand-transfer inhibitor [INSTI]) and long-acting rilpivirine (a nonnucleoside reverse-transcriptase inhibitor [NNRTI]) are safe,¹⁷ non-inferior to standard oral therapy for maintaining HIV viral suppression,^{18,19} and a

compelling alternative to oral therapy for persons who struggle with adherence to daily ART pills, including PWID. But pivotal phase three long-acting injectable (LAI) ART studies excluded persons with substance use disorders at the discretion of the study investigator.^{18,19} Although expected to be effective, the acceptability of LAI ART among HIV-infected PWID has not been explored.

LAI ART (hereinafter referred to as “LAI”) has been approved for use by the United States Food and Drug Administration²⁰ and the European Medicines Agency,²¹ and may soon be approved for use in low- and middle-income countries, including Vietnam. As global availability of LAI expands, examining the barriers and facilitators of integrating LAI into existing HIV care systems is essential to inform implementation strategies for this novel, highly efficacious HIV treatment modality. Therefore, to identify and characterize these barriers and facilitators in the context of Vietnam, we conducted a qualitative study among stakeholders to understand their perspectives on LAI as a potential treatment modality.

Methods

Conceptual framework

We applied the Consolidated Framework for Implementation Research (CFIR) to guide study design and analysis.²² CFIR is a theoretically-informed taxonomy of constructs

likely to influence successful implementation of complex interventions (Figure 1). The framework includes 39 constructs across five domains. Its comprehensiveness is well-suited for systematically characterizing the implementation context during the developmental, pilot, and scale-up of interventional research.

We used CFIR to conduct a pre-implementation assessment of LAI in Vietnam. We sought to characterize feasibility and acceptability of LAI implementation at individual, organizational, and systems levels. Specifically, we explored perceptions of current ART policy and practice, potential individual-, clinic-, and systems-level barriers and facilitators to LAI uptake, perceived acceptability and utility of LAI as an alternative to daily oral ART for PWID with HIV, and stakeholders’ considerations for successful implementation.

Data collection

We conducted semi-structured in-depth interviews (IDIs) in Hanoi, Vietnam between February and November 2021. Participants were purposively sampled to provide a wide range of opinions and experiences, including policymakers across government agencies in Vietnam; HIV clinic staff (physicians, counselors, and pharmacists); and PWID, including PWH enrolled in ART care, recently diagnosed with HIV but not yet on ART, and previously enrolled in ART but defaulted. Patient and provider participants were recruited from

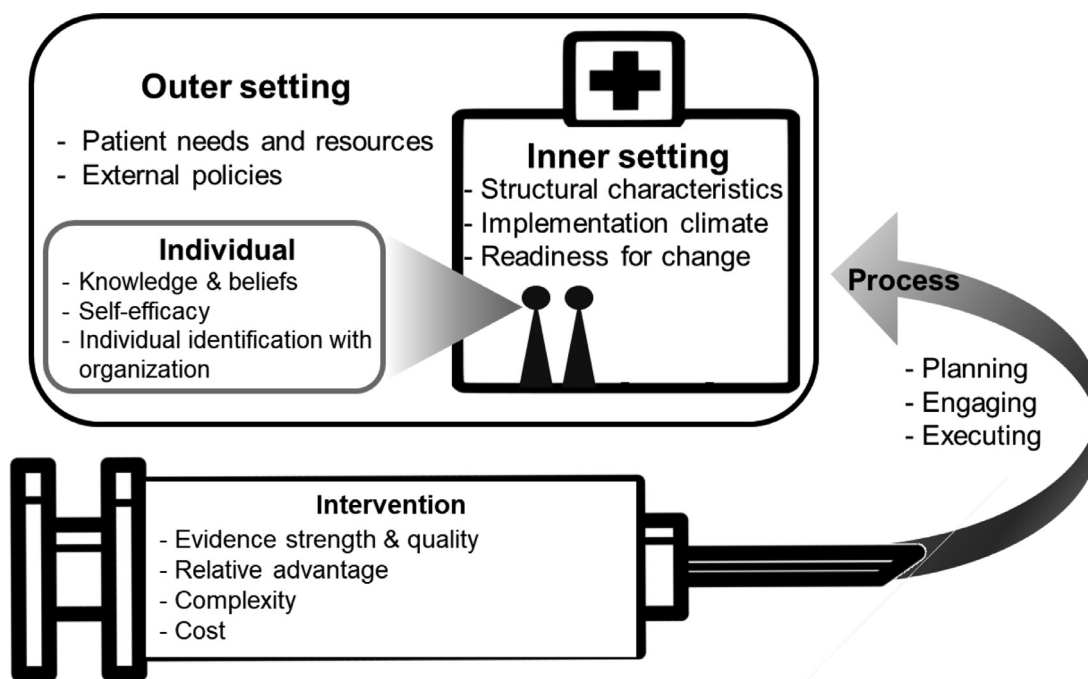


Figure 1. Examining determinants of LAI implementation among PWID in Vietnam using the Consolidated Framework for Implementation Research.

government-run public ART clinics and had to be ≥ 18 years old. Participants received standard compensation in line with local practices.

IDI guides followed a similar structure for each stakeholder group. In part one of the interview, participants shared their perspectives on current ART practice in Vietnam. Participants were then provided a brief synopsis of LAI (i.e., that it is a new alternative to daily oral ART that is injected gluteally monthly). Interviewers were instructed not to provide details about LAI effectiveness, side effects, cost, storage logistics, or related factors initially so that participant questions and concerns would arise organically. In part two, participants shared their perspectives on the feasibility and acceptability of LAI and compared this new technology with oral ART. PWID also completed a brief demographics survey.

All interviews were conducted by trained interviewers in-person and lasted between 45–60 minutes. Participants provided written consent. Interviewers verbally administered a brief demographic and drug-use survey to PWID before beginning the interviews. All interviews were conducted in Vietnamese, audio-recorded, transcribed, and translated into English.

Data analysis

We summarized survey responses using descriptive statistics (STATA version 13.1, College Station, Texas, USA). Analysis of the transcripts was grounded in Braun and Clarke's thematic analysis approach²³ and proceeded in two phases. In phase one, two investigators (SER and ALS) applied open, thematic coding to develop and iteratively refine codebooks. Separate codebooks were developed for patient and non-patient (i.e. provider, policymaker) participants. The resulting codebooks reflect a mix of deductive codes (e.g. adherence facilitators) drawing from the IDI guide and inductive codes (e.g. deference to medical authority) based on emerging themes from the interviews. Three transcripts were then coded by three investigators (SER, ALS, HEH) to test the robustness of the codebook. The investigators met after each coded transcript to discuss discrepancies and achieve consensus on coding decisions. Subsequently, HEH independently coded all interview transcripts. Dedoose (version 7.0.23, Los Angeles, CA, SocioCultural Research Consultants, LLC) was used to organize and index codes and facilitate the coding process. The second phase involved discussion of the key themes and subthemes characterizing barriers and facilitators to LAI implementation, and mapping of these themes to subdomains of the CFIR framework (e.g., *LAI/daily oral comparison* code was analyzed and described within the CFIR *relative advantage* construct). Only CFIR constructs addressed by participants during the interviews were included in analysis.

Ethics statement

The University of North Carolina at Chapel Hill Biomedical Institutional Review Board and the Hanoi Medical University Institutional Ethical Review Board approved this study.

Role of the funding source

This work was supported by the United States National Institutes of Health. Funders were not involved in study design, data collection, analysis, or manuscript writing.

Results

We interviewed 38 stakeholders, including 19 PWID living with HIV (Table 1), 14 ART clinic staff, and 5 HIV/AIDS policymakers. Among PWID, four were ART naïve and one had previously defaulted from ART care, the remainder were currently receiving ART. We did not observe notable differences in responses according to ART use exposure. Providers included prescribing physicians ($n=4$), counselors ($n=3$), pharmacists ($n=3$), and clinic directors ($n=4$). Findings are organized using CFIR domains, with corresponding participant quotes numbered within Table 2.

CFIR domain one: characteristics of the intervention

Key characteristics of an intervention influence its appeal to implementers and likelihood of success; this CFIR domain was a main focus in our IDIs and constructs of complexity and relative advantage were addressed *a priori* in the guides. Other constructs, such as cost, emerged organically during interviews.

Relative advantage. PWID patient, clinic providers, and policymakers were enthusiastic about the convenience of LAI compared to daily oral ART. PWID patients and providers described multiple appealing features of LAI, including discreet administration, relief from worry about remembering a daily pill, and less frequent dosing intervals. Most PWID respondents expressed confidence in LAI's relative benefits, indicating preference for the injectable modality if it were available (Table 2, #2).

While the longer dosing interval was generally perceived to be a positive feature, a minority of PWID and providers expressed skepticism about the durability of a single monthly injection to effectively suppress viral replication. Largely in response to a perceived lack of effectiveness, some PWID expressed preference for oral ART, citing familiarity with their own pill-taking experience, but also more generally identifying the therapeutic benefits of oral pills among their friends as a source of reassurance (Table 2, #4).

The mode of administration was also a drawback; though no PWID expressed concern about pain or

Characteristics	Median [IQR], (range) or n (%)
<i>Sociodemographics</i>	
Age (years)	41 [39,45], (34-47)
Male	17 (89.6%)
<i>Employment</i>	
Stable	2 (10.5%)
Part-time	1 (5.3%)
Self-employed	11 (57.9%)
Not working	5 (26.3%)
<i>Injection drug use</i>	
Years since first injected	20 [9,24] (2-28)
Injecting daily in last 3-months	7 (36.8%)
On methadone assisted therapy	11 (57.9%)
<i>HIV</i>	
Years since diagnosis	11 [2,18] (0-23)
Currently on ART	14 (87.5%)
One or more missed doses in prior month	5 (35.7%)

Table 1: PWID participant characteristics, n=19.
ART: antiretroviral therapy; IQR: interquartile range.

lingering discomfort from injections, and nearly all providers noted “high pain tolerance” among PWID, some respondents suggested that LAI may trigger a relapse to injection drug use (Table 2, #5).

Overwhelmingly, the most common concern was uncertainty regarding extent and severity of LAI side effects (e.g. headaches, nausea, fatigue). Some PWID recalled the plethora of adverse effects they or others experienced when starting oral ART or methadone, and several providers queried specifically about “anaphylactic reactions” to injections.

Complexity. Nearly all PWID quickly noted that their current visit frequency was monthly and thus would be unchanged with LAI. In contrast, policymakers perceived LAI would increase visit frequency, describing an intended visit schedule of every-3-months for oral ART. Providers also described the need for additional or revised reminder systems and raised concerns regarding operational adjustments, noting LAI implementation created additional staffing needs. Providers and policymakers cited concerns regarding complexity of adopting LAI, including logistics of preparing, scaling, and distributing injectable, particularly as these activities exerted additional workload. Most of these challenges were identified as surmountable with additional resources including dedicated space, additional training, and integration of LAI into national HIV treatment guidelines.

Evidence strength and quality. Many PWID expressed a desire to see LAI deployed more broadly before committing to switch, waiting to see other PWH use it first

before agreeing to replace their oral ART. In contrast, most providers and policymakers were confident in the government’s robust scientific review that would be completed prior to adoption.

Cost. PWID rarely expressed concerns about the cost of LAI, in absolute terms or compared to oral ART. However, policymakers, and to a lesser extent providers, were quick to identify cost as a substantial potential barrier to LAI implementation, citing current affordability of oral ART. Several policymaker and provider participants noted that, even if LAI proved acceptable and effective, uptake would depend on its incorporation into the relatively new national insurance system, which may be untenable if the price is not comparable to current options. One policymaker noted that PWID, in particular, would be unlikely to pay for LAI (Table 2, #8).

CFIR domain two: outer setting

The “outer setting” summarizes a myriad of external influences relevant to LAI implementation, including how patient needs are perceived by the organization, and how or if existing policies, regulations, or guidelines are anticipated to impact availability and accessibility of LAI.

Patient needs and resources. Stigma was identified by PWID, provider, and policymaker stakeholders as an important facilitator for LAI use among PWID; many PWID described challenges associated with daily oral ART related to hiding medications and preference for traveling long distances to clinic to avoid being seen at an ART clinic in their own community, dismissing concerns about travel cost or time. Providers and PWID also noted the challenge of incarceration interfering with ART adherence. The criminalization of PWID, frequently jailed or sent to mandatory rehabilitation in Vietnam, was identified as a major barrier to oral ART adherence, and possibly an advantage of LAI by providers and policymaker participants, though this issue was not raised by PWID.

External policies. As LAI is not currently available in Vietnam, there are no existing policies guiding implementation. However, ART care delivery is government-led, standardizing the scope of HIV clinical practice. Providers and policymakers expressed deference to future ART guidelines and confidence that adequate resources and trainings would be devoted if LAI was adopted, with recommendations dictated by dedicated scientific research committees.

Policymakers noted that major shifts in HIV treatment policy and health financing could have important implications for LAI implementation. Vietnam is

CFIR domain and construct	Representative quotes
Domain one: characteristics of the intervention	
Relative advantage	<p>(1) [Patients] hide [ART] from everyone, but they're still worried because they're afraid that they'll not be able to comply with the medicine because, for example, when they return to their hometown, because they hide it so they don't dare to bring the medicine bottle with them. – <i>HIV counselor</i></p> <p>(2) Because I still use drugs and I often forget to take the oral pills. This medicine is very great, I only need to tell my family to remind me to get injections once a month. I think I can do that, taking medicine every day is quite difficult for me now. – <i>44 year old male PWID, not on ART, lost to follow-up</i></p> <p>(3) I think if this injectable type is available now, I will be the first one to ask for the injections, and then I can say if this type is okay or not, I will be the first one to support this program. It saves me time taking medicine every day and it doesn't cause any trouble at all. – <i>36 year old male PWID, on ART</i></p> <p>(4) I've seen people taking oral medications for ten years but I haven't seen anyone use injections, so I don't want to change anything, I still think oral medicine is effective, I will choose to take oral pills. – <i>43 year old male PWID, on ART</i></p> <p>(5) There are many situations that make me think about drugs, when I'm too sad or too happy I also think about it. There're many things that can make me think about it. The needles will also remind me of it. – <i>36 year old male PWID, on ART</i></p> <p>(6) The injectable type has the advantage that it doesn't take time and I don't forget to take the medicine, but it does have a problem that many people will have pain. Some people are afraid of injections, in general, like with normal injections, we also feel pain, for example, some people are afraid of needles, that is its drawback." – <i>36 year old male PWID, on ART</i></p>
Complexity	<p>(7) ...in my opinion, the injectable ART will be much more difficult than TLD in implementing. ...in terms of facilities, I think it's not too difficult to adjust guiding documents, but it's difficult to adjust their services. Why? The services of TLD and TLE [tenofovir, lamivudine, efavirenz] are the same. The way patients get TLD now is the same as the way they got TLE in the past, nothing has changed. But when the injectable medicine is put into treatment, the problems are that, where to set up injection rooms, how the accompanied services run if an event of shock happens, where the pharmacy is located, how to transport the medicine, who will dispense the medicine, and how to give the injections. ...in current procedure, patients come here every 3 months to get medicine, now it will be adjusted to be once a month, it is clear that there is a need to establish a mechanism to remind patients. The doctors themselves have to remember the days that patients need to return to the clinics for injections. All of these will have to be adjusted. So obviously, it's much more difficult than the transition from TLE to TLD. – <i>Policymaker (MOH)</i></p>
Cost	<p>(8) Acceptability in terms of cost depends on patients, depends on each patient group, and if the cost is high, no group will accept it. If the price is high but it's good, other groups may accept it, however, it is difficult for the addict group to accept the high price.- <i>Policymaker (MOH)</i></p>
Domain two: Outer setting	
Patient needs and resources	<p>(9) It [TLD] only has one weakness, that is, patients often get questions from other people such as "Why do you have to take medicine every day." If the oral pills can also solve the problem of such questions, I think they will choose the oral option rather than the injection. – <i>policymaker (MOH)</i></p>
External policies	<p>(10) I suggested that we should prioritize HIV-infected people who inject drugs so they could receive cards even when they lost their identity cards, identity papers. ...I also suggested that because [PWID] didn't have enough money to co-pay the 20% of the treatment fee. ...when they don't take medicine, that means the viral load in their blood increases and they are very contagious to others. But many people in other Ministries said that in terms of priority, it isn't called a priority because priorities will be given to people with meritorious services to the revolution, families of martyrs, etc. Those groups are just high-risk groups that we have to pay attention to. – <i>Policymaker (VAAC)</i></p>
Domain three: Inner setting	
Structural characteristics	<p>(11) I think that [my colleagues] will support it. We are expecting something more convenient for patients. I know that the beginning phase will be so hard however gradually it will be better. For injections, we will only need to counsel patients who have an appointment for the injection. We won't have to counsel as much and do it every day as now. – <i>provider (clinic director)</i></p>
Implementation climate	<p>(12) I think that, for patients who are on treatment now, especially patients who use opiates or who use drugs, we find that the oral treatment model now is very effective. ...currently in Hanoi, the percentage of patients who achieve the viral load results under the viral load threshold is 98%.- <i>Policymaker (MOH)</i></p>

Table 2 (Continued)

CFIR domain and construct	Representative quotes
Readiness for change	<p>(13) Our clinic has changed the treatment methods many times. Up to now, it's changed 103 times, then mother-child transmission treatment. There are many projects with a lot of technologies, but as long as we're well trained, we will work well, our staff here are used to it, we do this job, so we always need to update new knowledge with new technology, there's nothing to be confused about. <i>Provider (physician)</i></p> <p>(14) For this [injectable medication], I can see that when we have new medicine and introduce it to patients, they'll be very excited and I'm myself also very excited. Firstly, I know its effects. I have to learn about the its effects first, find out if it has been approved by any agency or has been announced by the World Health Organization. Secondly, when we have a new medicine like this, I will discuss it with the patients to see how they react. For medical staff like us, we think it's very good." – <i>Provider (clinic director)</i></p> <p>(15) I am happy if it is good for patients. If the injectable ART is good and has fewer side effects than oral forms, patients will prefer it. When we switched from TLE to TLD, it's better because the TLD pill is smaller and only needs to take once a day, and has no side effects. So patients choose it without a doubt. For the injection, injection causes pain and it isn't simple as taking pills. But if patients get an injection monthly, have no side effects, no drug reaction, and the time to get the injection is flexible, I think that patients will choose injections. And I will be happy for them. – <i>provider (clinic director)</i></p>
Domain four: characteristics of individuals	
Knowledge believe and self-efficacy	<p>(16) [O]ur clinic has changed the treatment methods [for HIV] many times. Up to now, it's changed 103 times, then mother-child transmission treatment. There are many projects with a lot of technologies, but as long as we're well trained [on administering LAI], we will work well, our staff here are used to it, we do this job, so we always need to update new knowledge with new technology, there's nothing to be confused about –<i>Provider (physician)</i></p> <p>(17) It's not difficult at all to counsel injectable medicine for a new client. Because for people who inject drugs, the most difficulty is taking pills every day. It's easier for me to convince them to get monthly injections. If they know about cases that get injections and have no side effects, that's fine. But if their friends get injections and have side effects, they will consider it." <i>Provider (clinic director)</i></p>
Individual identification with organization	<p>(18) In general, I really believe in the treatments offered here, whatever they counsel me, it's because they just want the best for me, that's what I see. That is, if the medical staff here counsel me about this treatment, this treatment must be good, so I completely trust the medical staff here. – <i>41 year old male PWID, on ART</i></p>
Domain five: implementation process	
Engage	<p>(19) Let me take an example like when we provide methadone treatment, patients have to come to take it every day. But when we switched to giving it once every 3 days, though it was a good idea that patients would not have to travel a lot, but in reality, there were not many patients to choose this option. Although it was very good when testing, but when it is applied on a large scale, patients didn't choose, so we have to evaluate whether patients accept it or not. – <i>Policymaker, Hanoi Center for Disease Control</i></p>
Executing	<p>(20) We never categorize the HIV-infected people into any group, whether they are drug users or whatever, they're all HIV patients, and for any HIV-infected patient, no matter what group they belong to, they have equal access to the same treatment. This means that all are provided with counseling, testing, and the benefits of treatment are the same, regardless of the target group. – <i>policymaker (MOH)</i></p>

Table 2: Representative quotes reflecting perceptions of long-acting injectable antiretroviral therapy implementation among HIV-infected persons who inject drugs in Vietnam using consolidated framework for implementation research domains and constructs.
ART: antiretroviral therapy; CFIR: Consolidated Framework for Implementation Research; MOH: ministry of health; PWID: person who injects drugs; TLD: tenofovir, lamivudine, dolutegravir; TLE: tenofovir, lamivudine, emtricitabine; VAAC: Vietnam Administration for HIV/AIDS Control.

currently transitioning away from a government-sponsored system to one where patients maintain insurance to cover healthcare costs. All drugs covered by insurance must first be approved by the Drug Administration and added to the formulary – described as a tedious and lengthy process that considers effectiveness, cost, and

expected impact on care. Although some policymakers clarified that the government would still pay for services for persons unable to afford insurance, the shift may impact how lower income patients engage with healthcare. One policymaker described his advocacy for PWID to receive waivers for drug co-pays but reported

pushback from other officials whom he described as less interested in prioritizing services for PWID (Table 2, #10).

CFIR domain three: inner setting

The “inner setting” domain examines implementation climate and preparedness for LAI vis-à-vis structural characteristics of integrating LAI into clinical practice.

Structural characteristics. Provider participants raised logistical concerns, including scheduling patients and space for administering injections, and quickly identified ways LAI may increase work burden, framing concerns against already stretched staffing resources. Despite PWID reporting monthly clinic visits for ART refills, providers felt LAI would increase the workload associated with drug distribution (monthly instead of every three months). Despite this, most providers felt workload concerns were addressable with adequate investment in personnel, training, and other clinic resources. Providers also recognized that the growing pains of LAI implementation would be finite; injectable ART could reduce workload in the long-term, requiring less adherence counseling during clinic visits (Table 2, #11).

Besides staff capacity, additional provider-identified barriers included physical space, storage (particularly refrigerated storage and supply chain), modified patient education, and management of side effects, with the most common concern being anaphylactic shock requiring personnel to attend to life-threatening events. Notably, anaphylaxis was not observed in any of RCT nor mentioned during the interview as a potential adverse effect of LAI.

Readiness for change. Citing a history of adapting to new treatments, including changing to dolutegravir, provider participants typically embraced innovation and change as an exciting part of their practice. LAI aligned with providers’ normative beliefs in which they prioritized interventions that would have the best outcomes for their patients (Table 2, #15).

Implementation climate. The most salient theme of this domain was that of *tension for change*. Nearly all providers, most policymakers, and the majority of PWID identified a key advantage of LAI as providing novel choice for PWH. Across all three groups, most respondents also acknowledged that for PWH who struggle with ART adherence, specifically PWID, LAI provided an advantage over oral therapy. However, a few policymakers contrasted this perspective, describing the state of HIV care in Vietnam as overwhelmingly effective as is, even among persons with substance use disorders,

and viral failure as an exceptionally rare occurrence, under which impetus to switch to LAI was minimal (Table 2, #12).

CFIR domain four: characteristics of individuals

Individuals’ experiences, behaviors, knowledge, and self-efficacy shape attitudes and beliefs and influence the successful implementation of an intervention

Knowledge, beliefs, and self-efficacy. Providers and policymakers noted the importance of robust information and training to better equip both providers and patients with information regarding the efficacy and safety of LAI. Providers were generally confident in their ability to talk to patients and counsel regarding the potential benefits of LAI.

PWID indicated confidence in their ability to receive LAI as prescribed (i.e., come to the clinic monthly). But some providers and policymakers were concerned about the reliability of PWID to show up on time or at all for appointments, noting the need for additional scheduling reminders or support for patients that are not self-motivated.

Providers expressed a similar confidence to that conveyed by patients, describing their ability to implement LAI if given the appropriate support, including guidance on when and how to administer LAI. Some providers drew parallels to other implementation experiences, noting the ways their clinic has had to pivot to deliver new medical technologies in the past.

Individual identification with organization. In general, PWID described positive relationships with clinic staff where they felt encouraged to take medicines and engage in care without feeling forced. Most PWID described deference to authority in selecting the appropriate ART option (Table 2, #18).

CFIR Domain five: Implementation process

The “implementation process” domain captures key steps including planning, engaging, executing, and evaluating implementation. Although some policymakers provided concrete feedback regarding stages of approval for LAI, one of the more complex emerging themes was LAI patient selection.

Planning. Policymakers described a multi-step regulatory process necessary to accomplish widespread LAI availability—specifically, the development of Ministry of Health guidelines, addition of the drug to national insurance formularies, and trainings and procedures for handling the injections, including management of adverse events. Many felt that approval by the European Medicines Agency and/or the United States Food and

Drug Administration would help pave the way for approval in Vietnam. The biggest hurdle appeared to be adding LAI to the list of covered drugs, given the need to demonstrate clinical equivalence and effectiveness, at a similar or cheaper cost.

Engaging. Providers emphasized the importance of engaging opinion leaders and evaluating demand among target recipients. Some described scale-up of methadone treatment as an example of an intervention that they had previously attempted to implement without first engaging patients or community members. One example offered by a provider included their experience with methadone dosing: they assumed PWID would prefer less frequent every three-day dosing, but after consultation with patients, discovered daily dosing was easier for patients to remember and adhere to (Table 2, #19).

Executing. Identifying the appropriate patient population for receipt of LAI is an important step in efficient and effective implementation. While all but one provider suggested PWID would be an ideal group to target given perceived poor adherence and frequent failure with oral ART, most policymakers expressed the importance of equality in access, with opposition to a distribution strategy targeting specific risk groups (Table 2, #20).

This risk factor-agnostic approach from policymakers contrasted many providers who identified PWID as a group that struggled with adherence and for whom providers found difficult to engage in effective counseling. Providers often described unique barriers to ART adherence among PWID, citing these patients as having less control over their own behaviors and/or being more forgetful when it came to daily ART due to ongoing drug use. There was one exception - one provider explicitly identified PWID as a group they would choose not to prioritize for LAI, explaining that the challenges this subpopulation face are not limited to daily adherence, but engagement and retention in care more broadly - challenges they believed monthly injections would not eliminate.

Discussion

Our study identified high interest for LAI among PWID, ART providers, and policymakers in Vietnam, and exposed important barriers and facilitators to implementation across domains and constructs of the CFIR model. Although some considerations were expected, such as need for revision of ART guidelines and updated training for providers, our findings exposed important and unanticipated considerations for implementation of LAI for PWID in Vietnam that may

improve development of evidence-based, acceptable implementation strategies of LAI for PWH globally.^{24–26} These strategies, and associated policies, are critical to translate the efficacy observed in Phase three clinical trials to improved treatment outcomes,²⁷ particularly for vulnerable PWID with high rates of viral failure.

Some of the most concrete barriers to LAI were structural characteristics pertaining to investment in personnel and complexity of implementation, shifting workloads and requiring additional resources including refrigerated storage space/transport and injection rooms. Navigating clinic staffing, infrastructure, and other logistics has previously been described as part of essential multi-level considerations for LAI implementation.²⁴

Framed through the construct of *relative advantage*, all PWID, providers, and policymakers readily acknowledged the benefits of a less frequent dosing paradigm as an effective strategy to reduce missed doses. PWID and providers identified adherence challenges driven by stigma associated with being seen taking pills, and providers described advantages of LAI including confidence that the patients who received injections had adequate drug to suppress viremia. Despite enthusiasm for potential therapeutic benefits, several PWID described hesitancy to change from a treatment strategy they knew worked (daily oral ART) before observing the effectiveness of LAI among peers. Patient and provider education will be crucial for effective implementation, particularly given a novel ART ‘choice’ paradigm. PWID expressed being comfortable with clinic staff, likely contributing to their described deference to provider recommendations when choosing between LAI and oral therapy. This choice highlights the importance of developing guidance around ART selection that accounts for patient and provider expectations and preferences regarding shared decision-making.

Shifting HIV treatment policies in Vietnam that are transitioning away from government-sponsored treatment to individual insurance was a salient theme in the *external policies* construct. Drug co-pays and coverage could especially impact PWID, described as a financially unstable group. Unsurprisingly, cost of the novel LAI therapy is expected to far exceed that of generic first-line oral ART. Identifying cost-effective implementation strategies is essential for sustainable and acceptable integration of LAI into Vietnam treatment guidelines. In sub-Saharan Africa, introduction of LAI is only likely to be cost-effective if explicitly targeted to PWH who would be expected to have poor adherence to, and viral failure on, oral ART.²⁸ In Vietnam, PWH who expected to have poor adherence includes PWID.^{29,30}

Poor treatment outcomes of HIV-infected PWID, and general enthusiasm among interviewed providers and PWID, indicate this group may be ideal to prioritize for LAI. The numerous adherence barriers specific to PWID were perceived to be mostly addressable through

LAI. But the *tension for change* seemed less salient to policymakers, who were more likely to feel comfortable with the daily oral status quo. Despite providers distinguishing the relative barriers to adequate adherence, policymakers emphasized principles of equity, opposing LAI implementation strategies that prioritized or targeted PWID above or separate from other PWH. Policymakers may be more removed from the day-to-day struggles that providers described in engaging and counseling PWID regarding ART adherence, or may feel compelled to support current government treatment initiatives. Indeed, our study revealed a marked discrepancy in policymaker and provider perceptions of HIV outcomes among PWID. The provider/policymaker discordance in both perceived need and appropriateness of a PWID-directed LAI implementation strategy exposes a critical and previously unexplored tension relevant to ART optimization strategies for this vulnerable population. Cost-effectiveness of LAI likely hinges on improving treatment outcomes, not just maintaining suppression for persons already accomplishing this via daily oral ART.²⁸ Although it is unclear whether these oppositional stakeholder views represent all policymakers, understanding the pervasiveness of these perspectives is critical. Developing implementation strategies that prioritize persons at highest risk of failure while accommodating highly valued equity principles is key for success and widespread acceptability among key stakeholders.

Our study was not without limitations. Due to travel restrictions during the COVID-19 pandemic, data collection was restricted to Hanoi, and we were unable to conduct planned interviews in rural Khanh Hoa province as had been initially intended. Our findings may not generalize to other areas in Vietnam where perceptions of LAI could differ, nor to other sub-populations of PWH in Vietnam who may also struggle with ART adherence and could benefit from LAI.^{31,32} Although our survey captured basic information regarding injection drug use, we did not specifically inquire regarding methamphetamine use, which has been shown to be associated with higher rates of viral failure among PWID.³³ Further, we were only able to recruit one PWID lost to ART care; further research is warranted to elicit the perspectives of this group and particularly whether LAI might encourage reengagement among those who previously used daily oral ART. All PWID interviews were conducted in clinics, and, despite interviewers having no relationship to provision of clinical care, participants' generally positive LAI perceptions may in part reflect acquiescence in an authoritative setting. In the absence of available LAI, we relied on hypothetical preferences rather than behavioral assessments, but were able to explore constructs in light of other interventions (e.g. TLD). Finally, the interview guides were not designed to exhaustively address every CFIR construct; that certain constructs are missing from our

results could be considered an artifact of our interview protocol rather than a reflection on the importance of these themes.

To our knowledge, this is the first study to explore PWID preferences and attitudes towards LAI. Our findings reinforce conclusions from other pre-implementation studies, highlighting the importance of stakeholder engagement, training, and systems that minimize staff burden.³⁴ Although results may generalize to other highly stigmatized populations, policymakers' perceptions shed important light on unexpected and likely context-specific determinants of LAI in Vietnam, providing a vital foundation for developing and testing LAI implementation strategies.

Contributors

SER, HVT, LMG, WCM, JJE, CLG and VFG conceptualized the original research question and study design. TTDN, HVT, LMG, MN contributed to data collection and project administration. SER, ALS, HEH and VFG conducted initial transcript analysis and coding and drafted the first version of the manuscript. All authors contributed equally to manuscript review and editing and approved the final version.

Data sharing statement

Deidentified participant data, including transcripts with all identifying information removed, can be made available after publication to interested parties who have obtained appropriate regulatory review and approval. Our full study protocol can also be available upon request.

Declaration of interests

The University of North Carolina at Chapel Hill receives research funding from ViiV Healthcare and Gilead for studies on which JJE is an investigator. JJE also receives consulting honoraria from ViiV, Gilead, and Merck.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.lanwpc.2022.100603](https://doi.org/10.1016/j.lanwpc.2022.100603).

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