Multisite Study of Women Living With HIV's Perceived Barriers to, and Interest in, Long-Acting Injectable Antiretroviral Therapy

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Background: Adherence to antiretroviral therapy (ART) is imperative for viral suppression and reducing HIV transmission, but many people living with HIV report difficultly sustaining long-term adherence. Long-acting injectable (LAI) ART has the potential to transform HIV treatment and prevention. However, little LAI ART–related behavioral research has occurred among women, particularly outside of clinical trials.

Setting: Six Women's Interagency HIV Study sites: New York, Chicago, Washington DC, Atlanta, Chapel Hill, and San Francisco.

Methods: We conducted 59 in-depth interviews with women living with HIV across 6 Women's Interagency HIV Study sites (10 per site; 9 at Washington DC). We interviewed women who were not included in LAI ART clinical trials but who receive care at university settings that will administer LAI ART once it is approved. Interviews were recorded, transcribed, and analyzed using thematic content analysis.

Results: Most women enthusiastically endorsed monthly LAI ART and would prefer it over pills. The following 3 reasons emerged for this preference: (1) convenience and confidentiality, (2) avoiding daily reminders about living with HIV, and (3) believing that shots are more effective than pills. Challenges remain, however, specifically around (1) medical mistrust, (2) concerns about safety and effectiveness, (3) pill burden for HIV and other conditions, and (4) barriers to additional medical visits.

Conclusions: Most women preferred LAI ART over daily pills given its benefits, including convenience, privacy, and perceived effectiveness. Future research should incorporate more women into LAI ART trials to better understand and align development with user concerns and preferences to enhance uptake.

Key Words: long-acting injectable, biomedical prevention, HIV antiretroviral therapy, women, adherence

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INTRODUCTION

Nearly one-quarter of people living with HIV (PLWH) in the United States are women. Of these, 89% know their diagnosis, 65% receive care, and 51% are virally suppressed.[1] Women living with HIV (WLWH) have historically been underrepresented in HIV treatment research and face myriad barriers, including gender-specific barriers, to HIV care continuum progression.[2,3] Despite oral antiretroviral therapy

(ART), in 2016, only 58% of diagnosed WLWH were virally suppressed, in part due to suboptimal adherence. WLWH have poorer adherence,[4,5] viral suppression,[6,7] and long-term clinical outcomes[8,9] than men and are more likely to receive a simultaneous HIV and AIDS diagnosis (ie, a late diagnosis).[6,7] Although women face unique adherence barriers, they are underrepresented in HIV clinical trials, and the trial data that are primarily from men do represent their needs. As such, women do not equally benefit from technological advances that aim to improve HIV prevention and treatment.[10]

In addition to individual health benefits, the treatment of PLWH decreases transmission (ie, treatment as prevention), and although studies remain limited, research suggests that increased treatment coverage is associated with declines in the community viral load in South Africa,[11] San Francisco,[12] and British Columbia.[13] Mathematical modeling suggests it would also be successful in Washington DC.[14] Obtaining and maintaining this reduction in the community viral load, however, requires medication adherence over the lifespan. Demonstrated barriers to adherence include side effects,[15] substance use,[16] mental health,[17] provider- and clinic-level challenges (eg, medical mistrust or poor communication),[18,19] and social and structural barriers (eg, stigma,[2,3] care access,[20] and gender norms[21]). Many PLWH face structural barriers that constrain adherence (eg, homelessness and food insecurity), yet most behavioral interventions to promote adherence focus solely on the individual level. As such, most behavioral adherence interventions have not been successful. Given the importance of ART in maintaining the health of PLWH, and limiting the risk of further HIV transmission, new strategies are needed to facilitate adherence.

With a goal to address these barriers, phase III clinical trials are currently testing the efficacy of long-acting injectable (LAI) ART [eg, Antiretroviral Therapy as Long-Acting Suppression (ATLAS[22]) and First Long-Acting Injectable Regimen (FLAIR[23])]. The results to date indicate noninferiority to oral ART in terms of viral suppression and low frequency of virologic failure.[22] Participants report that the side effects (eg, fatigue, fever, headache, and nausea) have been generally well tolerated and only rarely led to discontinuation.[22–26] Trial participants reported a high preference (97% in FLAIR and 91% in ATLAS) for LAI ART over oral ART. ATLAS data have already been submitted to the US Food and Drug Administration for approval; ATLAS-2M, which is exploring the efficacy of bimonthly shots, is ongoing.[22–26] In their current form, these injections require visits with HIV providers; however, over time, they may be administered in pharmacies or by other types of providers.

LAI ART may help alleviative some barriers to oral medication, but significant challenges remain because its current form requires one or more injections per visit and frequent injections (ie, monthly visits were tested in ATLAS and bimonthly visits in ATLAS-2M).[30] Most LAI ART trials include primarily men, particularly men who have sex with men and white participants: in ATLAS, only one-third were women; in FLAIR, about one-fifth were women; and in LATTE-2, only 8% of participants were women.[22–26] Although oral ART has improved, WLWH still face significant barriers to daily pill taking, some of which are gender specific. These include at the individual level (eg, forgetfulness,[2,3] pill fatigue,[2,3] and drug use),[27,28] interpersonal level (eg, caretaking responsibilities that complicate clinic visits, stigmatization,[2,29] and unintended disclosure),[30,31] clinic level (eg, medical mistrust and patient–provider communication), and structural level (eg, unstable employment, transportation, food insecurity,[32] and care access).[30,31] Some of these multilevel barriers might be addressed, or alleviated, by LAI ART.

Given the myriad levels of factors that impact WLWH's interest in, and access to, LAI ART, we applied Bronfenbrenner's[33] ecological model, adapted from a model tailored to pre-exposure prophylaxis uptake,[34] to frame our analytic approach (Fig. 1). To better understand women's unique experiences with HIV medication adherence and care access, and to explore their interest in LAI ART, with a focus on perceived barriers and facilitators to uptake, we conducted interviews with WLWH in 6 sites across the United States.

METHODS

Data were collected from the Women's Interagency HIV Study (WIHS), the largest national prospective cohort study of women living with and at risk for HIV infection.[35] WIHS participants are followed biannually, and study visits include a physical examination, interviewer-administered questionnaire, and ascertainment of the medical history and psychosocial factors.

Six WIHS sites were included in this qualitative substudy (Atlanta, Georgia; San Francisco, California; Washington, DC; Chapel Hill, North Carolina; Bronx, New York; and Chicago, Illinois). Details of the WIHS have been previously described.[36] The 59 in-depth interviews (10 at each site and 9 in Washington DC) were conducted from November 2017 to October 2018. The sites recruited participants to ensure that they varied by characteristics that might influence their interest in and willingness to use LAI ART (eg, age, job status, caregiving responsibilities, and time since diagnosis). The interviews lasted approximately 60 minutes, were digitally recorded, and transcribed verbatim. Interview questions were open-ended and explored women's experience with injectable medication, related knowledge and attitudes, and the perceived barriers and facilitators toward using injectable HIV medications for ART. Participants provided informed consent and were compensated $50. The institutional review boards at all participating sites provided approval.

Data were analyzed using the constant comparative method[37,38] to explore women's responses to LAI ART, with a focus on barriers and facilitators. Three individuals conducted line-by-line open coding on the first 5 interviews to develop a provisional coding scheme that focused primarily on identifying women's perceived barriers and facilitators toward LAI ART uptake. Subsequently, thematic codes based on the existing literature were added to ensure that theory-based and emergent concepts were included. The team members then crosscoded a random sample of 10 additional transcripts to refine the code dictionary and develop a codebook. This codebook was reviewed and amended by other team members.[39] Two coders independently applied this final coding scheme to all interview transcripts, and any discrepancies were resolved during team meetings.

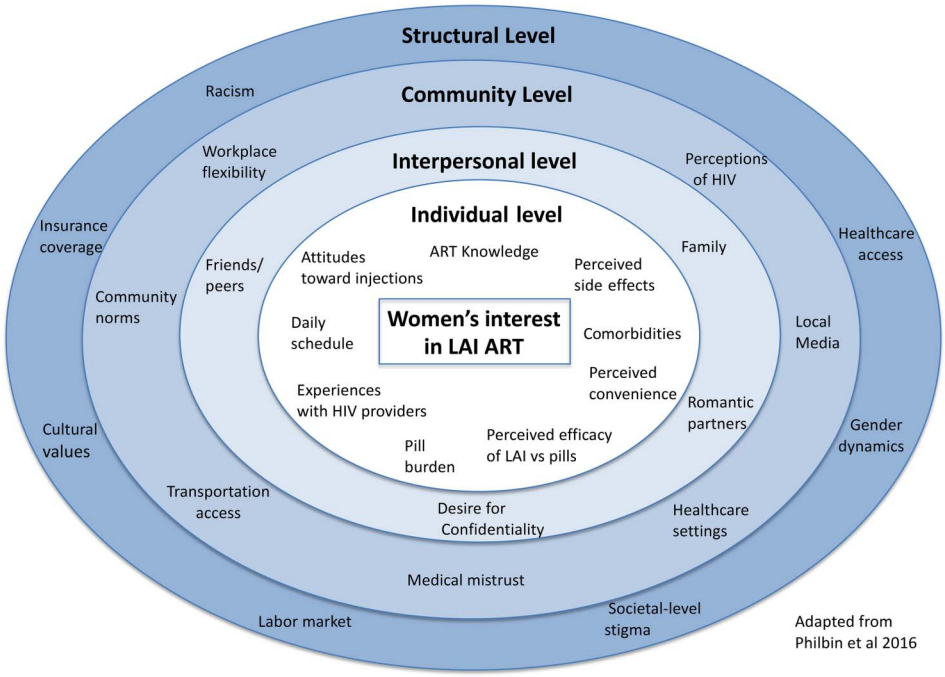

FIGURE 1. Ecological model of factors that impact women's interest in LAI ART. full color online

RESULTS

Participants' median age was 53 years (range 32–72 years), and the majority were women of color (96%). One-third had less than a high school education, whereas just under one-third had a high school diploma or some college, and 15% had a graduate degree. Most women were unemployed (66%) and earned <$12,000/year (59%) (Table 1).

More than half (33/59) responded that they would choose LAI over daily pills, expressing sentiments such as, "Once a month? And I don't have to take no damn pill no more? Man, shoot me fast" *(45, Black, Atlanta)*. WLWH identified 3 primary factors that would facilitate LAI ART uptake: (1) convenience and confidentiality over daily pills, (2) pill fatigue and avoiding daily reminders of their serostatus, and (3) believing shots were more effective than pills. The following 4 primary factors were found to limit enthusiasm for LAI ART: (1) medical mistrust, (2) potential side effects, (3) incomplete pill burden reduction, and (4) additional medical visits.

Facilitators of LAI ART Uptake

Convenience and Confidentiality

Women nearly uniformly described how LAI ART would make HIV medication more convenient. Specifically, LAI ART could be adopted in ways that would not interfere with their daily lives: "If I'm at my brother's house and I forgot my meds, that nightmare. If [the shot] were there, you travel for a week, then you don't have to worry" *(50, Black, DC)*. LAI ART would eliminate the need to carry daily medication because it would only require a monthly doctor's visit. This focus on convenience was particularly relevant for WLWH who had struggled with adherence to oral ART. Participants identified subgroups of WLWH who would most benefit from LAI ART, including youth, those with unstable housing, and incarcerated women.

WLWH also described LAI ART as a way to maintain confidentiality that is often challenging with pills. They frequently used words such as "discreet" and "privacy" to describe LAI, which was important because of "nosy" friends: "Nobody knows you're going to get a shot every month. [But if] you got any stuff jingling in your bag. A person there: "What you got in there?" Some pills. This is the stuff I've heard. That's a plus for it [LAI], the discreet part" *(34, Black, Chapel Hill)*. Another woman described how other medication-related items in her house could reveal her HIV status, which limited her social life: "I don't have people over because I don't want them to see the massive fucking 36 binders of paperwork I have. I don't care what anybody says, but there is a stigma, and it sucks" *(51, Mixed race, San Francisco)*. These sentiments demonstrate how LAI might ameliorate the ways that women's HIV status can govern how they interact with others and help them lead "normal" lives.

Pill Fatigue and Daily Reminders of Being HIV-Positive

In addition to LAI ART being more "discreet," women focused on how it might eliminate pill taking: "Once a month! I don't have to take pills that associate me with HIV. It's awesome! I'm stuck once a month and no pills! I'm so tired of taking pills" *(50, Black, Bronx)*. Eliminating pills was particularly important because the pills provided a daily reminder of women's HIV status and HIV-related stigma. This stigma challenged their ability to remain adherent and maintain viral suppression: "Some days I get depressed and I'm like, "Why did this have to happen to me? I'm a good person." That could break you to a point where you might

TABLE 1. Participant Demographic Characteristics

Characteristic	Total (N = 59	Median	Percentage
Age in years (range: 32–72 years)		53	
34–39	7		12
40–49	14		24
50–59	28		47
60+	10		17
Race			
Black/African American	45		76
White	2		3
Hispanic	4		7
Mixed	6		10
Others	2		3
Education			
Less than high school	12		20
Completed high school/GED	19		32
Some college	18		31
College or graduate school	10		17
Household income		$15,876	
$0–$11,999	24		41
$12,000+	34		58
Relationship status			
Single	27		46
Dating <6 months	1		2
Dating >6 months	12		20
Married/long-term partnership	19		32
Children			
Has children	43		73
Does not have children	16		27
Insurance			
Uninsured	4		7
Public insurance	51		86
Private insurance	3		5
Other insurance	1		2
Year diagnosed with HIV			
1980–1989	14		24
1990–1999	16		27
2000–2009	22		37
2010–2019	7		12
No. of years on ART		12	
0–9	25		42
10–19	20		34
20+	12		20

GED, General Educational Development.

say, 'I'm tired of taking the medicine. I got to be on this stuff for the rest of my life'" *(62, Black, Atlanta)*. Using shots would also eliminate a tangible symbol of women's illness—namely the pills: "It would make you feel more normal, because you don't have to think about it every day, when I take my medicine, I'm like, 'I got to take this because I'm HIV-positive.' With a shot I just know it would be so much better" *(43, Black, Chapel Hill)*.

Many WLWH had been HIV-positive for decades and described their frustration and struggle with daily pill taking, "I used to be so good about it, and I noticed that within the last year I started not giving a shit. It's almost like being a brat, thinking, 'Ha, ha. I didn't take my pills.' Like I get so tired of having to do all of these things that I never wanted to do and don't want to deal with" *(51, Mixed race, San Francisco)*. Women who struggled with viral suppression frequently noted the challenges of pill fatigue and how LAI ART could help alleviate that and increase their adherence. Other women shared this fatigue with daily pill taking and juxtaposed it directly with the perceived convenience of monthly shots: "A shot you know the date, you know to go get it and you ain't got nothing else to worry about" *(61, Black, Bronx)*. This suggests that LAI could potentially lower HIV-related stigma because women would not have daily reminders of their HIV status, and that it could also facilitate adherence because it would help address pill fatigue.

Shots Were More Effective Than Pills

Women were also excited about LAI because they believed that shots were more effective than pills, and that they worked faster. "I think it's more effective in a shot… That's just from drug use, there's a difference between injecting cocaine and snorting it or smoking it, because you get everything that's in there. You know it got into your system" *(65, Black, San Francisco)*. These beliefs around the shot's perceived effectiveness and efficiency are important to note given the fact that women also described injection-related fears, described below.

Barriers to LAI ART

Medical Mistrust

Many WLWH described a mistrust of the medical system, particularly the fear of new—and perceived untested—injectable products. Women frequently expressed a desire to wait before considering LAI ART to ensure its safety. This was particularly true because women already took medication they knew was effective: "I want to make sure it has the same efficiency as my drugs I'm taking now. I would hate if I stop taking my medicines for a month while I'm testing this out, and my viral load shoots up because it's not doing the same thing my cocktail is doing" *(56, Black, DC)*. Finally, a few women described a fear that speaks to the history of how medicine has engaged with marginalized communities, "I heard about injectable HIV medication, I immediately thought, 'Here it comes. They're going to kill us off. They're going to try to force us to take this injection and it's going to end us.' And that way they won't have to pay for these pills, it's just an easy way to kill us off" *(51, Mixed race, San Francisco)*. Thus, although women described injectable medication as more convenient, certain historical precedents might dampen their enthusiasm and uptake.

Potential Side Effects

When asked about potential side effects, women described fears of injection-site pain, bruising, and nausea. One-third of women (39%) were somewhat or very concerned about potential injection site pain and responded with: "Shit, I know it's going to hurt. Ouch" *(57, Black, Atlanta)* and "Not even very. Extremely concerned" *(42, Hispanic, Bronx)* in

contrast, some women were not concerned and referenced familiarity with other shots and tattoos. Some women also worried about whether their age might impact their body's ability to heal: "The older you get the longer it takes you to heal and stuff. I'd hate to have all this bruising or marks from 6 months of shots" *(58, Caucasian, San Francisco)*. Approximately one-third (27%) said that the injection-site location (ie, the buttocks) would influence their decision to use LAI ART, with 24% noting that they would be more likely to use LAI ART if the injection could occur in the arm or stomach; 51% said the injection location made no difference.

In addition, some women shared a fear that they would have little recourse with side effects because the shot lasted for such a long time and could not be removed: "With a pill— if I have a reaction, I can immediately go and flush it through my urine. With a shot, that stuff is in your blood stream which goes to your heart. That's mind-boggling. I'd stick with the pill" *(60, Black, DC)*. This was in direct contrast to the pill, which somebody could simply stop taking the next day. Finally, a few women with a history of injection drug use worried that taking an injectable medication may serve as a "trigger" and inadvertently facilitate reoccurrence of drug use.

Incomplete Pill Burden Reduction

Women frequently took pills for multiple conditions and reported mixed feelings about whether they would use LAI ART if it could only eliminate some of their pills (eg, medication for HIV but not blood pressure). Specifically, some WLWH expressed that taking fewer pills was not helpful; they would need all pills eliminated to use LAI ART: "I have bunch of medication to take, just because that one medication is injected, that doesn't save me any trauma. I still have to worry about all these pills" *(50, Black, DC)*. Similarly, another woman described how, "You take all or you don't take none. So, if you can't take all my medicines away, I don't want it" *(36, Black, Atlanta)*. This was particularly challenging for older individuals with co-occurring conditions that required daily pills because LAI would not eliminate all pills and also add additional medical visits.

Additional Medical Visits

Although most said that the time spent attending additional medical visits would not be a burden, many expressed wariness about accessing the clinic. Women, particularly in more rural sites (eg, North Carolina) or in some communities (eg, Atlanta), who may face transportation barriers, voiced concerns about getting to their appointments: "People that don't have the transportation to get back and forth. Are they going to be able to get where they need to get these shots? Do they have the support system to get back and forth?" *(58, Black, Chapel Hill)*. It was also challenging for women with full-time jobs who might be unable to miss work with the frequency required for LAI medication. A number of women shared that they might prefer LAI ART if the doctor's visits were less frequent, but that every month would be challenging, "It sounds promising. Only issue for me is the once a month. If it was more like every 3 months, every 4 or 5 months, I could do that. But once a month, no. I'm not anti the shot, it's just the frequency" *(34, Black, Atlanta)*. This suggests potential geographic disparities in LAI ART uptake because of women's clinic access. Please see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B448, for additional quotes.

DISCUSSION

This article explored perceived multilevel barriers and facilitators to LAI ART uptake as reported by WLWH across 6 distinct geographic areas in the United States. HIV medication has improved drastically, resulting in fewer side effects and the "one pill once a day" option. However, ART adherence is still a significant challenge.[40] Researchers have, therefore, worked to develop LAI HIV therapy to improve individual patient outcomes and curb population-level HIV transmission.

Most women in this study would prefer LAI ART, particularly because of its convenience, privacy, and perceived effectiveness. Similar to other studies, participants described "forgetting" as a common reason for pill nonadherence, particularly while traveling, suggesting that eliminating daily pills may improve adherence.[41] Injections could also occur in a doctor's office, eliminating participants' fears about friends discovering their medications. The focus on privacy points to the continued salience of HIV stigma in the lives of PLWH. Previous work has established a link between stigma and adherence to ART, suggesting that improved privacy may facilitate adherence.[3,17,42]

In addition, participants described "pill fatigue" and the challenge of constant reminders of their HIV status. Women described monthly injections as an innovation that would allow them to more freely live their lives without the constant burden of treating their HIV. Treatment fatigue and increased regimen complexity are associated with decreased adherence to oral ART, which LAI ART may reduce and thus improve adherence.[40,43,44] However, individuals who take daily pills to manage other conditions (eg, mental health and diabetes) may prefer to continue their current regimen instead of adding monthly clinic visits to receive injections.

Many women expressed concerns about potential side effects and safety, and approximately one-third of women questioned whether the medication was safe. As HIV disproportionately affects communities of color who have a history of mistreatment by the medical system, medical mistrust should be a consideration when implementing LAI ART.[45–47] These findings are consistent with the previous qualitative work among men that found concerns over the safety of newer treatment modalities.[48] In addition, anticipated stigma in health care settings can also negatively impact ART adherence, raising concerns that the increased frequency of clinic visits may pose a problem if patients feel stigmatized by health care providers.[2] This highlights the continued work that is necessary to address HIV-related stigma, particularly related to medication adherence.

Transportation challenges were also salient, although this varied by geography. Some felt that monthly visits would be a challenge, particularly for individuals who work hourly

wages, have children, and live in areas without public transportation (often in the south).[49] The previous work has demonstrated low adherence among rural and low-income mothers, supporting the notion that myriad socioeconomic factors may particularly disadvantage mothers.[49,50] This also suggests that LAI ART uptake might improve if it could also be offered in additional accessible locations, such as a local pharmacy or urgent care. In sum, findings demonstrate that LAI ART uptake and use will be most successful if potential barriers at all levels of the ecological framework are addressed. Specifically, our findings show the importance of incorporating individual-level factors such as perceived side effects and current pill burden, interpersonal-level factors such as the need for confidentiality and caregiving burden, community-level factors such as workplace flexibility and ability to access transportation, and structural-level factors such as gender dynamics.

Current LAI ART clinical trials predominantly include men, and qualitative research has primarily explored men's perceptions of LAI ART.[22,23,48] Although most men in LAI ART clinical trials reported injection-site side effects,[51] they remained enthusiastic about LAI ART and preferred it over oral ART.[52,53] However, clinical trials frequently include participants with high adherence whose experiences may not mirror the general population. For example, only 49% of WLWH in the WIHS would be eligible for AIDS Clinical Trials Group trials.[36] A focus group study in the general population also found that PLWH were less enthusiastic about LAI ART than clinical trial participants.[54] In addition, qualitative research with LAI ART clinical trial participants included only 2 women; WIHS women are representative of WLWH in the United States, and it is imperative to explore their opinions regarding LAI ART because women have identified gender-specific challenges to oral ART uptake that may be ameliorated by LAI ART. These included disclosure concerns, difficulty obtaining childcare for more frequent doctor's visits, and fears regarding whether the medication would influence women's ability to get pregnant or subsequent fetal development.[28] Specific to women, prior work suggests that nondaily contraceptive methods (eg, Depo-Provera) increase adherence among women of childbearing age; these findings are potentially applicable to LAI ART.[54,55,56]

Future research should explore how diverse populations (eg, by age, race/ethnicity, and sexual orientation) perceive LAI ART, considering their disproportionate rates of HIV incidence. Trial-recruiting efforts should be expanded to include more women of color.[6,7] Research should be expanded to include younger women, particularly those who are newly diagnosed and therefore lack the experience of pill taking and women of childbearing age who may have unique concerns. Finally, survey research with larger populations should be conducted so that those results can be synthesized with qualitative findings.

Strengths and Limitations

Interviews were conducted among women in 6 geographically diverse sites and could capture the experiences of women across various contexts (eg, urban vs. rural and north vs. south). We also included women whose experiences might more accurately mirror those of the US population—one study found that approximately 50% of women in the WIHS would not be eligible for inclusion in clinical trials.[57] Despite this strength, this study is limited by the fact that the sample population was older, and most individuals had been HIV-positive for many years and subsequently developed multiple coping and adherence strategies. Participants may therefore have different relationships to pills compared with younger HIV-positive individuals. We recruited women who varied by characteristics that could influence interest in the WIHS, including those who face challenges attending clinic visits. We were only able to speak with women who presented at the clinic for their interview. Consequently, we may not have reached women who are less adherent to treatment and face transportation and geographical barriers, although we provided transportation funding to attend the interview. Although women described a range of facilitators and barriers to LAI ART use, it is possible that WLWH across the United States may be less enthusiastic about LAI ART than the women we interviewed.

CONCLUSIONS

This study demonstrates that WLWH are open to LAI ART, and many believe it will provide distinct benefits over daily pills. Women shared many of the same concerns as men; however, they described unique challenges such as medical mistrust, the role of children and childbearing, caregiving responsibilities, and privacy that LAI might help alleviate. LAI might also facilitate confidentiality and minimizing time spent dealing with pills or pharmacy refills. Efforts should be made to incorporate more women into LAI ART trials to better understand and align development with user concerns and preferences with a goal to enhance uptake. This highlights the need to tailor the scale-up of LAI ART to specific subpopulations; additional research should further explore potential differences in WLWH's LAI ART interest by a subgroup to further tailor specific interventions. For example, patient–provider communication strategies should include details about LAI ART efficacy and side effects and explicitly address medical mistrust; community-level and structural-level factors could be addressed through expansion of locations and times where LAI ART is administered. To realize the potential of LAI ART, future research needs to examine whether LAI ART can be integrated into the lives of WLWH across all levels of the ecological framework.

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