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Patient and Physician Preferences Regarding Long-Acting Pre-Exposure Prophylaxis and Antiretroviral Therapy: A Mixed-Methods Study in Southern California, USA

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Abstract

Antiretroviral therapy (ART) and pre-exposure prophylaxis (PrEP) are key strategies in ending the HIV epidemic. However, poor adherence to daily ART and PrEP increases the risk of HIV transmission and acquisition. Long-acting ART and PrEP formulations attempt to improve adherence through providing long-lasting forms of the medication delivered through different routes of administration: oral (potentially monthly), injection (1–6 months), and subdermal implant (up to annually). This study explored patient and physician preferences for long-acting ART and PrEP as well as adherence support strategies. Adult patients ($n = 42$) with experience taking ART or PrEP participated in individual interviews or focus groups. Physicians ($n = 13$) currently prescribing ART and/or PrEP completed an online questionnaire. Rapid qualitative analysis systematically synthesized qualitative data, and descriptive statistics examined survey responses. Patients supported improved adherence as a top potential advantage of long-acting ART and PrEP, and reduced internal stigma as a strong benefit specific to long-acting ART. Annual coverage offered through subdermal implants had strong appeal; however, oral was the preferred modality for long-acting ART and PrEP. Patients preferred injectable ART and PrEP if concurrently receiving hormone therapy injections. Side effects, medication cost, and treatment accessibility were potential barriers. Patients preferred calendar tracking and text messages/phone reminders for adherence supports. Physicians reported that they would reduce clinic visits and HIV testing for all patients on long-acting PrEP, except men who have sex with men who would continue to complete HIV testing every 3 months. Physicians were mixed on whether they believed long-acting ART and PrEP would improve patient adherence. Overall, findings demonstrate the potential benefits of long-acting ART and PrEP, while highlighting the need to obtain additional information to address treatment concerns.

Keywords: HIV, pre-exposure prophylaxis, antiretroviral therapy, long-acting antiretrovirals, medication adherence, qualitative

Introduction

Approximately 1.2 million people in the United States are currently living with HIV.[1] At the end of 2019, nearly 35,000 new HIV infections and 15,000 deaths among people with HIV (PWH) were documented.[1,2] The U.S. national plan, *Ending the HIV Epidemic in the U.S.*, identifies strong adherence to HIV treatment and prevention strategies as key targets in the race to end the HIV epidemic.[3] Antiretroviral therapy (ART) is a well-established HIV treatment regimen that is taken daily to achieve an undetectable viral load, which improves the individual's health and nearly

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eliminates the risk of HIV transmission.[4,5] New HIV infections can also be prevented with use of pre-exposure prophylaxis (PrEP), which has been delivered up until now as a once daily oral medication regimen. PrEP is a powerful HIV prevention medication that can reduce the risk of HIV infection by 90% among men who have sex with men (MSM).[6–8]

Despite the strong efficacy of ART and PrEP, many individuals experience difficulty adhering to these daily medication regimens. Nationally, only 65% of PWH were able to maintain strong ART adherence needed to reach HIV viral suppression,[2] and studies show adequate PrEP adherence (i.e., 4+ doses per week) ranging between 34% and 84% among MSM and transgender women.[9] Furthermore, only 25% of PrEP-eligible individuals within the United States are prescribed PrEP, highlighting the need to promote alternative medication modalities that may improve PrEP uptake.[10]

There have been numerous identified barriers to ART and PrEP adherence, including stigma, substance use, unstable housing, and insurance coverage/medication cost.[11–13] In particular, internalized stigma (i.e., applying social stigma to oneself) and anticipated stigma (i.e., the experience of stigmatization from external sources)[14] have been shown to be unique barriers to ART and PrEP adherence.[12,13,15] Among PWH, those who endorsed shame regarding their HIV status (i.e., internalized stigma) reported avoiding taking ART medications around others as it inadvertently reveals their HIV status and elicits fears of disrupting interpersonal relationships (i.e., anticipated stigma).[15]

Similar concerns have been reported among PrEP users expressing concerns that PrEP medication would expose their sexual orientation to others.[12] Conversely, health care accessibility, trust with provider, and utilization of adherence support strategies (e.g., text messaging/telephone reminders, behavioral routines) have been associated with improving medication adherence.[12,13,16–19] Notably, reducing patient burden through lowering the number of daily medication doses has been directly linked with enhanced adherence.[13,18] Long-acting formulations of ART and PrEP aim to improve adherence by further reducing dosing to monthly (oral or injectable agents), 2–6 months (injectable), or annually (subdermal implant).[20] Various long-acting ART and PrEP modalities are currently at various stages of investigation or implementation.[20,21]

Given the new conceptualization of long-acting ART and PrEP formulations, it is unknown how patients and physicians will respond to these novel interventions. Understanding patient perspectives on long-acting ART and PrEP may help health care providers optimally introduce these new interventions to patients and identify strategies to support adherence. Even with long-acting ART and PrEP formulations, patients will still need to regularly attend clinic appointments, maintain adherence to the long-acting dosing schedule, and potentially visit the clinic to receive injections. In addition, engaging with physicians to identify how long-acting ART and PrEP may impact patient care practices, such as frequency of clinic visits and HIV testing, may provide insights into a potential shift in clinic operations.

This study conducted a mixed-methods investigation among patients and physicians in San Diego County, CA. Physicians had current experience prescribing ART and/or PrEP, and patients were currently or previously on ART or PrEP. The aims of this study were as follows: (1) understand patient preferences and identify potential advantages and barriers to long-acting ART and PrEP; and (2) understand physician treatment preferences (i.e., frequency of clinic visits and HIV testing) for long-acting ART and PrEP. Given the exploratory nature of this study, no other direct hypotheses were assumed.

Materials and Methods

Participants and eligibility

A total of 42 patients and 13 physicians were recruited through outreach by University of California San Diego (UCSD) AntiViral Research Center between November 2020 and July 2021. Physician participants were eligible if they were aged ≥18, and reported having at least one patient on current ART panel and/or providing ongoing care for at least one patient on PrEP. Physician participants were ineligible if they did not provide informed consent or did not complete the online survey in the allocated time. As shown in Table 1, the majority of physicians had experience prescribing ART and PrEP for patients (76.9%) with a range of 0–20+ years in practice. Among the long-acting ART and PrEP formulations, injectable was the most commonly known modality followed by oral agents and subdermal implant, respectively.

Patient participants were eligible if they were aged ≥18 years, and reported either strong or variable adherence to ART or PrEP. Patients were considered to have strong adherence if they self-reported >90% adherence to PrEP, or were engaged in HIV clinic care for the past year and self-reported HIV viral load of ≤100 copies/mL. Patient participants were considered to have variable adherence if they were eligible for ART or PrEP but not taking them, self-reported <90% PrEP adherence, or self-reported a HIV viral load of >100 copies/mL.

All patients were ineligible for study participation if they were diagnosed with HIV within the past 6 months, did not agree to be audio recorded, and/or could not provide informed consent. To protect participant confidentiality, no other demographic information (e.g., age, race, gender identity) was collected for participants. This decision was made in consultation with UCSD Institutional Review Board, which approved all study procedures.

Table 1. Descriptive Statistics for Provider Responses (N = 13)

	n	%
Years in practice		
0–10	7	53.8
10–20	4	30.8
20+	2	15.4
Types of patients seen		
HIV infected for treatment	2	15.4
HIV uninfected for pre-exposure prophylaxis	1	7.7
Both	10	76.9
Knowledge of long-acting antiretroviral modalities		
Injectable	13	100
Oral agents	7	53.8
Subdermal implant	6	46.2

Patient interview and focus group procedures

A total of eight individual interviews and four focus groups were conducted for all patient participants utilizing a semi-structured interview guide, which could be used to assess long-acting PrEP or ART separately (see Supplementary Appendix SA1 for semistructured interview guide). Patient participants were assigned to discuss long-acting PrEP if they self-reported to be HIV negative, and had current or past experience taking PrEP; whereas patient participants were assigned to discuss long-acting ART if they self-reported having HIV and experience taking ART.

The interview guide asked questions to assess participants' experience with ART or PrEP, preferences among the three long-acting ART or PrEP modalities (i.e., oral agent, injectable, subdermal implant), anticipated advantages and barriers to long-acting ART or PrEP, and preferences for adherence support strategies. Patients were assigned to participate in the focus groups if they self-reported to be highly adherent to ART or PrEP, and were assigned to participate in individual interviews if they reported challenges with adherence, or if they were eligible but not currently taking ART or PrEP. Interviews or focus groups were a maximum of 90-min duration and conducted virtually in accordance with UCSD COVID-19 safety precautions. Patients received $50 for their participation.

Physician survey procedures

Physicians completed an online survey to assess their preferred frequency for patient clinic visits and HIV and renal functioning testing. The survey also assessed physician anticipated patient treatment barriers, beliefs on how to best enhance patient adherence, and anticipated patient adherence to long-acting ART and PrEP. Physicians received $100 for completion of the 15-min online survey.

Data analysis

We utilized a rapid analytic approach[22] to analyze all qualitative data obtained from deidentified patient interview and focus group transcripts. Rapid qualitative analytic approaches deliver valid and timely findings that are highly similar to traditional qualitative analyses.[23] For the rapid qualitative analysis, we developed a transcript guide to identify the main research questions (i.e., ART and PrEP preferences, anticipated treatment advantages/barriers, and adherence support preferences were collected into these categories (Supplementary Table S1).

Two doctoral research team members confirmed consistency in the use of this transcript guide before implementation to extract key topics (''domains'') into summary templates. Completed summary templates were subsequently transposed into a matrix table (respondent × domain) to systematically analyze breadth and depth of information for each study domain. All physician survey responses were analyzed utilizing descriptive statistics.

Results

Patient preferences

Long-acting ART and PrEP modality. All patients expressed a preference for long-acting ART and PrEP modalities that provided the longest duration of coverage (i.e., annual). However, only four patients indicated a preference for the subdermal implant needed to achieve this annual coverage. As depicted in the quotations below, many patients struggled with the idea of an implanted device, often eliciting concerns of potential pain or discomfort. Across long-acting ART and PrEP modalities, oral agents were the preferred route of administration followed by injectable with subdermal implant being the least preferred modality:

> **Patient regarding long-acting ART**: ''Implants scare the hell out of me, but I guess I can be open minded. If I don't have to deal with this for a year that would be pretty awesome.''
>
> **Patient regarding long-acting PrEP**: ''If implant wouldn't give that much discomfort then I would prefer the implant. But if I was told that the implant would be uncomfortable when you lay down a certain way. Then I would prefer the shot instead.''

Of note, patients were more likely to express their preference for injectable ART or PrEP, if they were concurrently receiving injections for hormone therapy. As indicated in the quotation below, patients currently engaged in injectable hormone therapy appreciated the ability to consolidate treatments:

> **Patient regarding long-acting PrEP**: ''Injection only because I do injections now [for hormone therapy]. So, it's pretty easy.''

Long-acting ART and PrEP advantages. Patients identified greater convenience, potential to enhance medication adherence, and potentially reducing clinic visits and testing as the greatest advantages for long-acting ART and PrEP. For patients currently prescribed ART, an additional advantage of long-acting ART was the potential to reduce reminders of their HIV status. As described below, PWH described taking their daily ART medication as a constant reminder of past mistakes or living with a chronic disease:

> **Patient regarding long-acting ART**: ''I would be open to the implant and mainly because of the convenience of not having to worry about it in the daily or even monthly basis. I would just go about my life and not be reminded about the mistakes I've made in the past or things I've done that got me in this situation in the first place.''
>
> **Patient regarding long-acting ART**: ''…taking a pill every day is just a constant reminder that you're HIV positive.''
>
> **Patient regarding long-acting ART**: ''Although taking one pill a day is not a huge inconvenience, it is a constant reminder that I do have this chronic disease, and I need to take a pill to not get sick.''

Long-acting ART and PrEP barriers. Across all patients, there were clear concerns related to potential side effects and efficacy of long-acting ART and PrEP. As long-acting PrEP and ART modalities deliver the medication over a longer period of time (i.e., monthly to annually), there were also concerns on how to discontinue treatment if side effects became intolerable. Other highly identified barriers to both long-acting ART and PrEP were insurance coverage and medication cost.

Specific to injectable ART and PrEP, patients also stated concerns regarding who would administer these injections (e.g., health care provider vs. self-administered), and if that would result in increased clinic visits. As described by two

Table 2. Physician Preferences for Clinic Visits and Testing Frequency

	Oral agents		*Injectable*		*Subdermal implant*	
	N	%	n	%	n	%
Visit frequency						
Every 3 months	10	68.8	6	46.2	5	38.5
Every 6 months	2	12.5	4	30.8	6	46.2
Annually	0	0.0	0	0.0	2	15.4
Other	1	7.7	3	23.1	0	0.0
HIV testing frequency						
Every 3 months	11	84.6	8	61.5	6	46.2
Every 6 months	1	7.7	3	23.1	6	46.2
Annually	1	7.7	0	0.0	1	7.7
Other	0	0.0	2	15.4	0	0.0
HIV testing—men who have sex with men						
Every 3 months	12	92.3	9	69.2	11	84.6
Every 6 months	1	7.7	1	7.7	2	15.4
Annually	0	0.0	0	0.0	0	0.0
Other	0	0.0	3	23.1	0	0.0
HIV testing—women who have sex with men						
Every 3 months	9	69.2	7	53.8	8	81.5
Every 6 months	4	30.8	4	30.8	5	38.5
Annually	0	0.0	0	0.0	0	0.0
Other	0	0.0	2	15.4	0	0.0
Renal function testing						
Every 3 months	4	30.8	2	15.4	2	15.4
Every 6 months	8	61.5	10	76.9	9	69.2
Annually	1	7.7	1	7.7	2	15.4
Treatment barriers						
Limited insurance coverage	11	84.6	12	92.3	13	100
High medication cost	9	69.2	10	76.9	10	76.9
Patient adherence	10	76.9	9	69.2	7	53.8
Limited pharmacy access to medication	6	46.2	5	38.5	5	38.5
Consistent management across physicians	5	38.5	6	46.2	5	38.5
Side effects	3	23.1	4	30.8	6	46.2
Adverse reactions	1	7.7	2	15.4	2	15.4

patients below, the logistical considerations of increasing clinic visits for injectable ART and PrEP were identified as potential treatment barriers:

> **Patient regarding long-acting PrEP**: ''…my concerns are more administrative: Would I have enough time to go to the clinic to get the injection? If I leave for a longer duration, how would that work? It's not as simple as going to the pharmacy. I think those barriers would really influence my decision.''
>
> **Patient regarding long-acting ART**: ''I heard about the monthly thing, that it has to be done in office. That it's like a deep muscular, intramuscular injection. It had me on the fence because is it more convenient to just take a pill every night? Which I do without thinking about it. Do I want to go to the office? It's just an extra doctor visit. That's what kind of put me on the fence, the fact that I can't do it myself.''

Adherence supports. The majority of patients identified multiple adherence support strategies for long-acting ART and PrEP, including, text messages reminding of upcoming doses or appointments ($n = 21$), calendar tracking ($n = 14$), smartphone reminders ($n = 8$), patient portal messages ($n = 2$), and yearly pillbox ($n = 1$).

Physicians' preferences

Clinic visits and testing frequency. Injectable and subdermal implant ART or PrEP were associated with reduced clinic visits and HIV testing (Table 2). However, physicians preferred MSM patients continue to complete HIV testing every 3 months regardless of long-acting PrEP modality. Across all long-acting modalities, all physicians indicated a preference for renal functioning testing every 6 months. Physicians reported a preference for the following professions or people to administer injectable ART or PrEP: nurse (92.3%), pharmacist (61.5%), patient self-administer (30.8%), and provider (7.7%).

Long-acting ART and PrEP patient barriers. Physicians identified insurance coverage and high cost of medications as the greatest patient barriers to long-acting ART and PrEP (Table 2). Physicians reported other long-acting barriers in the following order: patient adherence, limited pharmacy access to medications, consistent management across physicians, side effects, and adverse reactions. Identified patient barriers remained consistent across all long-acting ART and PrEP modalities.

Table 3. Physician Beliefs on Anticipated Patient Adherence

	n	%
Anticipated patient adherence		
Oral agents		
Excellent (>90%)	5	38.5
Good (70%–90%)	5	38.5
Moderate (50%–70%)	3	23.1
Injectable		
Excellent (>90%)	4	30.8
Good (70%–90%)	7	53.8
Moderate (50%–70%)	2	15.4
Likelihood to attend annual visit		
Subdermal implant		
Very likely	4	30.8
Likely	8	61.5
Neutral	1	7.7
Unlikely	0	0.0

Anticipated patient adherence. For oral and injectable ART and PrEP, the majority of physicians anticipated that patient adherence would be either excellent (>90%) or good (70%–90%; Table 3). For subdermal implant ART and PrEP, physicians reported that patients would be likely (61.5%) or very likely (30.8%) to make an annual visit.

Adherence supports. The top identified patient adherence support strategies were as follows: (1) text message reminders, (2) calendar tracking, (3) mobile app reminders, (4) telephone calls, and (5) patient portal messages. E-mail was the least favored adherence support strategy for patients. Physicians reported consistency in preferred patient adherence supports across all long-acting ART and PrEP modalities, although there was a greater preference to utilize telephone calls for subdermal implant annual appointment reminders.

Discussion

This study identified patient and physician preferences for long-acting ART and PrEP, anticipated treatment advantages and barriers, and strategies to support patient adherence. Findings from patient qualitative data suggest that route of administration surpasses duration of coverage preferences when deciding among various long-acting ART or PrEP modalities. Although patients expressed their interest in the annual coverage provided by subdermal implants, the vast majority preferred oral agents with patients eliciting concerns related to potential pain or discomfort associated with an implanted device. These findings align with other studies demonstrating that individuals prefer oral and injectable long-acting ART and PrEP modalities compared with implants.[24–26]

Interestingly, patients were more likely to prefer injectable ART or PrEP if they were currently receiving other injectable treatments, such as hormone therapy. This highlights the importance of integrating health care services to ease patient burden and enhance adherence to ART or PrEP, particularly among those seeking gender-affirming treatments who often experience stigmatization in nongender-affirming clinical settings.[27–29]

Overall, patients perceived long-acting ART and PrEP as convenient with the potential to enhance adherence while reducing the frequency of clinic visits and HIV testing. Similarly, physicians reported that they would reduce frequency of clinic visits for patients prescribed long-acting ART and PrEP as well as HIV testing frequency for all patients on long-acting PrEP, except for MSM patients. The preference to maintain HIV testing every 3 months for MSM patients even while on long-acting PrEP indicates the need for standardized guidance on the recommended intervals of HIV and sexually transmitted disease testing for MSM on long-acting agents. Physicians also reported mixed beliefs on whether long-acting ART or PrEP would enhance patient adherence, revealing that more evidence from real-world implementation of these interventions is needed.

One particularly promising advantage to long-acting ART is the potential it has to reduce experiences of internalized HIV stigma and provide ''Freedom!'' as one PWH participant expressed. Patients currently on ART reported that the daily ART medication regimen was a constant negative reminder of their HIV status or ''past mistakes.'' PWH often experience internalized HIV stigma that results in negative views of themselves due to their HIV status.[30] Long-acting ART offers PWH a break from a daily routine that evokes internalized HIV stigma among patients, which may improve adherence outcomes and overall quality of life.[15,31]

Despite numerous potential advantages of long-acting ART and PrEP, both patients and providers identified insurance coverage and medication cost as the greatest barriers to treatment. This echoes ongoing issues with patients discontinuing ART or PrEP due to lack of insurance or limited insurance coverage leading to increased risk of HIV infection, transmission, and morbidity.[32–34]

In addition, patients expressed concerns related to the efficacy of long-acting ART and PrEP modalities and potential side effects, particularly how to promptly discontinue treatment if needed. Health care providers may benefit from discussing these potential topics of concern when introducing these novel interventions to patients to enhance treatment confidence and self-efficacy. In addition, patients may benefit from psychoeducation on how long-acting ART and PrEP modalities are evaluated for tolerability before administration (e.g., optional monthly oral lead-in for injectable ART and PrEP).[35,36]

Finally, in our increasing technology-driven world, it is not surprising that patients and physicians expressed preferences for technology-based adherence support strategies, including, text messages, smartphone reminders, and electronic calendar tracking. Technological interventions, such as individualized for texting adherence building, have been helpful in promoting adherence to daily oral ART and PrEP, and may similarly support patients in the context of long-acting formulations.[19,37]

Future research is needed to test the effectiveness of adherence support strategies to help patients smoothly transition from daily to long-acting ART and PrEP dosing schedules. Future research may also benefit from modifying existing medication adherence support systems to align with long-acting dosing schedules.

This study is not without limitations. The small sample size and restriction of recruitment to Southern California may limit generalizability to other patients and physicians. In

addition, this study did not obtain demographic information on patient participants, which inhibited our ability to draw any associations related to race, ethnicity, age, sex, gender, or sexual orientation. However, sociodemographic determinants related to ART and PrEP adherence have been well established in the literature, and were considered beyond the scope of this study.

This study relied on self-report of hypothetical treatment preferences rather than observed behaviors. It is possible that as long-acting ART and PrEP modalities are adopted in health care settings, different treatment preferences may emerge. Finally, this study included four focus groups, and there is potential that group thinking occurred during these sessions. Group cofacilitators attempted to reduce group thinking by providing instructions at the beginning of the group discussion that a diversity in responses was encouraged and there was no expectation the group would reach a consensus.

Conclusions

This mixed-methods study reveals patient preferences for oral agent long-acting ART and PrEP, and highlights the potential advantages of long-acting ART and PrEP modalities to improve patient adherence while reducing patient and clinic burden. In particular, long-acting ART has promising potential to reduce internalized HIV stigma, which may result in strong adherence among PWH. Given the novelty of these interventions, additional information is needed to determine treatment affordability and changes in patient care practices. Health care providers and clinics would benefit from utilizing these findings to inform development, selection, or adaptation of adherence support strategies (e.g., text messages, telephone reminders) to help patients prescribed long-acting ART or PrEP.

Authors' Contributions

S.Y. conducted qualitative and quantitative analysis as well as prepared and edited the manuscript. J.L.M. helped designing the study, assisted with data collection, conducted qualitative analyses, and edited the article. L.B. and K.C. assisted with data collection and edited the article. D.J.M. and S.M. helped designing the study, assisted with data collection, oversaw data collection, and edited the article.

Author Disclosure Statement

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Supplementary Material

Supplementary Table S1
Supplementary Appendix SA1

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