Long-acting Injectable PrEP: A Scoping Review

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Executive Summary

Long-acting injectable (LAI) pre-exposure prophylaxis (PrEP) is a novel HIV prevention option that is likely to be available soon in Australia. It will be critical that Australia is ready for the introduction of LAI PrEP. Implementation issues will need to be addressed to ensure the successful and systematic introduction and scale-up of LAI PrEP in Australia.

In April 2022, we conducted this scoping review to identify and summarise published data on LAI PrEP and CAB-LA relating to acceptability, willingness, preferences, and implementation. Using PubMed and Google Scholar, 402 records were screened, and 121 records were included in the final review.

Awareness, Interest and Willingness

Low awareness of LAI PrEP was common across all studies reviewed, except for one study in which 51.9% of men who have sex with men (MSM) PrEP-users from the United States (US) were aware of LAI PrEP. High levels of interest were commonly reported ranging from 55.7% to 85.7% among MSM, transgender populations, sex workers, drug users, current PrEP-users, and women in Sub-Saharan Africa. Willingness to use LAI PrEP was generally high among all studies (n=23) ranging from 31% to 96%. Willingness was particularly high among youth in Sub-Saharan Africa (82% to 96%), MSM from the US, China, and Nigeria as well as among samples of drug-users, transgender women, women experiencing intimate partner violence, and US men not willing to use daily oral PrEP.

Preferences

The majority (n=24/33) of studies that measured preferences for PrEP modalities rated LAI PrEP as their preferred choice over other PrEP modalities. Listing LAI PrEP as a preferred choice was most common among samples of MSM from the US and women from Sub-Saharan Africa. The most common reasons study participants preferred LAI PrEP included: easier alternative to a daily oral pill; convenience and ease of use; efficacy and improved adherence; privacy and discreteness; dosing frequency; and route of administration (including disliking pills and not wanting to take pills if not sick). The most common barriers to LAI PrEP included: fear/dislike of needles; fear of pain from injections; concerns about side effects; logistical difficulties with clinic appointments; fear that efficacy may wane before next appointment; and prohibitive costs. Other preference results revealed: location of buttock injection may not be ideal for users; current injection dosing frequency (bi-monthly) was acceptable, but options for longer duration were preferable; receiving injections in clinics was acceptable, but LAI PrEP needs to be widely accessible and available; self-injection is preferred by some; and costs need to be low/equal to oral PrEP.

Acceptability

There were six trials that captured acceptability insights of LAI PrEP based on experience using the product. Across all studies, satisfaction, acceptability, willingness to continue/use LAI PrEP in the future, and willingness to recommend LAI PrEP to others was generally high. Attributes that increased acceptability included number, frequency, location, protection, and duration of injection. Other benefits of LAI PrEP included “peace of mind” and decreased worry about adherence for themselves and their partners as there is no need to remember a daily pill. Across all studies, injection site pain post injection was the most commonly reported adverse event, however, participants reported high tolerability to

injection site pain. Other LAI PrEP disadvantages included: the large needle size; and embarrassment about having to show ones' buttocks to receive the injection.

Provider Opinion

There was a gap in data (n=3) on perceptions and opinions from PrEP providers about LAI PrEP. In general, US medical practitioners were supportive of LAI PrEP as a critical tool in HIV prevention that should be made widely accessible. They were also cautious that LAI PrEP may not be right for everyone and sceptical that current oral PrEP-users would switch to LAI PrEP to improve adherence. Medical providers for women in Sub-Saharan Africa were also generally supportive of LAI PrEP, particularly if it could be combined with contraception as a multipurpose prevention technology (MPT) or be synchronised with contraception injectables such as the Depo-Provera shots. PrEP-providers also noted that the introduction LAI PrEP would create more workload for clinics and some providers may be cautious to prescribe LAI PrEP over daily oral PrEP as it is more clinically difficult to manage.

Cost-effectiveness and Epidemiological Impact

There were six papers that used cost-effectiveness models to determine the financial impacts of introducing LAI PrEP. Seven studies used mathematical modelling to determine potential reductions of new HIV infections with the availability of LAI PrEP. Most of these (n=10/13) were based on sample populations from Sub-Saharan African countries. Generally, across all the studies, LAI PrEP was shown that it could be cost-effective when prioritised to women in Sub-Saharan Africa. However, providing LAI PrEP was only cost-effective when drug prices were low. If low prices are not feasible, providing LAI PrEP only to women at high risk of HIV infection may be an alternative strategy. Mathematical modelling studies in SSub-Saharan Africa predicted reduced HIV rates ranging from 10%-28%.

Implementation

Thirty-two studies provided insight into LAI PrEP implementation opportunities and challenges. Several insights were taken from LAI antiretroviral therapy (ART) studies and were included in this review due to the potential learnings and similarities between LAI ART and LAI PrEP. In general, LAI PrEP was viewed as an exciting new HIV prevention tool that offers more choice to patients and the potential to improve adherence. Many were cautiously optimistic, noting that there were many implementation issues to be addressed including unique management challenges and the need for future implementation research. Key implementation considerations included: introducing strategies to adopt flexible modes of delivery and simplification of LAI PrEP administration; defining strategies, policies, and collaboration; addressing complexities of drug resistance and the pharmacokinetic tail; high-level planning for clinical support; prescribing and operational considerations for clinicians and clinics; manufacturing logistics; addressing systemic barriers for consumers; and research requirements. Suggestions to investigate learnings from other recent biomedical interventions was common.

Introduction

Pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention option that has revolutionised HIV prevention in Australia. There are two PrEP modalities currently available in Australia: daily oral PrEP (one pill per day) and “on-demand” PrEP (taking PrEP around the time of sex) with long-acting injectable (LAI) PrEP on the way. LAI PrEP has recently been proven safe and superior to daily oral PrEP[1,2]. The HIV integrase strand transfer inhibitor, cabotegravir (CAB), is the only drug currently used as LAI PrEP. Long-acting cabotegravir (CAB-LA) reduces risk of non-adherence by enabling the controlled release of PrEP over an extended duration of time to prevent HIV-1 infection.[3] CAB-LA is administered to people who are HIV-uninfected, at a dose of 600mg, intramuscularly, four weeks apart for the first two injections and every eight weeks thereafter for the prevention of HIV acquisition.[4] As of August 2022, CAB-LA has been approved for use in the United States, Australia, and Zimbabwe. In 2022, CAB-LA was recommended by the World Health Organisation (WHO) to ‘be offered as an additional prevention choice for people at substantial risk of HIV infection, as part of combination prevention approaches’.[4]

Preclinical studies in macaque models using CAB-LA administered as a single agent demonstrated protection against simian/human immunodeficiency virus regardless of exposure route.[5-8] Phase II (ÉCLAIR and HPTN-077) and then Phase IIb/III (HPTN083 and HPTN084) studies were then held to confirm safety in humans. Data from Phase II trial HPTN077 demonstrated that CAB-LA dosing intervals of 600mg every 8 weeks consistently met pharmacokinetic targets for people assigned male or female at birth, informing optimal dosing intervals for humans which were used in the Phase IIb/III trials.[9]

The Phase IIb/III trials, HPTN083 and HPTN084, were concurrently held and both stopped early in 2020 after demonstrating efficacy outcomes had been met. Both trials showed CAB-LA was superior to daily oral tenofovir disoproxil fumarate–emtricitabine (TDF-FTC) for PrEP.[1,2]

HPTN083 was a randomised, double-blind, double-dummy, noninferiority trial that compared the efficacy of CAB-LA (600mg intramuscularly every eight weeks) with daily oral TDF-FTC for PrEP in at-risk cisgender men who have sex with men (MSM) and transgender women who have sex with men.[1] HPTN083 sites were across the United States, Latin America, Asia, and Africa.[1] HPTN084 was a randomised, double-blind, double-dummy, active-controlled, superiority trial that evaluated the safety and efficacy of CAB-LA (600mg intramuscularly every eight weeks) compared to daily oral TDF-FTC, for PrEP in HIV-uninfected women in Sub-Saharan Africa.[2]

Both studies demonstrated high HIV risk reduction in the CAB groups compared to the TDF-FTC groups of 66% in HPTN083 and 88% in HPTN084.[1,2] In total there were 13 incident infections in the CAB group in HPTN083 and four in HPTN084 with five integrase strand transfer inhibitor resistance mutations in the CAB groups in HPTN083 and zero in HPTN084.[1,2] Across both studies injection site reactions were the most common adverse event reported by participants in the CAB arms (81.4% and 38% for HPTN083 and HPTN084, respectively).[1,2] Injection site reactions contributed to 2.4% of injection discontinuations in HPTN083 and zero injection discontinuations in HPTN084.[1,2] In

HPTN084 there were 29 confirmed pregnancies in the CAB group and no neural tube defects or congenital anomalies were observed.[2] Both these studies confirmed that CAB-LA is well tolerated, has an acceptable safety profile and increases adherence and thus reduces HIV risk among cisgender MSM and heterosexual women (cisgender and transgender).[1,2] However, it is important to note that both trials were conducted in settings where adherence to daily oral TDF-FTC PrEP was known to be or likely to be suboptimal. The key insight for settings with high adherence to oral PrEP is that both CAB-LA and daily oral TDF-FTC PrEP were found to be highly efficacious and substantially reduced HIV incidence.

In August 2022, the Australian Therapeutic Goods Administration (TGA) approved CAB-LA as PrEP, with the brand name Apretude, and thus Australia became the second country globally with regulatory approval.[10] This will be followed by a submission to the Pharmaceutical Benefits Advisory Committee (PBAC) for public subsidy on the Pharmaceutical Benefits Scheme (PBS). The availability of LAI PrEP in Australia will offer more choice to those at risk for HIV and could increase the number of people on PrEP, thereby bringing Australia closer to the national goal of virtually eliminating HIV transmission by 2030.[11] It will be critical that Australia is ready for the introduction of LAI PrEP and implementation issues are addressed to ensure the successful introduction and scale-up of LAI PrEP in Australia.

Methods

The aim of this scoping review was to identify and summarise the available evidence on LAI PrEP with a focus on CAB-LA. We sought to identify key concepts, definitions and relevant findings on acceptability, willingness, preferences, and implementation. This scoping review was guided by the following research questions:

1. What are the existing pre-clinical and clinical trials on injectable PrEP and CAB-LA?
2. What are key populations' and service providers' acceptability, values, and preferences for LAI PrEP?
3. What are the key areas of consideration for implementation of LAI PrEP?

Initially, our primary aim for the search strategy was any literature written on CAB-LA as PrEP, other LAI forms of PrEP, and other potential future PrEP modalities (e.g. once a month/once a week pill, implants, vaginal ring). We used the search terms in Table 1 below. Our secondary aim was any literature on LAI HIV treatment, especially using CAB, however only to the extent that it was relevant to PrEP. We included literature on acceptability, clinical adaptations/issues, implementation issues and clinician perspectives, using the terms in Table 2 below.

In April 2022, a search was performed using PubMed and GoogleScholar for all available papers using the terms in Table 1 and Table 2. Approximately 1,410 results were screened by title/abstract and separated into LAI PrEP, other modalities (i.e. LA pills, gel, films, implants, vaginal rings) of PrEP, or excluded. Due to the large number of articles, the research team decided to narrow the focus of the scoping review to only include available evidence on LAI PrEP (with a focus on CAB-LA) retaining the additional data sources collected on other PrEP modalities for future work. Further restrictions on the search were added by language (English only) and year (2015 onwards).

In total, 402 records were screened (238 from PubMed and 279 from GoogleScholar) after 115 duplicates were removed. Our criteria included primary research on: pre-clinical or clinical trial data; acceptability, values and preferences data; and primary, secondary and opinion data on implementation. There were 189 records that did not meet the primary research criterion or did not provide sufficient data and hence were not included in the final analysis. Of the 213 records remaining, each full-text article was reviewed and categorised into a Microsoft Excel spreadsheet by key characteristics. These included: year, author, publication title, study type, study size, year of data collection, population group, country, PrEP modalities, and high-level results. Of these, 121 studies were included in the final review, 79 on preferences and opinions (summarised in Tables 3 to 8) and 42 on implementation considerations (summarised in Tables 9 to 12). A modified PRISMA flow diagram of the literature search is shown in Figure 1.[12]

It is important to note that this review was not a comprehensive systematic review, but rather a scoping review to assist knowledge translation on the evidence of LAI PrEP and CAB-LA.

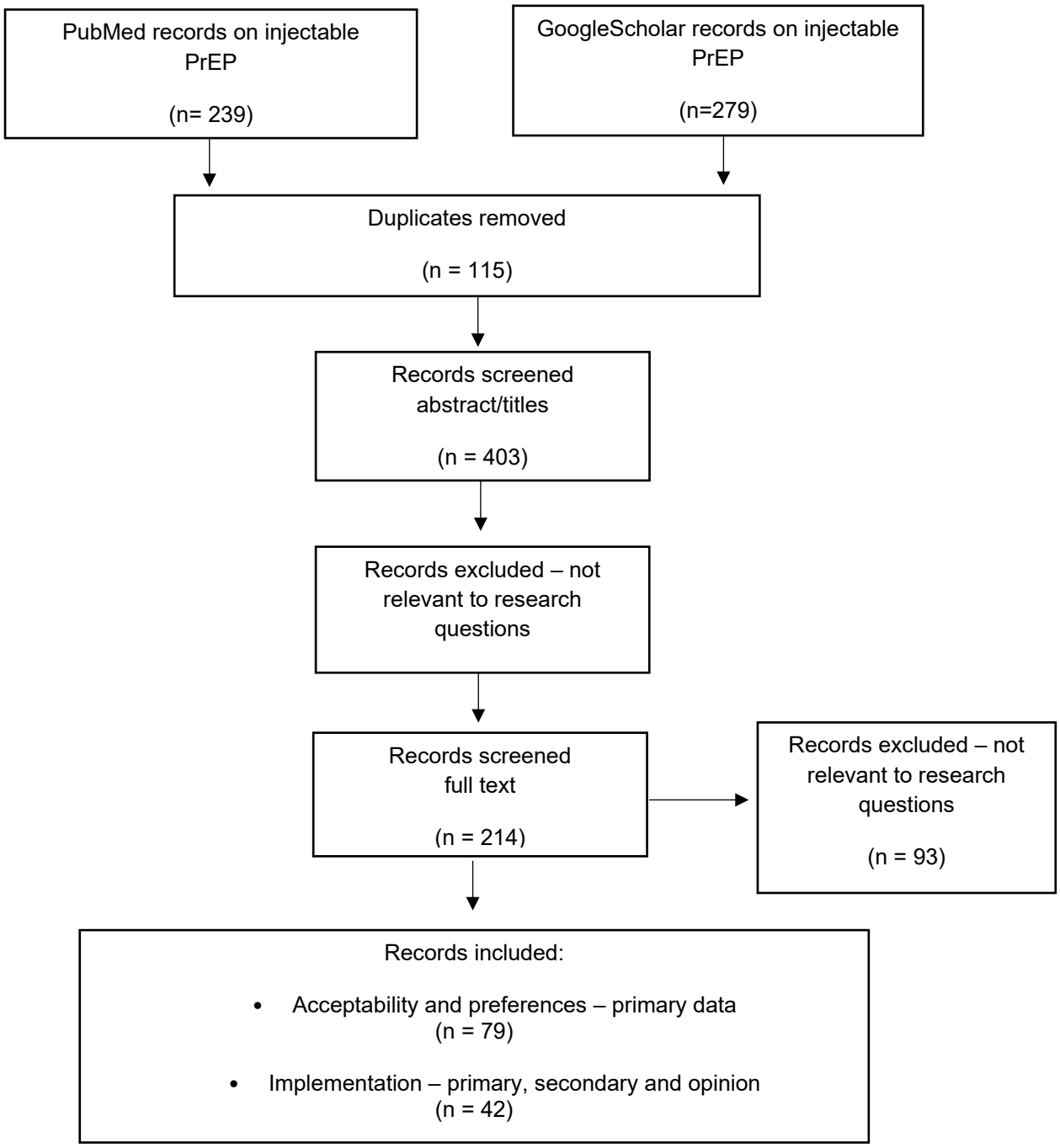
Table 1 Primary Aim Search Terms

PrEP
"HIV PrEP" OR "Pre-Exposure Prophylaxis" OR "Pre Exposure Prophylaxis" OR "HIV Prevention" OR "PrEP products" OR "PrEP"
AND
Modalities
"CAB-LA" OR "Cabotegravir" OR "long-acting injectable cabotegravir" OR "long acting cabotegravir" OR "long-acting" OR "long-acting PrEP" OR "Injectable PrEP" OR "lenacapavir" OR "islatravir" OR "dapivirine vaginal ring" OR "vaginal ring" OR "vaginal insert" OR "vaginal film" OR "vaginal gel" OR "TAF/EVG" OR "tenofovir alafenamide and elvitegravir" OR "rectal gels" OR "modalit*" OR "innovation" OR ""multipurpose prevention technologies"

Table 2 Secondary Aim Search Terms

HIV Treatment
"treat* of HIV" OR "HIV treat*" OR "treat* for HIV"
AND
Modalities
"CAB-LA" OR "Cabotegravir" OR "long-acting injectable cabotegravir" OR "long acting cabotegravir" OR "long-acting" OR "long-acting PrEP" OR "injectable" OR "Injectable PrEP" OR "lenacapavir" OR "islatravir" OR "dapivirine vaginal ring" OR "vaginal ring" OR "vaginal insert" OR "vaginal film" OR "vaginal gel" OR "TAF/EVG" OR "tenofovir alafenamide and elvitegravir" OR "rectal gels" OR "modalit*" OR "innovation"
AND
Area specifics
"acceptability" OR "clinical adaptions" OR "adaptions" OR "clinical issues" OR "issues" OR "implementation issues" OR "clinician perspectives"

Figure 1 Modified PRISMA Flow Diagram



Findings

Perceptions and Opinions

1. Knowledge and Awareness of Injectable PrEP

Five quantitative studies measured awareness of LAI PrEP (Table 1).[13-18] Low awareness of LAI PrEP was common across all studies reviewed, except one.[13] Awareness ranged from 3.9% to 25.6%. While lower proportions of awareness were more common there was a 2018 US study that reported the highest rate of LAI PrEP awareness (51.9%) among MSM who were current PrEP-users.[13] MSM in this study who had been on PrEP for more than a year were 10 time more likely to be aware of LAI PrEP then those who had recently initiated PrEP.[13]

Studies from outside of the US were more likely to report lower levels of LAI PrEP awareness. The lowest rate of LAI PrEP awareness was reported in a 2019 sample of Ugandan adolescent girls and young women in which 3.9% of respondents had ever heard of LAI PrEP.[14] Within a sample collected in 2015 - 2016 of French MSM, 7% reported awareness of LAI PrEP.[15] A subset of this sample analysed LAI PrEP awareness among MSM who reported engaging in transactional sex in which 13.3% were aware of LAI PrEP.[16]

Table 3 Studies reporting LAI PrEP awareness 2015 - 2022

First Author / Year	Country	Year/s of data collection	Sample Characteristics	Awareness of LAI PrEP %
John S A 2018 [13]	United States	2018	MSM current PrEP users	51.9
Shrestha R 2020 [18]	United States	2018 - 2019	Drug users	25.6
Peng L2019 [17]	China	2018 - 2019	MSM	7.1
Goedel W C 2018 [15]	France	2015 - 2016	MSM	7.0
Lunkuse J F 2021 [14]	Uganda	2019	Adolescent girls and young women	3.9
Note: MSM = men who have sex with men				

2. Willingness to use Injectable PrEP

Twenty-three studies reported proportions of respondents who were willing, intending, or likely to use LAI PrEP (Table 4). Willingness to use LAI PrEP was generally high among all studies, ranging from 31% to 96%. Our definition of willingness incorporated terms of 'likelihood' and 'intention' but did not include interest (reported separately below) due to differing motivations these terms may reflect in respondents' potential future actions.

2.1 MSM

Willingness was high (52.7% to 88.0%) among MSM in the US,[19-24] China,[17,25,26] and Nigeria.[27] One study conducted in 2017 – 2018 with a sample of Chinese MSM reported 38.5% of respondents were willing to use LAI PrEP while the majority were more willing to use daily oral PrEP.[28] Rates of willingness were slightly lower among MSM in France[15] (44.4%) and Brazil[29] (47.48%), however it is important to note that these surveys were conducted in 2016.

2.2 Adolescents and Youth

Samples of Sub-Saharan adolescents and youth reported the highest rates of willingness to use LAI PrEP within the studies reviewed, ranging from 82% to 96%.[14,30,31] It is important to note that the study reporting the highest level of willingness (96%) was taken from a 2017 - 2019 sample of youth (18-24 years) in South Africa; the percentage of willingness may be elevated as this response included willingness to use LAI PrEP and implants.[30] In comparison, a 2018 study of African-American US students reported lower rates with 57% of participants stating that they were willing to use LAI PrEP if it was administered every 2 months and 51% if it was administered monthly.[32]

2.3 Other Populations

Other samples of priority populations within HIV prevention, such as people who use drugs and trans and gender diverse people, reported high willingness to use LAI PrEP. There were two studies of these populations, including a 2018 – 2019 US study, reporting that 73.5% of drug users were willing to use LAI PrEP.[18] The second, a 2020 study among Thai transgender women, reported a 74.1% willingness to use LAI PrEP.[33] There was one 2017 – 2018 study in the US of heterosexual women, in which 55.5% of the sample were Black, Hispanic and/or another non-white race and an overall 43.1% experiencing intimate partner violence (IPV).[34] After learning about LAI PrEP, 42% of study respondents with IPV experiences intended to use LAI PrEP in the future.[34] One study reported LAI PrEP willingness among a 2015 sample of US men who were currently not willing to try daily oral PrEP in which 73% of respondents were willing to use LAI PrEP.[35]

2.4 Willingness to Switch from Daily Oral to LAI PrEP

Two studies reported rates of willingness to use LAI PrEP among current daily oral PrEP-users. Among one US study of current PrEP-users in 2017, 31% of respondents reported willingness to use LAI PrEP as their first choice.[36] In this same study, 45% of respondents ranked their willingness to use long-acting PrEP implants as their first choice.[36] Another study from the US reported 66.7% of the study sample would switch from daily oral PrEP to injectable PrEP once made available.[37] Respondents in this study that had a moderate income ($30,000–$50,000) and high injection tolerance were more likely to consider switching from daily oral PrEP to LAI PrEP.[37] Within this study, other factors such as age, race/ethnicity, sexual orientation, education, insurance status, factors related to partnership type, or whether or not the participant was a current PrEP-user were reported to be not associated with intention to switch from daily oral PrEP to LAI PrEP.[37]

2.5 Factors Influencing Willingness

There were 16 studies that reported factors that contributed to LAI PrEP willingness. Six studies reported common reasons for willingness to use LAI PrEP. These included: reducing pill burden,[14,36,37] convenience,[36,37] efficacy,[26,37] increased adherence,[26,37] timing and dosing frequency,[36] and the perceived benefits of PrEP.[33] In a 2014 sample of 314 MSM from the US, 88% of respondents were willing to use LAI PrEP if it was available for free or covered by health insurance.[19] Conversely, four studies with samples of either MSM who were current PrEP-users or adolescents reported the most common reasons respondents were not willing to use LAI PrEP, such as: disliking/fear of needles,[36,37] concerns of side effects,[14,31] logistical difficulties with the requirement for frequent appointments,[36,37] concerns of post-injection pain,[37] and concerns about safety or effectiveness.[36]

Common characteristics of respondents who were willing to use LAI PrEP were reported by 15 studies. The most common characteristic among respondents willing to use LAI PrEP was being at increased risk for HIV such as reporting: frequent sexual partners, inconsistent condom use, and condomless anal intercourse.[15,18,19,25,27,29] Of these studies that reported high willingness to use LAI PrEP among respondents at increased risk for HIV, five were taken from samples of MSM and varied geographically (France, US, China, Nigeria and Brazil). One sample was of drug-users in the US. Other common characteristics reported among respondents who were willing to use LAI PrEP, included: having used oral PrEP in the past;[18,19,22] having knowledge about PrEP;[26,28,29] being engaged in healthcare;[18,27] and reporting a previous STI diagnosis.[29,33]

Table 4 Studies reporting willingness to use LAI PrEP 2015-2022

First Author / Year	Country	Method	Year/s of data collection	Sample Characteristics	Willingness LAI-PrEP %
Minnis A M 2020 [30]	South Africa	Quantitative	2017 – 2019	Youth (18-24)	96.0 (implant or LAI)
Lunkuse J F 2021 [14]	Uganda	Quantitative	2019	Adolescent girls and young women	89.5
Levy M E 2017 [19]	United States	Quantitative	2014	MSM	88.0 (if free or covered by health insurance)
Ogunbajo A 2022 [27]	Nigeria	Quantitative	2019	MSM	88.0
Levy M E 2021 [21]	United States	Quantitative	2017	MSM	84.0
Kidman R 2020 [31]	Malawi	Quantitative	2017 – 2018	Adolescents	82.0
Su X 2020 [26]	China	Quantitative	2018	MSM	77.0 (implant or LAI)
Meyers K 2018 [25]	China	Quantitative	2013 – 2014	MSM	76.0
Himma L 2021 [33]	Thailand	Quantitative	2020	TGW	74.1
Mansergh G 2021 [22]	United States	Quantitative	2018	MSM	74.0
Beckham S W 2021 [20]	United States	Quantitative	2019	MSM	74.0
Shrestha R 2020 [18]	United States	Quantitative	2018 – 2019	Drug-users	73.5
Beymer M R 2018 [35]	United States	Quantitative	2015	MSM not willing to try daily PrEP	73.0
Meyers K 2018 [37]	United States	Mixed Methods	-	MSM PrEP-users	66.7 (switch from oral to injectable)
Patel R R 2018 [24]	United States	Qualitative	2014 – 2016	MSM African American	65.38
Peng L 2019 [17]	China	Quantitative	2018 – 2019	MSM	62.8
Okeke N L 2021 [32]	United States	Quantitative	2018	African American Students	57 (2-mth LAI) 51 (1-mth LAI)
Hall E W 2016 [23]	United States	Quantitative	2015	MSM	52.7
Torres T S 2018 [29]	Brazil	Quantitative	2016	MSM	47.48

Goedel W C 2018 [15]	France	Quantitative	2016	MSM	44.4
Willie T C 2020 [34]	United States	Quantitative	2017 – 2018	Heterosexual Women with IPV experience	42.0
Chen W 2021 [28]	China	Quantitative	2017 – 2018	MSM	38.5
Ellison J 2019 [36]	United States	Quantitative	2017	MSM PrEP-users	31.0
Note: MSM = men who have sex with men, TGW = transgender women, IPV = intimate partner violence					

3. Interest in LAI PrEP

Eleven quantitative studies measured participants interest in LAI PrEP, summarised in Table 5. High levels of interest (>50% of participants in all studies) were commonly reported, ranging from 55.7% to 85.7%. Six of these studies were conducted in the US with samples of: MSM,[38,39] trans and gender diverse people,[38] drug-users,[40,41] and female sex workers.[42] Other samples were from various geographical locations globally, including: MSM (China, Vietnam, Australia),[43-45] female bar workers,[46] (Tanzania), and young women (Kenya)[47].

A 2017 sample of 979 MSM in China reported the highest rates of interest in LAI PrEP (85.7%).[43] Overall, this sample reported high interest in PrEP use generally; 77% of participants reported interest in using daily oral PrEP, with 93.9% (n=705/751) also interested in using LAI PrEP.[43] Of the remaining 23% who were not interested in daily oral PrEP, 57.5% (n=131/228) were interested in using LAI PrEP.[43]

Two additional studies reported that interest in LAI PrEP was more likely among respondents who were currently using daily oral PrEP.[39,45]

Table 5 Studies reporting interest in LAI PrEP 2015-2022

First Author / Year	Country	Method	Year/s of data collection	Sample Characteristics	Interest LAI-PrEP %
Huang W 2019 [43]	China	Quantitative	2017	MSM	85.7
Harling G 2019 [46]	Tanzania	Quantitative	2017	Female Bar Workers	79.0
Biello K B 2018 [38]	United States	Quantitative	2016	MSM, TGM, TGW	73.2
Assoumou S A 2021 [40]	United States	Quantitative	2016 - 2017	Drug-users	71.0
Reisner S L 2021 [48]	United States	Quantitative	2017	TGM	70.0
Oldenburg C E 2016 [44]	Vietnam	Quantitative	2015	MSM	69.8
Timmins L 2021 [39]	United States	Quantitative	2018 - 2019	Black MSM	Gay SMO: 52.0 Gay SWM: 62.5 Bisexual SMO: 50.0 Bisexual SWM: 39.4
Ngure K 2021 [47]	Kenya	Quantitative	-	Young women	58.5

Chan C 2022 [45]	Australia	Quantitative	2019-2020	MSM previous of current PrEP-user	59.7
Rosen J G 2022 [42]	United States	Quantitative	2016-2017	cis FSW	Quarterly arm: 56 Quarterly abdomen: 29
Schneider K E 2021 [41]	United States	Quantitative	2018	Injecting drug-user	55.7
Note: MSM = men who have sex with men, TGM = transgender man, TGW = transgender women, SMO = Had sex with at least one man and no women in the past 6 months, SMW = Had sex with at least one woman and at least one man in the past 6 months.					

4. LAI PrEP Preferences

There were 51 studies published between 2015 and April 2022 that measured preferences for LAI PrEP (Table 6). Studies ranged geographically; just over half (n=26)[13,18,19,21,24,32,36,38,48-65] of all studies were conducted in the US, followed by countries in Sub-Saharan Africa (n=11),[27,31,47,66-76] Asia (n=4), [28,43,44] and Europe (n=4).[15,77-80] There were two studies from Australia[45,81] and one from Canada.[82] Most studies involved MSM (n=26), followed by women (n=10).

Thirty-three studies measured preferences for PrEP modalities, offering LAI PrEP as an available choice. The majority (n=24) reported that respondents rated LAI PrEP as their preferred choice over other PrEP modalities. Levels of preference ranged from 5.5% to 81%, however, 17% to 75% is a more accurate representation due to differences in study design (i.e. the study reporting 81% combined implant, injection and ring preferences,[66] while the study reporting 5.5%[28] noted that the description of LAI PrEP provided in the study may have led to decision bias among respondents, as it stated injections causes serve pain).

It was common for MSM from the US[13,19,21,24,38,48,50,52,53] and women from Sub-Saharan Africa[47,66-70,72] to rate their preference for LAI PrEP highly and as their preferred choice over other PrEP modalities. In a sample of 234 people who use drugs in the US, 67.9% rated LAI PrEP as their preferred PrEP modality compared to daily oral (15.8%) or neither (16.2%).[18] Adolescents and students in Sub-Saharan Africa[31] and the US[32] were also more likely to prefer LAI PrEP over other PrEP modalities.

4.1 Common reasons for preferring LAI PrEP

There were 27 studies that provided insight into common reasons respondents preferred LAI PrEP. The most common reported reason was that LAI PrEP was an easier alternative to a daily oral pill.[36,38,44,45,56-58,60,66,69,70,72,73,79,80] Of the 15 studies that reported this preference, the view that LAI PrEP was an easier alternative to the daily oral pill was common among samples of MSM from the US,[36,38,56-58] Australia,[45] England,[80] and, Vietnam[44,79] as well women from Sub-Saharan African[66,69,70,72,73] and the US.[57,60]

The second most common reason for preferring LAI PrEP was convenience and ease of use.[36,55-58,60,61,68,72,83] This was commonly reported by women. Other common themes for preferring LAI PrEP included: efficacy, improved adherence (including protection duration and less user reliance);[24,55,56,62,69,71,73-76,83] privacy and discreteness (including partners not needing to know);[44,55,66,68,69,73,75,83] dosing frequency;[36,55-57,60,70,73,75] and route of administration (including disliking pills and not wanting to take pills if not sick).[24,50,51,66,69,80]

Another reason for preferring LAI PrEP, raised in a 2014 -2016 qualitative study with a sample of 26 African American MSM in the US, was that using LAI PrEP to prevent HIV was similar to prevention of other medical conditions, which often require injections/vaccines.[24]

There were 18 studies that analysed common or statistically significant characteristics of respondents who preferred LAI PrEP. Approximately 20 different characteristics were identified by these studies, however, only four reported similar or the same characteristics. Of the characteristics that were reported by separate studies more than once, the most common was reporting a self-reported risk for HIV (i.e. inconsistence condom use, multiple partners, and engaging in condomless anal intercourse).[32,38,54,71]

Reporting oral PrEP experience (currently using daily oral PrEP or having had used it in the past) was another common characteristic.[38,56,67] However, one 2015 - 2016 US study with a sample of people who have sex with men (including cis and trans men and cis women), with prior oral PrEP experience, had a greater preference for daily oral pills. These participants reported that they trusted daily oral pills as an effective HIV prevention method. Within this study it was the PrEP-naïve participants who expressed greater interest in LAI PrEP.[53] In a 2013 - 2014 study of 200 MSM in China, of respondents who were unwilling to consider oral PrEP, over half (53.5%, n=49/52) stated they would consider LAI PrEP.[25]

Other common characteristics of those who preferred LAI PrEP included: having previous experience with injectable mediations;[56,62,70] being younger;[38,52,77] having higher education levels; [52,55,77] having less than a bachelor's degree;[13,38] and having PrEP knowledge.[24,43] There were two studies with samples of US women with current or previous experience of injecting drug use which both observed that people who currently inject drugs may be particularly willing to use LAI PrEP.[60,83] These studies also suggested that people who currently inject drugs, or who are also experiencing housing instability and unpredictability, could find it challenging to take daily oral pills.[60,83] The option to use LAI PrEP might be more suitable to ensure adherence and prevention.[60,83]

4.2 Common barriers or concerns of LAI PrEP

There were 22 studies that provided insight into barriers or concerns participants had about LAI PrEP. The most common barrier or concern participants had about LAI PrEP was a fear/dislike of needles.[18,24,31,36,55,56,69,78,83] Some studies found that fear/dislike of needles did not entirely preclude the possibility of using LAI PrEP; participants felt that the infrequent dosing made having an injection worthwhile, and fear of needles was often a visual reaction rather than fear of actual physical pain.[24,68] However, fear of pain from injections was also commonly raised.[31,53,61,69,75] In comparison, a 2015 - 2016 US study with a sample of 104 MSM current PrEP users found that fear of needles was of least concern to participants.[13]

Side effects from LAI PrEP was the second most commonly reported barrier or concern.[13,31,50,53,61,62,69,83] Concerns about whether the side effects would dissipate or would last the entire effective period of the injection was commonly raised as well as the concern of having less control over potential side effects.[53,60] This theme links into a concern raised by participants in two studies that compared to the daily oral pill, LAI PrEP was perceived as potentially reducing bodily autonomy.[60,78]

Logistical difficulties, such as having to regularly return to a clinic, and attend routine appointments on time, were also common concerns raised by participants who may be

suitable for future LAI PrEP use.[13,18,31,36,53,62,65] Others included: fear PrEP efficacy may wane over time (incomplete protection);[13,18,24,36,53] prohibitive costs;[18,53,62,65] distrust of medical systems and injections;[53,59,78] potential long term health effects;[13,18,50] fear of potential interactions with other medication regimens, including hormone replacement therapy injections;[60-62] privacy issues;[31,63,65] and a fear injections could be 'triggering' for people who inject drugs.[59,83] Concern about weight gain was raised by participants in one qualitative study of 112 South African men and women.[73] In one 2016 - 2017 qualitative study, with a sample of 18 transgender women from New York City, participants reported they disliked being informed that an oral lead-in would be required to initiate LAI PrEP.[62]

4.3 Preferences for anatomical site location for injection

There was only one study that quantitatively measured respondents' preferences for where on the body they would prefer to receive LAI PrEP. Within this sample of 406 MSM and men who have sex with women (MSW) from South Africa, 37% said that the outer arm was their most preferred location for injections, with 43% rating their buttocks as their least preferred location for injections.[76] Another qualitative study among LGBTQ youth of colour noted that 'young people had a lot of questions about why the shot needed to be in the butt?'[61] A concern raised by trans women in two studies was the fear that LAI PrEP injections in the buttock would interact with silicon buttock implants/injections.[61,62]

4.4 Preferences for Injection dosing frequency

There were 11 studies that provided insight into how often potential LAI PrEP-users would prefer LAI PrEP to be administered. A minimum of at least one month between LAI PrEP was acceptable, however, options for longer duration were most preferable.[24,69,80] The exception was among one 2017 - 2018 study from China with a sample of 550 MSM, which found that the majority of respondents preferred LAI PrEP once a month (49.5%), followed by once every 3 months (35.4%), and once every two months (15.1%).[28] Apart from this study, studies reported that LAI PrEP every 3 months was the most preferred dosing frequency among US MSM.[24,50] In one study in 2016 - 2017, in which 33 people who inject drugs were interviewed, participants suggested that LAI PrEP every two months would increase PrEP adherence compared to a daily oral pill.[59] Another qualitative study from 2015 - 2016, in which 36 MSM (including trans men) and women who have sex with men were interviewed, participants suggested that quarterly injections may be more manageable and increase adherence.[53] Longer term dosing of every six months was raised in three studies (mostly women, including trans women) as the preferred option over every three months.[31,60,62]

A common theme raised in relation to dosing frequency was the possibly of coinciding LAI PrEP with LAI contraception, which was seen as a benefit among women in the US and Sub-Sharan Africa.[57,73] Coinciding LAI PrEP with other injectable medications was also raised by trans youth in the US who noted in a 2016 - 2017 qualitative study that injectable PrEP would be convenient if it can be taken at the same time as injectable hormones.[61]

4.5 Where to get injections and who will administer them

Of the studies reviewed, seven provided insights into the locations at which potential LAI PrEP users would prefer to receive their injections. A further five provided insights into who participants would prefer to receive their LAI PrEP from. Preference for receiving an injection at a health clinic was common.[31,63-66,79] In a 2013 - 2014 qualitative study with a sample of 68 women from Sub-Saharan African countries, participants described that receiving LAI PrEP

at a clinic would increase adherence.[66] These participants also revealed that clinic-administered PrEP was attractive as it provided privacy; they would not need to worry about storing or hiding PrEP in their own home and fear risk of discovery.[66]

Other themes that emerged from these studies where that some participants would prefer to receive LAI PrEP in clinics that they already routinely accessed and/or are MSM-friendly.[63-65,79] These participants recommended that that LAI PrEP must be widely accessible and available in locations where it is convenient and easy to obtain.[63-65,79] In comparison, participants from a 2016 - 2018 qualitative study of 18 transgender women from New York City, reported that visits to healthcare providers for LAI PrEP were cumbersome and inconvenient.[62] Participants who were experienced with injecting medication reported a preference to have the option to self-inject LAI PrEP.[62] In another qualitative study among 41 young MSM, self-injection of LAI PrEP was also preferred, if provided training, and described as 'convenient and an empowering option to avoid PrEP stigma.'[56] Another theme raised by participants was the need for those administering LAI PrEP to be competent in injecting (i.e. must have training and skills).[63]

4.6 Cost

In the studies reviewed, four reported concerns of potentially high costs of LAI PrEP as a common barrier to potential uptake.[18,53,62,65] In a 2017 - 2019 sample of 406 South African men (47% MSM, 53% non-MSM), 6% of respondents said that they were not willing to pay for LAI PrEP.[76] Another theme raised in two studies among MSM in the US was a preference for LAI PrEP to be equal to or less than the cost of daily oral PrEP, and that if LAI PrEP were to cost more, this would be a barrier for future users.[19,58]

Table 6 Studies reporting LAI PrEP preference over other PrEP modalities 2015-2022

First Author / Year	Country	Method	Year/s of data collection	Sample Characteristics	Preference over other PrEP modalities %	Other LAI Preferences
Studies reporting LAI preferences by %						
Luecke E H 2016 [66]	South Africa Zimbabwe Uganda	Mixed methods	2013 - 2014	Women	**Implant, injection or ring: 81.0** Vaginal film or suppository: 28.0 Oral tablets: 22.0 Vaginal gel: 16.0	-
Siedner M J 2018 [67]	Eswatini	Quantitative	-	Primary health clinic attendees (86% female)	**LAI: 75.0** Daily oral: 25.0	-
Patel R R 2018 [24]	United States	Qualitative	2014 - 2016	MSM African American	**LAI: 71.43**	Preferred LAI: ○ Better adherence ○ Dislike taking pills Concerns included: ○ Fear of needles ○ Perception that there would not be therapeutic levels for a long duration Preferences: ○ Ranged from weekly to annually. Longer dosing intervals of three

						months was preferred
Shrestha R 2020 [18]	United States	Quantitative	2018 - 2019	Drug-users	**LAI: 67.9** Daily oral: 15.8 Neither: 16.2	
Levy M E 2017 [19]	United States	Quantitative	2014	MSM	**LAI: 67.0** Daily oral: 24.0 Neither: 9.0	
Levy M E 2021 [21]	United States	Quantitative	2017	MSM	**LAI: 67.0** Over oral	
Minnis A M 2018 [68] & Shapley-Quinn M K 2019 [69]	Kenya South Africa *Trio Study*	Qualitative	2015 - 2016	Women	**LAI: 65.0** Tablets: 18.0 Ring: 17.0	Concerns: ○ Needle size Preferences for LAI: ○ Saved time ○ Discreetness
Van der Straten A 2018 [70]	Kenya South Africa	Quantitative	2015 - 2016	Women	**LAI: 62.0** Daily oral: 15.0 Ring: 12.0 Condoms: 10.0	
Kidman R 2020 [31]	Malawi	Quantitative	2017 - 2018	Adolescents	Girls - **LAI: 60.6** Pill: 39.3 Boys - **LAI: 59.3** Pill: 40.6	Preferences for dosing and location: <u>Health Clinic</u> 3 monthly - Girls: 60.6 Boys: 59.3 6 monthly – Girls: 64.5 Boys: 63.3 <u>Home</u> 3 monthly – Girls: 50.1 Boys: 49.8 Girls: 53.0 Boys: 53.8
Reisner S L 2021 [48]	United States	Quantitative	2017	Trans MSM	**LAI: 51.2** Daily oral: 22.1 Anal gel/lube:14.6 Blood transfusions w/ antibodies: 9.1 Anal douche: 3.0	
MacGibbon J 2019 [81]	Australia	Quantitative	2019	Gay bisexual men	**LAI: 40.0** Daily oral: 22.0 Event-based pills: 19.0 Implants: 18.0	
Philbin M M 2021 [83]	United States	Qualitative	2017 - 2018	WLHIV and HIV-negative women at risk of HIV	**LAI: 50.0** Daily oral: 23.0 Neither: 23.0	Preferences: ○ Used to injections ○ Belief LAI are more effective than pills ○ Ease ○ Convenience ○ Confidentiality Concerns: ○ Injection burden ○ Fear of needles ○ Triggering for IDU ○ Fear of new—injectable products ○ Side effects (e.g. injection-site pain, nausea).
Cheng C Y 2019 [71]	South Africa	Quantitative	2015	Heterosexual Men	**LAI: 48.0** Daily oral: 33.0 Condoms: 20.0	
Biello K B 2018 [38]	United States	Quantitative	2016	MSM & TGW	**LAI: 47.2** Daily oral: 16.8 Unsure: 36	

Gill L 2020 [72]	South Africa	Quantitative	2015 - 2017	Heterosexual Women	**LAI: 46.1** Ring: 27.1 Pill: 10.1 Condoms: 4.5	
Parsons J 2016 [50]	United States	Quantitative	2014	MSM	**LAI: 46.0** Daily oral: 14.3 Whichever is most effective: 21.7 No preference: 10.1 Neither: 7.8	Dosing: ○ 1m: 43.2 ○ 3m: 53.6
Ogunbajo A 2022 [27]	Nigeria	Quantitative	2019	MSM	**LAI: 44.0** Daily oral: 21.0 Lubricant:17.0 Like all equally: 10.0 Implant: 6.0	
Elopre L 2022 [51]	United States	Quantitative	2019 - 2020	Black cis-gender women	**LAI: 41.4** Daily oral: 40.0	
Okeke N L 2021 [32]	United States	Quantitative	2018	African American Students (75% women)	**LAI (every 2 months): 38.0** Daily oral: 29.0 not sure: 19.0	
Dubov A 2019 [52]	United States	Quantitative	2015	MSM	**LAI: 37.9**	
Huang W 2019 [43]	China	Quantitative	2017	MSM	Rectal microbicides: 39.2 **LAI: 36.3** Daily oral: 24.6	
Ngure K 2021 [47]	Kenya	Quantitative	-	Young women – PrEP experienced	**LAI: 36.0** oral pills: 34.2 Implants: 22.0 vaginal ring: 14.6	
Ellison J 2019 [36]	United States	Quantitative	2017	MSM PrEP-users	Implants: 45.0 **LAI: 31.0** Daily oral: 21.0 Rectal microbicides: 1.0 Antibody Infusions: 1.0	
John S A 2018 [13]	United States	Quantitative	2015 - 2016	MSM	**LAI: 30.8** Daily oral: 26.9 Whichever most effective: 34.6 No preference: 7.7	
Chan C 2022 [45]	Australia	Quantitative	2019	MSM – PrEP experienced	**LAI: 30.5** PrEP implants: 26.3 Daily oral: 21.4 Event-driven PrEP: 21.2	
Biello K B 2018 [53]	United states	Mixed methods	2015 - 2016	MSM WSM Trans MSM	**Quarterly LAI: 30.0** Precoital gel: 22.0 Daily pill: 14.0 No response: 33.0	
Irie W C 2022 [54]	United States	Quantitative	2019	Black cis-gender women	Daily pill: 51.1 **LAI: 25.7** Vaginal gel: 16.5 Vaginal ring: 6.7	
Greene G J 2017 [55]	United States	Mixed Methods		MSM	Daily oral: 35.5 Non-visible implants: 34.3 **LAI: 25.2** Visible implants: 4.3	

John S 2021 [56]	United States	Mixed Methods	2020	Young MSM	Daily oral: 35.4 Implant 1: 34.4 **LAI: 25.2** Implant 2: 4.3	Preferences: ○ Experienced PrEP users approved of LAI-PrEP more ○ Easy to remember ○ Convenience ○ Used to injectables ○ Protection duration ○ Self-injection more acceptable if provided training Concerns: ○ Invasive
Calabrese S K 2020 [57]	United States	Quantitative	2017	Heterosexual Women	Daily oral: 24.9 **LAI: 24.3** Invisible Implants: 14.9 Event-driven:10.7 Vaginal film: 10.1 Vaginal ring: 5.7 Visible implant: 3.2 Vaginal or anal suppository 2.5 Daily vaginal or anal gel: 2.3 Event-driven vaginal or anal gel: 1.4	
Goedel W C 2018 [15]	France	Quantitative	2016	MSM	Daily oral: 4.8 Event driven pills: 11.0 **LAI: 21.8** Penile microbicide gel: 8.3 Rectal Microbicide: 6.6 Whichever is most effective: 31.7 No preference: 4.6 None: 11.6	
Oldenburg C E 2016 [44]	Vietnam	Quantitative	2015	MSM	Rectal microbicide gel: 65.7 **LAI: 17.0** Daily oral: 17.3	
Chen W 2021 [28]	China	Quantitative	2017 - 2018	MSM	Daily oral: 41.4 **LAI: 5.5 (**Note: survey mentioned that injectable PrEP causes severe pain at the injection site which may have potentially led to a bias in the decision on PrEP preferences among participants)	Preferences of those willing to use LAI PrEP (38.5): ○ 1m: 49.5 ○ 2m: 15.1 ○ 3m: 35.4
Other reported preferences by year						
Calder B J 2018 [58]	United states	Qualitative		MSM	Benefits: ○ simplify lives Preference: ○ one large dose shot over multiple Concern: ○ Cost - especially if LAI not covered (or no financial assistance available) or cost more than daily oral	
Dubov A 2018 [77]	Ukraine	Quantitative	2016	MSM	DCE - Group 5 was at highest risk for HIV and preferred LAI were more likely to be young and educated.	
Govender E 2018 [73]	South Africa	Qualitative		Men and Women	Preferred LAI due to: ○ Longer period of HIV protection	

					○ Easily adopted into contraceptive routines ○ Doesn't require daily administration ○ Less user reliance ○ Safe ○ Requires minimal negotiation or partner support Concerns were: ○ Weight gain ○ Sex outside of relationship	
Quaife M 2018 [74]	South Africa	Quantitative	2015	Adult men and women Adolescent girls FSW	DCE All groups demonstrated a strong preference for LAI.	Preferences were: ○ Protection and efficacy ○ MPT
Biello K B 2019 [59]	United States	Qualitative	2016 - 2017	PWID	The majority of PWID interviewed believed LAI-PrEP would be acceptable.	Preferences: ○ Injections every 2m would reduce barriers to daily oral PrEP adherence, including forgetting while "high" and safeguarding pills when homeless. Concerns: ○ medical mistrust, ○ a concern that injections could alter their 'high' or be 'triggering' for PWID.
Footer K H A 2019 [60]	United States	Qualitative	2016 - 2017	Women IDU FSW	Women with existing pill regimens felt that adding an additional pill would be the most convenient for them. However, both groups recognised that for less stable women, in particular women getting high or with no permanent place to stay, a daily pill regimen could be challenging.	Preferences included: ○ Convenience and ease of use ○ Frequency of administration, ○ Less frequent delivery methods (6m vs 3m) Concerns: ○ Less control over potential side effects ○ Reducing women's agency over their bodies ○ Potential interactions with other medication regimens
Carillon S 2020 [78]	France	Qualitative	2018 - 2019	PrEP-users and PLHIV (only reporting on PrEP-users)	Offers simplification compared to oral PrEP Concerns: ○ Specificities of the mode of administration ○ Administration modality ○ Long-acting action in the body ○ Fear of injections ○ Potential loss of body autonomy and control of side effects ○ Wary of effectiveness of LAI	
Golub S A 2020 [61]	United States	Qualitative	2016 - 2017	LGBTQ Youth of Colour	Concerns: ○ Anatomical site of injection ○ Injection site pain and post injection pain ○ Interactions with HRT / silicon butt implants Preferences: ○ Convenient if it works with injectable hormones	

Laher F 2020 [75]	South Africa	Qualitative	2018	Previous HIV vaccine trial participants	Preferences included: ○ Infrequent administration - lasting 1m at least reasons for this included: - forgetfulness when using daily methods - daily methods interfered with lifestyle - costliness of transportation for methods that required frequent clinic visits - product inaccessibility because of clinic operating times ○ Route of administration linked with efficacy, discreet, and long-lasting. ○ Women recommended that HIV prevention strategies – the method itself and any related adverse effects – should not be visible to male partners. Concerns: ○ Injections were perceived to be painful
Rael C T 2020 [62]	United States	Qualitative	2016 - 2017	TGW	Participants were overwhelmingly positive about long-acting HIV prevention strategies, though they had some apprehensions. Preferences: ○ Help address adherence challenges ○ Familiarity with injections made LAI more acceptable ○ Experience and preference to self-inject. ○ Injections should last for a prolonged period of time - i.e. 6m to 1 year Concerns: ○ Logistics ○ Presence in the body ○ Interaction with HRT / silicone implants or injections ○ Scaring or marking ○ Visits to healthcare provider cumbersome and inconvenient. ○ Dislike of oral lead-in ○ Side effects ○ Prohibitively expensive
Montgomery E T 2021 [76]	South Africa	Quantitative	2017 - 2019	MSM and MSW	Preferences influenced by: ○ Efficacy: 94.0 ○ Access/location: 88.0 ○ Frequency: 87.0 ○ Removable 85.0 ○ Location of injection 59.0 Location preference (most preferred): ○ Outer arm: 37.0 ○ Buttocks: 30.0 ○ Inner upper arm: 16.0 Location preference (least preferred): ○ Buttocks: 43.0 ○ Inner thigh: 13.0 ○ Inner upper arm: 7.0 Cost willingness ○ 6.0 not willing to pay
Nguyen L H 2021 [79]	Vietnam	Qualitative	2018	MSM	Preferences: ○ Easier to adhere ○ Preferred to receive LAI in civil business organisations and MSM-friendly clinics, Concerns: ○ Pharmacy stores are not suitable for PrEP administration due to lack of trust and fear of fake drugs
Rael C T 2021 [63]	United States	Qualitative	2019	TGW	Preferences: ○ Competence among those delivering LAI PrEP i.e. must have the training and skills

					○ Convenience, must be easy to obtain Concerns: ○ Privacy and fear of judgement from clinicians
Tan D H S 2021 [82]	Canada	Quantitative	2016	MSM	Minimum efficacy for PrEP options to be preferred over usual care: ○ Monthly injections: 40.1 ○ Monthly injection with side effects: 34.3
Arnold-Forster D 2022 [80]	England	Qualitative	2014 - 2016	MSM	Preferences: ○ Injection every month or couple of months ○ Easier than remembering pills ○ Don't feel like they have chronic diseases by having to take pills every day.
Gutierrez J I 2022 [64]	United States	Quantitative	2020	MSM in Military	Access / Location preferences: ○ Smartphone, military injection: 69.6 ○ Remote, military injection: 67.9
Valente P K 2022 [65]	United States	Qualitative	2020 - 2022	Young MSM	Concerns: ○ Parent's findings out / privacy ○ Logistical difficulties (moving around, not knowing where to go, parents' insurance) ○ Costs
Note: MSM = men who have sex with men, WLHIV= women living with HIV, TGW = transgender women, WSM = women who have sex with men, FSW = female sex workers, PWID = people who inject drugs, IDU = injecting drug users, PLHIV = people living with HIV, LGBTQ = lesbian, gay, bisexual, transgender, queer, MSW = men who have sex with women, DCE = discrete choice experiments.					

5. Acceptability of Injectable PrEP

Of the studies reviewed, there were eight sources that reported on acceptability of LAI PrEP based on actual experience using the product (Table 7). All eight sources researched acceptability, tolerability and satisfaction among participants from five different clinical LAI PrEP trials. These clinical trials included:

1. ÉCLAIR: A Phase IIa Study to Evaluate the Safety, Tolerability and Acceptability of Long Acting Injections of the HIV Integrase Inhibitor, GSK1265744, in HIV Uninfected Men (ECLAIR)
2. HPTN076: Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for Pre-Exposure Prophylaxis (PrEP)
3. HPTN077: A phase IIa Study to Evaluate the Safety, Tolerability and Pharmacokinetics of the Investigational Injectable HIV Integrase Inhibitor, GSK1265744, in HIV-uninfected Men and Women
4. HPTN083: A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral Tenofovir Disoproxil Fumarate/Emtricitabine (TDF/FTC), For Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women Who Have Sex with Men
5. NCT03422172: An Open Label, Phase 1 Study to Evaluate the PK, Safety, Tolerability and Acceptability of Long Acting Injections of the HIV Integrase Inhibitor, Cabotegravir (CAB; GSK1265744) in HIV Uninfected Chinese Men

Satisfaction was specifically reported within two studies and was rated generally high by respondents who had participated in the ÉCLAIR clinical trial.[84,85]

Acceptability was commonly reported across studies and it was generally reported that LAI PrEP was very acceptable to users.[84,86-88] Attributes that increased acceptability included number, frequency, location, protection, and duration of injection.[86-88] One study reported

that participants felt it was neither inconvenient nor difficult to receive the study medication as recommended.[84]

It was also common for clinical trial participants to report high rates of willingness to: continue using LAI PrEP; [84,89] use LAI PrEP in the future;[85,86,89] and recommend LAI PrEP to others.[84,89] In a 2015 - 2017 study of women's experiences of LAI PrEP in the HPTN076 trial, 79% strongly endorsed the statement that they would 'definitely use an injectable PrEP product for some time.'[86] This increased to 88% of women if LAI PrEP could be combined with pregnancy prevention.[86] Within these studies, it was common for respondents who had now had experience using LAI PrEP to state that they preferred LAI PrEP to daily oral PrEP.[84,85,87,88] One study from the ÉCLAIR trial reported that most participants receiving consecutive injections (74%) preferred CAB injections over oral CAB.[84]

Injection site pain was the most commonly reported adverse event.[84-88] In the ÉCLAIR trial, 6% of participants in the CAB arm reported pain/discomfort from injections 'a very great deal.'[84] Injection intolerability led to withdrawal of four participants (4%) receiving CAB injections in this study.[84] In another analysis of a sub-set of participants from the same ECLAIR trial, injections were described as 'not always pleasant.'[85] Despite this, participants expressed that the side effects were worth the pain if long-acting PrEP was found to be effective.[85] These respondents raised other disadvantages of LAI PrEP including the large needle size and embarrassment of having to show ones' buttocks to receive the injection.[85]

Participants from the ÉCLAIR and NCT03422172 trial reported relatively high tolerability for side effects of LAI PrEP (66% and 91% respectively) and pain/discomfort (64% and 78% respectively).[89] Within a subset of participants of HPTN076, respondents acknowledged that while injection site pain was a negative aspect, they concluded that the pain was temporary and subsided, on average within a day or two.[88] These respondents reported other experiences of side effects such as headaches, dizziness and nausea.[88]

Within a subset of 26 participants of the ÉCLAIR trial, respondents provided further insights on the benefits of LAI PrEP.[90] Respondents stated that LAI PrEP gave them 'peace of mind', allowing them to feel less worried about adherence for themselves and their partners.[90] These respondents from the US also raised the issue of cost. Respondents said they would be willing to pay on average $100 USD a month for LAI PrEP with the expectation it would be covered by insurance through a co-pay.[90] Other insights from these respondents suggested LAI PrEP should be available in locations similar to how the trial worked, such as doctor offices and clinics, as well as mobile outreach to reach those less likely to access care.[90] Respondents supported pharmacy-led administration of LAI PrEP, noting that injection administrators would need to be trained and skilful.[90] Few respondents said that they would see themselves administrating their own injections.[90]

Early findings on participant experiences and preferences within HPTN083 reported on facilitators and barriers to attending LAI PrEP appointments. Facilitators included motivational factors such as: preservation of health; desire to contribute to research; use of reminders; social support and clinical factors (e.g. flexibility).[91] Barriers included: financial constructs, travel to clinic, homelessness and time constraints.[91]

Table 7 Studies reporting LAI PrEP acceptability 2015-2022

First Author / Year	Country/s	Method	Year/s of data collection	Study Trial
Murray M 2016 [84]	United States	Quantitative	2014 - 2016	ÉCLAIR
Montgomery E T 2019 [88]	South Africa	Qualitative		HPTN076
Tolley E E 2019 [86]	Zimbabwe South Africa United States	Quantitative	2015 - 2017	HPTN076
Tolley E E 2020 [87]	United States Brazil Malawi South Africa	Qualitative		HPTN077
Kerrigan D 2018 [90]	United States	Qualitative	2015	ÉCLAIR
Meyers K 2018 [85]	United States	Qualitative		ÉCLAIR
Psaros C 2021 [91]	United States	Qualitative		HPTN083
Han K 2022 [89]	China	Quantitative		NCT03422172

6. PrEP Providers Opinions

We identified three studies on perceptions and opinions of PrEP providers on LAI PrEP (Table 8). Two studies were from the US and interviewed four clinical trial providers from the ÉCLAIR study,[90] and 24 medical practitioners who had a high-case load of MSM.[58] The final study interviewed 24 health care providers in Kenya and South Africa as part of the tablets, ring, injections as options (TRIO) study.[92]

In general, the US medical practitioners were supportive of LAI PrEP as a critical tool in HIV prevention that should be made widely accessible.[58,90] Practitioners were cautious that LAI PrEP may not be right for everyone, and were sceptical about whether current oral PrEP-users would switch to LAI PrEP to improve adherence.[58,90] Clinical providers from the ÉCLAIR study indicated that some medical practitioners may be cautious to prescribe LAI PrEP over daily oral PrEP, as it is more clinically difficult to manage.[90] These providers also acknowledged the dilemma that while LAI PrEP may theoretically seem more suitable for those with adherence challenges, these adherence challenges are not eliminated as patients will still need to attend regular appointments.[90] Additionally, US medical practitioners with a high caseload of MSM believed that LAI PrEP would not encourage people to start PrEP, and that simplifying lifestyles rather than improving adherence may be the main reason MSM would switch from daily oral to LAI PrEP.[58]

In comparison, medical providers of women in Sub-Saharan Africa were generally supportive of LAI PrEP, particularly if it could be combined with contraception as a multipurpose prevention technology (MPT), or synchronised with contraception injectables such as the Depo-Provera shots.[92] Medical providers had concerns that the introduction of MPTs would create more workload for clinics and that once available, clinicians will need to be trained, and clinics will need to have stable stock distribution available for wide distribution.[92]

However, if MPTs were developed, clinicians raised concerns over potential increases in STI prevalence, as women may decrease condom use.[92] Clinicians preferred for product length of duration to last for a minimum of three months to a maximum of three years.[92] They raised that women will be wary of the side effects and will require education support on the side effects of LAI PrEP.[92]

Table 8 Studies reporting LAI PrEP providers opinions 2015-2022

First Author / Year	Country/s	Method	Sample Characteristics	High-level results
Calder B J 2018 [58]	United States	Qualitative	Clinicians with high caseload of MSM	Recognised that LA PrEP methods (injections and implants) could provide better adherence. However, sceptical that achieving better adherence would be a reason for MSM to choose them over the pill. Believed that the availability of LA PrEP (injections or implants) would not encourage people to start PrEP.
Kerrigan D 2018 [90]	United States	Qualitative	Clinical providers from the ÉCLAIR study	Important option for HIV prevention that needs to be widely accessible however some providers may be cautious of prescribing due to harder clinical management. Also noted while it may assist patients who have adherence challenges there is still the dilemma that patients need to make appointments on time. Some also raised the concern that CAB-LA may not encourage “mindfulness” and reflection around sexual decision making, relationships and planning for HIV prevention.
Lutnick A 2019 [92]	South Africa Kenya	Qualitative	Clinical providers from the TRIO study	Supportive, especially if LAI PrEP can be combined with LAI contraception. Will increase workload and prefer products to last for 3 months to 3 years. Noted women will be concerned of side effects.
Note: MSM = men who have sex with men, LA = long acting.				

Mathematical Modelling Studies

1. Cost-effectiveness of LAI PrEP

Of the studies reviewed, there were six papers that used types of cost-effectiveness models to determine the financial impacts of introducing LAI PrEP to certain countries (Table 9). Most (n=5) studies were based on populations in South Africa[93-97] and one was based in the US.[98] As all studies used different forms of modelling and parameters, comparison across studies was difficult. In general, studies demonstrated that LAI PrEP could be cost effective, particularly when prioritised to young women in South Africa. The exception was one study that estimated providing PrEP to heterosexual South African men was not cost-effective, at the current cost-effectiveness thresholds it used.[97] It was noted that prioritisation of LAI PrEP uptake will be vital to maximise benefits, and that without prioritisation, benefits could erode, and costs may increase.[94]

The following information highlights some of the key cost analysis findings of interest. One study model demonstrated that compared to daily oral PrEP, LAI PrEP was very cost-effective ($150/life-year saved), and over five years would cost $1.6 billion when provided to 50% of eligible women in South Africa.[95] Another study from South Africa reported that prioritisation of LAI PrEP to 80% of the population at highest behavioural risk achieved comparable prevention (4%-8%) at <1% overall coverage, costing $298-$1242 per HIV infection prevented.[94] The study from the US modelled cost-effectiveness reporting that at 10 years, LAI PrEP could achieve an incremental cost-effectiveness ratio of at most $100 000 per quality-adjusted life-year, compared with generic PrEP at a maximum price premium of $3700 per year over generic PrEP (CAB-LA price <$4100 per year).[98]

In a recent preprint research paper that has not yet been peer reviewed, modelling showed that LAI PrEP averted 15%-28% of new infections compared to daily oral at 5%-8%, and cost per infection averted was $4,471-$6,785.[93] This model relied on the need for cost per LAI PrEP dose to be less than twice that of a 2-month supply of daily oral PrEP to remain as cost-effective, with threshold prices ranging between $9.03/injection and $14.47/injection.[93] Another study also stated in its findings that to be considered potentially cost-effective the annual LAI PrEP drug price should be <$16, and/or ART coverage remains at <85% in 2030.[96] This same study concluded that providing LAI PrEP was only cost-effective when drug prices were low, and if low prices aren't feasible providing long-acting PrEP only to women at high risk of HIV infection will become important.[96]

2. Epidemiological Impact

There were seven studies that used mathematical modelling to determine potential reductions of new HIV infections with the availability of LAI PrEP (Table 9). Four of these studies were based in South Africa,[93,95,96,99] one in Kenya,[100] one in the US[101] and one was unknown.[102] Across all studies, potential reduction in new HIV infections were promising. As all studies used different mathematical models to determine predictions of reductions in new infections, they cannot be compared directly. The following will outline key findings of interest.

Predicted reduction rates modelled in South Africa found relatively similar percentages ranging from 10% - 28%.[93,95,96,99] One study predicted that delivering LAI PrEP to 10% of the adult population of South Africa could avert more than 15% of new infections from 2023 to 2050.[103] A research paper from South Africa that has not yet been peer reviewed found a similar result, estimating that LAI PrEP averted 15% - 28% of new HIV infections.[93] One study predicted 21,000 (17,000 to 26,000) or 9.8% (8.9% to 10.6%) of new HIV infections could be prevented by LAI PrEP by 2030.[96] In another South African study using an optimistic scenario where LAI PrEP is 70% effective, LAI PrEP was predicted to prevent 17% of HIV infections in women aged 20 - 29 years over a 10 year period.[99]

Within a study modelled on the HIV epidemic in Kenya, a cascade prevention model predicted that LAI PrEP had a drop-off in HIV infections averted of 95.9% under pessimistic assumptions and 78.6% under optimistic assumptions.[100] There was one study that conducted modelling within a US population and predicted a lower estimate of HIV infections reduced than compared to Sub-Saharan African studies estimated. This study predicted that if 50% of the reference population (MSM from south-eastern US with behavioural indicators for PrEP) used LAI PrEP, 4.3% (95% simulation interval: -7.3% to 14.5%) of infections would be averted over 10 years.[101]

One study used a mosaic effectiveness model to measure effectiveness of long-acting PrEP modalities (e.g. implant, injectable or microbicide) in addition to daily oral.[102] Using mock data, it was predicted that if 40% of the population adhere to daily oral TDF-FTC PrEP and 30% adhere to long-acting PrEP as directed, HIV can be averted by 44 HIV infections per 5,000 person years by TDF-FTC PrEP and 34 HIV infections per 5,000 person years by LA PrEP.[102]

One study from South Africa also modelled the number of deaths averted if LAI PrEP was introduced, finding that compared with no PrEP and standard PrEP with LAI PrEP, 15 and 16 deaths per 1000 women at high risk for infection were averted, respectively, over 5 years.[95]

Table 9 Studies reporting mathematical models of potential impact of LAI PrEP 2015-2022

First Author / Year	*Country*	*Type*	*High-level results*
Glaubius R L 2016 [94]	South Africa	Cost-effectiveness	Compared with no PrEP, prioritized scale-up of RPV PrEP in KwaZulu-Natal could be very cost-effective or cost-saving, but suboptimal PrEP would erode benefits and increase costs.
Walensky R P 2016 [95]	South Africa	Cost-effectiveness Projected Impact	Measured on a lifetime basis, both standard PrEP and long-acting PrEP were cost saving, compared with no PrEP.
Van Vliet M M 2019 [96]	South Africa	Cost-effectiveness Projected Impact	Based on HIV epidemic in Limopo. LAI could prevent 21,000 new HIV infections by 2030 but to be considered cost-effective the annual long-acting PrEP drug price should be <$16, and/or ART coverage remains at <85% in 2030.
Vogelsang M 2020 [97]	South Africa	Cost-effectiveness	Study provides estimates of the incremental cost-effectiveness of providing oral PrEP, injectable PrEP, or a combination of both to heterosexual South African men to assess whether providing PrEP would efficiently use resources.

Jamieson L 2022 [93]	South Africa	Cost-effectiveness Projected Impact	This preprint research paper has not been peer reviewed. CAB-LA is potentially game-changing for HIV prevention. However, for its implementation to be financially feasible across low- and middle-income countries with high HIV incidence, CAB-LA must be reasonably priced.
Neilan A M 2022 [98]	United States	Cost-effectiveness	Compared with generic daily oral PrEP, CAB-LA increased life expectancy among those at very high risk. At 10 years, CAB-LA could achieve an incremental cost-effectiveness ratio of at most $100 000 per QALY compared with generic daily oral at a maximum price premium of $3700 per year over daily oral (CAB-LA price <$4100 per year).
Glaubius R L 2016 [99]	South Africa	Projected Impact	Prioritized scale-up of injectable PrEP among women in KwaZulu-Natal could reduce HIV infections, but suboptimal effectiveness could promote the spread of drug resistance.
Glidden D V 2018 [102]	-	Projected Impact	The ultimate impact of the new product will depend, not on its effect alone, but on its ability to add to a milieu of biomedical preventions by engaging at-risk populations that do not use or desire oral PrEP
Bershteyn A 2020 [100]	Kenya	Projected Impact	Long-acting PrEP had the highest population-level impact, even after accounting for possible delays in product availability, primarily because its effectiveness does not depend on drug adherence.
Maloney K M 2021 [101]	United States	Projected Impact	Aim of paper was to assess the population impact of LAI PrEP when available concurrently with daily oral PrEP using a reference model representing current HIV epidemiology and daily oral PrEP among US MSM.
Smith J A 2021 [103]	South Africa	Projected Impact	If efficacious, a CAB-LA intervention could have a substantial impact on the course of the HIV epidemic in South Africa. Uptake by those at the highest risk of infection, particularly young women, could improve the efficiency of any intervention.
Note: MSM = men who have sex with men, RPV = Rilpivirine, ART = antiretroviral therapy, QALY = quality-adjusted life-year.			

Implementation

There were 32 studies that provided insight into LAI PrEP implementation opportunities and challenges (Table 10). Several insights were taken from LAI ART studies and were included due to the potential learnings and clear similarities between LAI ART and LAI PrEP. In general, authors were in opinion that LAI PrEP was as an exciting new tool to be added to the HIV prevention landscape that offers more choice to patients and potential to improve adherence. Many presented a cautious optimism noting that there were many implementation issues to be addressed including unique management challenges ahead and the need for future implementation research. Of the papers reviewed, the majority were limited to a focus on implementation considerations within the US and within lower income countries, particularly Sub-Saharan Africa. Key learnings presented by authors are thematically described below.

1. Opportunities, Challenges and Considerations for Implementation

1.1 Flexible models of delivery and simplifying administration

The most common implementation opportunity raised by authors was the opportunity to develop innovative and flexible models of LAI PrEP delivery.[57,104-108] [40,107,109-114] Suitability of co-location of LAI PrEP delivery with other health services and simplifying injection administration were described as potential opportunities to increase adherence and uptake. Strategies commonly suggestions by authors included:

- Delivery alongside sexual health clinics and existing contraceptive practices (i.e. contraceptive injections);[57,105-108]
- Delivery within alternative/non-clinical healthcare settings such as: needle syringe programs,[107,108,111,112], drug detoxification centres,[40,107,109] community centres and mobile outreach,[111,112] pharmacies,[83,109] infusion therapy sites,[109] non-public sector facilities,[110] foodbanks,[109] and minute clinics;[83]
- Injection administration by lay providers,[109,115] including nurse-led PrEP delivery,[109,116] and pharmacists;[108-110] and
- Flexible strategies such as: home visits,[109] self-injection,[109] same-day initiation,[108] walk in visits,[108] and telehealth with home testing.[108]

In one study of user experiences of LAI ART, participants reported that ‘frequent clinic visits could worsen HIV stigma and stigmatisation, increase the risk of unwanted disclosures, lead to increased costs from co-pays and travel and may be difficult organise time off work to attend.’[113,114] The author suggested that innovative and flexible modes of LAI ART delivery should be considered to address these concerns and ensure equitable access.[113] This will be particularly important in the US, as one author noted that some health care organisations plan to deliver LAI PrEP in specialised clinics rather than primary care which will create further barriers for users.[108] This may also create the misimpression that PrEP is specialty rather than routine care.[108] Another author noted that ‘lessons from countries in Africa that adopted WHO-recommended task-shifting from physicians to nurses and community-health workers to manage the scale up of ARV treatment could be usefully applied.’[111] It was also suggested that ‘blurring of boundaries represents an opportunity to re-structure patient-focused care,’ however noting that restructuring must be addressed at the systems-level before they can be addressed by individual providers or in clinical settings.[111]

1.2 Learnings from recent biomedical interventions

Investigating and building on the opportunities and challenges experienced in the expansive scale up of other recent biomedical interventions was commonly suggested by authors. Interventions suggested to investigate included:

- Family planning,[117] such as injectable contraception,[110,118,119] long-acting reversible contraceptive,[118] and voluntary medical male circumcision;[110,117]
- HIV treatment and prevention including oral PrEP,[107,110,111,117], treatment as prevention,[117] and prevention of vertical transmission;[110]
- Mental health, including long-acting antipsychotics;[109,118] and
- Testosterone home self-injection.[109]

1.3 LAI PrEP does not require cold chain

Unlike LAI ART, which is a combination of Cabotegravir/Rilpivirine, in which the Rilpivirine component needs refrigeration, LAI PrEP solely consists of Cabotegravir and does not require cold chain considerations. This may have the effect of reducing additional implementation difficulties.

1.4 Strategy formulation

Strategic considerations were also suggested as an important component of LAI PrEP implementation. Authors suggested that ideally, LAI PrEP should be an *additional* choice for HIV prevention, and offered as a first-line choice rather than a restricted second-line option.[120,121] Authors cited learnings from contraception, which demonstrated that more choice allows for more uptake of prevention and adherence,[120,121] and the availability of new PrEP modalities may attract new users.[83] Authors did note that cost will impact this potential.[122]

Clear definitions of implementation targets were discussed by authors. Setting PrEP targets was acknowledged as useful for decision-makers, service providers and data managers to strategise on the direction of the PrEP program.[117] It also supports formulation of strategic prioritisation of where, by whom, to whom, and how services will be introduced and scaled up.[117] Caster et al.[117] suggested the following parameters to define LAI PrEP as a health intervention:

1. Actor (who will deliver each component of the intervention).
2. Action (what each actor does to deliver the intervention).
3. Action target (what is the relevant target for each intervention component).
4. Temporality (when does each component of the intervention occur).
5. Dose (how often is the intervention component provided).
6. Implementation outcome affected (what is the specific outcome each component will affect).
7. Justification (what is the evidence for the intervention component).[117]

1.5 Policy and collaboration

High-quality policy and collaboration were viewed as critical to the implementation of LAI PrEP. Authors suggested the development of the following policies for successful implementation:

- National PrEP policy and guidelines using defined targets and developed through collaborative efforts of healthcare providers, government, pharmaceutical industry, and global agencies;[101,107,122,123]

- Policy innovation that decreases cost related access issues of LAI PrEP (particularly in the US, such as manufacturer assistance program or subscription models);[108,124]
- Public health program planning and financing, including coordination with regulatory agencies for CAB-LA approval;[117]
- Research into health policy initiatives and patent protections including incorporating intersectionality-enhanced frameworks;[112]
- Developing monitoring and evaluation systems to track against targets, and monitor and evaluate for safety, effectiveness and impact;[117]
- National communication strategies ensuring consumer voice in communication strategies and messaging, and health providers voice in science information.[109,117] Creative and evidence-informed communication strategies are recommended including language that uses less biomedical terms, tailoring to low literacy levels, targeted communications (i.e. potential PrEP users and non-typical PrEP providers), and ensuring communications is empowering rather than fear based.[111,119]

1.6 Complexities of LAI - drug resistance and the pharmacokinetic tail end

Authors noted that the pharmacokinetic complexities of LAI PrEP, which require specific strategies to reduce risk for drug toxicity and resistance (i.e. oral lead in, consistent adherence and managing the tail), will pose implementation challenges for the roll out of LAI PrEP.[106,110,120,125] In addition, once current LAI PrEP is administered it cannot be recalled or dialysed, potentially exposing patients to intractable adverse events.[107] Authors have suggested the following implementation considerations to address the pharmacokinetic complexities of LAI PrEP:

- Rigorous and increased laboratory monitoring to identify drug resistance (such monitoring is not routinely performed in current programs);[104,104]
- Appropriate knowledge and counselling around the specifics of LAI PrEP (i.e. when to switch, stop, start, adherence/follow up visits, managing the tail);[111,117]
- Ensuring other prevention methods are available for patients ceasing LAI PrEP;[106,126]
- Managing side effects and reducing discomfort;[104,110] and
- Ensuring continued use and inclusion of oral formulations to ensure safety in the initial phase of LAI use.[117]

1.7 Clinical Support

Several key implementation issues for clinics in planning for introduction, scale up and institutionalisation of LAI PrEP were described. The added burden of increased patient visits and testing, and the management requirements on the health system were the most common clinical considerations for implementation raised by authors.[107,108,111,113,115] Data collected from insights of HPTN083 and HPTN084 reported challenges with the extensive preparation time of injections and highlighted that this challenge could be exacerbated in lower resourced settings.[117] In contrast, findings from implementation studies of LAI ART conducted with US health providers, have shown that workload/time requirement concerns reduced over time.[115,127]

Authors suggested the following clinical planning strategies to assist LAI PrEP implementation including:

- Staff training on administration, guidelines and science behind LAI PrEP,[109,115,117,123,128] including cultural competence training;[118]

- Operational protocols such as prescribing guidelines, screening assessment tools, and patient centred communication tools.[109,111,115,119,128] This will assist in accurate prescribing, and minimising confusion and errors.[90] Other opportunities for clinics include developing information and reminder systems such as desktop/mobile applications to facilitate provision and adherence.[119]
- Planning and ensuring appropriate disposal of biological waste due to increase use of syringes.[117]
- Engaging staff, including clinic administration workers in communication and information about LAI PrEP to patients.[109]

1.8 Prescribing and operational considerations from LAI ART

Prescribing and operational considerations for LAI ART are useful when considering implementation of LAI PrEP, these are described below.

- Risk versus benefit discussions with patients.[129]
- Establishment of guidelines such as patient screening processes and patient flow charts (see NASTAD infographic here).[129,130]
- Consideration of patient psychosocial factors, such as:
    - Patient needs to be contactable;[129]
    - Patient has a means to access medication affordably and consistently;[129]
    - Any transportation or scheduling barriers preventing attendance of follow- up appointments;[129] and
    - Patient being able to adhere will be vital as some may have to return to pills if they forgot a dose or choose to discontinue.[131]
- Consider certain patient populations for whom it may be best to avoid prescribing including:
    - Patients who are pregnant and/or could become pregnant (i.e. of childbearing age and not participating in safe sex practices);[129]
    - Patients with hepatitis B co-infection;[129] and
    - Patients with extended travel plans.[129]
- Planning to address clinic and staff logistics, such as:
    - Staff training for Z-track injection methods;[129]
    - Determining appointment duration, availability of examination rooms, whether walk-ins can be provided and if there will be need to extend clinic hours to accommodate increased patient visit volume;[129]
    - Stock procurement to ensure stable stock access and flow, and determining a system of whether the clinics have their own stock, clinics order in specifically for patients, or whether patients purchase LAI PrEP from general pharmacies/specialist pharmacies;[129] and
    - Consideration of how additional visit volumes may impact frontline registration and support staff, and whether additional staff need to be hired or existing staff are designated to managing administration such as appointment reminders and/or follow-up for missed injection appointments.[129]
- Potential for administration of LAI PrEP by trained laypeople outside health-care settings such as pharmacists, non-clinical staff, peer workers, and family members.[113]
- Addressing structural barriers for patients using LAI PrEP (such as the lack of access to transportation and housing) that may hinder patients from successfully attending required monthly appointments.[109]

1.9 Manufacturing and availability

Authors highlighted that the introduction of a new drug requires new manufacturing capacities to consider within implementation and roll-out.[110] Kanazawa et al.[132] noted that LAI PrEP will be 'less impacted by uptake and adherence, but it is instead dependent on product availability in the short term and retention in the long term' meaning timely product approval and rollout will be critical to maximise the impact of LAI PrEP.[132] In lower income countries, new technologies will need to meet the manufacturing requirements of resource limited settings (lack of cold-chain dependence, cost of manufacturing, safety in pregnancy, and compatibility with tuberculosis medications) to avoid delays in access between high and lower income countries.[104,110,117,133] The importance of partnering with generic antiretroviral manufacturers was also raised.[115]

1.10 Systemic barriers

An important implementation consideration will be acknowledging and addressing systemic barriers that prohibit access to LAI PrEP including: socioeconomic barriers, healthcare and insurance access, medical mistrust, perceived risk, clinical support and wraparound services, caregiving demands, food insecurity, drug use, stigmatisation, transportation, and employment.[112] The cost of LAI PrEP in the US in December 2021 is about 71 times more than generic oral PrEP.[108] Marcus et al. states that in the US, high costs 'will force public and private insurers to restrict access and people without insurance to navigate assistance programmes, which often cover only the cost of medication, and not laboratory testing or provider visits.'[108] Ensuring global availability of LAI PrEP will be important for implementation. Systemic barriers will pose difficulties for accessibility in lower income countries in which, if not addressed, costs, feasibility, and care delivery structure will impact implementation efforts.[110,115]

1.11 Research requirements

There has been clinical efficacy research on LAI PrEP however further research in other domains will be required to support the successful implementation. Research suggested by authors include:

- Implementation science research.[101,115,117,122,125,134,135]
  Specific recommendations by authors include:
  - Integration of social and behavioural scientists (including upskilling of local researchers in LMICs) into clinical trial design and subsequent implementation studies;[112,122]
  - Blending of implementation research into clinical trials earlier, so that the public health community is armed with tested implementation strategies to maximise access and impact when new medications become available;[134] and
  - Optimise the implementation of LAI PrEP in different settings, consider effective service delivery models, and ensure program sustainability.[122]
- Behaviour and social science research.[111,112,136 90,118]
  Specific recommendations by authors include:
  - Expanding scientific understanding of end-user needs, motivations, acceptability, attitudes, intentions, desires, and contexts to improve LAI PrEP product development;[111,123,128,136]
  - Develop tools and approaches to support LAI PrEP regimen choice, use, and care retention;[136]

  - Advance innovative healthcare delivery models to maximise equitable access and reduce complexities of LAI PrEP;[108,136] and
  - Address access and uptake within healthcare settings, and potential for unconscious and implicit biases in provider decision-making and behaviour.[112,128]
- Safety studies with priority populations not traditionally included in trials such as:
  - Pregnancy,[111,120,123,125]
  - Breastfeeding,[111,123,125]
  - Infants and children,[111,123]
  - Adolescents,[111,123,125,137]
  - Trans and gender diverse individuals,[111]
  - People experiencing homelessness,[123]
  - Injecting drugs users,[111,123] and
  - Sex workers.[111]
- Modelling studies on epidemiological and economic impact of LAI PrEP on various communitties.[108,110]
- Studies to identify the risk of CAB resistance[105] and effects of long-term use.[105]

Other future research raised for LAI ART that will also be useful for LAI PrEP contexts, include research that:

- Explores barriers contributing to poor adherence;[131]
- Identifies alternative injection sites (i.e. develop subcutaneous injections) to allow self-administration and allow LAI PrEP to be accessible to patients with buttock implants and/or fillers (who were excluded from the clinical trials);[122]
- Develop low volume injections to decrease pain;[131]
- Supports decentralisation of LAI PrEP service delivery through expansion to lay providers.[122,138]

Table 10 Studies reporting implementation considerations of LAI PrEP 2015-2022

First Author / Year	Themes covered
Glidden D V 2020 [139]	Statistical and design issues in developing LAI products for HIV prevention and treatment.
Azhar S 2021 [140]	Reaching priority populations (racial/ethnic minorities) in research.
Morton T 2021 [136]	Research gaps that behavioural and social science research can address to strengthen future use of LAI treatment and prevention.
Kerrigan D 2018 [90]	Need for guidelines to assist patient decision-making. Research gaps on the acceptability of CAB-LA among men and women at higher risk for HIV in different settings.
Xavier Hall C D 2021 [119]	Implementation opinions from providers including population targeting, communication strategies, guidelines, and a need for further interventions to facilitate provision, and adherence.
Landovitz R J 2016 [106]	Highlights the investment required to deploy and scale up LAI PrEP in South Africa, issues of toxicity and the potential to combine an injectable contraceptive with long-acting injectable PrEP.
Barnhart M 2017 [104]	Highlights the pros and cons of long-acting HIV treatment and prevention. Author suggests for further implementation to explore improving injection approaches such as simplifying administration, reducing cost and discomfort. Important to consider the needs of lower-income countries from the start to ensure LAI PrEP is implemented in a feasible, affordable, and accessible way. Medications to meet requirements for lower resource settings to avoid delays between high-income and low-income access.
Benitez-Gutierrez L 2018 [133]	Highlights the importance for LAIs to be implemented in a feasible, affordable and accessible way, particularly in lower-income countries.
Czarnogorski M 2019 [134]	Author suggests that by using more hybrid implementation-effectiveness study designs in phase III trials, researchers can accelerate the availability of implementation data closer to the initial introduction of novel treatments into community settings.

Nachman S 2019 [123]	Discusses need to focus on strategies and principles to ensure that the needs of children, adolescents, and pregnant and lactating women are considered when developing long-acting formulations. Research should focus not only on how best to transition long-acting products to these populations but also on early engagement across sectors and among stakeholders.
Mugwanya K K 2019 [121]	Author discusses the potential impacts and challenges of increased PrEP modalities in particular CAB-LA as PrEP noting that user preferences will vary, across individuals and populations, and if multiple PrEP options can be developed, the result will be increased reach, coverage, and impact.
Scarsi K K 2020 [120]	Author discusses the issue with the pharmacokinetic tail of CAB-LA and notes that it must be considered during the implementation of LAI PrEP. Emphases the important of understating safety of LAI drugs during pregnancy and the vitalness to have systematic collection of data. Suggests CAB-LA will not be suitable for everyone and that we should be moving away from a one all approach with HIV.
Bavinton B R 2021 [141]	Further research required to understand long-term patterns of PrEP use and what people at risk of HIV want in a product. The long delay between efficacy evidence and scale-up, as occurred with daily oral PrEP, must be avoided.
Cohen M S 2021 [142]	Discusses how there may be increased benefit of LAI PrEP beyond adherence as novel agents and delivery methods may attract new PrEP users. Notes that modelling studies of PrEP shine a light on the benefits and limitations of the intervention and on new agents such as CAB-LA, but they are perhaps too narrow in their scope.
Karim Q A 2021 [143]	Suggests strategies to increase LAI PrEP use such as innovative outreach services and need for real world implementation studies. Also highlights drug resistance concerns for LAI users who discontinue use or are not adherent to injections.
Boffito M 2022 [115]	Highlights need for efficacy research in other minority populations and for implementation research. Discussion of potential challenges to implementation of LAI PrEP.
Hojilla J C 2022 [113]	Opportunities for innovative delivery and outreach services within non-healthcare settings. Challenges and learnings from LAI ART for implementation discussed. Need for inclusion of other priority populations such as pregnant women, youth and people experiencing homelessness.
Sharfstein J M 2022 [124]	Raises issues of prohibitive costs and that the potential for public health benefit can be jeopardized by the cost and complexity of the US health care system. Also calls for policy innovation in regard to the introduction of CAB-LA.
Marcus J L 2022 [108]	Highlights structural changes needed in the US to increase cost, access and equity of LAI PrEP for all minority populations.
Mudzingwa E K 2022 [105]	Further research needed of the long-term effects of CAB-LA and to investigate the risk of CAB resistance in real-world settings with non-optimal adherence. Once implementation strategies around the required oral lead-in period are optimised, CAB injections could be easily administered alongside existing contraceptive injections.
Meyers K 2015 [111]	Importance of addressing implementation issues at three levels: patient, provider, and system.
Myers J 2015 [135]	Implementation of LAI PrEP must consider lessons and possible solutions from injectable contraception.
Nyaku A M 2017 [107]	Discusses challenges and requirements of LAI PrEP.
Kapogiannis B G 2018 [137]	Inclusion of adolescents in research and implementation studies.
Goedel W C 2019 [118]	Highlights need for acceptability research, learning from LAI contraception, incorporating clinical cultural competence and reducing costs to promote patients making non-financial choices.
Castor D 2020 [117]	Suggest the use of implementation science frameworks and investigating individual-level, population-level, and health systems-level opportunities and challenges. Learnings from previous scale up of other biomedical interventions (i.e. LAI ART, oral PrEP, LAI contraception).
Meyers K 2020 [128]	Highlights the need for provider training including developing tools to support patient-centred communication. Intervention research and research into understanding affective processes impacting PrEP attitudes and intentions.
World Health Organization 2020 [125]	Safety studies in adolescents, among pregnant and breastfeeding women are needed. Open-label extension studies will need to be considered to understand the most effective and acceptable implementation approaches. Also discusses the need for research on real-world implementation issues such as issues with the pharmacokinetic tail.
Chandiwana N C 2021 [110]	Uncertain costing, scale-up manufacturing, complex delivery systems and implementation challenges are potential barriers when considering the scalability of long-acting ARVs for global use.
Howe Z W 2021 [129]	Discussion on implementation considerations and logistical challenges of LAI ART. Clinics will need to address barriers related to management of clinic workflow, procurement, reimbursement, and nonadherence.

Kanazawa J T 2020 [132]	Discussion on implementation considerations of LAI ART. Authors used PRISM implementation science framework and results posed multiple questions for consideration in the development of an optimal implementation strategy for LAI ART in the US. These questions revealed the necessity for more data, including acceptability of LAI ART among many different subgroups of people living with HIV, cost effectiveness, patient satisfaction, and patient-reported outcomes, as well as more detailed information related to the external environment for optimal LAI-ART implementation.
Ariyo O E 2022 [131]	Discussion on implementation considerations of LAI ART.

2 Implementation learnings from injectable contraception

Looking to learnings from other LAI biomedical interventions to assist informing implementation considerations for LAI PrEP was recommended by multiple researchers during this review, in particular, learnings from injectable contraception (known as the Depo shot). Table 11 outlines the key learnings from injectable contraception that may be relevant for informing LAI PrEP. Most of these learnings have been informed by Julie E Meyers, Tanya M Ellman and Carolyn Westhoff's 2015 review '*Injectable agents for pre-exposure prophylaxis lessons learned from contraception to inform HIV prevention'* as well as various other referenced sources.

Table 11 Key learnings from injectable contraception

Theme	Learning
More contraceptive choice generated increased use	Expansion of contraception modalities (i.e. oral pills, condoms, injectables, IUDs, vaginal rings, implants) has been recognised by family planning research as a key factor associated with increased uptake and use of contraception over time. Choice allows for more individual preferences with different products appealing to different populations over the reproductive lifetime. Comparatively to HIV prevention, availability of multiple modalities would result in greater acceptability and uptake with users able to tailor methods to their prevention needs.[111]
Success of nurse-led task sharing	In the contraception field nurses provide almost all contraception services, with experience in providing many contraception modalities (such as oral pills, injectables, vaginal rings and implants) in multiple settings.[116] Within the HIV prevention field, nurse expertise and experience could be built on allowing authorised nurses to deliver LAI PrEP.[116]
User-dependant vs provider-dependant	Within the contraceptive field there is a distinguishment between user-dependent (e.g. pill, condom) and provider-dependent (e.g. injectables, IUDs) modalities. Research supports increased adherence thus significant reduction in failure rates among provider-dependant modalities. This would also be the case for LAI PrEP and as described by Meyers & Golub 'adherence may be operationalized as "retention in care," and will not depend on day-to-day behaviour, but on navigation of health care systems and related contexts.'[111]
Highly acceptable but acceptability research required	LAI contraception acceptance was rapid after it was introduced.[135] Common patient reported benefits included high praise for its efficacy, convenience and privacy/confidentiality it provided to women.[135] There will be clear similarities in benefits for LAI PrEP users but extensive acceptability work will be important and required in parallel to LAI PrEP product development.[135]
Discontinuation is high and longer duration products are optimal	One large-scale study in 2011 in the US reported over 40-60% of participants discontinued LAI contraception in the first year.[144] A common reason for discontinuation was due to menstrual disruption, which is not an issue for LAI PrEP, however the need for frequent reinjection in clinical settings was noted by Meyers et al. as likely also contributing to high discontinuation rates.[144] It is important to note that 2008 data from the US pharmacy databases show that these continuation rates are not much higher than other contraceptives including the oral pill.[145] Myers et al. suggests from these findings that 3-monthly intervals may be too often and LAI contraception products that offer longer duration (such as one year) may be more optional for consumers.[135] This is likely to be a similar preference for individuals using LAI PrEP which is a shorter duration of every two months.
Prioritisation to reach vulnerable populations	Ensuring LAI PrEP access to the most vulnerable populations will be essential as difficulty providing access to the most vulnerable populations in need of LAI contraception have limited its impact.[135] This is evident as Myer et al. explains that discontinuation of LAI contraception is higher among the lowest income women, possibly meaning that poverty may decrease access to reinjection visits.[135] It will be important to develop strategies to reduce these barriers particularly around cost to support LAI PrEP users to continued access.
Gaps in data on provider attitudes	There is scare data on provider attitudes towards LAI contraception. LAI PrEP researchers should prioritise future research in this area to not replicate these gaps.

HIV risk limits uptake of LAI contraception	One of the greatest barriers to further scale-up of LAI contraception is the ongoing controversy about whether it increases risk of HIV acquisition.[135] Research knowledge on significant risks in associated with LAI PrEP (one study of PrEP providers[92] mentioned sub-Sharan African women will want to know LAI PrEP won't increase or decrease fertility as this could be a potential barrier to uptake) will be vital to address to support scale up efforts.
There is high appeal to offer alternative injection administration	Expert opinion in the contraception field suggests that subcutaneous formulations allowing self-injection or pharmacist administration outside of clinical settings would be 'game-changer'.[135] These alternative injection administration opportunities have also been raised by multiple experts within HIV prevention for LAI PrEP.
Interventions to improve continuation rates have been unsuccessful	Various interventions to improve continuation (including intensive reminders for upcoming repeat injections) have been ineffectual with the exception of one study,[146] using an intensive, structured counselling intervention that addressed menstrual irregularities.[135] This knowledge can be used to inform LAI PrEP continuation interventions.

3. Implementation science trials for LAI ART

3.1 CUSTOMIZE – Clinical Trial

CUSTOMIZE is a phase IIIB-hybrid III implementation study that was conducted between 2019 and 2022 to identify and evaluate strategies for successful implementation of the Cabotegravir + Rilpivirine long-acting injectable (LAI ART) regimen in the US. Recent results were presented at the 11th IAS Conference on HIV Science in 2021 by Maggie Czarnogorski. At this point in time (August 2022) no published papers on findings of this study were found. Findings reported results from interviews and surveys (at baseline, month 4 and month 12) with patients and health staff (including clinics, nurses/injectors and front desk staff/administrators) from eight clinics across the US.[134] Overall, healthcare staff found LAI ART acceptable, appropriate, feasible, and sustainable to implement across diverse US clinic types, with most feeling that optimal implementation was achieved in one to three months.[134] Patients reported minimal barriers to receiving LAI ART and 94% preferred LAI ART over oral dosing for HIV ART.[134] Further key results presented by Czarnogorski are outlined in Table 12.

Table 12 Key results from the CUSTOMIZE trial presented at the 11th IAS Conference on HIV Science in 2021 by Maggie Czarnogorski

Theme	Learning
Provider concerns reduced over time	As perceived by healthcare staff, all barriers to implementation (top three included ability of patients to keep monthly visits, obtain transportation and flag missed visits) decreased by month 12 except for patient/injection soreness.
Optimal implementation was achieved in 1–3 mths	78% of healthcare staff felt optimal implementation was achieved in 1 to 3 months.
Patients reported low interference with ability to receive LAI ART	Participants reported fewer factors interfering with their ability to receive LAI ART compared with healthcare staff. At month 12, 74% of participants reported that nothing interfered with their ability to receive LAI ART.
Most common factor interfering with ability to receive LAI ART was injection pain or soreness	The most reported factor for interfering with participants ability to receive injections was injection pain or soreness (15%).
Monthly visits were seen as positive for healthcare staff	70% of healthcare staff interviewed at month 12 expressed that monthly visits added benefit for patients. Benefits included: improving patient engagement and relationship with providers; discussing and/or screening for STIs; patients becoming more aware of their health; addressing issues such as adverse events; monitoring higher-risk patients; counselling patients about alcohol; and reminding patients about routine care.
Key educational and support items for patients	At month 12, participants endorsed the following as very or extremely useful: verbal information (98%); information and resources (89%); reminder calls (88%); and reminder text messages (80%).

Key strategies for successful clinic implementation	1. Good staff communication 2. Teamwork 3. Use of web-based treatment planner.
Key implementation strategies for patient adherence	1. Good communication about dosing window 2. Effective appointment reminder systems 3. Designated staff for appointment tracking.
Clinicians may have underestimated adjustments required to facilitate LAI ART	High feasibility score at baseline with slight decrease at month 4 due to healthcare staff realising some adjustments may be needed in the clinic but by month 12 feasibility scores increased demonstrating that after a few months of initial implementation support, healthcare staff found ART to be very feasible in clinics.
Key changes made by clinics	Infrastructure changes: extended clinics hours; increased coordination with other departments; purchased new refrigerators; and sourced available room space. Attitude changes: mitigated concerns regarding leadership support; a good tracing and reminder system addressed concerns regarding patients keeping their appointments; short wait times and increased patient-provider touchpoints eased concerns regarding length of injection visits and patients' zealous acceptance of treatment was a great surprise.
Summary of best practices implemented by clinics	• Calling the patient 2 days after the first injection to check in is reassuring to the patient and clinic staff. • Adding the Physician in Charge to their morning huddles, • Utilising telehealth portal to send videos and product information to patients. Scheduling visits as far out as the clinic schedule allows. • Booking >1 month in advance to prevent frequent overbooking. Designing their own EMR template for injection visits. • Designating before and after-hours time slots for walk-in injections for people who must reschedule a visit.

3.2 CARISEL- Clinical Trial page

CARISEL is the European companion study to CUSTOMIZE and is also an open-label, hybrid type phase IIIb trial evaluating implementation strategies for long-acting Cabotegravir/Rilpivirine administered every two months in select European healthcare settings. The one-year study was launched after CUSTOMIZE in late 2020. It's aim is to build on the body of evidence collected in the US by spanning the study across 18 diverse practice sites throughout different healthcare systems in France, Spain, Belgium, Germany, and the Netherlands. Results will evaluate both qualitative and quantitative measures across arm, clinic type, provider type, and country to determine the most effective implementation strategies and to identify barriers, facilitators, and solutions.[147] In addition to findings on implementation, clinical data on the efficacy and safety of Cabotegravir/Rilpivirine will be evaluated.[147] As of August 2022, results are yet to be released.

Discussion

This review summarises the recent studies exploring acceptability, willingness, preferences, and implementation for LAI PrEP among populations at risk of HIV infection. Overall, 121 studies were included, providing a strong breadth of research as a strength of this review which aimed to identify key studies related to LAI PrEP. Limitations of this review is that it was not undertaken as a comprehensive systematic review but rather a scoping review to assist knowledge transfer and discussions about implementing LAI PrEP in Australia.

Findings on interest and willingness to initiate or switch to LAI PrEP were generally high among priority populations for HIV prevention. LAI PrEP was often listed as the preferred choice over other PrEP modalities particularly among MSM from the US and women from Sub-Saharan Africa. Potential LAI PrEP end-users described LAI PrEP as a convenient alternative to a daily oral pill. This simplicity coupled with the high rate of efficacy and improved adherence benefits of LAI PrEP were listed as influencing end-users' preferences. Privacy and discreteness offered by LAI PrEP was an important factor, particularly for women.

These results can inform health professionals that there may be considerable demand for LAI PrEP. It will be important to consider if these findings on interest, willingness, and preference results, in reality, will translate into tangible uptake and continued use of LAI PrEP. It is also important to note that most of these studies didn't include or describe the potential complexities of LAI PrEP use to participants, such as the oral lead in and pharmacokinetic tail. This could further altercate correlations between LAI PrEP interest, willingness, and preferences with real-world uptake and adherence. Encouragingly, results from acceptability studies based on participants from the LAI PrEP clinical trials found that LAI PrEP was highly acceptable among users, but strategies to address injection site pain will be important. There were notable gaps in research among perceptions and opinions of PrEP providers of LAI PrEP. Provider knowledge with local and international collaboration and engagement will be vital for successful roll out and implementation of LAI PrEP.

Extensive learnings and insights were explored highlighting the vast amount of implementation considerations required to successfully roll out and scale up LAI PrEP. These will include: introducing strategies to adopt flexible models of delivery and simplification of LAI PrEP administration; defining strategies policies, and collaboration; addressing complexities of drug resistance and the pharmacokinetic tail; high-level planning for clinical support; prescribing and operational considerations for clinicians and clinics; manufacturing logistics; addressing systemic barriers for consumers; and future research requirements. Learning and building on the evidence from other recent biomedical interventions such as injectable contraception and LAI ART implementation science results from the CUSTOMIZE study are valuable to inform implementation considerations for LAI PrEP. Once published, findings from the CARISEL study will be useful due to the closer comparison between European health systems and the Australian health system.

This scoping review identifies and summarises the types of available evidence on acceptability, willingness, preferences, and implementation of LAI PrEP. LAI PrEP has the potential to rejuvenate the HIV prevention landscape in Australia and worldwide by offering more choice to those at risk for HIV and increasing the number of people taking PrEP. These potential benefits of LAI PrEP need to be prioritised to allow momentum towards the elimination of HIV transmission. It will be critical to look to the available evidence within this review to inform health professionals and ensure Australia is ready for the introduction of LAI PrEP.

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