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Advancing use of long-acting and extended delivery (LAED) HIV prevention and treatment regimens

Guest Editors: José A. Bauermeister, Sinéad Delany-Moretlwe, Charles Flexner
Supplement Editor: Alberto Rossi

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EDITORIAL

Advancing use of long-acting and extended delivery HIV prevention and treatment regimens

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Long-acting and extended delivery (LAED) HIV treatment regimens are becoming increasingly accessible to consumers. After more than a decade of clinical research, long-acting antiretroviral formulations have been approved for treatment and prevention [1, 2]. Long-acting injectable cabotegravir (CAB)-rilpivirine has begun to receive regulatory approval for HIV treatment across the globe, including the United States, the UK, Europe, Australia and Canada. Similarly, new LAED regimens are securing regulatory approval for HIV prevention. A monthly dapivirine vaginal ring (DVR) for women at high risk for HIV acquisition has received regulatory approval in several African countries, a positive opinion from the European Medicines Agency, and is under consideration by other regulatory agencies. Following the successful HPTN 083 and 084 trials, the U.S. Food and Drug Administration approved a bimonthly injection of long-acting injectable CAB for Pre-Exposure Prophylaxis (PrEP) in 2021 [3], with subsequent approvals being secured or pursued across other countries. The United States Agency for International Development is supporting large demonstration projects for both the DVR and CAB to facilitate rollout in multiple sub-Saharan African countries. These strategies represent the forefront of numerous new LAED product candidates and delivery strategies now advancing in early-stage development or clinical trials.

LAED regimens have the potential to reshape the HIV treatment and prevention landscape through dosing schedules that are measured in months rather than days. To realize their maximum impact, it is important to recognize that product innovations in HIV and other areas of medicine face a variety of challenges when moving to wide-scale implementation [4, 5]. An instructive example is found in oral PrEP [6, 7], where meaningful access and use have lagged regulatory approvals in many settings due to patient, provider and healthcare system factors. Steep inequities in uptake and early discontinuation continue to limit the global public health impact of oral PrEP.

There are questions about whether future LAED regimens could face similar challenges in their delivery, uptake and persistent use, as well as concerns about facilitating access in resource-constrained environments and in key populations. LAED regimens have the potential to overcome many of these challenges, but questions remain about how best to offer HIV prevention and treatment choices, how to manage product switching and what constitutes optimal service delivery while using LAED products. For this supplement, we invited scholars to submit multidisciplinary articles designed to advance the development, future use and equitable delivery of LAED regimens for HIV prevention and treatment. We received several abstracts spanning original research, commentaries, reviews and viewpoints. After careful review and deliberation, the editorial team selected 16 contributions that illustrate current LAED advances and challenges to improve the development, retention and equitable delivery of LAED regimens across low-, middle- and high-income countries.

Users' desires and choices may also impact LAED uptake and persistent use. As illustrated by the studies included in the first section of our supplement, a deeper understanding of end-users' preferences can guide the development of new LAED and service delivery models and emphasize their significance in creating demand for LAED products.

Graham et al.'s [8] study examined the preferences for potential long-acting antiretroviral therapies (LA-ART) regimens among people with HIV in the United States. Using a discrete choice experiment, they found that LA oral tablets were the only mode preferred over the current daily oral treatment. Annual implants and injections were the next most preferred LA-ART options. Longer time between doses was preferred, and administration at home was preferred to clinics, which were preferred to pharmacies. Future research should investigate the sources of preference heterogeneity and actual uptake of and adherence to LA-ART products when available.

Biello et al.'s [9] research article focused on the correlates of preferences for next-generation HIV prevention products among a national U.S. sample of young men who have sex with men (YMSM). Given the low uptake of daily oral PrEP, it is essential to understand end-users' preferences and concerns about PrEP products to ensure high acceptability and penetration. In a series of conjoint analyses, participants prioritized efficacy, absence of side effects and costs when considering different PrEP products. Interestingly, their analyses found that age, insurance status, sexual behaviour, PrEP use history, HIV and Sexually Transmitted Infections (STI) testing

history, and STI diagnoses influenced YMSM's decisions to prioritize next-generation modalities over daily oral PrEP.

Finally, Lorenzetti et al.'s [10] review examined the values and preferences regarding the use of injectable PrEP to prevent HIV acquisition. Their review highlighted that there is often a preference for injectable PrEP across populations, but variation within and across groups and regions was also observed. While many stakeholders indicated that injectable PrEP could help address adherence challenges associated with daily or on-demand dosing for oral PrEP and may be a better lifestyle fit for individuals seeking privacy, discretion and infrequent dosing, end-users identified concerns related to injectable agents, including fear of needles, injection site pain and concerns about body location for the injections, logistical challenges and waning or incomplete protection.

Taken together, these studies underscore the importance of acknowledging choice as a key tenet of the increasing availability of HIV prevention and care products and ensuring that programmes help address users' needs and concerns to maximize their appeal and behavioural congruence.

For LAED to achieve its potential impact on the HIV epidemic, it needs to reach populations with the greatest need. These populations often face disparities in health access, either within countries or regions where health resources are limited. Mgodi and colleagues' commentary [11] focuses on these challenges and provides recommendations to advance the use of LAED for HIV prevention and treatment in sub-Saharan Africa. In addition to discussing concerns about LAED costs, they highlight the need to train and retain more healthcare providers, implement task shifting, invest in healthcare infrastructure and integrate healthcare services. They call for innovation in laboratory diagnostics and the development of non-injectable long-acting formulations for the region.

Recognizing these constraints, four manuscripts focus on cost considerations as a critical barrier to access and discuss strategies that can be leveraged to overcome these challenges. Gaayeb and colleagues [12] discuss voluntary licensing ahead of patent expiry as a strategy to accelerate access to affordable HIV treatment and prevention products. They propose 10 enablers of voluntary licensing of Intellectual Property (IP) rights, with special consideration given to early identification of products designed for low- and middle-income country contexts, technology transfer and innovative partnerships for product development, strategies to optimize regulatory review and de-risking mechanisms.

Meyer-Rath et al. [13] extend this focus on cost and access by considering demand and supply-side factors that can accelerate CAB access in low- and middle-income countries, using South Africa as an example. They argue that guaranteed market volumes based on stimulating and sustaining demand for HIV prevention products like CAB through scaled-up national programmes can encourage price reductions if coupled with expanded manufacturing capacity.

Jenkins et al. [14] echo many of these sentiments in their roadmap for investment decision-making and product introduction based on learnings from product introduction models for contraceptives, Tuberculosis (TB) treatment and dolutegravir. They reiterate the importance of partner alignment, the need for advance preparation by national programmes with a focus on policies and guidelines, the importance of community engagement to ensure demand and acceptable service delivery models, the critical role of generic manufacture and expedited regulatory reviews. Castor and colleagues [15] supplement our understanding of cost barriers through a scoping review that analyses PrEP cost study data and identifies gaps in cost information for implementation domains. The authors argue that limited cost information has the potential to undermine product introduction and scale-up in access. In situations where resources and budgets are constrained, greater consideration may need to be given to budget allocation to priority implementation domains that can yield health system efficiencies.

Warren et al. [16] emphasize the importance of accelerating the design of CAB implementation studies that adequately address priority knowledge gaps. As additional long-acting HIV prevention products become available over the next 5 years, the delivery of multiple regimens may become more complex. Therefore, expanded stakeholder engagement and ongoing coordination with the WHO will accelerate the adoption of evidence-based policies and wide-scale implementation, and lessons from the Biomedical Prevention Implementation Collaborative (BioPIC) may inform strategies to introduce these new long-acting HIV prevention products across settings. These considerations must also align with a country's HIV epidemiologic profile. Stansfield et al.'s [17] research article highlights how high PrEP coverage with CAB-LA might substantially reduce HIV in settings that experience high HIV incidence. However, the paper also serves as a reminder that LAED regimens may not be a silver bullet and that careful consideration of the epidemiological context is essential as part of the introduction and scaling of LAED regimens.

Ongoing research and evaluation will help inform best practices as the menu of HIV prevention and care regimens is implemented and scaled. As the final section of our supplement highlights, these efforts will require multisectoral partnerships throughout the LAED development and dissemination pipeline and must ensure that all communities who could benefit from LAED regimens are included and represented.

Kim et al. [18] argue that there is a need for a robust, multidisciplinary research agenda that produces additional long-acting treatment options, in addition to strategies that support their effective and equitable use. A robust and multilevel LAED research agenda will require multisectoral partnerships to advance innovations in long-acting regimen development, clinical monitoring, behavioural support interventions and implementation science.

Grimsrud et al.'s [19] commentary reminds us that the development of new LAED should be based on consideration of how people currently receive HIV treatment and prevention services, if we are to achieve improvements in access and outcomes. Future positioning of treatment and prevention LAED is likely to be different. For treatment, LAED regimens may address challenges with adherence, but their delivery should provide clear advantages over existing oral products to be scaled. For prevention, LAED regimens expand a potential PrEP user's choice of methods, but like other methods, they need to be delivered in a manner that allows for re-initiation for individuals whose risk profiles may vary over time.

Celum et al.'s [20] commentary reinforces the importance of learning lessons from oral PrEP as we consider how to

optimize the delivery of long-acting PrEP methods. Strategies that expand PrEP delivery options, including telePrEP, pharmacy-based PrEP, key population-led services and mobile venues, need further evaluation. Integrated delivery models that include STI testing and treatment, contraception for people not desiring to become pregnant, PrEP for pregnant women in high HIV prevalence settings, and gender-affirming hormones and support for transgender persons are needed. The lessons learned from the delivery of oral PrEP about demand creation, informed client decision-making, provider training, adherence support and service delivery models are relevant to the delivery of long-acting PrEP and integration with other services.

Three manuscripts serve as a reminder to ensure that the benefits of LAED accrue to populations that are frequently left behind. Hosek et al.'s [21] viewpoint reminds us that the needs of LAED regimens must be centred around the needs and experiences of adolescents and young adults. Given the persistent disparities in HIV outcomes among youth, the authors renew a call to support the development, effective implementation and equitable delivery of LAED products for HIV prevention and treatment by aligning new technologies with existing youth-focused programmes. White et al.'s [22] viewpoint also notes the importance of including pregnant and breastfeeding people in trials of novel LAED PrEP agents, and discusses the work needed to overcome community and regulators' concerns about the inclusion of pregnant women in trials. Success in the development and implementation of LAED requires partnership with communities to build confidence and foster inclusion of populations traditionally regarded as vulnerable. Gandhi et al.'s [23] viewpoint reflects the challenge of evaluating LAED in viraemic patients who experience adherence challenges for social and structural reasons. The authors argue for a new approach to trial design that would allow evaluation of LAED in this population and aid in implementation in real-world settings.

Taken together, the contributions to this supplement highlight the opportunities and synergize the rollout and scale-up of LAED regimens across the globe. The manuscripts in this supplement note how structural, policy, community and healthcare contexts might facilitate or hinder the delivery of LAED regimens. Like other prevention and care efforts, the success of LAED regimens will require countries to allocate the appropriate resources required for a tailored strategy that maximizes LAED access and persistent use among its constituents. As illustrated by the manuscripts in this supplement, these tailored efforts will require an understanding of users' needs across settings, collective buy-in from stakeholders and communities, and comfort in creating evidence-based implementation guidelines to support patients' switches between HIV prevention and care regimens. Moreover, while the existing data indicate the potential of LAED regimens to help achieve global HIV prevention and care goals, continued investments are needed to ensure equity in access among key populations. LAED regimen research with understudied and/or excluded populations should remain a priority to ensure their inclusion in regulatory guidelines. We hope that the key considerations raised in this supplement will serve to advance the field as existing and emerging LAED regimens are approved and implemented.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

JAB and SD-M contributed to the initial draft of the manuscript. CF provided feedback, reviewed and edited the draft, and approved the final version prior to submission.

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RESEARCH ARTICLE

U.S. patient preferences for long-acting HIV treatment: a discrete choice experiment

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Abstract

Introduction: Recent advances in long-acting antiretroviral therapy (LA-ART) could provide new options for HIV treatment and reduce adherence barriers, if regimens are acceptable to patients. We elicited preferences for key attributes of potential LA-ART regimens among people with HIV (PWH) in the United States, focusing on four treatment modes (oral tablets, subcutaneous injections, intramuscular injections, and implants), product characteristics and location of administration.

Methods: A discrete choice experiment was conducted among PWH aged ≥18 years recruited from HIV clinics in Washington State and Atlanta, Georgia from March 2021 to June 2022. Participants responded to 17 choice scenarios, each with three options: two systematically generated hypothetical LA-ART regimens and a constant opt-out (their current daily oral treatment). LA-ART regimen descriptions included treatment mode, pain, dosing frequency, location, pre-treatment time with undetectable viral load, pre-treatment negative reaction testing and "late-dose leeway" (i.e. flexibility or forgiveness in timing the next dose). We used conditional logistic regression, with an interaction between treatment mode and pain, to estimate preference weights for all attribute levels.

Results: Seven hundred participants (350 at each site) enrolled, with median age 51 years (range 18–73); 70% identified as cisgender male, 24% as cisgender female and 6% as non-binary or transgender. LA oral tablets were the only mode preferred over current daily oral treatment, with annual implants and injections the next most preferred LA-ART option. Longer time between doses was preferred, and administration at home was preferred to clinics, which were preferred to pharmacies. Attributes with less impact on preferences included oral lead-in treatment to achieve viral suppression or test for negative reactions and late-dose leeway around the prescribed dosing interval. Participants in Atlanta were more likely to prefer their current daily oral ART than participants from Seattle.

Conclusions: PWH in the United States may soon have several options for LA-ART. Our results suggest that LA oral tablets will be preferred by many patients over their current daily oral treatment, while implants and injections with longer duration may be acceptable to some. Future research should investigate sources of preference heterogeneity and actual uptake of and adherence to LA-ART products, when available.

Keywords: antiretroviral agents; antiretroviral therapy; choice behaviour; delayed-action preparations; HIV; patient preference

Additional information may be found under the Supporting Information tab of this article.

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1 | INTRODUCTION

In 2020, the Centers for Disease Control and Prevention estimated that for every 100 people who were diagnosed with HIV, only 74 had received HIV care and 65 were virally suppressed, based on their most recent viral load result [1]. Disparities in U.S. HIV care cascade outcomes (i.e. HIV diagnosis, engagement in care and viral suppression) have been reported among adolescents and young adults [2, 3], Blacks [2–5], Hispanic persons [6], injection drug users [3], women [3], heterosexual men [3, 4], foreign-born persons [4] and those of low socio-economic status [3]. New approaches to optimizing antiretroviral therapy (ART) uptake, adherence and retention are clearly needed, in order to overcome challenges that undermine treatment success, such as HIV stigma, treatment fatigue, missed visits or refills, forgetfulness and side effects [7–9].

Recent advances in long-acting antiretroviral therapy (LA-ART) could provide new options for HIV treatment and reduce adherence barriers, if regimens are acceptable to

patients. Initial results from the first LA-ART regimen to reach the market have been promising. In the LATTE-2 randomized, open-label phase 2b trial, participants were randomly assigned (2:2:1) to receive two intramuscular injections of long-acting cabotegravir plus rilpivirine at 4- or 8-week intervals or a comparable daily pill-based regimen [10]. The regimen at either frequency was as effective as daily oral combination therapy at maintaining HIV viral suppression through 96 weeks [10]. This regimen was well accepted and tolerated, with 97% of 254 participants reporting 5 or 6 on a 6-point scale of treatment satisfaction and 99% stating they would be "highly satisfied to continue" their long-acting injectable (LAI) ART [10]. In a qualitative study associated with this trial, 39 in-depth interviews were conducted with participants and providers from the United States and Spain [11]. Despite commonly experienced injection site reactions [10], participants were generally tolerant of the regimen, finding injections convenient, with reduced potential for HIV disclosure and elimination of the "daily reminder of living with HIV" [11].

Due to the early success of the cabotegravir/rilpivirine regimen, research on patient acceptance and preferences has focused on injectable regimens. For example, Williams and colleagues surveyed 400 adults taking daily ART at two clinical sites, reporting that 61%–85% would "definitely or probably" try LAI ART, depending on the dosing interval, with over one quarter saying they would try an injectable regimen even if it cost "much more" than their current regimen [12]. In a survey conducted by an Italian patient advocacy group [13], Rusconi et al. reported that 55% of the 488 respondents knew about LAI ART and 83% would appreciate not taking pills on a daily basis. Furthermore, 30% said they would benefit even if hospital-based injections were required every month and an additional 39% would benefit if hospital-based injections were required every 2 months [13]. While the injectable cabotegravir/rilpivirine regimen was first on the market, a number of promising LA-ART products are in development that could result in effective combination regimens with less frequent administration, fewer injections or other potential advantages [14]. Our recent interviews with key informants involved in HIV drug development and clinical trials revealed that experts thought implants, subcutaneous injections and long-acting oral tablets could also become available for HIV treatment in the near future [15]. Data on patient preferences for this wider range of LA-ART modalities are currently sparse.

Discrete choice experiments (DCEs) are used to measure and quantify preferences in the absence of revealed preference data from field studies [16, 17]. In a DCE, individuals are asked to choose between different hypothetical alternatives, each defined by a set of attributes with varying levels. Responses can be used to determine whether participants' preferences are significantly influenced by the attributes, the relative importance of each attribute and the trade-offs (i.e. marginal rates of substitution) patients are willing to make among attributes [18]. DCEs may be particularly helpful when interventions are still in development or when a comparison of multiple different options in observational studies or trials would be too costly or impractical. Therefore, the results of a DCE conducted at an early stage of product development can generate important insights for product developers and help inform features that will increase acceptability.

To obtain patient preferences on a range of potential long-acting treatment modalities without over-emphasizing the first LA-ART regimens on the market, we conducted key informant interviews to identify treatment modalities most likely to become available in the next 5–10 years [15]. Based on this qualitative work and our prior research on LAI ART acceptability with both patients and providers [19, 20], we developed and pilot-tested a DCE to capture the preferences of patients engaged in HIV care with respect to key attributes of these long-acting regimens [21]. The results of the pilot testing informed the experimental design of a fully deployed DCE at research sites in Seattle, Washington and Atlanta, Georgia. Our objective in this analysis is to present the results of this fully deployed DCE, which investigated preferences related to four different treatment modalities (oral tablets, subcutaneous injections, intramuscular injections and implants) and their characteristics, compared to patients' current daily oral HIV regimen.

2 | METHODS

2.1 | Population and setting

We recruited DCE participants from the University of Washington HIV clinics in Bremerton, Everett, Federal Way, Olympia, and Seattle, Washington and from Emory University's Infectious Diseases Program in Atlanta, Georgia. Recruitment was conducted between March 2021 and June 2022 through outreach to patients by e-mail or telephone using contact information from the HIV patient registries at each site, or in person at their regular clinic appointments. Our target enrolment was 350 at each site, for 700 participants overall. Eligibility criteria included living with HIV, age ≥18 years, established care at one of the research sites, fluency in English and ability to provide informed consent. Exclusion criteria included currently taking an LAI regimen and being an "elite controller" who has a very low viral load without requiring ART (approximately 0.1%–2.5% of all HIV infections worldwide [22]). In addition, individuals judged to be cognitively impaired or under the influence of drugs or alcohol during in-person screening were excluded.

2.2 | Ethical oversight

The University of Washington (UW) and Emory University reviewed and approved the study protocol and informed consent documents, with the UW serving as the single institutional review board of record (STUDY00007390). All participants provided electronic informed consent.

2.3 | DCE design

We developed our DCE based on feedback from key informants about potential treatment modes and their likely frequency of administration [15]. This feedback led to the selection of four LA-ART treatment modes (long-acting oral tablets, subcutaneous injections, intramuscular injections and implants) and six additional attributes: dosing frequency, location of treatment administration, pain with administration/insertion, pre-treatment time undetectable (should viral

suppression be required before initiating LA-ART), pre-treatment "negative reaction" testing (implementing an oral lead-in to assess tolerability or to exclude reactions such as "an allergic rash or abnormal liver test results" should this be required before starting LA-ART) and "late-dose leeway" (i.e. flexibility or forgiveness in dosing timing before breakthrough viremia). These concepts were carefully explained to DCE participants in the survey introduction (details in Supporting Information 1).

Attribute levels were restricted based on what key informants considered feasible. For long-acting oral medications, attributes were restricted to: no pain, administration at home and frequency 1 or 4 weeks. For subcutaneous injections, attributes were restricted to: no or mild pain; administration at home, clinic or pharmacy; and frequency 1, 4, 8 or 12 weeks. For intramuscular injections, attributes were restricted to: mild or moderate pain; administration at clinic or pharmacy; and frequency 4, 8 or 12 weeks. For implants, attributes were restricted to: mild or moderate pain, insertion at clinic and frequency 26 or 52 weeks. If the location was clinic or pharmacy, the dosing frequency was restricted to ≥4 weeks. The other attributes had no restrictions. Choices for pre-treatment time undetectable were 0, 3 and 6 months. Negative reaction testing was needed or not needed. Late-dose leeway was a duration of time set at 50% or 100% of the dosing interval for that specific LA-ART option, with 50% referred to as a "short" late-dose leeway and 100% referred to as a "long" late-dose leeway.

2.4 | Survey components

The DCE survey (Supporting Information 1) was pilot tested with 50 participants over a series of waves with iterative improvements [21]. The survey started with an overall introduction, then introduced each treatment mode or "option," along with visual images. The ability to remove an implant if a negative reaction occurred was included in the description of that treatment mode. Because effective HIV treatment requires two or more antiretroviral medications and to avoid mixing treatment modes, we advised participants that each hypothetical LA-ART regimen would require two products, both administered by the same mode [15]. This introduction was followed by three comprehension questions about these treatment options to ensure understanding. Next, the first three attributes or "features," including location of treatment, frequency of dosing and pain experienced, were introduced. Participants were also asked to make the following assumptions as they considered their choices: (1) all options would work equally well (i.e. could suppress viral load but not cure HIV); (2) there would be no difference in costs compared to participants' current regimen; and (3) the safety of treatment administration locations would not be impacted by COVID-19. An instructional video with narrative descriptions explaining how the choice sets were to be read presented a practice choice set with only the treatment modes and the first three attributes. After this practice choice set, pre-treatment time undetectable and pre-treatment negative reaction testing were introduced, followed by a comprehension question, then finally late-dose leeway was introduced, followed by its own comprehension question. Another instructional video introduced the more complicated choice sets with all these attributes, followed by another practice choice set.

DCE participants responded to 17 choice scenarios, each with three options: two systematically generated hypothetical LA-ART regimens and a constant opt-out (i.e. the participant's current daily oral treatment). Figure 1 presents an example of the choice sets used. Participants were randomized to 1 of 4 blocks of 16 choice scenarios (out of 64 possible), which were presented in a random order. The 17th question presented two different types of long-acting oral regimens that were compared to the same constant opt-out. The DCE was designed using Ngene software (ChoiceMetrics, Sydney, Australia). The experimental design was unlabelled, and was constructed using a modified Federov algorithm and D-optimal main effects [21].

2.5 | Data collection

Individuals could access the survey at home through an e-mailed invitation link or in a private area within the clinic (after COVID-19 restrictions on in-person research were lifted). Research staff were available for assistance if needed, either by telephone or in-person (for clinic participation). Participants were screened for eligibility and consented, if eligible, using a questionnaire available in REDCap, an electronic data capture tool hosted by the UW. After consenting, participants were linked from REDCap directly to the DCE survey, which was administered in SurveyEngine (SurveyEngine GmbH, Berlin, Germany), an online data collection platform specifically designed for preference research. After the introduction described above and before being presented with the 17 choice scenarios, participants were asked questions about their HIV history, their current and past ART regimens, and their experience with injections, pill storage and clinic visits. At the end of the choice sets, additional data were collected on quality of life, provider support, social support, socio-demographic characteristics and preferences for reminders about clinic visits or treatment administration. In addition, six questions on internalized stigma were included, based on a validated scale [23]. If the participant consented to chart linkage, clinical data, including the participant's current HIV regimen, most recent CD4 count, most recent viral load and number of HIV and non-HIV medications taken daily, were also abstracted from the medical record.

2.6 | Data analysis

Descriptive statistics were used to summarize participant characteristics, overall and by site, with comparisons across sites using independent-sample *t* tests for continuous variables and Chi-square or Fisher exact tests for categorical variables. Each HIV stigma question was scored from 1 (no stigma) to 4 (high-level stigma), and an average score for all stigma questions answered was calculated. Conditional logistic regression was used to analyse the participants' choices across all tasks using attribute levels as the covariates. Data were clustered by participant, to account for intra-individual correlation. All attribute levels were categorical effects-coded, with the omitted level estimated from the negative sum of all other levels in the model. The primary endpoints were all

	Option A	Option B	Option C - your current HIV regimen
Treatment type - How do I take this treatment?	Long-acting oral pills 	Injections under the skin 	
Location - Where would I get this treatment?	Home	Local pharmacy	
Frequency - How often would I get this treatment?	Once a week	Once a month	
Pain - How much pain would I feel?	None	Mild	
Pre-treatment time undetectable - How long would I need to be undetectable on daily pills before starting this treatment?	3 months	None	
Pre-treatment negative reaction testing - Would I need to take daily pills to check for negative reactions before starting the treatment?	Needed	Not needed	
Late dose leeway - How late can I be for a dose of this treatment and still remain undetectable?	1 week	1 week	
Which do you prefer?	○	○	○

Figure 1. Example choice set presenting two different long-acting antiretroviral therapy (LA-ART) regimens (Option A and Option B) and the constant Option C opt-out (current daily oral regimen). For each LA-ART option, attributes presented included treatment type, location, frequency, pain, pre-treatment time undetectable, pre-treatment negative reaction testing and late-dose leeway. "Long" late-dose leeway was defined as 100% of the dosing interval and "short" late-dose leeway was defined as 50% of the dosing interval for that specific treatment option.

attribute-level preference weights, with 95% confidence intervals (CI). Log likelihood ratio tests and Akaike's Information Criterion were used to assess model fit [24]. Due to restrictions on the pain attribute by treatment mode, we included an interaction between treatment mode and pain. The best fitting model coded injection mode as a single type (combining subcutaneous and intramuscular) while restricting implants to 6- or 12-month frequency. We conducted similar analyses stratified by site, in order to explore differences between preference weights for the participants in Georgia and those in Washington State. Mean preference-weight estimates relative to the mean attribute effect normalized around zero and with 95% CI were graphed for each attribute. All data analyses were performed using Stata version 17.0 (StataCorp LLC, College Station, TX) or R version 4.2.2 (https://www.r-project.org/about.html).

3 | RESULTS

Seven hundred participants enrolled, with 350 at each site. Table 1 presents the characteristics of this population, overall and by site. The median age was 51 years, ranging from 18 to 73. Overall, 70% of participants identified as cisgender male, 24% as cisgender female and 6% as non-binary, transgender or other. There were large differences by site, with Atlanta participants less likely to be of Hispanic ethnicity and more likely to be Black, female, heterosexual, unemployed or uninsured. Participants in Atlanta had had HIV and been on ART for a longer duration, had lower recent CD4 counts, were more likely to report having been diagnosed with AIDS and were less likely to have undetectable viral load, despite being more likely to take only one HIV pill per day. In addition, Atlanta participants were more likely to choose their current daily oral regimen over the LA-ART options presented and were more likely to take the DCE survey in the clinic with assistance from research staff.

Table 2 presents the mean preference weights for each attribute and level in the entire study population, along with 95% CI that allow comparison of utility across attribute levels. These results are also summarized in Figure 2. Across all participants, LA oral tablets were the only mode strongly preferred over current daily oral treatment, with a preference weight of 0.89 (95% CI 0.75, 1.04) for LA oral tablets, compared to 0.03 (95% CI −0.11, 0.18) for current treatment. Annual implants (preference weights −0.08 [95% CI −0.25, 0.08] and −0.03 [95% CI −0.18, 0.11]) for those with mild and moderate pain, respectively) and injections with no pain (preference weight −0.06 [95% CI −0.15, 0.03]) were next most preferred, with 95% CI for each overlapping current daily oral treatment. Longer time between doses was preferred, with clear separation between the 95% CI

Table 1. Characteristics of 700 participants by study site

	Total (*N* = 700)	Atlanta (*n* = 350)	Seattle (*n* = 350)	*p* Value for comparison
Age (years)				
Mean (SD)	48.6 (12.1)	49.3 (12.2)	48.0 (12.0)	0.15
Median [min, max]	51 [18, 73]	51 [18, 72]	50 [22, 73]	
Hispanic ethnicity, *N* (%)				
No	623 (89.0%)	325 (92.9%)	298 (85.1%	0.001
Yes	61 (8.7%)	17 (4.9%)	44 (12.6%)	
Missing	16 (2.3%)	8 (2.3%)	8 (2.3%)	
Race, *N* (%)				
White	259 (37.0%)	23 (6.6%)	236 (67.4%)	<0.001
Black	331 (47.3%)	295 (84.3%)	36 (10.3%)	
Other/Mixed	94 (13.4%)	24 (6.9%)	70 (20.0%)	
Prefer not to say	16 (2.3%)	8 (2.3%)	8 (2.3%)	
Gender, *N* (%)				<0.001
Woman	168 (24.0%)	135 (38.6%)	33 (9.4%)	
Man	493 (70.4%)	197 (56.3%)	296 (84.6%)	
Transgender woman	15 (2.1%)	8 (2.3%)	7 (2.0%)	
Transgender man	6 (0.9%)	4 (1.1%)	2 (0.6%)	
Other	10 (1.4%)	3 (0.9%)	7 (2.0%)	
Prefer not to say	8 (1.1%)	3 (0.9%)	5 (1.4%)	
Sexual orientation, *N* (%)				<0.001
Heterosexual	227 (32.4%)	173 (49.4%)	54 (15.4%)	
Lesbian, gay or bisexual	419 (59.9%)	143 (40.9%)	276 (78.9%)	
Prefer not to say	30 (4.3%)	24 (6.9%)	6 (1.7%)	
Missing	24 (3.4%)	10 (2.9%)	14 (4.0%)	
Employment, *N* (%)				<0.001
Full time	192 (27.4%)	55 (15.7%)	137 (39.1%)	
Part time	79 (11.3%)	33 (9.4%)	46 (13.1%)	
Not working	407 (58.1%)	248 (71.0%)	159 (45.4%)	
Prefer not to say	22 (3.1%)	14 (4.0%)	8 (2.3%)	
Any health insurance, *N* (%)	577 (82.4%)	237 (67.7%)	340 (97.1%)	<0.001
HIV stigma score	2.17 (0.79)	2.14 (0.80)	2.20 (0.77)	0.33
Time on ART (years)				0.035
Mean (SD)	15.6 (8.7)	16.3 (8.9)	14.9 (8.5)	
Missing	10 (1.4%)	3 (0.9%)	7 (2.0%)	
Time with HIV (years)				0.026
Mean (SD)	17.9 (9.8)	18.7 (9.9)	17.0 (9.6)	
Most recent CD4 count (cells/mm^3)				0.0006
Mean (SD)	601 (316)	558 (338)	641 (289)	
Missing	30 (4.3%)	25 (7.1%)	5 (1.4%)	
Self-reported AIDS diagnosis, *N* (%)[a]	292 (41.7%)	164 (46.9%)	128 (36.6%)	0.0006
Viral load undetectable, *N* (%)	500 (71.4%)	224 (64.0%)	276 (78.9%)	<0.001
HIV pills per day, *N* (%)				<0.001
One tablet	390 (55.7%)	230 (65.7%)	160 (45.7%)	
Two tablets	200 (28.6%)	72 (20.6%)	128 (36.6%)	
Three or more tablets	92 (13.1%)	39 (11.1%)	53 (15.1%)	
Prefer not to say/missing	9 (2.6%)	9 (2.6%)	18 (9.2%)	
Number of scenarios in which Option C (the constant opt-out) was chosen, Mean (SD)	5.4 (6.4)	6.3 (7.0)	4.6 (5.7)	0.0004

(*Continued*)

Table 1. (Continued)

	Total (*N* = 700)	Atlanta (*n* = 350)	Seattle (*n* = 350)	*p* Value for comparison
Respondents selecting Option C (the constant opt-out) at least once, *N* (%)	381 (54.4%)	181 (51.7%)	200 (57.1%)	0.149
DCE participation site, *N* (%)				<0.001
Home	299 (42.7%)	34 (9.7)	265 (75.7)	
Clinic	376 (53.7%)	312 (89.1)	64 (18.3)	
Other	25 (3.6%)	4 (1.1)	21 (6.0)	

Note: Comparisons were made across sites using independent-sample *t* tests for continuous variables and Chi-square or Fisher exact tests for categorical variables. SD: standard deviation; DCE: discrete choice experiment.
[a]Data were missing for 14 participants, 9 from Atlanta and 5 from Seattle.

Table 2. Point estimates and 95% confidence intervals (CI) from conditional logistic regression for preference weights, entire study population

	Preference weight	95% CI
Current therapy (alternative-specific constant)	0.03	−0.11, 0.18
Long-acting oral—no pain*	0.89	0.75, 1.04
1-year implant —mild pain	−0.08	−0.25, 0.08
1-year implant—moderate pain	−0.03	−0.18, 0.11
6-month implant—mild pain	−0.15	−0.27, −0.02
6-month implant—moderate pain	−0.34	−0.51, −0.17
Injectable—no pain	−0.06	−0.15, 0.03
Injectable—mild pain	−0.09	−0.18, −0.01
Injectable—moderate pain	−0.13	−0.24, −0.02
Frequency—3 months	0.41	0.35, 0.46
Frequency—2 months	0.22	0.16, 0.27
Frequency—1 month	−0.14	−0.18, −0.09
Frequency—1 week*	−0.49	−0.57, −0.40
Location—clinic	−0.01	−0.06, 0.04
Location—pharmacy	−0.14	−0.20, −0.09
Location—home*	0.16	0.08, 0.23
Time undetectable—6 months	−0.05	−0.09, −0.02
Time undetectable—3 months	−0.04	−0.07, −0.01
Time undetectable—none*	0.09	0.06, 0.13
Negative reaction testing—needed	−0.06	−0.09, −0.04
Negative reaction testing—not needed*	0.06	0.04, 0.09
Late-dose leeway—long[a]	0.07	0.05, 0.10
Late-dose leeway—short*[a]	−0.07	−0.10, −0.05

Notes: Thin lines separate the different attributes assessed. Preference weights are relative to the mean effect. Non-overlapping 95% confidence intervals for preference weights of different levels of the same attribute indicate significantly different utilities between the two levels compared.
[a]Late-dose leeway was defined as the flexibility or "forgiveness" in dosing timing before breakthrough viremia, with long leeway defined as 100% of the dosing interval and "short" leeway defined as 50% of the dosing interval for that specific treatment option.
*For each attribute, the omitted level, which was estimated from the negative sum of all other levels in the model, is indicated by an asterisk.

for 3 monthly, 2 monthly, monthly, and weekly, but overlap between 95% CI for 6- and 12-month implants regardless of the pain. Administration at home (preference weight 0.16 [95% CI 0.08, 0.23]) was preferred to clinics (preference weight −0.01 [95% CI −0.06, 0.04]), which were preferred to pharmacies (preference weight −0.14 [95% CI −0.20, −0.09]), again with separation between the 95% CI for these three attribute levels. Attributes that impacted preferences less included oral lead-in treatment to achieve viral suppression or test for negative reactions and late-dose leeway around the prescribed dosing interval, although in each case, there was a clear preference (for no pre-treatment requirements and for longer late-dose leeway), with non-overlapping 95% CI.

In general, Seattle participants had stronger preferences for LA-ART regimens than Atlanta participants (Tables S1 and S2, and Figure S1). Most strikingly, while Seattle participants were somewhat negative about their current regimens (preference weight −0.26 [95% CI −0.46, −0.06]), Atlanta participants were more positive (preference weight 0.32 [95% CI 0.12, 0.52]). There was a clear preference for long-acting oral treatment among Seattle participants, while implants and injectable regimens had 95% CI overlapping that of current therapy, indicating similar utility. The four levels of dosing frequency each had clear separation from the others at this site, with a stronger preference for each increase in the dosing interval. Also among Seattle participants, there was a clear preference for treatment at home, but the 95% CI for pharmacy and clinic overlapped, indicating similar utility for each location. In Atlanta, the 95% CI for long-acting oral treatment overlapped that of current therapy, and implants were less preferred, with a 95% CI less than that of current therapy for all four implant options. The 95% CI for all injection options overlapped with that of current therapy, indicating similar utility. While longer dosing intervals were preferred in Atlanta, there was an overlap between 95% CI for 2 and 3 months and between 95% CI for 1 week and 1 month. There was a clear preference for clinic and home over pharmacy, but the 95% for clinic and home overlapped for Atlanta participants. Finally, although longer late-dose leeway was clearly preferred in Atlanta, participants at this site had no clear preference in terms of pre-treatment time undetectable and pre-treatment negative reaction testing.

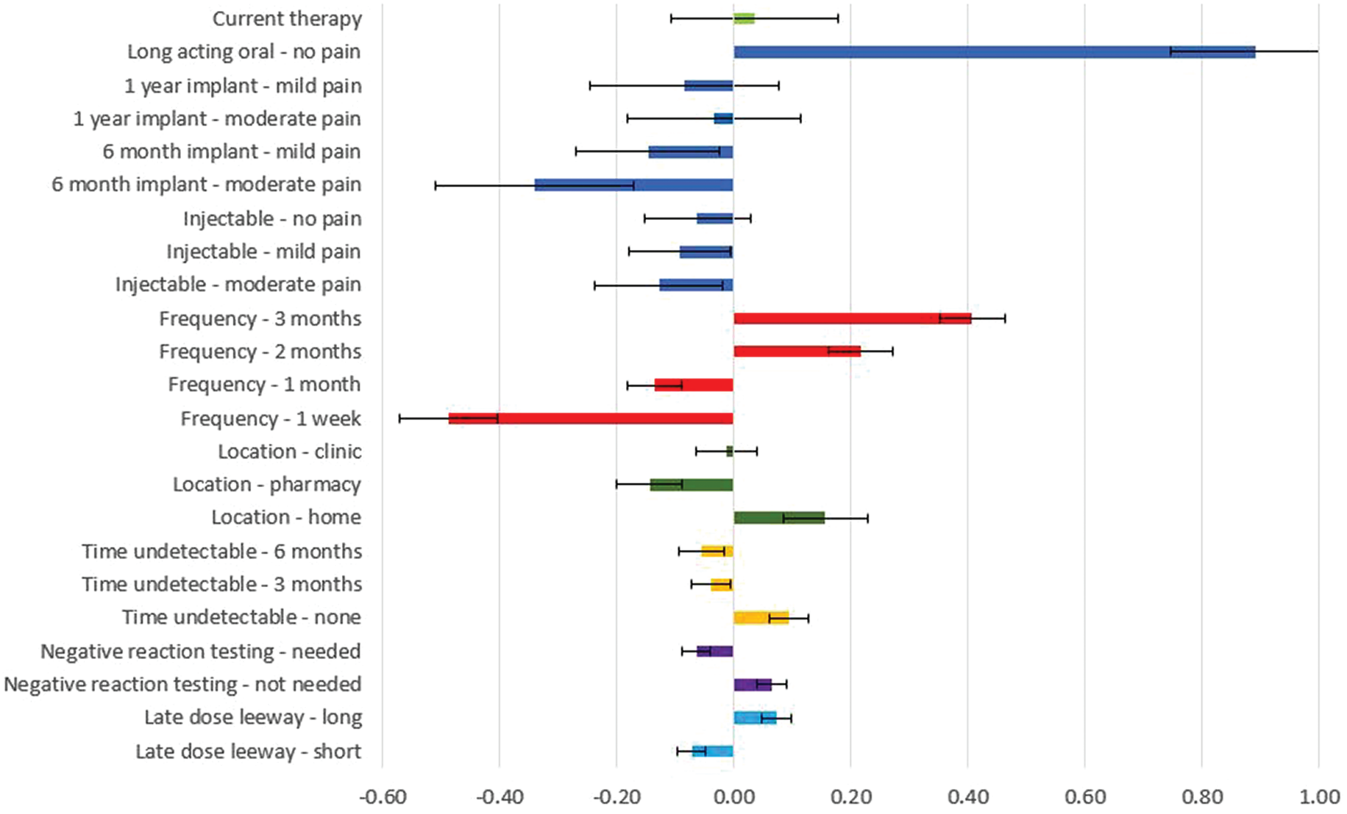

Figure 2. Long-acting antiretroviral treatment (LA-ART) preference weights from conditional logistic regression, entire study population. Mean preference-weight estimates for each attribute relative to the mean attribute effect are presented, normalized around zero. Black lines with bars indicate 95% confidence intervals for preference weights. Positive weights indicate higher preference relative to the other levels evaluated. The overall relative importance of an attribute overall is the difference between the largest and the smallest preference weights of that attribute. "Long" late-dose leeway was defined as 100% of the dosing interval and "short" late-dose leeway was defined as 50% of the dosing interval for that specific treatment option.

4 | DISCUSSION

In this diverse population of 700 people with HIV (PWH) engaged in care at our study sites, we found that participants strongly preferred long-acting preparations with longer intervals between dosing, less pain with administration, and greater privacy and convenience in terms of administration. In addition, participants preferred minimal barriers to LA-ART initiation (i.e. no lead-in testing for reactions or a requirement for viral load suppression) and greater tolerance for delays in product administration. There were differences in preferences across sites, with participants in Seattle more open to switching from their current daily oral regimen than in Atlanta. However, preferences for the different treatment modes when presented with the restrictions used in this DCE were fairly consistent, with more participants preferring long-acting oral tablets than injections, and more participants preferring injections than implants.

To our knowledge, this is the first DCE investigating the preferences of PWH in the United States with respect to a broad range of potential LA-ART regimens, including long-acting oral tablets, subcutaneous and intramuscular injections, and implants. One published study evaluated the acceptability of LA-ART in general, and asked participants to choose the one mode they would most prefer, "if all options cost the same and worked equally well" [25]. The options provided were oral pills, injections given every 1–2 months, implants inserted every 6–12 months or an intravenous infusion administered every 2–4 weeks. Among 374 participants, 61% reported that they were likely or very likely to use LA-ART; 41% preferred pills, 40% preferred injections and 18% preferred an implant, with only 1% preferring an infusion [25]. While these results are interesting, the method used did not include trade-offs between different products with varying attributes, such as frequency and site of administration, so results should be interpreted with caution. Our study extends that work and adds to the literature by using a rigorous DCE methodology to elicit patient preferences.

While long-acting oral tablets were most preferred overall in our study, it is unclear when a long-acting oral HIV treatment regimen will become available. Gilead Sciences and Merck have developed an LA-ART regimen composed of weekly oral lenacapavir combined with weekly oral islatravir; a randomized trial (NCT05052996) of this regimen among PWH with viral suppression at baseline is ongoing, with a lower dose of islatravir than initially planned (due to toxicity)

and an estimated completion date of December 2027 [26]. Currently, there is only one complete LA-ART regimen on the market: the cabotegravir/rilpivirine regimen (Cabenuva, Viiv Healthcare, Brentford, United Kingdom). This regimen was approved by the U.S. Food and Drug Administration in 2021 with a once-monthly dosing schedule [27], based on the ATLAS and FLAIR randomized controlled trials demonstrating the equivalence of this regimen to standard daily oral ART [28, 29]. The FDA approved every 2-month administration of injectable cabotegravir/rilpivirine in 2022 [30], based on results of the ATLAS-2 M study [31], which demonstrated the non-inferiority of this dosing schedule. Viiv Healthcare is working on drug delivery technology to enable the delivery of larger doses with less pain, leading to an "ultra-long-acting" product dosed every 3 months or longer [32]. Evidence suggests that these regimens are tolerable in practice: in the week 124 FLAIR study, while injection site reactions were the most common adverse event (occurring after 21.3% of injections across all participant visits), they were generally mild (grade 1 or 2), short-lived (median duration 3 days) and less frequent over time, and only 2.1% (11 of all 515 participants) discontinued LA cabotegravir/rilpivirine due to injection site pain or reactions [33]. While less frequent dosing and only mild pain could overcome concerns about injections, LA oral regimens have other advantages, such as greater convenience and privacy with home administration, that will likely influence preferences.

Participants in our DCE preferred LA-ART regimens without a requirement for viral suppression before initiation, although this attribute had a relatively weak influence on choices. While each potential LA-ART regimen we examined could lead to increased patient satisfaction if available, the extent to which LA-ART regimens will address gaps in ART adherence and help attain viral suppression targets remains unclear [34]. Of note, in the study by Dandachi et al. asking participants to select their most preferred LA-ART type, the likelihood of LA-ART use did not correlate with adherence or viral suppression [25]. An ongoing AIDS Clinical Trial Group study called "LATITUDE" (NCT03635788) is investigating the use of injectable cabotegravir/rilpivirine compared to daily oral therapy among patients with a history of poor adherence, who were specifically excluded from prior trials [35]. While LATITUDE was originally designed with an oral lead-in period of 6 months during which conditional economic incentives would promote viral suppression [35], new evidence suggests that viral suppression may not always be needed prior to starting cabotegravir/rilpivirine [36]. Results of the LATITUDE trial and other studies could provide important evidence on the extent to which LA injectable treatment may address current gaps in viral suppression. Further research on preferences for LA-ART that includes populations who have struggled with adherence and viral suppression, such as adolescents and those with substance use or mental health problems, will be important as new regimens become available.

Our DCE participants also preferred LA-ART regimens without a requirement for allergic reaction or other side effect testing before initiation and those with some "leeway" or forgiveness in dosing. Of note, the requirement for oral lead-in for "negative reaction" testing has been waived for injectable cabotegravir/rilpivirine, based on the week 124 FLAIR results [33]. While an oral lead-in period to identify and manage potential adverse drug reactions is no longer an issue for cabotegravir/rilpivirine, it may well be needed for other regimens. In addition, missed or late administration could lead to antiretroviral resistance mutations, regardless of treatment mode [34]. Resistance to injectable cabotegravir/rilpivirine has been reported for a small number of participants in recent clinical trials [37]. While they may be less influential for patients, concerns about managing adverse reactions and ensuring adequate leeway in the event of a missed dose will be key attributes influencing the preferences of providers.

Switching to LA-ART may not be of interest to patients who are doing well on their current daily regimen. Indeed, in a separate analysis exploring associations with selecting the "Option C" constant opt-out in this DCE, we found that PWH who were older, more adherent, more averse to injections and had lower educational attainment more frequently chose their current daily regimen in this DCE [38]. A striking finding of the current study is the difference in preferences by geographic site, which were evaluated nominally in stratified analysis for this manuscript, with no direct statistical comparison. Atlanta participants were more positive about their current daily oral regimen than were Seattle participants, and their preferences for treatment mode were less strong, with the 95% CI for current regimen overlapping those of long-acting oral treatment and injections. While they clearly did not prefer implants, they also did not have a preference for home over the clinic. Atlanta participants were more likely to be unemployed and uninsured, and gaps in insurance coverage have led to challenges implementing injectable cabotegravir/rilpivirine at the Atlanta site [39]. These structural problems may underlie patients' stronger preference for their current daily oral therapy, despite our request that patients assume there would be no difference in cost for the LA-ART options presented relative to their current daily oral regimen. Site differences may also have been influenced by the greater proportion of cisgender women in Atlanta and their experiences with injections and implants for contraception; in addition, women had higher stigma scores than men (2.27 vs. 2.13, $p = 0.04$), which may also have impacted preferences. Another possibility is that medical mistrust is more prevalent in the Atlanta participant sub-population, which was more likely to be Black. Of note, in an extension of the ATLAS study that investigated the safety of "direct-to-injection" cabotegravir/rilpvirine initiation as an option alongside the standard pre-treatment negative reaction testing, Black participants were less likely than White participants to opt for "direct to injection" [40]. Future studies of patient preferences for LA-ART options should consider including measurement of medical mistrust and evaluating structural barriers to treatment access that may alter preferences.

This study has a number of limitations. First, we only targeted patients who were engaged in HIV care at our clinical sites, and so missed PWH in the study areas who were not diagnosed or engaged in care. In addition, patients who volunteered for the study, especially those who participated online, may differ from those who did not. Second, our work was conducted in only two U.S. regions and our study population is, therefore, not representative of PWH in other geographic

areas or settings. While an online study could potentially reach a larger group of PWH, there is a trade-off between the challenges of online recruitment and recruitment from clinical settings in which HIV status can be confirmed and other clinical data are available. Third, we may have excluded potential LA-ART products (e.g. infusions of broadly neutralizing antibodies) that may come on the market eventually or included product modalities that may turn out not to be feasible. That said, we developed our DCE based on feedback from 12 experts in the field in the year immediately prior to study launch, using the best information available at the time. Fourth, we were unable to fully examine differences between subcutaneous and intramuscular injections due to the complexities of the restrictions used and did not compare regimens that included mixed modalities due to concerns about cognitive overload. In addition, because the home location was restricted to those modes that could be self-administered with ease, we could not distinguish preference for home location from preference for self-administration. Fifth, DCEs ask individuals to make hypothetical choices, which may differ from choices patients would actually make when opportunities arise in the real world, especially if recommended by their physician. Finally, our focus was to provide a comprehensive assessment of preferences within the study sample, and additional exploration is needed in order to assess preference heterogeneity across participant sub-groups; this work will be forthcoming. Despite these limitations, the present analysis builds on prior patient preference research on LA-ART by expanding the options participants considered beyond the injectable products first on the market, and is, therefore, a unique and valuable contribution.

5 | CONCLUSIONS

In conclusion, PWH in the United States may soon have several options for LA-ART. Our results suggest that LA oral tablets will be preferred by many patients over their current treatment, while implants and injections with longer duration may be acceptable to some patients. Future research should investigate sources of preference heterogeneity and actual uptake of and retention on products, when available.

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COMPETING INTERESTS

BH is an employee of Pfizer. SMG has received support from Gilead and Cepheid for her research. VCM has received investigator-initiated research grants (to the institution) and consultation fees (both unrelated to the current work) from Eli Lilly, Bayer, Gilead Sciences and ViiV. The other authors declare that they have no competing interests directly relevant to the content of this article.

AUTHORS' CONTRIBUTIONS

SMG, JMS, BH and DB designed the study; SMG and JMS acquired funding; VCM oversaw the Atlanta site; ATB and the Emory PREFER Team collected data; DB and ES analysed the data; ACC and RJYH contributed expertise in long-acting treatment development and testing; and SMG wrote the initial manuscript. All authors contributed to and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

De-identified data will be made available in the Harvard Dataverse upon publication.

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SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article:

Supporting Information 1. Project PREFER SurveyEngine Questionnaire & DCE

Figure S1A. Long-acting antiretroviral treatment (LA-ART) preference weights from conditional logistic regression for Seattle participants.

Figure S1B. Long-acting antiretroviral treatment (LA-ART) preference weights from conditional logistic regression for Atlanta participants.

Table S1. Point estimates and 95% confidence intervals from logistic regression for preference weights, Seattle participants.

Table S2. Point estimates and 95% confidence intervals (CI) from conditional logistic regression for preference weights, Atlanta participants.

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RESEARCH ARTICLE

Who prefers what? Correlates of preferences for next-generation HIV prevention products among a national U.S. sample of young men who have sex with men

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Abstract

Introduction: Pre-exposure prophylaxis (PrEP) has been available for young people for over a decade, yet only ~15% of young people in the United States with indications for PrEP have a prescription for it. Next-generation PrEP modalities may address some of the challenges of daily oral PrEP. However, preferences for these products are unknown.

Methods: From October 2020 to June 2021, we conducted an online survey of 737 cisgender, young men who have sex with men (age 15–24 years) without HIV across the United States who reported same-sex attraction or consensual sex with another man in the past 6 months. Participants completed a conjoint experiment comparing daily oral pills, event-driven oral pills, event-driven rectal douches, intramuscular injections, intravenous broadly neutralizing antibody (bnAb) infusions and subcutaneous implants. Participants ranked the products from most to least preferred. Exploded logit models examined the association between ranked preferences of PrEP modalities and socio-demographic and behavioural characteristics.

Results: Participants' mean age was 21 years (SD = 2.3), and 56% identified as White. Nineteen percent were currently taking daily oral PrEP, and another 9% had previously taken it. Participants prioritized efficacy, absence of side effects and costs in the conjoint analyses. Daily oral PrEP had the highest preference ranking, followed by event-driven oral (OR = 0.89, p = 0.058), injectable (OR = 0.83, p = 0.005), implant (OR = 0.48, $p < 0.0001$), bnAb infusions (OR = 0.38, $p < 0.0001$) and rectal douches (OR = 0.24, $p < 0.0001$). There were differences in PrEP preferences across age, insurance status, sexual behaviour, PrEP use history, HIV and sexually transmitted infection (STI) testing history, and STI diagnoses (omnibus tests: $p < 0.05$). Participants also provided reasons for selecting their top product choice: ease of use for those who chose daily oral (99%) and daily event-driven (98.5%); feel more protected against HIV for those who chose injectable (95.4%) and implants (100%); not worrying about forgetting to take it for those who chose bnAbs (93.8%); and being able to stop taking it when they want for those who chose rectal douche (90.9%).

Conclusions: Next-generation modalities were less likely to be preferred over daily oral PrEP, with differences in the magnitude by socio-demographic and behavioural characteristics. Given the low uptake of daily oral PrEP, end-users' preferences for and concerns about PrEP products must be understood to ensure high acceptability and penetration.

Keywords: men who have sex with men; adolescents; HIV prevention; pre-exposure prophylaxis; conjoint experiment; product preferences

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1 | INTRODUCTION

HIV incidence continues to be a major public health concern among young men who have sex with men (YMSM) in the United States, who account for 24% of new infections among MSM [1]. In May 2018, the antiretroviral combination tenofovir-emtricitabine, prescribed as a daily oral pill, was approved by the U.S. Food and Drug Administration (FDA) for HIV pre-exposure prophylaxis (PrEP) for adolescents weighing at least 77 lb (35 kg), almost 6 years after approval for adults [2, 3]. With greater than 90% efficacy when taken as prescribed, PrEP is an essential tool in ending the HIV epidemic [4, 5]. However, PrEP uptake has been low among adolescents and young adults [6–9]. Only 2% of individuals 13–26 years old meeting indications for PrEP have been prescribed the medication in the United States [10], with adolescents under 18 years old accounting for less than 1% of all PrEP prescriptions [11].

Moreover, a recent meta-analysis showed that, across studies, about one-third of YMSM who initiated PrEP have

suboptimal adherence [6, 7, 12]. Barriers to PrEP uptake and adherence among YMSM are multi-level and include individual (e.g. forgetting/hectic lifestyles and concerns about side effects) [13–17], interpersonal (e.g. stigma and discrimination from family, friends and sexual partners) [13, 17, 18] and structural (e.g. access to health insurance and concerns about cost) factors [13, 15, 19, 20].

New PrEP formulations, including implants and long-acting injectable products, may help address challenges individuals face adhering to a daily oral pill [21–24]. Diverse drug delivery mechanisms could offer choices based on YMSM's socio-cultural context and facilitate uptake of and adherence to products that are behaviourally congruent with their sexual practices. For example, rectal douches may be congruent with cleansing practices and behaviours regarded as normative before participating in activities where the probability of engaging in receptive anal intercourse is high [25, 26]. Similarly, long-acting injectable formulations or episodic oral PrEP might be more compatible with a complex lifestyle when taking a pill daily is unrealistic.

Achieving consistent and correct use among the product's consumers will require researchers to develop desirable and acceptable products to end-users within the context of clinical trials and in the real world [27–29]. However, YMSM's recruitment in these next-generation PrEP studies has been limited [3], and little is known about how YMSM perceive next-generation prevention modalities or the factors that influence the acceptability of these products in this population. Thus, even if found to be efficacious, the absence of YMSM's perspectives on product characteristics could lead to acceptability and adherence challenges once they become available as HIV prevention strategies.

We conducted an online survey with U.S. YMSM examining PrEP modality preferences to address this gap. In this study, we aim to examine the (1) preferences for features of PrEP products *within* YMSM participants via conjoint analyses and (2) across PrEP product preferences and correlates of these preferences *between* YMSM participants (via rank-choice selection).

2 | METHODS

2.1 | Participants and procedures

YMSM in the United States were recruited for an online survey from social media platforms, dating apps and targeted mailing lists between October 2020 and June 2021. Participants were eligible for this study if they were 15–24 years old, were assigned male sex at birth and currently identified as male, self-reported being HIV negative or did not know their HIV status, reported same-sex attractions or consensual sexual behaviours with other men in the past 6 months, lived in the United States and spoke English.

Interested individuals completed an online screener to ascertain eligibility. We used automatized (e.g. CAPTCHA validation) and manual methods (e.g. time to complete screener) to verify the legitimacy of responses and checked phone numbers and email addresses to identify duplicate entries, as recommended by previous research [30–32]. Eligible individuals then received a unique, password-protected link to an online survey developed and pilot-tested with a Youth Advisory Board of sexual and gender minority youth. Individuals were randomized to a brief conjoint experiment exploring preferred attributes of one of five different next-generation modalities (i.e. event-driven oral, intramuscular injections, subcutaneous implants, intravenous infusions of broadly neutralizing antibodies [bnAbs] and rectal douches). Conjoint experiments can shed light on HIV prevention decision-making by examining how product attributes (e.g. efficacy and side effects) influence choice preferences [33]. Following the conjoint experiment, the survey assessed ranked preferences across daily oral and next-generation PrEP modalities, and socio-demographic and behavioural characteristics. The survey was designed to be completed in ≈45 minutes.

The Institutional Review Board at the University of Pennsylvania approved study procedures and materials. Informed consent/assent was obtained from all participants, and a waiver of parental consent was obtained for participants 15–17 years old. Participants received a USD$40 gift card for participation.

2.2 | Measures

2.2.1 | *Conjoint experiment*

Definitions of PrEP products and images for the product features were reviewed by participants prior to the conjoint experiment. Definitions and images were developed through cognitive interviews with YMSM (reported previously [34]). Given that many of the products are still under development, and that we were trying to assess optimal attributes, we did not include the frequency of recommended use in the descriptions (e.g. bimonthly for injectable PrEP). Participants then selected between 20 pairs of product profiles based on random combinations across five or six product-specific features. All conjoint experiments assessed HIV prevention efficacy, duration of protection, average cost and side effects. Additionally, event-driven oral PrEP experiments assessed pill size and timing of use; injectable experiments assessed deliverer; implant experiments assessed time for placement; bnAb experiments assessed infusion time; and rectal douche experiments assessed delivery device. Figure 1 shows a sample of a conjoint experiment.

2.2.2 | *PrEP modality preferences*

Following the conjoint experiment, participants were then asked to rank each modality (including daily oral PrEP) from best (1) to worst (6) if they provided equal protection against HIV transmission based on their preferences and how the product would fit their lifestyles.

We then asked participants to indicate on a 4-point scale their agreement with 11 reasons they selected their top-ranked PrEP modality. Sample reasons included, "It would be easy to use this product," "I would have fewer concerns about side effects," and "I feel more protected against HIV using this product." We further dichotomized responses to each

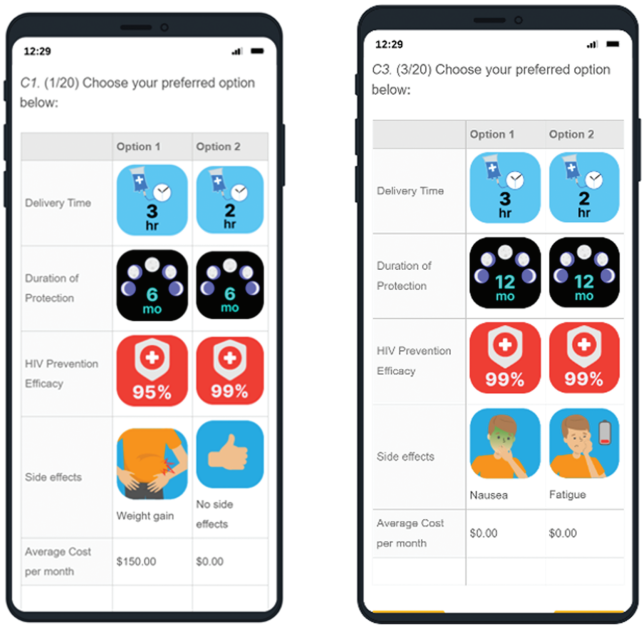

Figure 1. Sample of two product profiles from the conjoint experiment. Abbreviations: hr, hour; mo, month.

statement as agree/strongly agree versus disagree/strongly disagree.

2.2.3 | *Access to healthcare*

We classified health insurance status as uninsured, covered by their parents'/guardians' insurance plan and covered by their own insurance plan. We assessed whether participants had a primary care provider and the extent to which participants believed the healthcare services accessed met their health needs. Responses on a 5-point scale ranging from "never" to "always" were dichotomized as "usually/always" and "never/rarely/sometimes" meet health needs.

2.2.4 | *Access to HIV prevention care*

We assessed previous HIV and other STI testing, prior diagnosis of STIs, awareness of PrEP for HIV prevention and PrEP use (current use, prior use or never used).

2.2.5 | *Sexual and drug use behaviours*

Participants were asked about the number of men with whom they had condomless anal sex (CAS) in the past month, with responses dichotomized into any versus none. Participants were also asked about any use of the following non-prescribed substances in the past 30 days: cocaine/crack cocaine, stimulants, inhalants, sedatives, hallucinogens and opioids. Our composite measure of drug use included any use of these substances in the past 30 days. Lastly, participants were asked how frequently they had a drink containing alcohol in the past 30 days, which was dichotomized into 2+ drinks per week versus less than 2 drinks per week.

2.2.6 | *Socio-demographics*

We also assessed participants' age, race, ethnicity, sexual orientation, educational attainment and ZIP code (coded into Census regions). To measure food insecurity, we asked participants how often they or their families had to skip a meal in the past 3 months because there was not enough money for food. Responses on a 4-point scale ranging from "almost every week" to "never" were dichotomized into any versus no food insecurity.

2.3 | Analytic plan

We described frequencies and descriptive statistics for socio-demographic and behavioural characteristics.

Using Qualtrics Conjoint Experiment platform, we estimated the feature importance of each attribute in the participants' decision-making process. We also calculated YMSM's willingness-to-pay (WTP; i.e. average cost per month in $USD) for a feature based on trade-offs between different levels.

We described ranking frequencies and mean ranking across all six PrEP modalities and frequencies of endorsement of reasons for selecting the top-ranked PrEP modality. We used rank-ordered regression (e.g. exploded logit regression) to model the probability of ranking each modality highest [35], which we present alongside participant-reported top-ranked modality as they provide complementary information. Specifically, participant-reported top-ranked choices describes the one modality participants would choose if all options were accessible to them. In contrast, model-estimated probabilities account for the distribution of ranks across products, including bimodal ranking (e.g. a high percentage of both acceptance and rejection).

Rank-ordered regression is a generalization of conditional logit models that estimates the preference for a given PrEP modality compared to an arbitrarily defined reference category based on sets of ranked items. Following the procedures outlined by Allison and Christakis [36], we used partial likelihood procedures for proportional hazards to estimate rank-ordered models and examine heterogeneity in PrEP modality preferences across participant characteristics (e.g. if participants' socio-demographic characteristics are associated with modality preferences). In these models, variables of interest were included in regression models as interaction terms "variable*modality," and significance of associations was assessed by Wald chi-square tests of the hypothesis that all variable*modality terms are zero. Exponentiated regression coefficients of rank-ordered models are interpreted as odds ratios (ORs) of preferring a given next-generation modality over daily oral PrEP. Likewise, exponentiated differences in coefficients are interpreted as the odds of preferring a given modality over daily oral PrEP between levels of the variable of interest [36].

We used an exploratory approach to model building, first examining bivariate associations between modality preferences and several measures of socio-demographic characteristics, access to healthcare and HIV prevention, and sexual and drug use behaviours selected based on our previous research on acceptability and access to PrEP. We then retained variables with p-values <0.10 in bivariate analysis for adjusted

models. STI diagnosis and alcohol use were both excluded from the adjusted models due to high collinearity with HIV testing and drug use, respectively. Given that ORs in adjusted rank-ordered models assume reference levels of other covariates in regression models and that ORs are non-collapsible [37], the magnitudes of adjusted and unadjusted ORs are not comparable. We, therefore, present unadjusted ORs and report only *p*-values of adjusted ORs.

Analyses were done in SAS 9.4 and Stata 17.

3 | RESULTS

Table 1 shows sample characteristics. In brief, the mean age of our sample of *N* = 737 YMSM was 21.1 years (Standard Deviation = 2.27). Nearly, one-quarter (24%) identified as Latino. Over half (56%) identified as White, 19% as Black, 12% as Asian and 13% as Multiracial or some other racial identity. While nearly all (95%) were aware of PrEP, only 28% had ever used PrEP.

3.1 | Preferred attributes: a series of conjoint experiments

See Table 2 for the results of the conjoint experiments. Across all PrEP products presented in the conjoint experiment, the most important features were: efficacy (ranging from 33% to 42%), side effects (ranging from 18% to 33%) and average cost (ranging from 18% to 20%); however, side effects had a higher proportion for event-driven products (e.g. event-driven oral and rectal douche; 30% and 33%) compared to systemic products (e.g. injectable, implants and bnAb; 18%–23%). Duration of protection had greater feature importance for non-event-driven products (14%–18%) than for event-driven products (4% and 6%). Timing of use (e.g. around sex) or timing of delivery (e.g. length of infusion) demonstrated low feature importance (<3%) across all products, as did the mode of delivery (2%–6%).

The willingness to pay metric indicates that efficacy and side effects had the greatest cost trade-offs in participants' choices. YMSM were less willing to adopt a given technology in the presence of lower efficacy and certain side effects, whereas they were more forgiving of the mode of delivery, duration of HIV protection and timing of regimen use. For example, across products, participants were willing to pay >$250 more for a product with 95% efficacy compared to 50% efficacy. Additionally, a negative impact on kidney function was seen as a major trade-off for the event-driven products (>$200 compared to no side effects), as was weight gain for all products ($125–$176).

3.2 | Preferred products: rank orders

The complete ranks by each product are described in Table 3. Approximately one-quarter of participants ranked event-driven oral PrEP (28%), daily oral PrEP (27%) and injectable PrEP (24.6%) as their first choice of products, followed by PrEP implant (13%), bnAb infusion (4%) and a PrEP rectal douche (3%). When accounting for the complete rank order of the products (i.e. ranks 1–6), the model-estimated proportion of individuals selecting daily oral PrEP was 26%,

Table 1. Characteristics of an online sample of young men who have sex with men in the United States (*N* = 737)

	N (%)
Age (years)	
15–17 years	61 (8%)
18–20 years	200 (27%)
21–24 years	475 (65%)
Race	
White	412 (56%)
Black	139 (19%)
Asian	91 (12%)
Multiracial/Other	95 (13%)
Latinx/Hispanic	174 (24%)
Sexual orientation	
Gay	587 (80%)
Bisexual	111 (15%)
Queer	29 (4%)
Other	9 (1%)
Region	
South	251 (34%)
Northeast	209 (29%)
West	137 (19%)
Midwest	134 (18%)
Education attainment	
6–11 grade	67 (9%)
Graduated high school/GED	107 (15%)
Some college/technical school	250 (34%)
Graduated from 2- or 4-year college or technical school	224 (31%)
Some graduate school or higher	87 (12%)
Food insecurity (past 3 months)	134 (18%)
Insurance status	
Parents' insurance	450 (61%)
Own insurance	219 (30%)
Uninsured	57 (8%)
Don't know	9 (1%)
Has healthcare provider	591 (84%)
Healthcare meets health needs	568 (81%)
HIV test	
Ever	582 (79%)
Past 3 months	294 (42%)
STI test	
Ever	497 (71%)
Past 3 months	252 (36%)
STI diagnosis (ever)	172 (25%)
PrEP awareness	698 (95%)
PrEP use	
Current use	130 (19%)
Past use (not current)	66 (9%)
Condomless anal sex (past 6 months)	315 (45%)
Drug use (past month)	95 (14%)
Alcohol use, 2+ days per week (past month)	168 (24%)

Abbreviations: GED, General Education Development Test; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

Table 2. Feature preference for next-generation PrEP products among young men who have sex with men in the United States

	Douche (n = 139)			On-demand oral PrEP (n = 145)			Injectable PrEP (n = 139)			PrEP implant (n = 146)			bnABs (n = 144)		
Feature		Feature importance (%)	WTP (in $USD)		Feature importance (%)	WTP (in $USD)		Feature importance (%)	WTP (in $USD)		Feature importance (%)	WTP (in $USD)		Feature importance (%)	WTP (in $USD)
Average cost per month		20.2			18.8			20.3			17.8			20.00	
Delivery		6.3			2.1			3.1			3.6				
	Hose		−13.70	0.5 inch pill		Ref.	Self-injected		−12.20	Self-inserted		−19.00			
	Enema		Ref.	1 inch pill		−12.50	Provider		Ref.	Provider		Ref.			
	Bulb		6.40												
Duration		4.3			6.1			17.7			13.7			17.9	
	6–24 hours		Ref.	6–24 hours		Ref.	1 month		−37.30	1 month		Ref.	1 month		Ref.
	1–2 days		6.00	1–2 days		11.00	2 months		Ref.	2 months		33.80	2 months		38.70
	3–5 days		25.80	3–5 days		24.20	4 months		57.20	4 months		50.20	3 months		66.70
	6–7 days		32.20	6–7 days		33.50	6 months		95.80	6 months		84.00	6 months		96.10
							12 months		122.70	12 months		114.20	12 months		131.60
Efficacy		33.3			40.4			39.0			42.1			40.2	
	50%		−225.70	50%		−267.10	50%		−250.80	50%		−298.00	50%		−259.20
	65%		−185.00	65%		−185.90	65%		−181.80	65%		−212.50	65%		−181.90
	80%		−59.60	80%		−84.50	80%		−80.10	80%		−88.60	80%		−81.40
	95%		Ref.	95%		Ref.	95%		Ref.	95%		Ref.	95%		Ref.
	99%		49.70	99%		54.90	99%		39.90	99%		53.90	99%		45.20
Side effects		33.4			30.4			20.00			22.9			18.5	
	None		Ref.	None		Ref.	None		Ref.	None		Ref.	None		Ref.
	Nausea		−119.50	Nausea		−91.50	Nausea		−54.10	Nausea		−97.40	Nausea		−56.00
	Diarrhoea		−123.40	Diarrhoea		−114.80	Fever		−46.40	Fever		−70.70	Fever		−45.00
	Fatigue		−67.90	Fatigue		−50.80	Fatigue		−41.30	Fatigue		−60.20	Fatigue		−29.00
	Kidney decline		−261.70	Kidney decline		−214.50	Soreness at injection site		−27.50	Soreness at insertion site		−28.80	Soreness at injection site		−35.10
	Weight gain		−154.80	Weight gain		−123.80	Weight gain		−132.50	Weight gain		−175.60	Weight gain		−123.90

(*Continued*)

Table 2. (Continued)

	Douche (n = 139)			On-demand oral PrEP (n = 145)			Injectable PrEP (n = 139)			PrEP implant (n = 146)			bnABs (n = 144)		
Feature		Feature importance (%)	WTP (in $USD)		Feature importance (%)	WTP (in $USD)		Feature importance (%)	WTP (in $USD)		Feature importance (%)	WTP (in $USD)		Feature importance (%)	WTP (in $USD)
Timing of use		2.6			2.2										
	30 minutes before sex		Ref.	2–24 hours before sex + for 2 days after sex		Ref.									
	30–60 minutes before sex		1.70	1–2 hours before sex + for 2 days after sex		9.00									
	1–2 hours before sex		1.70	2–24 hours before sex + for 1 day after sex		11.40									
	2–4 hours before sex		−12.50	1–2 hours before sex + for 1 day after sex		16.60									
Timing for delivery														3.4	
													30 minutes		Ref.
													1 hour		−2.50
													2 hours		−9.10
													3 hours		−25.30

Abbreviations: bnABs, broadly neutralizing antibodies; PrEP, pre-exposure prophylaxis; USD, United States Dollar; WTP, willingness to pay.

Table 3. Next-generation PrEP product preference rankings among young men who have sex with men in the United States

Product	Ranking					
	1st	2nd	3rd	4th	5th	6th
Daily oral PrEP	27.1%	23.4%	18.8%	16.3%	10.2%	4.1%
Event-driven oral PrEP	28.0%	23.0%	14.1%	12.8%	18.0%	4.1%
Injectable PrEP	24.6%	19.7%	19.5%	19.0%	10.9%	6.3%
PrEP implant	12.6%	13.6%	17.3%	17.3%	21.9%	17.2%
bnABs	4.5%	11.6%	14.6%	22.6%	24.3%	22.3%
Rectal douche	3.1%	8.5%	15.8%	11.9%	14.6%	46.0%

Abbreviations: bnABs, broadly neutralizing antibodies; PrEP, pre-exposure prophylaxis.

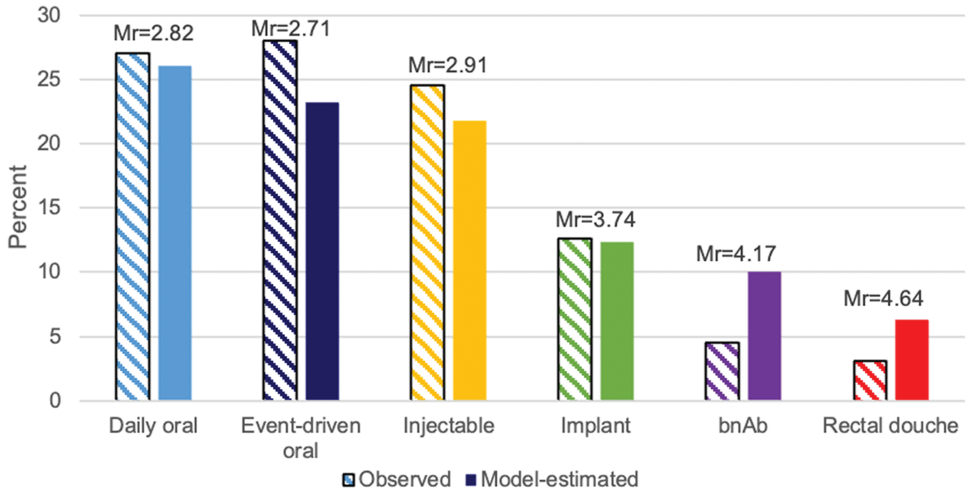

Figure 2. Observed and model-estimated top-ranked preferences of PrEP modalities among young men who have sex with men in the United States. Abbreviations: bnABs, broadly neutralizing antibodies; Mr, mean ranking.

23% for event-driven oral PrEP, 22% for injectable PrEP, 12% for PrEP implant, 10% for bnAb infusion and 6% for PrEP rectal douche. Figure 2 shows the observed and model-estimated top-ranked rankings of PrEP modalities.

In the rank order regression model, daily oral PrEP was preferred over all next-generation modalities (OR vs. daily oral PrEP: event-driven oral PrEP = 0.89, $p = 0.058$; injectable PrEP = 0.83, $p = 0.005$, PrEP implant = 0.48, $p < 0.0001$; bnAb infusion = 0.38, $p < 0.0001$; PrEP rectal douche = 0.24, $p < 0.0001$) (Table 4).

3.3 | Correlates of preferred products

While the magnitude differed across levels of the potential correlates examined (described below), the odds of selecting daily oral PrEP was not significantly lower than the odds of choosing any next-generation modality. Notably, over 90% of individuals ranking *daily oral PrEP* first agreed or strongly agreed that they chose this product due to ease of use, perceived protection against HIV and lack of discomfort (Table 5).

3.3.1 | *Event-driven oral*

Participants who reported any food insecurity in the past 3 months were 28% less likely to prefer event-driven versus daily oral PrEP than those who did not experience food insecurity ($p < 0.05$). Moreover, participants reporting CAS in the past 6 months were 33% less likely to prefer event-driven to daily oral PrEP ($p = 0.002$). Finally, compared to individuals who had never used PrEP, current users were 52% less likely to prefer event-driven over daily oral PrEP ($p < 0.0001$) (Table 4).

The highest endorsed reasons for ranking *event-driven oral PrEP* first included ease of use, ability to stop taking it, no impact on daily routine, perceived protection against HIV and lack of discomfort (Table 5).

3.3.2 | *Injectable*

Compared to individuals 15–17 and 18–20 years, participants 21–24 years old were 21% and 47% more likely to prefer injectable PrEP to daily oral PrEP ($p < 0.05$). Additionally, participants who had prior HIV tests were 74% more likely to prefer injectables to daily oral compared to those who had not been tested ($p < 0.001$), and participants reporting recent CAS were 27% less likely to prefer injectables to daily oral PrEP ($p = 0.02$).

In bivariate analysis, YMSM with their own health insurance had greater odds of preferring injectables over daily oral PrEP compared to those uninsured or covered by their

Table 4. Correlates of preferred PrEP modality rankings among young men who have sex with men in the United States

	Event-driven oral		Injectable		Implant		bnAb		Rectal douche		Omnibus omnibus tests		
	OR	*p*-value	OR	*p*-value	OR	*p*-value	OR	*p*-value	OR	*p*-value	Unadj. models	Adj. models	
Age											**0.0028**	**0.0278**	§
15–17 (ref.)	0.74	0.65	**0.78**	**0.03**	**0.37**	**0.006**	**0.35**	**0.06**	0.21	0.45			
18–21	0.87		**0.64**		**0.35**		**0.30**		0.28				
21–24	0.91		**0.94**		**0.55**		**0.43**		0.23				
Race											0.2942		
White (ref.)	0.88	0.90	0.81	0.74	0.45	0.49	0.33	0.05	0.21	0.11			
Non-White	0.90		0.85		0.49		0.43		0.27				
Ethnicity											0.8665		
Latino (ref.)	0.85	0.70	0.85	0.87	0.51	0.53	0.42	0.40	0.24	0.99			
Non-Latino	0.81		0.87		0.56		0.48		0.24				
Sexual orientation											0.6694		
Gay (ref.)	0.85	0.16	0.84	0.93	0.47	0.60	0.37	0.35	0.24	0.35			
Not gay	1.06		0.82		0.51		0.43		0.27				
Food insecurity											0.0857	**0.0261**	§
Yes (ref.)	**0.68**	**0.0455**	0.78	0.65	0.51	0.62	0.39	0.90	0.19	0.10			
No	**0.94**		0.85		0.47		0.38		0.26				
PrEP use											**<0.0001**	**0.0001**	§
Never (ref.)	**1.04**	**<0.0001**	0.80	0.56	**0.42**	**0.005**	**0.37**	**0.02**	**0.26**	**0.04**			
Current use	**0.50**		0.81		**0.51**		**0.29**		**0.16**				
Past use	**0.88**		1.02		**0.87**		**0.60**		**0.25**				
Ever HIV test											**<0.0001**	**0.0297**	§
Yes (ref.)	0.88	0.7	**0.94**	**<0.001**	**0.53**	**<0.001**	**0.42**	**0.002**	0.24	0.64			
No	0.93		**0.54**		**0.31**		**0.26**		0.23				
Ever STI diagnosis											**0.0002**		♯
Yes (ref.)	0.78	0.24	**1.05**	**0.03**	**0.68**	**0.001**	0.44	0.17	0.23	0.67			
No	0.93		**0.76**		**0.42**		0.36		0.24				
Condomless anal sex											**0.0014**	**0.0134**	§
Any (ref.)	**0.72**	**0.002**	**0.69**	**0.02**	0.49	0.6	0.34	0.22	0.23	0.53			
None	**1.06**		**0.95**		0.46		0.40		0.25				
Insurance											**0.0244**	0.3998	§
None (ref.)	0.74	0.53	**0.52**	**0.006**	**0.35**	**0.03**	0.33	0.14	0.21	0.81			
Own insurance	0.85		**1.10**		**0.60**		0.46		0.25				
Parents' insurance	0.93		**0.78**		**0.44**		0.35		0.24				
Primary care provider											0.8528		
Yes (ref.)	0.89	0.98	0.85	0.55	0.46	0.50	0.38	0.69	0.24	0.88			
No	0.89		0.76		0.52		0.41		0.25				
Healthcare needs met											**0.0418**	**0.0535**	§
Yes (ref.)	0.88	0.73	0.87	0.19	0.50	0.15	0.23	0.12	0.39	0.69			
No	0.93		0.70		0.39		0.30		0.37				
Any drug use											**0.0206**	0.273	§
Yes (ref.)	0.84	0.73	0.97	0.31	**0.77**	**0.003**	0.49	0.11	0.28	0.33			
No	0.90		0.80		**0.44**		0.36		0.23				

(*Continued*)

Table 4. (Continued)

	Event-driven oral		Injectable		Implant		bnAb		Rectal douche		Omnibus omnibus tests		
	OR	*p*-value	OR	*p*-value	OR	*p*-value	OR	*p*-value	OR	*p*-value	Unadj. models	Adj. models	
Alcohol use											**0.0371**		
2+ drinks/week (ref.)	0.45	0.13	0.22	0.55	**0.62**	**0.02**	**1.03**	**0.05**	0.92	0.74			♯
<2 drinks/week	0.36		0.25		**0.43**		**0.77**		0.88				

Notes: Odds ratios (ORs) in the table refer to the odds of selecting each of the modalities in comparison to daily oral PrEP (our reference category).
p-values in the modality columns refer to the hypothesis of whether ORs for modalities are equal across all categories of potential correlates we examined.
Omnibus tests (last two columns) examined the significance of each potential correlate across all modalities in unadjusted and adjusted models. *p*-values in these columns examine whether ORs were different between categories of potential correlates across all modalities.
Bolded values indicate results with *p*-value < 0.05.
Abbreviations: bnABs, broadly neutralizing antibodies; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infections.
[§]Included in adjusted regression models (Omnibus *p*-value < 0.10 in unadjusted models, except STI diagnosis and alcohol use).
[♯]Not included in adjusted models due to high collinearity with another variable.

Table 5. Reasons for top-ranked PrEP product among young men who have sex with men in the United States

	Agree/strongly agree with reasons for selecting top choice *N* (%)					
	Daily oral PrEP *n* = 191	Intermittent oral PrEP *n* = 197	Rectal douche *n* = 22	Injectable PrEP *n* = 173	PrEP implant *n* = 89	bnAbs *n* = 32
Would be easy to use	189 (99.0%)	194 (98.5%)	19 (86.4%)	160 (92.5%)	85 (95.5%)	29 (90.6%)
Would have less concerns about side effects	166 (86.9%)	160 (81.2%)	16 (72.7%)	117 (67.6%)	57 (64%)	22 (68.8%)
Would NOT impact daily routine	170 (89.0%)	189 (95.9%)	17 (77.3%)	160 (92.5%)	86 (96.6%)	28 (87.5%)
Would NOT be uncomfortable to use	177 (92.7%)	184 (93.4%)	17 (77.3%)	132 (93.1%)	78 (87.6%)	22 (68.8%)
Would NOT worry about remembering to take	107 (56.0%)	135 (68.5%)	18 (81.8%)	161 (93.1%)	88 (98.9%)	30 (93.8%)
Would NOT worry about having product stolen	152 (79.6%)	153 (77.7%)	17 (77.3%)	162 (93.6%)	86 (96.6%)	27 (84.4%)
Would NOT worry about people finding out I'm taking	134 (70.2%)	142 (72.1%)	17 (77.3%)	156 (90.2%)	85 (95.5%)	29 (90.6%)
Would NOT worry about my use of drugs and alcohol interfering with PrEP	106 (55.5%)	105 (53.3%)	16 (72.7%)	127 (73.4%)	53 (59.6%)	23 (71.9%)
Would make sex life more pleasurable	162 (84.8%)	160 (81.2%)	19 (86.4%)	156 (90.2%)	74 (83.1%)	21 (65.6%)
Would be able to stop taking when I wanted	171 (89.5%)	191 (97.0%)	20 (90.9%)	108 (62.4%)	27 (30.3%)	19 (59.4%)
Would make me feel more protected against HIV	187 (97.9%)	184 (93.4%)	18 (81.8%)	165 (95.4%)	89 (100%)	29 (90.6%)

Abbreviations: bnABs, broadly neutralizing antibodies; HIV, human immunodeficiency virus; PrEP, pre-exposure prophylaxis.

parents' plan. However, these differences did not remain significant in adjusted models ($p = 0.40$) (Table 4).

The highest endorsed reasons for ranking *injectable PrEP* first included perceived protection against HIV, not worrying about a stolen product, not worrying about remembering to take it, ease of use, no impact on daily routine, not worrying about people finding out they are taking PrEP, improved sex life and lack of discomfort (Table 5).

3.3.3 | Implant

Compared to individuals 15–17 and 18–20 years, participants 21–24 years old were 51% and 57% more likely to prefer implants to daily oral PrEP ($p < 0.01$). Participants reporting prior HIV tests were 74% more likely to prefer implants compared to those without prior tests ($p < 0.001$), and, compared to PrEP-naïve individuals, past PrEP users were 21% more likely to choose PrEP implants over daily oral PrEP ($p = 0.001$).

In bivariate models, the odds of choosing PrEP implants over daily oral PrEP were greater among individuals with their own insurance, and among individuals reporting any drug use in the past 30 days. Yet, these associations did not remain significant in adjusted models ($p = 0.40$ and $p = 0.27$, respectively) (Table 4).

Reasons for ranking *PrEP implants* first were perceived protection against HIV, not worried about remembering to take it, no impact on daily routine, not worried about stolen product, ease of use and not worried about people finding out they are taking PrEP (Table 5).

3.3.4 | bnAb

Participants 21–24 years old were 22% and 43% more likely to prefer bnAb infusions to daily oral PrEP compared to individuals 15–17 and 18–20 years, respectively ($p = 0.06$). Participants who had prior HIV test were 65% more likely to prefer bnAb to daily oral PrEP in comparison to individuals not previously tested ($p < 0.01$). Past PrEP users were 60% more likely to choose bnAb infusions ($p = 0.03$) over daily oral PrEP compared to individuals who had never used PrEP (Table 4).

For *bnAb infusions*, the highest endorsed reasons included not worried about remembering to take it, ease of use, not worried about people finding out they are taking PrEP and perceived protection against HIV (Table 5).

3.3.5 | Rectal douche

Finally, rectal douches were ranked lowest on average. Only PrEP use was a significant correlate of rectal douche preference, whereas current PrEP users were 38% less likely to prefer rectal douches over daily oral PrEP ($p = 0.01$) compared to never users (Table 4).

The only reason that was endorsed by ≥90% of participants who ranked rectal douche as their top choice was the ability to stop taking it (Table 5).

4 | DISCUSSION

The present study—which is to our knowledge the first to quantitatively explore in substantial depth the acceptability and preferences for a broad range of PrEP products among YMSM—used multiple innovative methods to explore both within and between product preferences.

Using a discrete-choice conjoint analysis, which simulates actual decision-making processes for existent and hypothetical PrEP formulations [33], we found that participants prioritized efficacy, absence of side effects and costs across all PrEP products. Additionally, for long-acting products (e.g. injectable, implants and bnAb), duration of efficacy was also prioritized. Conversely, delivery mechanism and timing of use or delivery did not demonstrate importance. Our findings are aligned with previous studies showing cost, efficacy and side effects to drive preferences for oral and injectable PrEP formulations among adult MSM and other at-risk U.S. populations [33, 38–40]. These findings should inform the development of these next-generation products and how interventions and public awareness campaigns introduce these products when they come to market. For example, research on women's contraceptive decision-making showing efficacy and side effects as key product attributes [41, 42] has informed the development of decision aids to facilitate contraceptive choices [43].

The rank-choice analysis demonstrated that daily oral PrEP was preferred over all next-generation modalities, which contradicts prior studies that demonstrated a preference for injectable PrEP among YMSM [24, 44]; however, these prior studies did not provide a broad array of PrEP options and did not take into account the full range of rankings, and as such may have over-estimated the preference for next-generation products. Importantly, our findings suggest that the next-generation products may not be, without additional efforts, a panacea to PrEP expansion. Efforts to address the underlying barriers to PrEP use among YMSM must not assume that simply changing technology will create demand. Rather, an interdisciplinary and multi-level approach is needed to remove barriers and improve communication about these products [45]. Resources to support these efforts should be prioritized to ensure the optimal uptake of oral PrEP and the newly FDA-approved bi-monthly injectable PrEP in the form of cabotegravir extended-release injectable suspension [3, 46].

Our study also found differences in preference rankings by socio-demographic and behavioural characteristics. Individuals who were older age, had prior HIV testing history and were insured were more likely to prefer long-acting PrEP products than their peers, suggesting that individuals with a greater connection to the healthcare system may be more open to long-acting next-generation modalities. Conversely, this also suggests that next-generation PrEP products may not reach, without additional efforts, those with higher HIV risk and larger barriers to PrEP care (e.g. food insecure and not on own insurance). Notably, while preferences for injectable PrEP were not different across PrEP use categories, compared to current PrEP users, individuals who had never used PrEP were significantly more likely to prefer event-driven oral PrEP and rectal douches. Previous work has shown that event-driven oral PrEP may appear appealing to some PrEP-naïve

individuals, but challenges related to planning sexual activity may make some of these individuals eventually switch to daily regimens [47]. Additionally, individuals reporting prior PrEP use were significantly more likely to prefer implants, bnAb and rectal douches, which may indicate an interest in novel modalities among individuals who have tried and discontinued daily oral PrEP due to challenges with daily regimens. This may inform how intervention strategies should differ for distinct groups (e.g. early adopters vs. late adopters), and that equity must be centred in all efforts to rollout new products (e.g. ensuring affordable access to next-generation modalities regardless of health insurance) [48]. Nonetheless, all groups continued to rank daily oral PrEP ahead of next-generation options, suggesting that in addition to the need for broad outreach as new products are developed and come to market, efforts to increase uptake and adherence to oral PrEP, which has proven efficacy and an established long-term safety profile, must be continued and strengthened.

These findings should be considered in light of some limitations. First, while this was a large, diverse, national survey, recruitment was primarily conducted online, and as such, the sample may not represent all YMSM in the United States. Further studies on modality preferences are needed with other key populations in the HIV epidemic, such as transgender women and people who inject drugs. Additionally, a number of these products are still in development and precise information on their efficacy, side effects and other characteristics was not available when our study was conducted, and as such were presented as hypothetical. Familiarity with next-generation products was not measured. Although we used descriptions of the products developed and tested in cognitive interviews with YMSM [34], preferences may differ if or when the products are available. Lastly, the conjoint experiments were designed to examine preferred features and willingness to pay for product features; however, because each participant was randomized to review one product, we could not quantitatively compare feature preferences across products.

5 | CONCLUSIONS

Both low rates of PrEP use and suboptimal adherence among YMSM [7, 10, 12] suggest that new modalities are needed to ensure those at risk for HIV acquisition have access to this potentially transformative prevention tool. While scientists are actively developing and testing the efficacy of new PrEP formulations [49], it is essential that end-users' preferences for and concerns about PrEP products are understood and considered. Ensuring the preferences for features within products and preferences across products are considered will increase the acceptability of these products and the eventual penetration and expansion of PrEP across communities.

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COMPETING INTERESTS

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AUTHORS' CONTRIBUTIONS

PKV, RD and WL performed the research. KBB, KHM, LH-W, DTdS and JB designed the research study. KBB, PKV and JB analysed the data. KBB and PKV led the writing of the paper. All authors provided edits to the paper, and have read and approved the final manuscript.

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DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REVIEW

Systematic review of the values and preferences regarding the use of injectable pre-exposure prophylaxis to prevent HIV acquisition

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Abstract

Introduction: Pre-exposure prophylaxis (PrEP) is an important HIV prevention option. Two randomized trials have provided efficacy evidence for long-acting injectable cabotegravir (CAB-LA) as PrEP. In considering CAB-LA as an additional PrEP modality for people at substantial risk of HIV, it is important to understand community response to injectable PrEP. We conducted a systematic review of values, preferences and perceptions of acceptability for injectable PrEP to inform global guidance.

Methods: We searched nine databases and conference websites for peer-reviewed and grey literature (January 2010–September 2021). There were no restrictions on location. A two-stage review process assessed references against eligibility criteria. Data from included studies were organized by constructs from the Theoretical Framework of Acceptability.

Results: We included 62 unique references. Most studies were observational, cross-sectional and qualitative. Over half of the studies were conducted in North America. Men who have sex with men were the most researched group. Most studies (57/62) examined injectable PrEP, including hypothetical injectables (55/57) or placebo products (2/57). Six studies examined CAB-LA specifically. There was overall interest in and often a preference for injectable PrEP, though there was variation within and across groups and regions. Many stakeholders indicated that injectable PrEP could help address adherence challenges associated with daily or on-demand dosing for oral PrEP and may be a better lifestyle fit for individuals seeking privacy, discretion and infrequent dosing. End-users reported concerns, including fear of needles, injection site pain and body location, logistical challenges and waning or incomplete protection.

Discussion: Despite an overall preference for injectable PrEP, heterogeneity across groups and regions highlights the importance of enabling end-users to choose a PrEP modality that supports effective use. Like other products, preference for injectable PrEP may change over time and end-users may switch between prevention options. There will be a greater understanding of enacted preference as more end-users are offered anti-retroviral (ARV)-containing injectables. Future research should focus on equitable implementation, including real-time decision-making and how trained healthcare providers can support choice.

Conclusions: Given overall acceptability, injectable PrEP should be included as part of a menu of prevention options, allowing end-users to select the modality that suits their preferences, needs and lifestyle.

Keywords: acceptability; injectable PrEP; long-acting injectable cabotegravir; pre-exposure prophylaxis; PrEP; values and preferences

Additional information may be found under the Supporting Information tab of this article.

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1 | INTRODUCTION

Despite the availability of HIV prevention tools, HIV remains a significant public health issue, with approximately 1.5 million people acquiring HIV in 2021 [1]. Pre-exposure prophylaxis (PrEP) is the use of antiretroviral drugs to reduce the risk of HIV acquisition among those not infected [2]. In 2021, an estimated 1.6 million people worldwide were using oral PrEP, which was under the United Nations 2025 target of 10 million people [3]. Further complicating the uptake of oral PrEP is the challenge of persistence. To be effective, oral PrEP does

not need to be taken continuously, but its impact relies on adherence during periods of risk. Clinical trials have demonstrated that effectiveness is substantially higher among more adherent participants compared to overall study populations [4–10]. Implementation studies have also demonstrated challenges to the effective use of oral PrEP during periods of risk [11], with uptake and persistence varying across at-risk populations [12, 13]. Daily pill-taking can be burdensome for some, including young people [14], contributing to ineffective use.

In January 2021, the dapivirine vaginal ring (DVR) became the second PrEP product recommended by the World Health Organization (WHO) [2]. Although women have expressed interest in the DVR, particularly in east and southern Africa, some have reported discomfort with ring insertion or difficulties with effective use [15]. Newer PrEP products, especially long-acting modalities, could increase PrEP uptake and use. In 2021, results from two randomized trials on the use of long-acting injectable cabotegravir (CAB-LA) as PrEP, HPTN 083 and HPTN 084, were published [16, 17]. These trials stopped early after demonstrating CAB-LA's statistically superior efficacy at preventing HIV acquisition compared to oral tenofovir/emtricitabine among cisgender men and women and transgender (trans) women. Although CAB-LA and oral PrEP were effective in both trials, adherence to CAB-LA was significantly higher than for oral PrEP. In HPTN 084, 93% of women took CAB-LA as prescribed compared with 42% of women taking oral PrEP [18]. In December 2021, CAB-LA as PrEP gained approval from the U.S. Food and Drug Administration (FDA) for adolescents and adults at risk for sexual acquisition of HIV [19], with WHO also recommending CAB-LA as PrEP in July 2022 [20].

Understanding acceptability, interest in and views about injectable PrEP from potential end-users is key to informing global guidelines to facilitate uptake, thereby increasing coverage of HIV prevention among populations at substantial risk. As such, we conducted a systematic review assessing end-user and stakeholder values, preferences and perceptions of acceptability related to injectable PrEP. We included peer-reviewed and grey literature examining all forms of injectable PrEP, including CAB-LA, placebo injections and hypothetical injectable PrEP use.

2 | METHODS

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [21]. A protocol was reviewed by the WHO and prospectively registered in PROSPERO (CRD42021285299). Database searches and article screening were conducted concurrently with a review on safety and efficacy of CAB-LA as PrEP (CRD42021290713) [22]. Results are reported separately.

2.1 | Databases and search terms

In October 2021, we searched for peer-reviewed and grey literature in databases that sourced clinical or social and behavioural research on the use of injectable PrEP globally. We worked with a reference librarian to construct a search strategy for the following databases: PubMed, Global Health, Cochrane Register of Controlled Trials, Embase and the Cumulative Index to Nursing and Allied Health Literature. Abstracts from the following conferences were searched: International AIDS Conference; International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention; Conference on Retroviruses and Opportunistic Infections; and HIV Research for Prevention Conference.

Within each database, we searched for articles published between 1 January 2010 and 27 September 2021. Because we searched for clinical as well as social and behavioural research, we opted for an inclusive search strategy that included three main constructs: injectable modalities AND PrEP/prevention AND HIV. (Supporting Information Appendix A includes a comprehensive list of terms.)

2.2 | Inclusion and exclusion criteria

Articles needed to meet eligibility criteria (Table 1). We included articles exploring values and preferences for injectable PrEP among diverse stakeholders regardless of language or location of intervention. We excluded articles that did not include primary data, those containing duplicative data or interim results if final results were available.

2.3 | Citation screening, data management and analysis

After conducting database searches, a de-duplicated list of references was uploaded into Covidence, a systematic review screening and data management software. Four reviewers used a multi-phase screening strategy to determine inclusion (stage 1: title/abstract review; stage 2: full-text review). Disagreements were resolved by consensus through team discussions. Quantitative and qualitative data were extracted independently by two reviewers using a standardized Excel-based form. Differences in data extraction were also resolved through consensus. We gathered the following from each included study: (1) study identification: authors, reference type and publication year; (2) description: objectives, location, population characteristics, intervention description, study design and sample size; and (3) outcomes: quantitative or qualitative measures, main findings, strengths, limitations and conclusions. We also coded references to relevant constructs from the Theoretical Framework of Acceptability (TFA; Table 2) [25].

Findings were summarized and reported in narrative and tabular formats. Results are organized by constructs from the TFA. Peer-reviewed articles were also assessed for risk of bias using the Joanna Briggs Institute (JBI) Critical Appraisal Tools [27], a suite of checklists available by study design. After selecting the appropriate checklist based on each study's design, the research team appraised each article and summarized the results.

3 | RESULTS

We identified 2277 records through our database search and 14 records through other sources, yielding 1462 unique

Table 1. Inclusion criteria for the review on values and preferences for injectable pre-exposure prophylaxis (PrEP)

Criteria	Eligibility
Article type	a. Published in peer-reviewed journal between 1 January 2010 and 27 September 2021; OR b. Presented as abstract at a scientific conference between January 2010 and September 2021; OR c. Unpublished work containing relevant data
Intervention	Studies reporting primary data on injectable PrEP, including CAB-LA, placebo products or hypothetical injectable PrEP use
Study population	a. Populations at substantial risk of HIV acquisition; OR b. Healthcare workers/stakeholders involved in any aspect of provision of injectable PrEP
Study design	a. Qualitative studies, including in-depth interviews or focus group discussions; OR b. Experimental or non-experimental studies quantitatively evaluating the use of injectable PrEP to prevent HIV among people at substantial risk of HIV infection
Key outcomes	a. Awareness of injectable PrEP b. Values and preferences related to injectable PrEP c. Feasibility[a], acceptability[b] or satisfaction[c] with injectable PrEP d. Concerns regarding injectable PrEP e. Willingness to use injectable PrEP f. Barriers and facilitators of injectable PrEP use

[a]Feasibility is defined as "the extent to which a new treatment, or an innovation, can be successfully used or carried out within a given agency or setting" [23, 24].
[b]Acceptability is defined as "a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention" [25].
[c]Satisfaction is "the state of being content or fulfilled with a service or intervention based on one's needs and desires or being content with the general service-delivery experience" [26]. Abbreviations: PrEP, pre-exposure prophylaxis; CAB-LA, long-acting injectable cabotegravir.

Table 2. Constructs of acceptability for injectable PrEP, adapted from the Theoretical Framework of Acceptability developed by Sekhon et al. [25]

Construct	Operationalization	Outcomes
Affective attitude	Overall feelings about an intervention	Satisfaction with, overall acceptability, liking or recommending injectable PrEP
Burden	Perceived amount of effort to participate in the intervention	Ease of use and facilitators; perceived challenges or concerns related to injectable PrEP
Ethicality	Extent of fit with an individual's value system	Discretion of product use; fitting with lifestyle preferences; perceived stigma
Intervention coherence	Extent that participant understands the intervention/how it works	Understanding how injectable PrEP prevents HIV
Opportunity costs	Extent that benefits, profits or values must be given up to engage in the intervention	Trade-offs of taking injectable PrEP
Perceived effectiveness	Perception that intervention is likely to achieve its purpose	Degree of protection; perceived ability of injectable PrEP to prevent HIV
Self-efficacy	Participant's confidence that they can perform the behaviours required to participate in the intervention	Ability to use/adhere to injectable PrEP; ability to regularly attend clinic visits to receive the injections

Abbreviation: PrEP, pre-exposure prophylaxis.

records (Figure 1). Ultimately, 100 records met inclusion criteria; 62 records (53 articles and 9 abstracts) were fully extracted and organized below by acceptability constructs and groups, with findings specific to CAB-LA also reported separately. Thirty-eight records briefly mentioned preferences for injectable PrEP (e.g. abstracts with few details, articles including only one question mentioning injectable PrEP) and were extracted separately (Supporting Information Appendix B).

3.1 | Study characteristics

Of 62 records, most were observational, cross-sectional and qualitative studies examining end-user values and preferences in approximately 41 countries (one report included participants from 29 unnamed countries), with over 50% of articles from North America and one-third from sub-Saharan Africa (SSA; Table 3). Most examined injectable PrEP

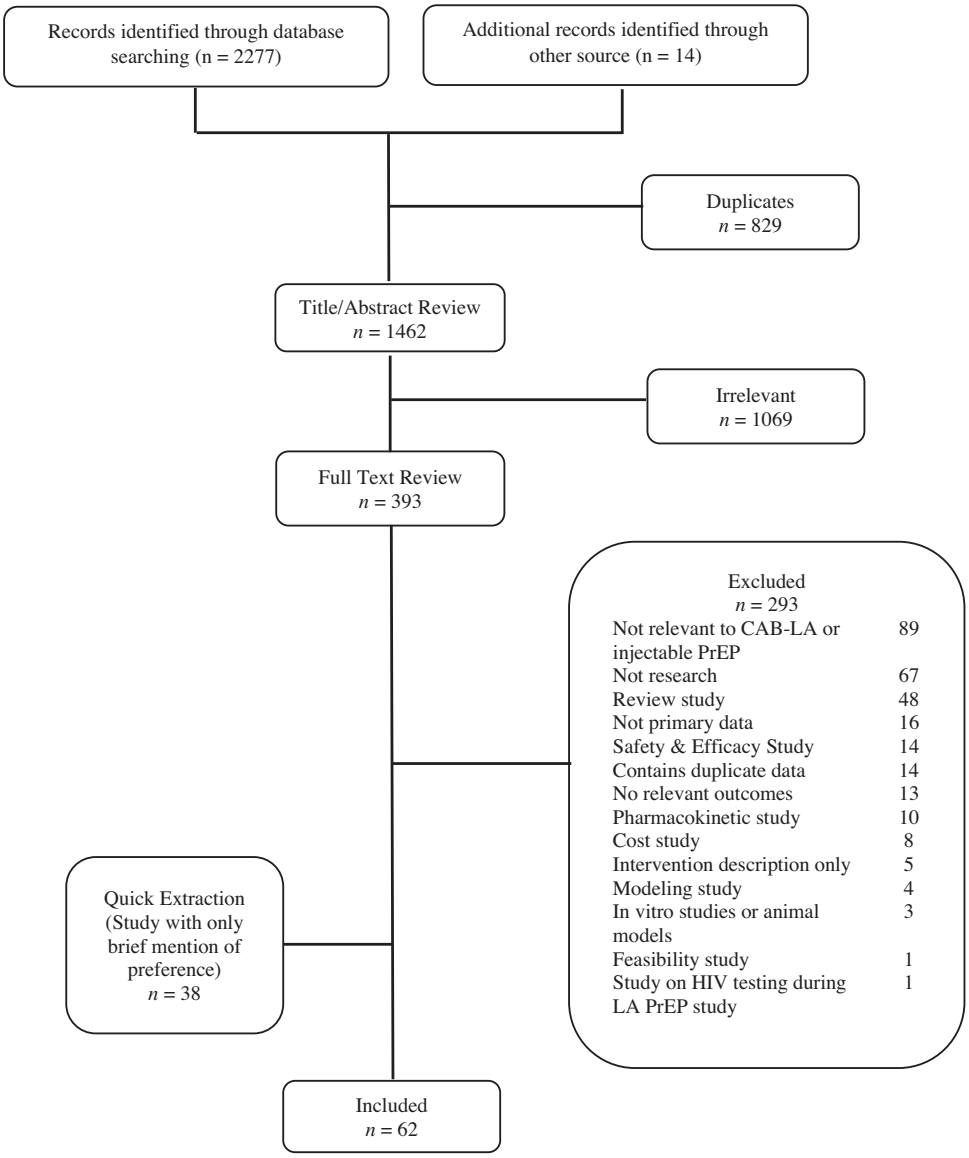

Figure 1. PRISMA diagram.

generally, including hypothetical or placebo injections. Six studies examined CAB-LA specifically. Men who have sex with men (MSM) were the most researched group. Table 4 summarizes the results from included studies.

3.2 | Quality assessment

We assessed 53 full-text articles for risk of bias using JBI criteria. Overall, included studies met most checklist criteria, indicating a low-to-medium risk of bias for individual studies. There were specific limitations by the study design/checklist. For example, across 27 qualitative studies, all lacked a statement locating the researcher culturally or theoretically. Only one mentioned the influence of the researcher on the research and vice versa. We applied the JBI checklist for cross-sectional studies to 22 references with quantitative outcomes. All used appropriate statistical analysis; however, five did not identify confounding factors or state strategies to address them. Four studies were assessed with the checklist for randomized controlled trials, but none met all criteria. The main limitation was a lack of clarity as to whether the outcome assessors were blinded to treatment assignments and if participants were analysed in the groups to which they were randomized.

3.3 | CAB-LA-specific findings

Six studies examined values and preferences for CAB-LA: three from the ECLAIR trial [40, 41, 43]; one each from HPTN 077 [88] and HPTN 084 [63]; and a qualitative study with sex workers (men, women, trans women) in India [74]. Across ECLAIR, a U.S.-based placebo-controlled trial among men at low risk for acquiring HIV, participants reported willingness to use or high satisfaction with CAB-LA [40, 41, 43].

Table 3. Characteristics of studies included in detailed extraction

Characteristics	*N* of studies (%)
Study type	
Peer-reviewed	53 (85)
Grey literature	9 (15)
Study design	
Observational study	58 (94)
Randomized control trial	4 (6)
Location[a]	
North America	35 (57)
Sub-Saharan Africa	19 (31)
East Asia and Pacific	5 (8)
Europe and Central Asia	5 (8)
Latin American and the Caribbean	2 (3)
South Asia	2 (3)
Modality	
Injectable (generic)	53 (85)
CAB-LA	6 (10)
Injectable multipurpose prevention technology	2 (3)
Rilpivirine	1 (2)
Group identifier[b]	
MSM	26 (42)
Women only	11 (18)
Adolescents and young people	8 (13)
Current PrEP users	8 (13)
Trans women and men	6 (10)
Care providers	5 (8)
People who inject drugs	5 (8)
Sex workers (male and female)	5 (8)
JBI checklist[c]	
Qualitative	27 (51)
Cross-sectional	22 (41)
Randomized control trial	4 (8)

[a]A study could include more than one location. Geographic locations were defined according to World Bank Classifications.
[b]A study could include more than one group identifier.
[c]Only full-text peer-reviewed articles were assessed with a JBI checklist. Abbreviations: PrEP, pre-exposure prophylaxis; JBI, Joanna Briggs Institute.

Injection pain was common [41], yet most reported satisfaction with the product despite side effects and pain/discomfort [43]. HPTN 084 participants overwhelmingly preferred CAB-LA to daily oral PrEP [63]. Most HPTN 077 participants found the number, frequency and location of injections initially acceptable [80], though future interest in CAB-LA was higher in non-U.S. sites. HPTN 077 participants in the placebo arm reported higher acceptability of physical experiences [88]; however, there was no relationship between injection site pain and future interest in CAB-LA [88]. ECLAIR participants and SSA women from HPTN 084 appreciated that CAB-LA afforded more privacy and improved adherence over pills [16, 63]. Finally, sex workers in India were willing to use CAB-LA, especially those with prior oral PrEP or depot-medroxyprogesterone acetate (DMPA) experience [74].

3.4 | Affective attitude

Nearly, all studies reported on affective attitude (Table 5). Most explored stated preference (i.e. preference for hypothetical products or attributes). Less common were reports of enacted preference (i.e. experimentation with multiple modalities and subsequent choice of a preferred product) or preference based on experience with placebos or active injectables. Where possible, we provide details to clarify enacted preference or preference based on experience.

3.4.1 | U.S.-based MSM

Injectable PrEP was often, though inconsistently, preferred among U.S.-based MSM. ECLAIR participants reported higher satisfaction with CAB-LA over oral PrEP and higher interest in future use [40, 43]. Although 25% of participants receiving CAB-LA were dissatisfied with the pain/discomfort associated with the injection, 74% were satisfied enough to continue CAB-LA [43]. Other studies also reported a willingness to receive injectable PrEP [28] or a preference for injectable PrEP compared to daily oral PrEP [32, 39, 44, 46], on-demand PrEP [35, 52], penile or rectal gels or anal suppositories [44, 52]. However, two studies reported a preference for subdermal implants over injectables [33, 46]. Others reported a preference for daily oral PrEP over injectables [33], since adherence to daily oral PrEP was already high [37]. Overall, there were conflicting reports about how oral PrEP experience influenced preferences. Two studies reported greater interest in potentially using injectable PrEP among oral PrEP-naïve versus oral PrEP-experienced participants [36, 50], but a third study reported daily PrEP users as more likely to endorse future injectable PrEP use [52]. Some MSM noted the value of long-acting PrEP could increase if proven more effective or lower cost than oral PrEP [37]. Three studies noted a preference for the most effective method [32, 33, 36].

U.S.-based adolescents assigned male at birth more often preferred condoms or yearly implants compared with injectables or quarterly implants [51]. More Black and Latino MSM youth preferred daily oral PrEP, followed by PrEP implants, then injectables [66].

3.4.2 | MSM in other regions

Globally, preferences for injectable PrEP among MSM varied. MSM in India preferred injectables administered monthly or every 2 months over daily oral PrEP [29]. In China, most were willing to use injectable PrEP over pills [42] or willing to use on-demand PrEP, followed by injectable PrEP, then daily oral pills [47]. Meanwhile, MSM reported a preference for rectal microbicide gels over injectables in Vietnam [31], oral PrEP over injectables in Kenya [34], injectables over implants in South Africa [48] and injectables followed by daily PrEP, then on-demand PrEP in Latin America [49]. Ukrainian choice-based analyses reported a stated preference for injectable PrEP for younger [45], well-educated MSM [38, 45] and those living off a lower income [38], with cost an important consideration.

Table 4. Summary of studies included in detailed extraction

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
MSM	Meyers, K. et al. (2014)	North America	Observational study	197	Injectable PrEP (hypothetical products)	1. Over 80% of participants stated that they would definitely or probably be willing to receive injectable PrEP if it could effectively prevent HIV aquisition. 2. Higher socio-economic status corresponded with lower willingness to use injectable PrEP (x2 = 5.38, df = 2, $p = 0.07$), as did some college education (x2 = 10.78, df = 2, $p = 0.004$). 3. In bivariate analysis, compared to those with a college or post-graduate degree, those with some college or technical school had higher odds of being willing to try injectable PrEP (OR = 3.9, 95% CI: 1.7–9.1); however, there was no linear trend across level of education. Those with no partners in the last 3 months had lower odds of being willing to use injectable PrEP as compared to those who reported two or more partners (OR = 0.4, 95% CI: 0.1, 0.9). In the multivariable model, education and number of partners retained significance at $p < 0.10$. 4. 79.2% ($n = 156$, $p < 0.001$) stated they would prefer an injection administered every 3 months. 5. From the bivariate model: if PrEP was accompanied by free sexual health services, one-on-one counselling around PrEP use and sexual health, text-based support, of if it was free, all had significantly higher odds of being willing to use injectable PrEP (ORs ranging from 3.0 to 4.6) than those who disagreed with those statements.	[28]
	Chakrapani, V. et al. (2015)	South Asia	Observational study	26	Injectable PrEP (hypothetical products)	1. Some MSM reported a preference for injectable PrEP administered monthly or every 2 months over daily oral PrEP. 2. An advantage of injections was that it could solve problems on where to safely store and conceal PrEP at home or how to carry pills during travel.	[29]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Meyers, K. et al. (2016)	North America	Observational study	62	Injectable PrEP (hypothetical products)	1. Sixty-eight percent of participants would "definitely" or "probably" switch to injectable PrEP if it were FDA approved. 2. Product-specific motivating factors for "switchers" included: convenience, not having to adhere to daily pill and not carrying pills around. Psychological factors included desire to eliminate anxiety around missed dosing and a belief that a shot would mean "less to think/worry about." 3. Those not willing to switch from oral to injectable PrEP cited scientific concerns, including safety, efficacy and waning protection. 4. Product-level disadvantages included pain and inconvenience of scheduling follow-up injections. Non-switchers reported that swallowing a pill daily made them feel like they were in control of their health and would not trust the shot's protection. They expressed satisfaction with oral PrEP and unwillingness to be an early adopter of a novel approach.	[30]
	Oldenburg, C. E. et al. (2016)	East Asia and Pacific	Observational study	548	Injectable PrEP (hypothetical products)	1. Reasons for preferring injectables included: easier to remember than a daily pill (71%) and easier to conceal from members of their community (58.1%). 2. Older participants had increased odds of preferring injectable PrEP (aOR 1.08 per 1-year increase in age, 95% CI 1.03–1.14). 3. Participants who were willing to pay more for PrEP had increased odds of preferring injectable PrEP (aOR 1.17 per 1-unit increase in amount of willing to pay for PrEP, 95% CI 1.01–1.35).	[31]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Parsons, J. T. et al. (2016)	North America	Observational study	948	Injectable PrEP (hypothetical products)	1. When asked about the acceptability of injectable PrEP in 1- and 3-month intervals, 43.2% found the 1-month version acceptable compared with 53.6% who found the 3-month dosing acceptable. 2. Forty-six percent expressed a preference for injectable PrEP (vs. 14.3% for oral PrEP and 21.7% for whichever turns out to be most effective). 3. Those who would not take PrEP at all were significantly older ($p < 0.05$) than those who preferred injectable PrEP and those who would take the most effective form. Those who would take the most effective form were also significantly younger than those who preferred oral PrEP. 4. Long-term health effects and concerns about side effects were the greatest concern for both oral and injectable PrEP. 5. Participants reported having to return for medical visits every 3 months as significantly less of a burden for injectable PrEP than oral PrEP.	[32]
	Greene, G. J. et al. (2017)	North America	Observational study	512	Injectable PrEP (hypothetical products)	1. Among PrEP modalities, the most preferred was the implant-1 (21.5%; two implants; 12-month duration; tactile, but not visible perception by others), followed by daily oral PrEP (17%), injectable PrEP (14.3%) and implant-2 (3.7%; two implants; 12-month duration; tactile and visible perception). 2. There was higher educational attainment reported by those preferring injections over those preferring condoms and pill ($p = 0.04$ and $p = 0.02$, respectively). 3. For those who preferred injections, frequently cited reasons were protection duration (49.5%), dislike/fear of other options (49.5%) and privacy (32.1%).	[33]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Ngongo, P. B. et al. (2017)	Africa	Observational study	165	Injectable PrEP (hypothetical products)	1. There was a difference of opinion on mode of administration, with healthcare providers and MSM preferring oral PrEP and other groups (FSW, youth) opting for injectable PrEP.	[34]
	Beymer, M. et al. (2018)	North America	Observational study	761	Injectable PrEP (hypothetical products)	1. Nearly, 75% of the sample indicated they would be more willing to try injectable PrEP than daily oral PrEP. 2. Those who had some college education or more had higher odds of willingness to try injectable PrEP (aOR = 2.92; 95% CI: 1.32–6.46).	[35]
	Biello, K. B. et al. (2018)	North America	Observational study	36	Injectable PrEP (hypothetical products)	1. Participants with prior PrEP experience expressed greater preference for daily pills as a trusted method and were uncertain about injectable dose and side effects. PrEP-naïve participants expressed greater interest in injectables due to longer intervals between doses. 2. Participants across groups agreed that injectable PrEP might be preferred for certain people/circumstances. Quarterly injections may be more manageable for those with adherence difficulties, those who engage in sex more frequently and may avoid stigma associated with PrEP use (more discreet). 3. Concerns about injectable PrEP were related to having to return for an injection every 3 months, missing medical appointments, diminishing levels of protection, experience of getting an injection and side effects.	[36]
	Calder, B. J. et al. (2018)	North America	Observational study	21	Injectable PrEP (hypothetical products)	1. MSM expressed that adherence to pill-taking was sufficient to ensure a high level of protection against HIV. Improved adherence associated with the usage of long-acting modalities (injections and implants) was not an advantage. 2. Some MSM saw value in injections and implants based on the belief that it could simplify their busy lives, but they were unsure if potential benefits would outweigh the disadvantages (e.g. having less control). 3. Although MSM saw oral PrEP as already effective, they would value long-acting modalities if they were more effective and less costly.	[37]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Dubov, A. et al. (2018)	Europe and Central Asia	Observational study	1184	Injectable PrEP (hypothetical products)	1. In a choice-based analysis, members of a group that had more students, live off a low income, well-educated (university level) ($n = 216$, 18%) had a strong preference for injectable PrEP. Most were influenced by cost.	[38]
	John, S. A. et al. (2018)	North America	Observational study	104	Injectable PrEP (hypothetical products)	1. 30.8% of the men specifically preferred injectable PrEP, and 34.6% preferred the most effective method. 2. Participants had the lowest amount of concern regarding fear/dislike of needles associated with injectable PrEP (M = 1.75, SD = 1.10, range 1–4), with the majority (61.5%) having no concern at all about fear/dislike of needles. 3. Men had less concern about returning for medical check-ups and injections every 3 months (M = 1.79, SD = 1.00, range 1–4), with 54.8% having no concern about quarterly medical visits. 4. Men reported moderate concern regarding long-term health effects of injectable PrEP (M = 2.63, SD = 0.97, range 1–4). Most had a moderate amount of concern about the potential side effects of injectable PrEP (M = 2.71, SD = 0.91, range 1–4). 5. Nearly, all (93.3%) expressed some level of concern about incomplete protection, and 40.4% of all men were very concerned about it. 6. In bivariate analyses, men with less than a bachelor's degree had higher odds of preferring injectable PrEP compared to those with more education. Concerns about incomplete HIV protection and possibility of protection wearing off were both associated with lower odds of injectable PrEP preference.	[39]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Kerrigan, D. et al. (2018)	North America	Observational study	26	CAB-LA (enacted preference)	1. Significant consensus that while the injections were "not always pleasant," side effects were worth the pain if injectable PrEP was found to be effective. 2. Most participants rated their satisfaction as "very high" and almost all indicated their interest in potentially using CAB-LA. 3. The main disadvantage of injectables: injection site reactions, large needle size and exposing one's buttocks to receive the injections. 4. Participants described receiving injections every 3 months as convenient. There was a perceived advantage over not having to worry about adhering to a daily oral regimen. 5. CAB-LA afforded more confidentiality and privacy than daily oral pills.	[40]
	Meyers, K. et al. (2018)	North America	Observational study	28	CAB-LA (enacted preference)	1. Eighty-eight percent ($n = 14$) reported they would definitely or very likely use CAB-LA, and 63% ($n = 10$) reported they would prefer to use CAB-LA every 12 weeks to daily oral PrEP. 2. Sixty-four percent ($n = 20$) felt anxiety before the first injection. This decreased to 29% ($n = 8$) by the second and third injections. Participants reported two sources of anxiety: needles (32%, $n = 9$) and expectation of injection pain (54%, $n = 15$). 3. Some expressed feelings of awkwardness and vulnerability associated with receiving injections in the buttocks (43%, $n = 12$). 4. Many participants (46%, $n = 13$) spoke about the importance of nurses and staff being caring, friendly and warm, and treating them like human beings rather than just study subjects. They also discussed the importance of providers managing patients' expectations and providing information about the process. Fourteen percent (4/28) of participants mentioned the importance of the skill-level of study nurses in terms of drawing blood and giving injections and the fact that they liked having the same person each time.	[41]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Meyers, K. et al. (2018)	East Asia and Pacific	Observational study	200	Injectable PrEP (hypothetical products)	1. Seventy-six percent (152/200) of the men said they would be probably or very willing to use injectable PrEP. 2. In multivariate analyses, higher education (aOR = 0.5, 95% CI 0.2–1.0), having a female partner (aOR = 3.1, 95% CI 1.0, 10.2), knowing a person living with HIV (aOR = 4.2, 95% CI 1.9, 9.2) and having a steady partner living with HIV (aOR = 0.0, 95% CI 0.0, 0.3) were significant predictors for having interest in injectable PrEP only. 3. Ninety-two (46.0%) respondents were unwilling to consider oral PrEP. Of these 92, 53.3% (49/92) would consider an injectable PrEP modality. 4. Of the men who found oral PrEP acceptable, 95.4% (103/108) were also open to injectable PrEP.	[42]
	Murray, M. I. et al. (2018)	North America	Randomized control trial	115	CAB-LA (enacted preference)	1. At week 30, participants were generally satisfied with the study medication (100% in placebo, 74% in CAB-LA). 2. Overall, participants reported a willingness to recommend the treatment (CAB-LA, 87%, placebo, 100%) and continue the study medication (CAB-LA, 79% and placebo, 100%). 3. Tolerability assessments of cabotegravir injections showed that 66% ($n = 57$) of participants were satisfied with the side effects and 64% ($n = 55$) were satisfied with the amount of pain/discomfort. 4. Throughout the study, 79% of participants in the cabotegravir group reported a level of satisfaction sufficient to continue with the study medication (Week 6, 88%; Week 18, 81%; Week 30, 79%). 5. When comparing views of treatment at Week 18, participants were more satisfied with injectable cabotegravir than with oral cabotegravir, particularly on items related to convenience, flexibility and lifestyle. 6. Approximately 25% of participants in the cabotegravir treatment group reported dissatisfaction with the amount of discomfort or pain associated with the study medication during the injection phase. However, 74% ($n = 67/91$) of participants were satisfied to continue treatment with injectable cabotegravir, and few (4%; $n = 4/94$) withdrew from the study because they reported injection intolerability.	[43]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Patel, R. R. et al. (2018)	North America	Observational study	26	Injectable PrEP (hypothetical products)	1. 17/26 MSM preferred injectable PrEP, regardless of frequency. Some respondents did not want an injection without discussing frequency. 2. Six participants mentioned that who administers the injection was tied to their preferences for an injectable modality. 3. Seven participants reported fear of needles when discussing preferences for injections versus other modalities. 4. When asked about acceptability for injectable PrEP (administered every 3 months), most interviewees (18/22) found injectable PrEP acceptable. Acceptability was related to familiarity with other medications that are in an injectable form, infrequent dosing, disliking injections and knowledge of efficacy. 5. Participants' preferences for injections factored in general dislike for needles, the frequency that they needed to receive an injection and not wanting to self-administer the injection. Preferred frequencies regarding injectable PrEP typically ranged from weekly to annually. Longer dosing intervals were proposed and preferred (3 months)	[44]
	Dubov, A et al. (2019)	Europe and Central Asia	Observational study	554	Injectable PrEP (hypothetical products)	1. Results from discrete choice experiment showed that Group 1 ($n = 73$)—described as average age of 41.2, 78% work full time, 96% has associate degree or higher, 86% White, 75% live in urban area—had equal preference for either daily pill or on-demand intermittent pills while strongly opposing injectable PrEP. 2. Group 2 ($n = 126$)—described as 72% working full time, 96% had an associate degree or higher, 86% White, 71% living in urban areas—put cost twice as important as dosing frequency, and preferred injectable PrEP. 3. Those preferring injectable PrEP are overall younger and better educated.	[45]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Ellison, J. et al. (2019)	North America	Observational study	108	Injectable PrEP (hypothetical products)	• In ranking the likelihood of using products, subdermal implants were most commonly selected as the first choice (45%), followed by injectables (31%) and daily oral PrEP (21%). • Among those who were somewhat or very interested in injectables, the most common reasons were: not having to take a daily pill (43%), convenience (30%) and timing or dosage frequency (11%). • Regarding the most important reasons for not wanting to use injectable PrEP, participants who were not very or not at all interested cited disliking needles (46%), concerns about safety or effectiveness (23%) and logistical difficulties (15%). • In multivariate analyses, Black and Hispanic MSM were more likely (OR: 2.45, 95% CI: 0.86–6.89) to prefer the injectable over daily oral PrEP. MSM with public insurance also had increased odds ([aOR]: 2.80, 95% CI: 0.71–11.1) of preferring injectable PrEP.	[46]
	Peng, L. et al. (2019)	East Asia and Pacific	Observational study	524	Injectable PrEP (hypothetical products)	1. Overall willingness to use any type of PrEP in the next 6 months was 84.9%, with a willingness rate of 60.1% for daily oral PrEP, 79.2% for on-demand PrEP and 62.8% for injectable PrEP. 2. Most participants intended to adhere to PrEP, with an intention rate of 70.2% for daily PrEP, 84.9% for on-demand PrEP and 71.2% for injectable.	[47]
	Minnis, A. M. et al. (2020)	Africa	Observational study	807	Injectable PrEP (hypothetical products)	1. Females and MSM both had greater preference for a single injection over an implant compared to MSW ($p = < 0.004$). Females and MSW also expressed more preference for two injections compared with implants ($p < = 0.009$). 2. All youth preferred insertion in the arm ($p<0.001$). Females disliked insertion in the thigh, and both MSW and MSM disliked insertion on the buttocks ($p = 0.01$). 3. If a clinic offered a 2-month long-acting PrEP product, females would be willing to go to a pharmacy if the pharmacy offered a product dosed every 3.8 months (95% CI 3.0, 5.5); if the clinic offered a 6-month long-acting PrEP product, they would be willing to go to the pharmacy if it offered a product dosed every 9 months (95% CI 7.7, 10.4).	[48]

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Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Torres, T. et al. (2020)	Latin American and the Caribbean	Observational study	19,457	Injectable PrEP (hypothetical products)	1. Overall, injectable PrEP was the first option for 42% (95% CI 41–43) of the respondents. In multivariable logistic regression, preference for injectable PrEP was associated with age >25 (aOR 1.32, 95% 1.22–1.44), PrEP awareness (aOR 1.23, 95% CI 1.15–1.32), having >5 male sexual partners (aOR 1.05, 95% CI: 0.99–1.12) and binge drinking (aOR 1.15, 95% CI 1:07–1.23)	[49]
	Gutierrez, J. I. et al. (2021)	North America	Observational study	429	Injectable PrEP (hypothetical products)	1. An injectable PrEP option did not alter participant interest rate among PrEP-experienced individuals but did garner a higher participation interest rate in those with no PrEP experience (80.5%).	[50]
	Macapagal, K. et al. (2021)	North America	Observational study	59	Injectable PrEP (hypothetical products)	1. Participants disliked how injections and removable implants require more frequent visits to healthcare providers and require greater commitment. 2. Participants liked when delivery methods were less perceptible or visible (e.g. injectable). 3. Participants most frequently discussed disliking the possibility of side effects (i.e. pain and scarring at the insertion or injection site). 4. Barriers to injectables: dislike of injection and frequency of the injection (every 2 months). To increase acceptability, participants suggested administration in their arm instead of buttocks, self-administration like some gender-affirming hormones and reduced injection frequency. 5. When asked to rank order preferred methods, most youth selected condoms (39.6%) and yearly implants (37.7%)—injection and quarterly implant were the least preferred.	[51]
	Mansergh, G. et al. (2021)	North America	Observational study	782	Injectable PrEP (hypothetical products)	1. Most men were likely to use PrEP in the future via injection (74%). 2. In multivariable analysis, current PrEP users (vs. non-users) were more likely to prefer injectable (aOR = 3.29, 95% CI = 2.12–5.11). Black (vs. White) men had lower odds for reporting likelihood of using injectable (AOR = 0.54, 95% CI = 0.34–0.84). MSM age 30–39 (vs. older men) had greater odds of endorsing an injection product (aOR = 1.89, 95% CI = 1.17–3.07). 3. Current daily PrEP users (vs. non-users) ranked injectable and daily oral PrEP higher, and condoms, event-based pills, anal gel and anal suppositories were ranked lower. White MSM ranked injectables higher than Black and other or mixed race/ethnicity men, but not compared to Hispanic/Latino men.	[52]

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Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Nguyen, L. H. et al. (2021)	East Asia and Pacific	Observational study	30	Injectable PrEP (hypothetical products)	1. One participant suggested that the injectable PrEP should be provided along with oral medication. It could be beneficial for the PrEP users as they did not need to remember taking the pill daily, which could increase uptake.	[53]
Women							
	Luecke, E. H. et al. (2016)	Africa	Observational study	68	Injectable PrEP (hypothetical products)	1. Most women (55 of 68, 81%) preferred long-acting formulations. 2. Women who did not complete secondary school were significantly less likely to prefer long-acting methods (70% vs. 94%, $p < 0.05$). 3. Women were very concerned about their ability to adhere to daily regimens and often expressed a preference for product formulations that are long-acting or on demand. 4. Product formulations administered at the clinic by providers were also attractive because women would not have store or hide products at home.	[54]
	van der Straten, A. et al. (2017)	Africa	Observational study	71	Injectable PrEP (hypothetical products)	This study was conducted within ASPIRE, a phase III randomized controlled trial of a vaginal ring, with all women being ring experienced. 1. The vaginal ring was most preferred by 94% of participants, followed by implants (39%), injectables (33%), male condoms (27%) and oral tablets (11%). 2. Product reversibility came up in discussions of safety and side effects. The potential for incompatibility between the drug and the body was seen as a major disadvantage of injections. 3. Preference for long-acting formulations was also explained by an appreciation for infrequent dosing, fewer clinic visits and less opportunities to forget doses, the ease of administering the product at the clinic, discreetness, and in the case of the implant and injection, non-vaginal administration. 4. Concerns with injections were: needle phobia, the pain or discomfort associated with the administration process, the reliance on skilled clinicians and the invasive procedure.	[55]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Minnis, A. M. et al. (2018)	Africa	Randomized control trial	258	MPT injections (placebo products)	1. Product ratings after 1 month of use were highest for injections (mean 4.26; 95% CI 4.14, 4.38). The mean rating for injections was significantly higher than those for rings and tablets (p <0.001); the mean rating for rings was also significantly higher than that for tablets (p = 0.015). 2. For women who expressed negative reactions to the injection, they discussed being afraid of pain with the injections when they first saw the needle; however, these feelings subsided after receiving them. 3. Participants who had completed secondary school reported a lower mean rating for tablets compared with those who had not completed secondary school (adjusted β −0.38; 95% CI −0.71, −0.06; p = 0.021), and a higher mean rating for injections (adjusted β 0.24, 95% CI 0.00, 0.49, p = 0.054). Ever-use of injectable contraceptives was associated with slightly lower injection ratings (adjusted β −0.24, 95% CI −0.48, 0.00, p = 0.054). 4. For injections, the level of acceptability of product-specific attributes was higher than for the other products. Women who indicated the injection's attributes tied to use were acceptable very consistently expressed positive views of the product, valuing the fact that it "saved time" and offered discreetness.	[56]
	Quaife, M. et al. (2018)	Africa	Observational study	609	Injectable PrEP (hypothetical products)	1. %1.Adult women and FSWs significantly disliked oral PrEP and favoured injectable products. Neither adult women nor adolescent girls found the vaginal ring appealing but an injectable product was favoured by all groups.	[57]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Minnis, A. M. et al. (2019)	Africa	Randomized control trial	523	MPT injections (placebo products)	1. Thirty-four percent of women who chose the injection after trying each of the three products ($N = 160$) had preferred another product at enrolment (25% tablets, 9% rings). 2. The injection achieved the highest adherence, which was also the most popular delivery form. Oral pills achieved the lowest adherence. 3. Although injections were the favoured delivery form, discrete choice experiment data estimated that a larger proportion of participants would choose an MPT ring or MPT tablets over injections that prevented only HIV.	[58]
	Tolley, E. E. et al. (2019)	North American, Africa	Observational study	136	Rilpivirine (enacted preference)	1. Although U.S. participants reported lower acceptability of injectable attributes than women from African sites, most participants rated injectable attributes as highly acceptable. Acceptability ratings were similar over time. 2. At baseline, 56% of U.S. participants and 81% of African participants preferred using a bi-monthly injectable to other prevention methods, including daily oral pills, a vaginal ring or gel. Interest increased in both regions over time. 3. At week 28, 79% of participants strongly endorsed that they would "definitely use an injectable PrEP product for some time" if it were available in the future. Even more women (88%) strongly agreed that they would be "more interested in using an injectable if it was both for HIV and pregnancy prevention." 4. In longitudinal univariate models, acceptability of product attributes and of physical experiences, altruistic and personal motivations for trial participation, and HIV risk perception, were associated with future interest in use. U.S. participants reported significantly lower levels of future interest in use than African women (OR = 0.14, $p < 0.001$) and those in the experimental group had lower future interest in use than those in the placebo arm (OR = 0.42, $p = 0.04$). Product attribute scores and being from a non-U.S. site remained the strongest predictors of future interest in use in multivariate models.	[59]

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Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Calabrese, S. K. et al. (2020)	North America	Observational study	563	Injectable PrEP (hypothetical products)	1. The strongest preference was for daily pills (29.4%) and injections (24.3%). 2. In multivariable analyses, women currently using injectable contraceptive method had higher odds of preferring PrEP injections than those never having used injectable contraceptives (aOR 8.45, 95% CI 4.22–16.91).	[13]
	Dauria, E. F. et al. (2021)	North America	Observational study	27	Injectable PrEP (hypothetical products)	1. Criminal justice-involved women expressed most interest in oral and injectable versions of PrEP due to familiarity with medication administered in this way.	[60]
	Philbin, M. M. et al. (2021)	North America	Observational study	59	Injectable PrEP (hypothetical products)	1. Fifty percent of women would prefer injectable PrEP over daily pills. 2. Many women compared HIV therapy to birth control options—these individuals focused primarily on how experience with injections would allow people to feel comfortable with future injections and did not feel that taking multiple injections at once would be a barrier. 3. Women with a history of frequent medication-related injection (e.g. insulin pumps, etc.) expressed reticence to add additional injectables to their regimen. Many women reported being terrified of needles and explained that they would not use injectable formulations no matter how much they disliked pills. 4. Among women who had history of injecting drugs, some stressed that they would avoid injectables because even the sight of a needle "can be a trigger," but some women with a history of drug use described how it would be an individual-level decision about whether a history of injection drug use might limit their willingness to use injectables. 5. Most women felt that people who currently inject drugs would be especially willing to try injectable modality for treatment and prevention.	[61]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Philbin, M. M. et al. (2021)	North America	Observational study	30	Injectable PrEP (hypothetical products)	1. Specific barriers to injectable PrEP uptake included medical mistrust (e.g. women expressed a desire to wait until injectable PrEP had been on the market for an extended period to ensure its safety and efficacy), injection-related side effects (e.g. interfering with a pregnancy), administration location and more frequent doctors' visit. 2. Facilitators included belief that shots were more effective than pills, convenience and confidentiality.	[62]
	Tolley, E. et al. (2022)	Africa	Observational study	68	CAB-LA (enacted preference)	1. Participants overwhelmingly preferred CAB LA to daily pills. 2. Regardless of risk category, women liked the injectable's privacy from husbands, boyfriends, sexual clients or just "nosey people." 3. At least half of participants worried about forgetting to take pills, describing previous mishaps with oral contraception or challenges with study pills. 4. Descriptions of pain were variable, but the most common concern with the injection. 5. Women in high-risk categories were more likely to mention "effectiveness" as a reason to prefer the injection.	[63]
Adolescents and young people							
	Mack, N. et al. (2014)	Africa	Observational study	133	Injectable PrEP (hypothetical products)	1. In South Africa, adolescents' concerns about injections included the potential to be painful, with some preferring an injection in the arm rather than buttocks. Several girls were uncomfortable with having to remove their pants/skirts to receive an injection. 2. Young women preferred injections over a pill because they thought injections would be safer, longer-lasting, more private and difficult to forget. Young women expressed less concerns over receiving an injection in the buttocks—some actually preferred that location since they were already accustomed to receiving contraceptive injections there.	[64]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Ngongo, P. B. et al. (2017)	Africa	Observational study	165	Injectable PrEP (hypothetical products)	There was a difference of opinion on mode of administration, with healthcare providers and MSM preferring oral PrEP and other groups (FSW, youth) opting for injectable PrEP.	[34]
	Quaife, M. et al. (2018)	Africa	Observational study	609	Injectable PrEP (hypothetical products)	Adult women and FSWs significantly disliked oral PrEP and favoured injectable products. Neither adult women nor adolescent girls found the vaginal ring appealing but an injectable product was favoured by all groups.	[57]
	Montgomery, E. T. et al. (2019)	Africa	Observational study	95	Injectable PrEP (hypothetical products)	1. Injections could address the issue of the ring potentially come out and causing embarrassment. They could allow for greater sexual freedom and pleasure. 2. Injectable-experienced women appreciated not having a daily product and felt that receiving the injection every 2–3 months was feasible. The injection was perceived to provide greater protection because it would be absorbed in their bodies, they would not forget to take it and it would not burst. 3. Experience of side effects was raised as the main complaint with using injectable PrEP. Some stated that injection site pain was also a disadvantage. 4. For some, high efficacy would override the importance of all other attributes. 5. Assuming high efficacy, the most favourable attribute among HIV prevention methods was invisibility, linked to long-acting modalities.	[65]
	Taggart, T. et al. (2019)	North America	Observational study	200	Injectable PrEP (hypothetical products)	1. Thirty-four percent said they prefer daily oral PrEP, 13% prefer PrEP injections and 14.7% prefer a PrEP implant. 2. Reasons for preferring PrEP injections over other modalities included: "long lasting" and "would not have to take a pill everyday."	[66]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Golub, S. A. et al. (2020)	North America	Observational study	93	Injectable PrEP (hypothetical products)	1. Young people want to understand how biomedical prevention products are going to protect them. 2. For injectable PrEP, young people had questions about why the shot needed to be "in the butt," what the shot feels like and whether there is soreness after. 3. Participants raised questions about the feasibility of injectable PrEP in the gluteus for those receiving gluteal silicone injections. For some, this was seen as a barrier for use, but participants immediately thought creatively about marketing long-acting gluteal injections as part of gender-affirming care.	[67]
	Kidman, R. et al. (2020)	Africa	Observational study	2085	Injectable PrEP (hypothetical products)	1. Over 80% of both genders would be willing to have an injection every 3 months. Both genders preferred to get an injection at a health clinic (59–65%) over taking a daily pill. When the alternative was giving themselves an injection at home, approximately half favoured an injection over a daily pill. 2. One-quarter of participants had concerns that might stop them from getting an injection: that it might make them sick (6%), privacy (5%) and they may forget to get it (4%). 3. Over 10% said that they had a fear of injections/needles or were concerned about the pain.	[68]
	Minnis, A. M. et al. (2020)	Africa	Observational study	807	Injectable PrEP (hypothetical products)	1. Females youth expressed more preference for two injections compared with implants ($p <= 0.009$). 2. All youth preferred insertion in the arm ($p<0.001$). Females disliked insertion in the thigh. 3. If a clinic offered a 2-month long-acting PrEP product, females would be willing to go to a pharmacy if the pharmacy offered a product dosed every 3.8 months (95% CI 3.0, 5.5); if the clinic offered a 6-month long-acting PrEP product, they would be willing to go to the pharmacy if it offered a product dosed every 9 months (95% CI 7.7, 10.4).	[48]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
PrEP users							
	Meyers, K. et al. (2016)	North America	Observational study	62	Injectable PrEP (hypothetical products)	1. Sixty-eight percent of participants would "definitely" or "probably" switch to injectable PrEP if it were FDA approved. 2. Product-specific motivating factors for "switchers" included: convenience, not having to adhere to daily pill and not carrying pills around. Psychological factors included desire to eliminate anxiety around missed dosing and a belief that a shot would mean "less to think/worry about." 3. Those not willing to switch from oral to injectable PrEP cited scientific concerns, including safety, efficacy and waning protection. 4. Product-level disadvantages included pain and inconvenience of scheduling follow-up injections. Non-switchers reported that swallowing a pill daily made them feel like they were in control of their health and would not trust the shot's protection. They expressed satisfaction with oral PrEP and unwillingness to be an early adopter of a novel approach.	[30]
	John, S. A. et al. (2018)	North America	Observational study	104	Injectable PrEP (hypothetical products)	1. 30.8% of the men specifically preferred injectable PrEP, and 34.6% preferred the most effective method. 2. Participants had the lowest amount of concern regarding fear/dislike of needles associated with injectable PrEP (M = 1.75, SD = 1.10, range 1–4), with the majority (61.5%) having no concern at all about fear/dislike of needles. 3. Men had less concern about returning for medical check-ups and injections every 3 months (M = 1.79, SD = 1.00, range 1–4), with 54.8% having no concern about quarterly medical visits. 4. Men reported moderate concern regarding long-term health effects of injectable PrEP (M = 2.63, SD = 0.97, range 1–4). Most had a moderate amount of concern about the potential side effects of injectable PrEP (M = 2.71, SD = 0.91, range 1–4). 5. Nearly, all (93.3%) expressed some level of concern about incomplete protection, and 40.4% of all men were very concerned about it.	[39]

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Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
						6. In bivariate analyses, men with less than a bachelor's degree had higher odds of preferring injectable PrEP compared to those with more education. Concerns about incomplete HIV protection and possibility of protection wearing off were both associated with lower odds of injectable PrEP preference.	
	Meyers, K. et al. (2018)	North America	Observational study	28	CAB-LA (enacted preference)	1. Eighty-eight percent ($n = 14$) reported they would definitely or very likely use CAB-LA, and 63% ($n = 10$) reported they would prefer to use CAB-LA every 12 weeks to daily oral PrEP. 2. Sixty-four percent ($n = 20$) felt anxiety before the first injection. This decreased to 29% ($n = 8$) by the second and third injections. Participants reported two sources of anxiety: needles (32%, $n = 9$) and expectation of injection pain (54%, $n = 15$). 3. Some expressed feelings of awkwardness and vulnerability associated with receiving injections in the buttocks (43%, $n = 12$). 4. Many participants (46%, $n = 13$) spoke about the importance of nurses and staff being caring, friendly and warm, and treating them like human beings rather than just study subjects. They also discussed the importance of providers managing patients' expectations and providing information about the process. Fourteen percent (4/28) of participants mentioned the importance of the skill-level of study nurses in terms of drawing blood and giving injections and the fact that they liked having the same person each time.	[41]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Meyers, K. et al. (2018)	North America	Observational study	105	Injectable PrEP (hypothetical products)	1. Two-thirds of participants reported they would definitely (36.2%) or probably (30.5%) switch from daily oral PrEP to injectable PrEP. 2. Those with moderate income ($30,000–$50,000) were more likely to consider switching, compared to those who reported higher income. 3. Respondents who identified as having high injection tolerance had higher odds of switching (OR = 1.64); those who were more concerned about post-injection pain had lower odds of switching (OR = 0.57). 4. Participants who felt more strongly that the injection interval was a disadvantaged of the shot had lower odds of intending to switch (OR = 0.30). However, some switchers mentioned that oral PrEP requires regular clinic visits anyway, so that regular visits for injections were not an additional burden. 5. Strong agreement with the statement "taking PrEP pills every day feels like an emotional burden" was associated with intention to switch (OR = 1.54). Assigning a higher score to the statement "Taking PrEP pills every day makes me feel responsible" (OR = 1.87) was associated with higher odds of switching. 6. Higher scores on the statement "Not taking a pill every day would make me feel less in control of my HIV prevention" were associated with lower odds of switching (OR = 0.55). 7. Participants expressed concerns about waning protection across the injection interval. 8. In multivariable analysis, two predictors negatively predicted switch intentions: negative ratings of product-level factors (injections interval [aOR = 0.37] and shot schedule [aOR = 0.31]), three psychosocial-level factors positively predicted switch intentions: identifying daily pill-taking as emotionally burdensome (aOR = 13.71), believing that PrEP signifies personal responsibility (aOR = 4.72) and self-identifying as an early adopter (aOR = 3.77).	[69]

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Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Ellison, J. et al. (2019)	North America	Observational study	108	Injectable PrEP (hypothetical products)	1. In ranking the likelihood of using products, subdermal implants were most commonly selected as the first choice (45%), followed by injectables (31%) and daily oral PrEP (21%). 2. Among those who were somewhat or very interested in injectables, the most common reasons were: not having to take a daily pill (43%), convenience (30%) and timing or dosage frequency (11%). 3. Regarding the most important reasons for not wanting to use injectable PrEP, participants who were not very or not at all interested cited disliking needles (46%), concerns about safety or effectiveness (23%) and logistical difficulties (15%). 4. In multivariate analyses, Black and Hispanic MSM were more likely (OR: 2.45, 95% CI: 0.86–6.89) to prefer the injectable over daily oral PrEP. MSM with public insurance also had increased odds ([aOR]: 2.80, 95% CI: 0.71–11.1) of preferring injectable PrEP.	[46]
	Montgomery, E. T. et al. (2019)	Africa	Observational study	95	Injectable PrEP (hypothetical products)	1. Injections could address the issue of the ring potentially come out and causing embarrassment. They could allow for greater sexual freedom and pleasure. 2. Injectable-experienced women appreciated not having a daily product and felt that receiving the injection every 2–3 months was feasible. The injection was perceived to provider greater protection because it would be absorbed in their bodies, they would not forget to take it and it would not burst. 3. Experience of side effects was raised as the main complaint with using injectable PrEP. Some stated that injection site pain was also a disadvantage. 4. For some, high efficacy would override the importance of all other attributes. 5. Assuming high efficacy, the most favourable attribute among HIV prevention methods was invisibility, linked to long-acting modalities.	[65]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Slama, L. et al. (2019)	Europe and Central Asia	Observational study	200	Injectable PrEP (hypothetical products)	1. PrEP users were significantly more likely than people living with HIV to mention being certain not to forget treatment ($p < 0.0001$) and no need to think of treatment every day ($p < 0.0001$) as perceived advantages. 2. PrEP users were more likely than PLWH to select loss of freedom ($p < 0.0001$), misgiving adverse effects ($p = 0.013$) as perceived drawbacks and less likely to select too much a constraint as perceived drawback ($p < 0.0001$).	[70]
	Carillon, S. et al. (2020)	Europe and Central Asia	Observational study	28	Injectable PrEP (hypothetical products)	1. The management of injectable PrEP was perceived both as apprehension and a simplification of patient's daily life. 2. For current daily oral PrEP users, changing treatment to injectable PrEP did not cause apprehension. 3. Some participants dreaded injection as a delivery mechanism.	[71]
Transgender men and women							
	Meyers, K. et al. (2018)	North America	Observational study	28	CAB-LA (enacted preference)	1. Eighty-eight percent ($n = 14$) reported they would definitely or very likely use CAB-LA, and 63% ($n = 10$) reported they would prefer to use CAB-LA every 12 weeks to daily oral PrEP. 2. Sixty-four percent ($n = 20$) felt anxiety before the first injection. This decreased to 29% ($n = 8$) by the second and third injections. Participants reported two sources of anxiety: needles (32%, $n = 9$) and expectation of injection pain (54%, $n = 15$). 3. Some expressed feelings of awkwardness and vulnerability associated with receiving injections in the buttocks (43%, $n = 12$). 4. Many participants (46%, $n = 13$) spoke about the importance of nurses and staff being caring, friendly and warm, and treating them like human beings rather than just study subjects. They also discussed the importance of providers managing patients' expectations and providing information about the process. Fourteen percent (4/28) of participants mentioned the importance of the skill-level of study nurses in terms of drawing blood and giving injections and the fact that they liked having the same person each time.	[41]

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Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Rael, C. T. et al. (2020)	North America	Observational study	19	Injectable PrEP (hypothetical products)	1. Participants were familiar with injections, since many have already administered gender-affirming hormones in this way and were open to receiving injectable PrEP. 2. Participants liked that they would not have to adhere to a daily product. 3. Participants worried that the medication contained in injections and implants could interact with gender-affirming hormones. Participants felt that clinical studies should examine the effects prevention strategies have on transgender women. 4. Some participants expressed concerns over injection in the gluteal muscles. 5. Participants felt that visits with their healthcare provider to administer injectable PrEP were cumbersome and inconvenient. Transgender women often already juggle multiple doctor's appointments. Other participants felt that intramuscular injections were something they could do at home. 6. The 30-day oral lead in required for the injection was unpopular among most participants. 7. Some participants were concerned about potential side effects of the medication contained in injectable PrEP. 8. Overall, participants were excited about the concept of long-acting HIV prevention strategies. Some felt that 6 months was reasonable, though this was the least amount of time anybody found acceptable.	[72]
	Appenroth, M. et al. (2021)	North America, Africa, East Asia and Pacific, Europe and Central Asia, Latin American	Observational study	50	Injectable PrEP (hypothetical products)	1. Despite some concern, injectable PrEP was most referred to as the preferred modality because it limits the chance of forgetting to take the daily medication and reduces the risk for trans people of carrying around drugs that might expose them as vulnerable to HIV or even being falsely assumed of being HIV positive in front of authorities. 2. Having to go back to see a medical provider regularly to receive the shots was as a limiting factor.	[73]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Ashodaya Samithi (2021)	South Asia	Observational study	165	CAB-LA (hypothetical products)	1. Most community members were excited about CAB-LA, particularly male sex workers and trans women sex workers. However, there were queries about CAB-LA side effects, HIV resistance, adherence support, and so on. 2. Trans women sex workers expressed that CAB-LA would be a good option if it does not interfere with gender-affirming hormones. Some expressed worry about the pain on the injection site. 3. Though many MSW and trans women sex workers were interested in CAB-LA, some were sceptical and would prefer to wait and see its use in India before they start taking it for themselves. 4. Many FSWs relate CAB-LA with Depo-Provera injection. The long-acting prevention tool would relieve them from the worry of getting HIV and would ensure the daily oral tablet is not required. 5. The primary concern regarding taking the injection from government hospitals remained long waiting times, compromise of confidentiality, access to the government clinics and "not remembering the date for a follow-up visit." 6. There was overall excitement about and willingness to use CAB-LA across all the groups of sex workers (female, male and transwomen). However, the willingness to use CAB-LA was more among the FSWs who have taken oral PrEP earlier and realized its benefits as well as those who have taken Depo-Provera contraceptive injection.	[74]
	Poteat, T. et al. (2021)	Africa	Observational study	36	Injectable PrEP (hypothetical products)	1. Dislike of daily dosing was a common theme and the most common reason for preferring injectable or topical over oral formulations. 2. Trans women mentioned a reduction in health facility visits as an advantage of injectable PrEP over oral PrEP, as reports of discrimination by healthcare providers were ubiquitous.	[75]

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Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Tagliaferri Rael, C. et al. (2021)	North America	Observational study	15	Injectable PrEP (hypothetical products)	1. With respect to self-injections, many participants liked that: (1) the process was similar to that used to self-injected hormones; (2) transgender women could inject themselves without relying on others; (3) self-injection eliminated a routine doctor's visit; and (4) injections could be administered in the comfort of one's own home. In their narratives, however, participants recognized that self-injections could carry a higher margin of error. 2. With respect to injections during drop-in hours, many transgender women liked: (1) the convenience of short wait/visit times and the flexibility of not needing an appointment, and (2) that it felt like for some people, injections given by providers were safer. On the other hand, participants disliked that they might see others from the community during drop-in hour.	[76]
Care providers							
	Ngongo, P. B. et al. (2017)	Africa	Observational study	165	Injectable PrEP (hypothetical products)	There was a difference of opinion on mode of administration, with healthcare providers and MSM preferring oral PrEP and other groups (FSW, youth) opting for injectable PrEP.	[34]
	Calder, B. J. et al. (2018)	North America	Observational study	21	Injectable PrEP (hypothetical products)	Medical practitioners recognized that injections and implants could ensure better adherence but were sceptical that achieving better adherence would motivate MSM to choose them over daily oral PrEP.	[37]
	Kerrigan, D. et al. (2018)	North America	Observational study	26	CAB-LA (enacted preference)	Some providers may be more cautious in prescribing injectable versus oral PrEP as it is harder to clinically manage and more difficult to discontinue quickly.	[40]
	Hershow, R. B. et al. (2019)	North America	Observational study	20	Injectable PrEP (hypothetical products)	1. Several providers felt that injectable PrEP would be preferred since PWID would have one less thing to worry about each day and would find adhering to a daily pill difficult. 2. Some providers mentioned retention issues when asked whether they thought PWID would prefer oral or injectable PrEP, stating PWID would have difficulty with injectable PrEP due to the need for regular visits to a provider. 3. Some providers expressed concerns around PWID developing resistance mutations if clients initiated injectable PrEP and were not regimented about attending follow-up visits.	[77]

(Continued)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Xavier Hall, C. D. et al. (2021)	North America	Observational study	11	Injectable PrEP (hypothetical products)	1. Injectables would lessen daily cognitive burden on users; however, elements of the regimen were seen as increasing complexity and reducing trialability. 2. All providers suggested that the dosing schedule and frequency of visits could be barriers. 3. A subset of providers favoured seeing patients more frequently to monitor progress.	[78]
PWID							
	Biello, K. B et al. (2019)	North America	Observational study	33	Injectable PrEP (hypothetical products)	1. Most participants were enthusiastic about injectable PrEP and expressed greater interest in injectables than daily oral PrEP. A primary reason for preferring injectable PrEP (over oral PrEP) was easier adherence. 2. For homeless or marginally housed PWID, participants discussed the benefits of not needing to carry or store medication. 3. Most participants perceived that getting an injection every 2 months would not be a major barrier, but some worried about attending appointments every 2 months for injections. They suggested adherence strategies, like appointment reminder calls and distributing injectable PrEP at local pharmacies. 4. Some participants felt they would need more information about injectable PrEP: who might give the injections, side effects and costs compared to oral PrEP. Some concerns were related to general mistrust of medical systems/providers and apprehension about being injected with unknown substances. 5. Some worried that injectable PrEP could affect their high.	[79]
	Footer, K. H. A. et al. (2019)	North America	Observational study	31	Injectable PrEP (hypothetical products)	1. Participants raised concerns that they would have less control over side effects with injectable PrEP. 2. In the context of discussing irregular visits to a primary healthcare provider, sex workers and PWID expressed a preference for a longer lasting injectable (6 vs. 3 months) and implantable (12 months) PrEP. Some PWID had concerns about forgetting to go back for renewed protection. 3. Long-lasting delivery methods removed the concerns about daily adherence.	[80]
	Allen, S. et al. (2020)	North America	Observational study	48	Injectable PrEP (hypothetical products)	1. Participants explained that the availability of a long-acting PrEP option, whether in pill or injectable form, would alleviate many of the barriers PWID face in taking PrEP.	[81]

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Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Shrestha, R. et al. (2020)	North America	Observational study	234	Injectable PrEP (hypothetical products)	1. 67.1% and 25.6% of participants reported having heard of oral PrEP and injectable PrEP, respectively. 2. The most frequently reported concern about injectable PrEP was the potential for long-term side effects (76.9%). Participants reported slightly less concern about the possibility of waning efficacy of injectable PrEP (37.6%) or incomplete protection against HIV (33.3%), followed by the cost of injectable PrEP (27.4%), fear or dislike of needles (24.8%) and having to return to the clinic for injection of injectable PrEP every 2 months (20.5%). 3. 73.5% reported that they would be willing to use injectable PrEP. Factors independently correlated with willingness to use injectable PrEP included female sex (aOR = 2.181, $p = 0.018$), being engaged in healthcare (aOR = 2.919, $p = 0.023$), having high perceived risk for HIV transmission (aOR = 3.255, $p = 0.007$) and having ever used oral PrEP previously (aOR = 3.284, $p = 0.017$).	[82]
	International Network of People Who Inject Drug (2022)	Not available	Observational study	Not available	Injectable PrEP (hypothetical products)	1. Several participants highlighted that although daily oral PrEP is already available through community-led organizations, other PrEP modalities, such as injectables (CAB-LA), are either not available to PWID or people are unaware of its availability or how to access it. This is despite preferences for such modalities due to greater perceived efficacy, tolerability and convenience when compared to daily oral PrEP	[83]
Sex workers							
	Mack, N. et al. (2014)	Africa	Observational study	133	Injectable PrEP (hypothetical products)	In Kenya, the majority of FSW preferred an injectable over other formulations because one dose would last for a prolonged period and require little user intervention. Injections were perceived as relatively private. A few women described alcohol use as potentially interfering with their ability to take daily pill but not posing a problem with injections.	[64]
	Quaife, M. et al. (2018)	Africa	Observational study	609	Injectable PrEP (hypothetical products)	1. Adult women and FSWs significantly disliked oral PrEP and favoured injectable products. Neither adult women nor adolescent girls found the vaginal ring appealing but an injectable product was favoured by all groups.	[57]
	Minnis, A. M. et al. (2020)	Africa	Observational study	807	Injectable PrEP (hypothetical products)	1. MSW expressed greater preference for two injections compared with implants ($p <= 0.009$). 2. MSW disliked injection on the buttocks ($p = 0.01$).	[48]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
	Ashodaya Samithi (2021)	South Asia	Observational study	165	CAB-LA (hypothetical products)	1. Most community members were excited about CAB-LA, particularly male sex workers and trans women sex workers. However, there were queries about CAB-LA side effects, HIV resistance, adherence support, and so on. 2. Trans women sex workers expressed that CAB-LA would be a good option if it does not interfere with gender-affirming hormones. Some expressed worry about the pain on the injection site. 3. Though many MSW and trans women sex workers were interested in CAB-LA, some were sceptical and would prefer to wait and see its use in India before they start taking it for themselves. 4. Many FSWs relate CAB-LA with Depo-Provera injection. The long-acting prevention tool would relieve them from the worry of getting HIV and would ensure the daily oral tablet is not required. 5. The primary concern regarding taking the injection from government hospitals remained long waiting times, compromise of confidentiality, access to the government clinics and "not remembering the date for a follow-up visit." 6. There was overall excitement about and willingness to use CAB-LA across all the groups of sex workers (female, male and transwomen). However, the willingness to use CAB-LA was more among the FSW who have taken oral PrEP earlier and realized its benefits as well as those who have taken Depo-Provera contraceptive injection.	[74]
	Footer, K. H. A. et al. (2019)	North America	Observational study	31	Injectable PrEP (hypothetical products)	1. Participants raised concerns that they would have less control over side effects with injectable PrEP. 2. In the context of discussing irregular visits to a primary healthcare provider, sex workers and PWID expressed a preference for a longer lasting injectable (6 vs. 3 months) and implantable (12 months) PrEP. Some PWID had concerns about forgetting to go back for renewed protection. 3. Long-lasting delivery methods removed the concerns about daily adherence.	[80]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
Other populations							
Adults reside in high-burden districts	Govender, E. et al. (2018)	Africa	Observational study	112	Injectable PrEP (hypothetical products)	1. Most women favoured injectable PrEP as it offered a longer period of protection against HIV, was easily adopted into existing family planning routines and did not require daily administration. Many wanted a product that was safer, less user-reliant and required minimal negotiation/partner support. 2. Product sensitivity with injectables and the intravaginal ring were raised by many men who were concerned about side effects and allergic reactions. Women were concerned that the injectable could lead to weight gain, causing them to not feel sexy.	[84]
Heterosexual men	Cheng, ChihYuan et al. (2019)	Africa	Observational study	202	Injectable PrEP (hypothetical products)	1. Forty-eight percent ($n = 85$) of participants chose injectable PrEP, with 33% ($n = 58$) and 20% ($n = 25$) choosing oral PREP and condoms, respectively. 2. Men with children had a 22% higher likelihood of choosing injectable PrEP relative to childless men. 3. Men who have ever had unprotected anal sex had a decreased probability of 42% of choosing injectable PrEP compared to those who never had unprotected anal sex. An increase of 1 point in the self-rated risk attitude score was associated with a 3% increased likelihood of choosing injectable PrEP.	[85]
Adults reside in fishing communities	Kuteesa, M. O. et al. (2019)	Africa	Observational study	805	Injectable PrEP (hypothetical products)	1. Among women, there were comparable levels of demand for oral PrEP, injectables and implantable products; however, the uptake of an intravaginal ring was predicted to be substantively lower. 2. Class 2 women (more likely to be younger and without prior intimate partner violence) had strong, positive preferences for the longer-lasting products compared to oral PrEP, and significantly valued secrecy of use.	[86]
HIV-uninfected healthy at-risk adults	Laher, F. et al. (2020)	Africa	Observational study	38	Injectable PrEP (hypothetical products)	1. Many participants voiced a need for an HIV prevention method requiring infrequent administration (lasting at least a month). Reasons cited included: forgetfulness when using daily methods; daily methods interfered with lifestyle priorities; costliness of transportation for methods that required frequent clinic visits; and product inaccessibility due to of clinic operating hours.	[87]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
						2. Injections were favoured by male and female participants and were perceived as advantageous because they were thought to work quickly systemically. There was general support for injectable PrEP and vaccine innovations. Although injections were perceived as painful, participants were willing to use them because they were a route of administration linked with efficacy, discretion and long-lasting protection.	
Healthy adults at low HIV risk	Tolley, E. E. et al. (2020)	North America, Africa, Latin American and Caribbean	Randomized control trial	199	CAB-LA (enacted preference)	1. At baseline, participants most liked the idea that a PrEP injectable would be easier to use than other methods, might protect against HIV and could provide a longer duration of protection than other methods. However, one-third expressed concerns about potential side effects and pain. 2. After receiving a first injection at week 6, at least 50% of participants in cohort 1 and approximately 75% or more of participants in cohort 2 rated the number, frequency, location and duration of injection as highly acceptable. 3. More non-U.S. participants reported pain to be unacceptable than did U.S. participants at both timepoints. Participants receiving CAB-LA injections were more likely to find the location of the injectable—in the buttocks—acceptable than those receiving saline injections. 4. After their first injection, approximately 40% of participants in the CAB-LA arm and 75% of cohort 1 placebo participants reported either experiencing no pain or pain that was highly acceptable. After each injection visit, participants in the placebo arm reported significantly higher acceptability of physical experiences than those in the CAB-LA arm. 5. Over the injection phase of the trial, 27 participants permanently discontinued injectable product use. Stated reasons for discontinuation included product-related side effects, inability or unwillingness to follow study procedures, abnormal lab values, reactive HIV tests and desire for pregnancy.	[88]

(*Continued*)

Table 4. (Continued)

Specific group	First author, et al. (year)	Region	Study design category	Sample size	Product assessed	Main findings	Ref.
						6. In univariate models, future interest in use was positively associated with non-U.S. versus U.S. region (OR 2.9, $p = 0.0002$), with higher levels of acceptability for product attributes (OR 4.77, $p < 0.0001$) and for physical experiences (OR 1.6, $p = 0.0002$), having higher levels of altruism (OR 1.96, $p < 0.0001$) and fewer total injection site reactions (OR 0.9, $p = 0.004$). Among participants born female, having ever used a contraceptive injectable was associated with a significant increase in future interest in use (OR 3.4, $p = 0.001$).	
						7. In multivariable models, future interest in use was strongly associated with the composite acceptability score for product attributes (OR 4.84, $p < 0.0001$). Non-U.S. participants (OR 2.9, $p = 0.0003$) and those with higher baseline levels of altruism (OR 1.52, $p = 0.005$) had higher future interest in use.	

Abbreviations: aOR, adjusted odd ratios; CAB-LA, long-acting injectable cabotegravir; CI, confidence interval; DCE, discrete choice experiment; FDA, Food and Drug Administration; FIIP, future interests in injectable PrEP; FSW, female sex worker; HIV, human immunodeficiency virus; MPTs, multipurpose prevention technologies; MSM, men who have sex with men; MSW, male sex worker; PrEP, pre-exposure prophylaxis; PWID, persons who inject drugs; WWID, women who inject drugs.

3.4.3 | *Trans men and women*

Values and preferences research among trans men and women was typically grouped with MSM, making it challenging to disentangle findings for the trans community. Of the disaggregated research on affective attitudes, trans women in SSA reported preferring injectables to oral or topical formulations [75], trans women sex workers in India reported excitement for CAB-LA [74], and trans men and women from various geographies in a multi-country report often referred to injectables as the preferred PrEP modality [73].

3.4.4 | *Cisgender adult women and adolescent girls*

Feelings towards injectable PrEP also varied among heterosexual, cisgender women. In the U.S., there was a slight preference for pills over injections in a study presenting different PrEP modalities [13] but a preference for injectable PrEP over daily pills in others [60, 61]. Some preferred injectables given familiarity with injections for other medications/drugs [60].

Interest in injectable PrEP also varied in SSA, though several studies highlighted a strong preference for injectables. In a qualitative sub-study assessing preferences for HIV prevention formulations among participants in a phase III trial of DVR, the ring was most preferred, followed by implants, injectables, male condoms, then oral pills [55]. In a discrete choice experiment, Ugandan women reported comparable levels of demand for oral PrEP, injectables and implants [86]. However, in several SSA studies, women reported preferences for injectable or implantable formulations over daily oral PrEP [34, 48, 54, 57, 64, 84]. Women in HPTN 084 reported an overwhelming preference for CAB-LA compared to daily oral PrEP [63]. African women in HPTN 076 (assessing rilpivirine injections) more strongly endorsed injectable PrEP than U.S.-based participants, and even more so if the injectable offered HIV and pregnancy prevention together [59].

In the TRIO study, which compared women's modality preferences for placebo multi-purpose prevention technologies (MPTs) in South Africa and Kenya, injections were the most popular modality (over oral pills or vaginal rings) and achieved the highest adherence [58]. However, more participants stated they would choose an MPT ring or pill over an injection that solely prevented HIV [58]. Sex workers in India had a higher willingness to use CAB-LA if they had previous exposure to oral PrEP or DMPA [74]. Finally, adolescent girls and young women in SSA [34, 64, 68] reported a preference for injections over daily pills. In a study of MPTs in SSA, participants rated the acceptability of injectables significantly higher than for rings or pills [89]. Malawian adolescents were particularly interested in facility-based injections [68].

3.4.5 | *PWID*

Compared to some groups, values and preferences research is lacking for persons who inject drugs (PWID). Among studies examining U.S.-based PWID, there was greater interest in injectables [79, 82] or implants [80] compared with daily oral PrEP, given irregular visits to primary health centres. PWID [81] and providers [77] reported that the availability of injectable PrEP could alleviate barriers to PrEP adherence for PWID. Some indicated that other PWID would be willing

Table 5. Overview of articles by acceptability constructs and groups

	MSM	Women	Trans men and women	Adolescents and young people	PWID	Care providers	Sex workers (male and female)
Affective attitude	[28, 31–45, 47–50, 52, 69, 85]	[34, 48, 55, 57–61, 63, 64, 74, 84, 86, 88]		[34, 51, 64, 66, 68]	[61, 77, 79-83]	[34]	
Burden—ease of use and facilitator							
Ease of use and convenience	[33, 37, 46, 71]	[62, 87]				[78]	
Injections circumvent daily pill-taking burden	[31, 53, 69]		[72, 75]		[79, 80]		
Fit with family planning		[61, 64, 74, 84]					[74]
Frequency of injection	[32, 44]	[48]	[76]	[51]			
Trained, sensitive providers	[44]	[55]					
Burden—concerns and challenges							
Dislike/fear of needles and pain	[33, 37, 39, 41, 44, 46]	[59, 61, 63, 65]			[61, 79]		[55, 64, 74]
Side effects	[32, 33, 36, 39, 40]	[62]			[79, 80, 82]		
Invasiveness and body location of the injection	[40, 41, 48]	[55]		[48, 64]			
Logistical challenges	[36, 46, 69, 73]	[62]	[36, 46, 73]	[51]			
Lack of control	[37, 69]	[55]					
Ethicality	[29, 31, 69]	[61, 62, 64, 65, 84, 86]	[72, 73, 75, 76]	[51]	[61, 79]		[64]
Intervention coherence				[67]			
Opportunity costs		[84]	[74, 82]		[79]		[74]
Perceived effectiveness	[36, 39, 40, 69]	[62]		[65]	[82]	[77]	
Self-efficacy				[68]	[79, 80]		[74]

Abbreviations: PWID, persons who inject drugs.

to try injectable PrEP given familiarity with needles [61, 79]. Despite low awareness of injectable PrEP, PWID from a multi-regional assessment reported a preference for injectable PrEP over daily oral PrEP due to greater perceived efficacy, tolerability and convenience [83].

3.5 | Burden—ease of use and facilitators

Following affective attitude, burden was the most commonly reported TFA construct (reported in 34 references), including ease of use, facilitators or challenges.

3.5.1 | *Ease of use and convenience*

ECLAIR participants reported relative ease of use of injectables compared to oral PrEP, which reduced long-term adherence concerns [40]. Among MSM, injectable PrEP was considered an easy-to-use, convenient option compared to daily pills [33, 46] that provided privacy and adequate duration of protection [33]. Some MSM noted that injectables presented a therapeutic simplification over oral PrEP that suited busy lifestyles [37, 71]. U.S.-based women also reported injectable PrEP as convenient [62]. South African women in a vaccine

efficacy trial reported that injectable PrEP fulfilled the need for an effective, discreet method requiring infrequent administration [87].

3.5.2 | *Injections circumvent daily pill-taking burden*

A major benefit of injectables was the reduced burden of daily pill-taking. Current PrEP users were more likely to see not forgetting doses as an advantage of injectables compared to people living with HIV (PLWH) [70]. ECLAIR participants and women in MTN-003D (assessed preferences for oral PrEP, gel and other formulations [54]) reported the relative ease-of-use of injectables and implantables reduced end-users' fears about maintaining long-term adherence. Women in HPTN 084 said injections circumvented fears of forgetting to take pills, which could happen due to lifestyle considerations, such as late-night work, travel or drinking alcohol [63]. Similarly, PWID reported that injectable PrEP reduced concerns about daily dosing [80] and more easily fit into clinical care schedules [79].

MSM in Vietnam [31, 53] and U.S.-based Black and Latino youth [66] and MSM [69] reported injectable PrEP as beneficial to reducing the anxiety of remembering to take a daily pill. Trans women in South Africa specifically noted that dislike of daily dosing was a common reason for preferring injectable formulations [75], while U.S.-based trans women appreciated not having to adhere to a daily product to have reliable protection [72]. Some U.S.-based providers said injections could reduce the burden of remembering to take daily pills for users, yet dosing schedules and frequency of visits were cautioned as adherence barriers [78].

3.5.3 | *Fit with family planning*

In the U.S. and South Africa, adult [13, 61, 84] and young women [64] reported that injectables fit into existing family planning routines and modalities for some (e.g. receiving contraceptive injectables in the buttocks), which was an important facilitator of injectable PrEP use. Some female sex workers (FSWs) in India compared CAB-LA with taking DMPA [74].

3.5.4 | *Frequency of injection*

Frequency of injection was an important attribute, including among U.S.-based MSM who found a 3-month (or longer) injectable preferable to shorter durations [32, 44]. Some South African women preferred receiving bimonthly injectable PrEP at a health facility but would consider a pharmacy if dosed less frequently [48]. For U.S.-based sexual and gender minority adolescents, ease of use would be supported by administration in the arm, reducing the number of annual injections, and—though not yet recommended—self-administration similar to gender-affirming hormones [51]. Many U.S.-based trans women also favoured self-injection, though acknowledged this could yield errors [76].

3.5.5 | *Trained, sensitive providers*

Some ECLAIR participants felt that friendly nurses trained to give intramuscular injections would improve injectable PrEP use [41]. Per U.S.-based MSM, attitudes or behaviours of personnel administering the injection could affect preferences for this modality [44]. Some women in SSA expressed concerns about the qualifications of clinical staff to perform "invasive procedures" like injections [55].

3.6 | Burden—concerns and challenges

3.6.1 | *Dislike/fear of needles and pain*

Dislike or fear of needles was mentioned by FSWs and other women in SSA and India [55, 64, 74], adolescents in Malawi [68] and South Africa [64], U.S.-based MSM [33, 41, 44, 46], and former injection drug users and other women in the U.S. [61, 63, 79]. Some former PWID found the use of needles "triggering," as they were reminders of their history of drug use. However, dislike/fear of needles was somewhat countered by the high level of protection provided by injectable PrEP [44]. Some experienced PrEP users also reported fear of poorly administered injections [71]. Several young women in an MPT trial in South Africa [89] and many women in the rilpivirine trial [59] noted fear of pain upon initially seeing the needle, though this typically subsided after experiencing the injection. Few rilpivirine trial participants reported pain as unacceptable [59]. South African women also acknowledged that pain is temporary following injection, and soreness subsides [65].

3.6.2 | *Side effects*

Concerns over side effects, including not having control over side effects, were mentioned by PWID [79, 80], adolescents [51] and MSM [32, 36, 39]. Some U.S.-based women reported that side effects, including potential interference with pregnancy, were barriers to uptake [62]. Despite concerns over side effects, ECLAIR participants noted a willingness to deal with CAB-LA side effects if found to be effective [40]. Beyond side effects, MSM [32, 39] and PWID [82] in the U.S. expressed concerns over the long-term effects of injectable PrEP.

3.6.3 | *Invasiveness and body location of the injection*

Invasiveness of injection location (i.e. buttocks) was a barrier for women shown hypothetical prevention modalities at the end of a DVR trial in SSA [55]. Adolescent girls in South Africa were uncomfortable with having to remove their skirts for the injection, instead preferring an injection in the arm [48, 64]. Several ECLAIR participants also noted embarrassment from needing to expose one's buttocks [40, 41], and some MSM and heterosexual men in South Africa had concerns about the buttocks as an injection site [48].

3.6.4 | *Logistical challenges*

MSM and trans people expressed logistical concerns, including needing to regularly return for appointments [36, 46, 73]. By contrast, regular visits were not considered a barrier by some U.S.-based MSM currently using oral PrEP since it also required regular clinical visits [69]. Logistics were a concern for men in a PrEP demonstration project inconvenienced by scheduling follow-up appointments [69]. U.S.-based women were concerned with appointment frequency [62], and

adolescents disliked how injectable PrEP has a short duration/coverage, requiring frequent appointments [51].

3.6.5 | *Lack of control*

MSM mentioned lack of control over their bodies and medication administration, particularly compared to pills that are fully under user control, as a disadvantage of injectables [37, 69]. Lack of control worried PrEP-experienced users [71], who were more likely to see the loss of control or adverse effects as barriers to injectables than PLWH [70]. In a PrEP demonstration project, men liked the control of taking a daily pill over using an injectable [69]. Women in SSA expressed concern about injectable reversibility, that is the ability to remove or discontinue product use if there are concerns about safety or side effects [55].

3.7 | Ethicality

Sixteen studies reported on ethicality [29, 31, 40, 51, 54, 61–65, 69, 79, 84, 86, 89, 90]. One of the most desirable aspects of injectable PrEP was its ability to be concealed. Women in the U.S. [62], FSWs in South Africa [64, 78] and young women using placebo MPTs in SSA [89] described injectables as offering discretion and confidentiality. Participants in CAB-LA studies also noted a preference for injectables by those valuing confidentiality, as injectables afford more privacy than pills [40, 63]. SSA women reported that longer-lasting products were more acceptable to women valuing secrecy [86], discretion and invisibility [65] as well as women needing maximum protection and minimal partner negotiation [84]. Facility-based administration was appealing for women hiding pills at home from partners, family or children [54]. MSM in several studies also reported that injectable PrEP obviates the need to conceal PrEP at home or carry pills while travelling [29, 31, 69]. Adolescents assigned male at birth also liked that injectables could be easily concealed and included as part of routine check-ups [51].

Injectable PrEP was typically considered a better fit for people comfortable with needles [40, 61, 79], though some studies challenged this assertion. Some PWID noted social or cognitive burdens in that some with a history of injection drug use, especially those in recovery, could be triggered by injections [61, 79]. Other PWID worried that injectable PrEP could "affect their high" [79]. Women with a history of medication-related injections (e.g. insulin pumps, steroid injections, etc.) expressed reticence to add another injectable to their regimens [61].

Finally, injectables may be appropriate for the unhoused [36], those engaging in more frequent sex or those looking to reduce perceived stigma related to oral PrEP [71]. Some oral PrEP users reported that, because injectables offered discretion, they could reduce social stigma [71]. Additionally, some trans people felt that injectable PrEP reduced the risk of carrying drugs that might expose them as being vulnerable to HIV or being falsely assumed as HIV positive [73]. Nevertheless, stigma was also a barrier for trans women attending drop-in hours at a health facility for injectable PrEP [76]. Trans women in South Africa said reducing the number of healthcare visits for injectables could mitigate discrimination from healthcare providers [75]. Some trans women reported feeling comfortable with the idea of self-administering at home, much like gender-affirming hormones [72].

3.8 | Intervention coherence

One study addressed intervention coherence. U.S.-based LGBTQ youth questioned how injectable PrEP would protect them, and in some cases, made incorrect assumptions about how biomedical prevention works [67]. Participants requested information about the rationale for the injection site and whether injectables would interfere with other recreational, over-the-counter or gender-affirming drugs [67].

3.9 | Opportunity costs

Six studies reported on opportunity costs [38, 45, 72, 74, 79, 84]. Trans women in the U.S. and India worried that injectables could interfere with gender-affirming hormones [72, 74], with some feeling more research was necessary to explore these interactions [72]. U.S.-based trans women also discussed the potential effect of injections in gluteal muscles due to silicone implants and concerns about scarring [72]. South African women reported concerns about weight gain and poor body image as a potential result of injectable PrEP [84]. U.S.-based PWID raised concerns over the monetary costs of injectables relative to oral PrEP [79], and European MSM [38, 45] noted cost as a major influencer when considering different hypothetical products, ranking cost as more important than dosing frequency.

3.10 | Perceived effectiveness

Nine studies addressed perceived effectiveness [36, 39, 40, 62, 65, 69, 71, 77, 82]. Some MSM were interested in CAB-LA [40] or injectable PrEP more generally [36] because it was perceived as an effective modality, particularly in instances of unexpected HIV risk or condomless sex. Some U.S.-based women perceived injections to be more effective than pills [62], and some South African youth perceived that injections provided greater protection than vaginal rings since the injection is systemic and readily absorbed [65]. However, others expressed concerns over the experimental nature of long-acting anti-retroviral therapy (ART) and PrEP, wanting more scientific evidence [71] or FDA approval [69] before using. MSM were concerned about diminishing, waning or incomplete protection associated with injectable PrEP [36, 39, 69]. Among men in a U.S.-based PrEP demonstration project, the biggest barrier to switching to injectables included concerns about safety, efficacy and not trusting protection from a single shot [69]. Some providers of PWID were concerned over ARV resistance if participants did not return for follow-up appointments [77]. However, PWID were less concerned about incomplete protection than longer-term health effects [82].

3.11 | Self-efficacy

Five studies addressed self-efficacy [68, 74, 77, 79, 80], which mapped to some logistical concerns noted under *Burden* given the focus on participant's assessment of their ability to adhere

to injectable PrEP. There was concern among PWID [79, 80] and their providers [77] over PWID's ability to consistently attend appointments. Participants countered concerns by discussing adherence strategies [76, 79]. Worry over forgetting appointments was also reported by some Malawian adolescents [68] and sex workers in India, who were challenged by long wait times at government hospitals and not remembering appointment dates [74].

4 | DISCUSSION

Since 2010, a wealth of literature has explored values, preferences and acceptability related to injectable PrEP. This review found an overall preference for and much interest in injectable PrEP, including CAB-LA. However, there was variation in preferences within and across groups and geographies. This is consistent with evidence that preference for injectable contraceptives also varies by location, with women in low-income countries more likely to prefer an injectable than women in high-income countries [91]. The variation also highlights the importance of including injectable PrEP in a menu of prevention options, allowing end-users to interface with providers to choose a PrEP modality that suits their lifestyle and supports effective use. Moreover, as this review included a variety of groups and regions, it is important to consider how individual risk perceptions are associated with interest in product use [92, 93] and acceptance [94], as has been demonstrated for oral PrEP use.

Most studies were conducted before CAB-LA efficacy data were published and CAB-LA had received regulatory approval, therefore, among participants who had not used CAB-LA. Participants were typically asked about preferences for hypothetical injectables compared with other PrEP products. More recent efficacy trials have tested placebo and active injectables, including CAB-LA, rilpivirine and lenacapavir (as a semi-annual subcutaneous injectable [95]). Evidence now suggests that CAB-LA is efficacious and safe for sexual exposure [96], thus receiving regulatory approval in the United States, Australia, Zimbabwe, South Africa and Malawi, which may overcome some concerns expressed within included studies. There is also increasing information on issues such as safety during pregnancy, although data remain limited.

When considering the rollout and scale-up of injectable PrEP, policy makers and healthcare providers should consider lessons learned from the slow and inequitable uptake of oral PrEP [1]. Assessing differentiated service delivery models, addressing provider bias and creating patient-centred decision tools may enable more equitable implementation of injectable PrEP [97], in addition to conducting research on how end-users make real-time decisions. Implementation plans are underway to offer CAB-LA alongside other PrEP options [98], providing opportunities to assess how people choose, continue and switch between products. It is important to offer a choice of products to potential end-users and that healthcare providers understand and respond to end-users' concerns, as identified here, to help make informed choices. As CAB-LA becomes available, future research might also explore end-user costs in accessing regular injections, including transportation fees to appointments, as cost was identified as a potential barrier to oral PrEP use [99].

Preferences for different modalities is driven, in part, by acceptability constructs. This is consistent with research indicating that preferences for prevention modalities depends on individual characteristics and may change over time [100]. Beyond affective attitude, for which there was no consistent pattern across groups and geographies, burden was most commonly described. Several concerns were raised, including fear of needles and/or injection site pain, side effects, invasiveness of injection location, logistical challenges and lack of control or reversibility. Nevertheless, facilitators of injectable PrEP included longer-lasting coverage and peace of mind. Preference for injectable PrEP may also be driven by age or ethicality, with different issues influencing acceptability across groups. Injectable PrEP may be beneficial for those seeking discretion or having challenges negotiating product use with sexual partners. It may fit within the lifestyles of those experienced with taking other medicine by injection (e.g. contraceptives or gender-affirming hormones), though unhappy associations with needle use may be concerning for PWID in recovery. Importantly, injectable PrEP presents a strong option for those having difficulty taking or unable to take daily or event-driven PrEP, including adolescents.

4.1 | Limitations

Strengths of this review include being the first to comprehensively assess acceptability for injectable PrEP. We included high-quality literature, as indicated by a low overall risk of bias, with findings organized by a theoretical framework identifying the most salient constructs related to acceptability. This review also presents insights for various geographies and groups, including under-researched groups like trans men and women. Although we used a systematic approach that reduced different sources of biases, some may still be present (e.g. publication bias). A key limitation is that most studies reported a preference for hypothetical products rather than enacted preference. The research was conducted prior to FDA approvals and the WHO recommendation, which affected end-user perceptions. Values and preferences may shift as end-users can use and choose between approved products.

Currently, CAB-LA is recommended to prevent HIV via sexual exposure. Animal models suggest efficacy to prevent parenteral exposure [101], but research is limited, and CAB-LA has not been specifically studied in PWID. Although PWID often have overlapping risk, this may influence their preferences. Another limitation is that certain groups or geographies are over-represented, while others are under-represented. We attempted to address this by stating the group/region reporting a preference, though findings suggest limited generalizability for certain groups. A limitation of CAB-LA studies was that none presented information on injection site discreetness or lack thereof (e.g. if the injection left a visible lump or scar). Lastly, this review contained studies with different sampling methods. The quality assessments noted limitations of varying approaches, though selection bias inherent in certain designs may have captured more favourable opinions of injectables. Yet, we feel this presents a low risk to

the review's interpretations given the variation in preferences reported across populations and geographies.

5 | CONCLUSIONS

This review found an overall preference for and interest in injectable PrEP, including CAB-LA, across groups and regions. Variation reinforces the inclusion of injectable PrEP as one of many prevention options offered to end-users, whose preferences and needs may shift over time. Injectable PrEP presents an opportunity to address adherence-related challenges associated with oral PrEP and may be a better lifestyle fit for individuals seeking discretion or are familiar with needles. However, end-users reported concerns related to fear/pain, logistical challenges and waning levels of protection. More research is necessary to explore enacted preference for end-users exposed to ARV-containing injectables.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

The study was conceptualized by RB, MR and RS. LL and ND drafted the study protocol with input from AVDS, VF and KR. LL, ND, VF and KR conducted the screening of citations, with AVDS helping to resolve differences in eligibility determination. LL and ND abstracted and analysed data. All co-authors contributed to data interpretation. LL drafted the initial manuscript, with all co-authors contributing to subsequent iterations. All co-authors have reviewed and approved the final version.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in the Supporting Information of this article.

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SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article:

Supporting Information Appendix A: Full search terms for included databases

Supporting Information Appendix B: Results from rapid extraction of 38 articles briefly mentioning preferences for injectables compared with other PrEP modalities

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COMMENTARY

Advancing the use of Long-Acting Extended Delivery formulations for HIV prevention in sub-Saharan Africa: challenges, opportunities, and recommendations

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Abstract

Introduction: The burden of HIV in sub-Saharan Africa (SSA) remains unacceptably high, and disproportionately affects girls and women. While the introduction of oral HIV pre-exposure prophylaxis (PrEP) in 2012 revolutionized HIV prevention, its effectiveness is dependent on user adherence and its implementation in SSA has faced numerous challenges. Patient-level, interpersonal and structural barriers, including, for example, daily pill burden, side effects, lack of partner support, testing and disclosure, and costs have been found to reduce adherence to oral PrEP.

Discussion: Long-acting extended delivery (LAED) formulations for PrEP, such as injectable long-acting cabotegravir (CAB-LA) and dapivirine vaginal ring (DPV-VR) are critical additions to the HIV prevention toolkit and are especially important for populations such as adolescent girls and young women (AGYW) and other key populations who remain at significant risk of HIV acquisition while facing substantial barriers to preventive services. These LAED formulations have been shown to result in better adherence and fewer side effects, with CAB-LA being superior to oral PrEP in reducing the risk of HIV acquisition. They can be used to overcome user burden and adherence challenges. However, the successful rollout of the DPV-VR and CAB-LA may be hampered by issues such as a shortage of healthcare providers (HCPs), inadequate parenteral medication infrastructure, increased workload for HCPs, patient concerns, the price of the medications and the possibility of drug resistance.

Conclusions: SSA must develop laboratory capabilities for monitoring patients on LAED formulations and enhance research on developing more non-injectable LAED formulations. There is a need to train and retain more HCPs, implement task shifting, invest in healthcare infrastructure and integrate healthcare services. To reduce costs and improve availability, the region must advocate for patent license waivers for LAED formulations and procure drugs collectively as a region.

Keywords: adolescent girls and young women; Africa; men who have sex with men; PrEP; prevention; stigma; long-acting

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1 | INTRODUCTION

1.1 | The burden of HIV in sub-Saharan Africa

Despite major advances in HIV prevention and treatment, the global burden of HIV remains unacceptably high. Approximately 38 million people are currently living with HIV. In 2021 alone, 650,000 people died from AIDS-related illnesses and there were 1.5 million new HIV acquisitions, representing a marginal decline of 31% since 2010 [1, 2], far below the target of a 75% reduction in new acquisitions for 2020 set by the United Nations General Assembly in 2016 [1, 2].

HIV/AIDS disproportionately affects sub-Saharan Africa (SSA). In 2021, 65% of all HIV-related deaths and 58% of all new HIV acquisitions occurred in SSA. Heterosexual women and girls in the region are especially burdened by HIV, accounting for 59% of all HIV acquisitions in SSA [1, 2]. This gender disparity starts at a young age with adolescent girls and young women (AGYW) aged 15–24 accounting for 25% of all new HIV acquisitions in the region despite representing just 10% of the population. Key populations (KPs) and their sex partners, including sex workers, men who have sex with men (MSM), people who inject drugs, and transgender people account for about half of new HIV acquisitions in SSA [1].

1.2 | Current progress with oral pre-exposure prophylaxis rollout

A decade after its approval for use among people at substantial risk of HIV acquisition, oral pre-exposure prophylaxis

(PrEP) access is still concentrated in a relatively small number of countries [3], and PrEP distribution within countries is not equal, resulting in a significant unmet need for PrEP [4]. To date, nearly 3.9 million people have initiated PrEP globally. While impressive, this is thought to represent only 10% of those who are at risk and could benefit from PrEP [3].

1.3 | Barriers to oral PrEP use in SSA

Underlying multi-level barriers have slowed the progress of PrEP implementation in SSA. Lack of adherence to oral PrEP has been associated with daily pill burden, side effects, stigma, fear of partner violence, religious beliefs and costs [5–7]. Long waiting times at health centres, dissatisfaction with care and reduced privacy due to inadequate consulting rooms are among the factors in the health system that hinder adherence [8]. Other health system factors that reduce adherence to PrEP include existing delivery practices requiring frequent healthcare facility visits for medication refills and negative attitudes by healthcare providers [9]. The uptake of healthcare services in general, and PrEP in particular, is lower among KPs in SSA due to widespread stigma, prohibitive legislation and discrimination [7]. In 2017, South Africa reported an oral PrEP uptake of 12% among sex workers and 43% among MSM [10]. Community-based distribution of oral PrEP is acceptable and may overcome barriers associated with clinic-based PrEP distribution and achieve high PrEP uptake and retention [11].

1.4 | The need for long-acting extended delivery formulations for HIV prevention

These challenges and unrelenting incident HIV acquisitions highlight the urgent need for a wider PrEP toolkit that includes long-acting extended delivery (LAED) PrEP formulations with more convenient dosing schedules [12]. However, only some of the PrEP delivery challenges will be addressed by these LAED formulations. In this article, we provide an overview of injectable long-acting cabotegravir (CAB-LA) and dapivirine vaginal ring (DPV-VR), discuss the possible implementation challenges and opportunities that SSA countries will likely face during the rollout of LAED PrEP and suggest recommendations to address the challenges.

2 | DISCUSSION

2.1 | Available LAED formulations

Table 1 summarizes the salient features of CAB-LA and DPV-VR. Cabotegravir is a second-generation integrase strand transfer inhibitor (INSTI) with a high barrier to resistance [20]. The HPTN-083 and 084 studies demonstrated that injectable CAB-LA was safe and superior to daily oral tenofovir/emtricitabine for HIV prevention across two cohorts at increased risk of HIV acquisition through vaginal and anal intercourse; cisgender women and cisgender men/transgender women who have sex with men, respectively [14, 21]. Compared to participants on oral PrEP, participants receiving intramuscular CAB-LA 600 mg once every 2 months had a 66% and 89% reduction in HIV acquisition in the two studies. CAB-LA was well tolerated and was demonstrated to have acceptable pharmacokinetic and safety profiles. Most adverse events were mild or moderate and balanced between the two study arms [13]. Injection site pain (ISP), headache, diarrhoea, nausea and exhaustion are a few self-limiting side effects of CAB-LA. ISP became less frequent with subsequent CAB-LA doses. There was high adherence to CAB-LA across the efficacy studies [13, 21].

Pregnancy incidence in HPTN-084 was 1.5 per 100 person-years in the CAB-LA group, with no congenital abnormalities reported. HPTN-083 data suggest that gender-affirming hormone therapy does not affect cabotegravir pharmacokinetics [13]; the World Health Organization (WHO) considers CAB-LA a safe and effective HIV prevention strategy for transgender women [15]. Data from these studies supported United States Food and Drug Regulatory Agency (FDA) approval and WHO recommendation for CAB-LA as PrEP, with subsequent registrations filed in the United States, Australia, Botswana, Brazil, Kenya, Malawi, South Africa, Uganda and Zimbabwe.

CAB-LA 600 mg is administered 4 weeks apart for the first two doses and every 8 weeks after that for PrEP [9]. The prolonged half-life of CAB-LA allows for a delay in follow-up dose of up to 8 weeks without dose alteration; however, if the follow-up injection is missed by more than 8 weeks or more, a higher loading dose will be required before returning to routine [22]. CAB-LA should not be co-administered with potent liver enzyme inducers like rifampicin and carbamazepine, which decrease its serum concentration by almost 60% [14]. CAB-LA is cost-effective when delivered with other preventive measures or given priority among certain populations, particularly women [15]. Participants in clinical trials reported overall satisfaction with CAB-LA [13]. More than 75% of participants in a study of women from the United States and Africa regarded long-acting injectables as highly satisfactory. The study concluded that women's demand for a long-acting injectable PrEP might be more significant in Africa than in US settings [16].

The DVR-VR is formulated as a flexible silicone ring that slowly releases the non-nucleoside reverse transcriptase inhibitor (NNRTI) dapivirine. The monthly vaginal ring is acceptable for use in SSA [17] and has the potential for better adherence than oral PrEP. It is a discreet, woman-initiated, easy-to-use intervention. To date, no related resistance has been reported. In July 2020, the European Medicines Agency announced a positive opinion about the ring for use by women 18 years and older to reduce their HIV risk [12]. The opinion was based on data from two large Phase III randomized trials which involved approximately 4,600 women in Malawi, Uganda, South Africa and Zimbabwe. Both studies demonstrated that the ring has a strong safety profile and reduced the risk of HIV acquisition by approximately 30%. Subsequent subgroup analyses among ASPIRE trial women who had high ring adherence according to residual drug levels in the DPV-VR suggested a greater HIV risk reduction of 50% or higher [18, 19].

The ring is now approved by several SSA countries. Though less efficacious than oral or injectable PrEP, it may be an essential risk-reduction tool for women unable, or unwilling

Table 1. Injectable CAB-LA and dapivirine vaginal ring for HIV prevention

Drug for HIV prevention	References	Type	Approval	Effectiveness	Side effects/safety	Route/dosing	Resistance	Other considerations
Long-acting injectable cabotegravir (CAB-LA) nanosuspension	[13–16]	Second-generation INSTI	Currently approved by WHO and FDA	More effective than oral PrEP with tenofovir/emtricitabine: 66%–89% reduction in HIV acquisition versus oral tenofovir/emtricitabine	Side effects include pain at the injection site, headaches, diarrhoea, nausea and exhaustion. Acceptable pharmacokinetic and safety profile	Route: intramuscular injection Dosing: every 4 weeks for 2 months, then every 8 weeks	Prolonged half-life Stable in the presence of frequent INSTI mutations	Cost-effective in some settings High acceptability among patients in SSA
Long-acting dapivirine vaginal ring	[17–19]	NNRTI	Licenced by FDA and WHO. Approved for use in Kenya, Malawi, Uganda, Rwanda, South Africa and Zimbabwe	29% HIV risk reduction versus placebo ring	Strong safety profile	Route: intravaginal insertion Dosing: monthly	No related resistance	Acceptable in SSA Potential to be combined with levonorgestrel for a single multipurpose ring. Stored at room temperature (no cold chain); 5-year shelf-life

Abbreviations: INSTI, integrase strand transfer inhibitor; WHO, World health organization; FDA, U.S. Food and drug administration; SSA, sub-Saharan Africa.

to take oral or injectable PrEP. The addition of the ring to the prevention toolbox strengthens the development of next-generation antiretroviral-based vaginal rings/films with the potential to be combined with levonorgestrel as a single multipurpose prevention technology [23].

2.2 | Challenges, opportunities and recommendations in the implementation

SSA will face several challenges in rolling out LAED formulations. Below, we discuss challenges related to infrastructure, trained personnel, product-related fears, HIV-related stigma, costs, drug resistance, guidelines and research, and then discuss opportunities and recommendations in the implementation of LAED in SSA.

2.2.1 | Infrastructure

Administration of injectable formulations, such as CAB-LA, requires adequate rooms for client confidentiality, needle supply and suitable disposal facilities for used needles. Some facilities may lack adequate space and the infrastructure to properly dispose of the increased volumes of used needles, increasing the risk of transmission of blood-borne infections [24]. To address the additional infrastructure needs, countries may need to integrate HIV services with other healthcare services, such as sexual and reproductive health services, antenatal/postnatal clinics and men's clinics [25]. A study conducted in Malawi to assess the integration of reproductive health services into HIV care revealed that such integration required minimal additional resources [26].

2.2.2 | Trained personnel

SSA has the world's lowest healthcare provider (HCP) to population ratio [25]. The need for intramuscular administration of long-acting injectables presents a problem in the region because registered nurses and doctors are required to administer the injections. These HCPs authorized to deliver parenteral medications are not present in adequate numbers across healthcare facilities in the region [25]. We recommend that SSA countries amend their policies to permit other HCPs, such as enrolled nurses and primary care nurses, to administer parenteral medications after proper training [25]. Additionally, we recommend that CAB-LA preparation be done at the point of injection just like other injectable medications like depot medroxyprogesterone acetate (DMPA), with special attention to body mass index calculation for needle size determination before administration.

A challenge that can arise when rolling out new interventions is an increased workload for the few available HCPs. Before delivering CAB-LA, clients must first be evaluated to determine their eligibility. Additionally, patients will require observation for at least 10 minutes following the injection [27]. Although community-based oral PrEP delivery models have increased the uptake of oral PrEP, the same models may be difficult to use in the administration of injectable LAED formulations. De-medicalizing the rollout of LAED formulations and appropriate task shifting may help to address this challenge. For example, community health workers could be trained on the safe administration of injections, and strategies devised for the safe disposal of the sharp materials used. While it is not possible to make use of community-based adherence groups that take turns going to the clinic or community product pick-up sites to collect the drugs for the whole group when using injectable LAED formulations, this approach may be feasible for DPV-VR.

HCP attitude and wellbeing are important attributes in health provision [8]. Countries in SSA should improve working conditions for HCPs and invest in the training of more HCPs to ensure that healthcare facilities are adequately staffed. This will improve staff morale and reduce the workload, ensuring that client waiting times are not long and resulting in improved client satisfaction. Satisfied patients are more likely to be adherent and have favourable management outcomes.

2.2.3 | Product-related fears and concerns

Some patients fear needles or are scared of ISP, hence might not be willing to switch from oral PrEP to injectable PrEP. Given the time it takes before the next injection, some patients might worry about insufficient protection. Furthermore, it could still be challenging to visit the medical facilities every 2 months for CAB-LA [15]; though there is potential for administration every 12 weeks, a schedule which would coincide with DMPA injection for contraception. In addition, patients should be well informed about the side effects of the long-acting formulations to improve compliance and reduce the discontinuation of the drugs without consulting HCPs [28].

2.2.4 | HIV-related stigma

HIV-related stigma can prevent patients from accessing services [29]. To reduce stigma and discrimination, communities should be engaged in formulating HIV programmes. This will make clients feel they are part of the programmes and improve implementation success [25]. Well-informed LAED messaging should be used to allay myths and misconceptions to reduce stigma and discrimination against those using them and improve uptake [25].

2.2.5 | Costs

Most SSA countries may not be able to afford CAB-LA and DPV-VR at the indicated cost of USD18/dose and USD6/ring, respectively, even though they may be considered cost-effective in some settings [25]. CAB-LA patent expires in 2031; if the manufacturers of long-acting formulations do not waive their patent licenses, it will take a long time for countries in SSA to be able to manufacture affordable generics [30]. Countries in SSA should, therefore, advocate for technology transfer and for drug developers to expeditiously waive their patent licenses so that cheaper generic forms can be produced regionally, ensuring that those at the greatest risk of HIV acquisition have access to PrEP. Furthermore, countries in SSA must procure the medications as a region to negotiate for more significant discounts with manufacturers.

2.2.6 | *Drug resistance*

CAB-LA has a half-life of 20–65 days and has been detected in some patients' blood up to 1 year after the last injection. However, the concentrations detected were suboptimal, which may lead to drug resistance [22]. Without robust follow-up of patients lost to follow-up, drug resistance may increase, driving HIV care costs up. Mathematical modelling shows that AIDS deaths are predicted to decline in 99% of scenarios where CAB-LA is implemented. However, INSTI resistance is of concern in SSA, where most first-line regimens include dolutegravir. Resistance may occur when CAB-LA is initiated in a recently infected individual with infection not yet detected by third-generation antibody tests used as the standard of care in SSA or as a breakthrough infection during CAB-LA use [31, 32]. To address this challenge, countries in SSA should build the capacity to monitor patients on long-acting injectable formulations for HIV transmission and drug resistance and invest in robust HIV testing algorithms that can detect incident HIV infections early.

2.2.7 | *Gaps in guidelines and research*

Several countries in SSA have now incorporated the DPV-VR in national PrEP guidelines. The CATALYST study will spearhead the two-stage implementation of an enhanced service delivery package providing a choice of oral PrEP, DPV-VR and CAB-LA among women at U.S. President's Emergency Plan for AIDS Relief (PEPFAR) delivery sites in several African countries [33]. The exclusion of DPV-VR from the Essential Medicines List for PEPFAR will likely delay widespread availability to beyond 2026 unless the Global Fund allows earlier procurement of the ring. The current lack of national guidance for CAB-LA means that healthcare facilities in SSA will take longer to embrace it and rollout may be further delayed. Guidelines for the rollout of LAED PrEP formulations are urgently needed and must be human rights-based, with guidance on appropriate task-shifting, and must normalize the use of the new products so those who need PrEP most can access it.

Data on the safety and efficacy of both CAB-LA and DPV-VR are not yet widely available among people who inject drugs, sex workers, pregnant and breastfeeding persons, gender-diverse populations and young people under 18 years. Implementation studies to address these gaps are planned for the Americas, Asia and SSA. SSA will also need to proactively engage KPs in the rollout of these new interventions to pre-empt socio-cultural barriers and gender inequalities that currently limit access to existing oral PrEP and other sexual reproductive health (SRH) services.

Currently, several novel, sustained-release next-generation drug delivery systems, such as implantable technologies and injectable depo systems, are at various stages of the research and development pipeline [12]. If these alternative vehicles of drug delivery are found safe and effective, they will reduce the frequency of administration, and potentially reduce the number of HCPs required for HIV care and the workload among HCPs [24].

3 | CONCLUSIONS

Long-acting formulations of PrEP, such as CAB-LA and DPV-VR, offer several advantages over daily oral PrEP. Nevertheless, the rollout of these long-acting formulations in SSA may face challenges, such as a shortage of HCPs, inadequate infrastructure for parenteral medication, increased workload for HCPs, patients' concerns, drug cost, stigma, drug resistance, and gaps in guidelines and research. To address these implementation challenges, we recommend that the region utilizes a multi-sectoral approach to build laboratory capacity for monitoring patients on long-acting formulations, and enhance research on the development of other controlled release technologies that are accepted by end-users and meet the needs of the community. SSA should provide a human-rights-based delivery service, train and retain more HCPs, invest in healthcare infrastructure, integrate health services, advocate for waiving patent licenses for long-acting injectables and procure drugs together as a region. We anticipate that this will accelerate efforts to expeditiously deliver CAB-LA and DPV-VR as part of a comprehensive HIV prevention package to persons who need it most, with the ultimate aim of improving the quality of life for at-risk populations in SSA.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

NMM—Conceptualization; Supervision; Writing original draft; GM—Writing original article; EM and CS–Writing original draft; GM, TD and JMB—Writing review and editing.

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COMMENTARY

Voluntary licensing of long-acting HIV prevention and treatment regimens: using a proven collaboration- and competition-based mechanism to rapidly expand at-scale, sustainable, quality-assured and affordable supplies in LMICs

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Abstract

Introduction: Emerging long-acting (LA) prevention and treatment medicines, technologies and regimens could be game-changing for the HIV response, helping reach the ambitious goal of halting the epidemic by 2030. To attain this goal, the rapid expansion of at-scale, sustainable, quality-assured, and affordable supplies of LA HIV prevention and treatment products through accelerated and stronger competition, involving both originator and generic companies, will be essential. To do this, global health stakeholders should take advantage of voluntary licensing of intellectual property (IP) rights, such as through the United Nations-backed, not-for-profit Medicines Patent Pool, as a proven mechanism to support broad access to existing HIV medicines across low- and middle-income countries (LMICs).

Discussion: While voluntary licensing may unlock the possibility for generic competition to take place ahead of patent expiry, there are additional elements—of amplified importance for more complex LA HIV medicines—that need to be taken into consideration. This paper discusses 10 enablers of voluntary licensing of IP rights as a model to rapidly expand at-scale, sustainable, quality-assured, and affordable supplies of LA HIV prevention and treatment regimens in LMICs:

1. Identifying promising LA technology platforms and drug formulations at an early developmental stage and engaging with patent holders
2. Consolidating a multidisciplinary network and strengthening early-stage coordination and collaboration to foster innovation
3. Embedding public health considerations in product design and delivery
4. Building innovative partnerships for product development and commercialization
5. Raising awareness of and creating demand for emerging LA products
6. Estimating the market size, ensuring sufficient competition and protecting sustainability
7. Using technology transfer and hands-on technical support to reduce product development timelines and costs
8. Exploring de-risking mechanisms and financial incentives to support generic manufacturers
9. Optimizing strategies for generic product development and regulatory filings
10. Aligning and coordinating efforts of stakeholders across the value chain.

Conclusions: Rapid access to emerging LA prevention and treatment regimens and technologies can be facilitated by voluntary licensing—catalyzed and supplemented by enabling collaborative and non-duplicative efforts of various other stakeholders. This can effectively lead to improved—accelerated and cheaper—access to quality-assured medicines for populations in LMICs.

Keywords: affordability; generic competition; global health; long-acting medicines; low- and middle-income countries; voluntary licensing

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1 | INTRODUCTION

Emerging long-acting (LA) prevention and treatment medicines, technologies and regimens could be game-changing for the HIV response [1–6]. The rapid expansion of at-scale, sustainable, quality-assured, and affordable supplies of LA treatments and technologies through accelerated and stronger competition between manufacturers will be essential. To support broad and timely access to LA medicines in low- and middle-income countries (LMICs), global health stakeholders should take advantage of voluntary licensing of intellectual property (IP) rights through the United Nations-backed, not-for-profit Medicines Patent Pool (MPP), as a collaboration- and competition-based mechanism that has proven successful to dramatically expand access to several antiretrovirals in immediate release oral formulations in 148 countries to date [7–10]. In 2020, MPP completed an exploratory phase to expand its mandate to LA technologies that could improve adherence and treatment outcomes [11, 12]. Some groups have also called on MPP to facilitate access to affordable LA medicines [13–16]. Accordingly, MPP started prioritizing LA medicines, formulations and technologies for in-licensing, and several LA technologies across the development pipeline have already been licensed [17–21].

2 | DISCUSSION

Outlining supporting elements of voluntary licensing of ip rights to unlock access to LA technologies and formulations in LMICs

Voluntary licensing of IP rights refers to "IP-holders voluntarily granting licences to their patents or other IP," allowing competition to take place ahead of patent expiry and supporting access to affordable medicines in LMICs [22]. Several enablers—of amplified importance for more complex LA HIV medicines and formulations—can complement and strengthen the impact of voluntary licensing [23, 24]. This paper discusses 10 enablers for products already on the market (such as cabotegravir LA, CAB-LA, for HIV pre-exposure prophylaxis—PrEP) and earlier-stage LA technology platforms and drug formulations. Some of these technologies are described in the MPP Long-Acting Therapeutics Patents and Licences Database (LAPaL [25]). Molecules with long half-life or high potency (but no formulation feature extending their activity) are beyond this paper's scope [26, 27], while a discussion on voluntary licensing of biotherapeutics is available elsewhere [28].

2.1 | Enabler 1: Identifying promising LA technology platforms and drug formulations at an early developmental stage and engaging with patent holders

Scoping, prioritizing and licensing promising LA technology platforms and drugs/formulations from the pipeline should take place at an early stage, well in advance of marketing authorizations, as early as phase 2 clinical trials, and in some cases at the pre-clinical stage [27–30]. There are at least four reasons for early engagement with patent holders:

1. It might be easier to negotiate access plans prior to exclusive agreements being secured between developing and commercializing entities (in particular, when developers are universities and small-to-medium biotechnology and pharmaceutical companies with limited commercialization capabilities). Earlier engagement with IP holders is an integral part of MPP's 2023–2025 strategy [31].
2. Early engagement can help address knowledge gaps and product design issues early [6]. It can emphasize the intended public health application(s), helping match prioritized active pharmaceutical ingredients (APIs)—such as those identified by Conference on Antiretroviral Drug Optimization (known as CADO) and Paediatric Antiretroviral Drug Optimization (known as PADO) processes—with promising LA drug delivery platforms or technologies [30].
3. As part of clinical research and product development, it may inform product specifications on needs and preferences of target populations—children and their caregivers, adolescents, pregnant and breastfeeding females, transgender individuals and people who may be on other therapies (including contraception and gender-affirming hormone therapies)—on issues such as injection sites or potential drug–drug interactions [32–39].
4. Early engagement may provide legal certainty that affordable generic versions of a product could become available in LMICs. This may be important for stakeholders in charge of downstream aspects of normative guidance, financing, procurement, rollout, uptake and scale-up, helping ensure comprehensive rollout plans are ready (and barriers that could cause unnecessary delays are addressed) by the time generics become available [6, 40, 41].

A caveat to early engagement is the inherent risk that a product might not prove safe and/or effective. In addition, the earlier in development a product is, the less clear costs of goods, indication(s) and market size are. These are risks that, if embraced by a coordinated global partnership, may lead to substantial benefits for timely and broad access to innovative LA products in LMICs. Accordingly, strategic investments and shared risk mechanisms should be put in place to support key stakeholders leading the development lifecycle [24].

2.2 | Enabler 2: Consolidating a multidisciplinary network and strengthening early-stage coordination and collaboration to foster innovation

There are few approved LA products for HIV prevention (the dapivirine monthly vaginal ring and CAB-LA) and treatment (CAB-LA with rilpivirine LA). However, the LA HIV research and development pipeline includes several dosage forms and routes of administration, such as implants and transdermal microarray patches [5, 25, 27, 42–44]. Several collaborative platforms, tools and projects aim at supporting and complementing upstream efforts, and pipeline navigation,

contributing to building a roadmap for access-friendly development of a range of LA products of promising impact in LMICs. These initiatives bring together key contributors, including affected communities, researchers, donors, and manufacturers investing in and developing those products:

1. Research and research-supporting initiatives, such as the Long-Acting/Extended Release Antiretroviral Research Resource Program (LEAP) and the Centre of Excellence in Long-Acting Therapeutics [45, 46].
2. Modelling tools, such as Teoreler, coordinated by the University of Liverpool and LEAP for pharmacokinetics modelling of LA medicines [47].
3. The dedicated Long-Acting Technologies Community Advisory Board, convened by AfroCAB and the Treatment Action Group (TAG), supporting meaningful community engagement and ensuring clinical studies of LA technologies are conducted in ways that are safe, ethical, appropriate and responsive to community priorities and needs [48, 49].
4. A recently launched project of the Clinton Health Access Initiative (CHAI) mapping the technical feasibility and programmatic utility of HIV medicines and platform technologies pairs based on specific target product profile (TPP) attributes (P. Domanico, CHAI, personal communication)—This project is aligned with a broader initiative led by the Global Accelerator for Paediatric Formulations (GAP-f) WHO network where GAP-f partners will be matching priority medicines with formulation and drug delivery innovations (which may include LA technologies) to maximize their potential impact and ensure that these become scalable and affordable to LMIC settings [50].
5. LAPaL [25], coordinated by MPP, a free online resource to support innovation, API-technology matching, and access to LA technologies and compounds that provides technical information on the development and IP status of selected LA therapeutics, as an interactive dashboard offering clinical trial and regulatory status data visualization.

2.3 | Enabler 3: Embedding public health considerations in product design and delivery

It is critical to engage early and through the product lifecycle, with end-user communities, caregivers and service delivery implementors (clinicians, nurses, pharmacists, community health workers and other people involved in delivering care) to include their perspectives, needs and preferences in the development of TPPs [35, 51–60]. Product features defined by such TPPs should inform product design for compatibility with resource-constrained settings, including to minimize the costs of starting materials as well as development, manufacturing, scale-up, distribution, supply chain costs, and other downstream implementation and service delivery requirements and challenges.

2.4 | Enabler 4: Building innovative partnerships for product development and commercialization

In addition to large pharmaceutical companies, engagement with originators (especially patent holders) should include smaller companies, academia and not-for-profit product development partnerships. Opportunities may exist for embedding broad access plans and pathways supporting scalability and economies of scale before downstream commercial agreements are in place. Sub-licensing to manufacturers might go beyond usual generic development, as there might not yet be any originator product with marketing authorization (and none for registrational phase 3 clinical trials too), implying that a sub-licensee may need to act as an "effective originator," as considered in the LONGEVITY project licensing agreement [18]. Progressing voluntary licensing early might also ease obtention of freedom to operate, as LA products may involve multi-layered patent protection: on the API, formulation (injectable, implant or other) and delivery device (as needed), in addition to multiple overlapping manufacturing process patents (e.g. on nanoparticle processes, polymers and excipients) possibly owned by several patent holders [11, 61]. Voluntary licensing terms may also support manufacturing supply chain security (e.g. for specific, sometimes proprietary, polymers and/or excipients and devices necessary to control the drug release rate) [21].

2.5 | Enabler 5: Raising awareness of and creating demand for emerging LA products

Downstream engagement with end-users and caregivers—including through dedicated focus groups, workshops, peer-to-peer communication, social media and early implementation studies—is also essential to raise awareness and sensitize potential end-users of emerging LA products ahead of their readiness for market entry [35, 62]. This is important to ensure product acceptability and create the necessary demand (including at the government, funder and procurement agency levels) to ensure that uptake at scale will transform into public health impact. As part of raising awareness, drug product literacy is an important element, and tools such as TAG's Illustrated Glossary for Long-Acting Technologies—as well as other community, product adoption and job aid resources (e.g. those developed to support the rollout of paediatric dolutegravir)—can be useful [63, 64].

2.6 | Enabler 6: Estimating the market size, ensuring sufficient competition and protecting sustainability

It is also critical to carefully estimate the market size and the geographic distribution of the expected demand across countries as a function of time to assure sufficient competition (i.e. a large enough number of manufacturers) while protecting sustainability (i.e. avoiding splitting the overall market into too many non-profitable parts). While drug price erosion correlates with the number of generic manufacturers in a given market [65], this has to be balanced with sustainability, where the maximum number of generics able to enter and

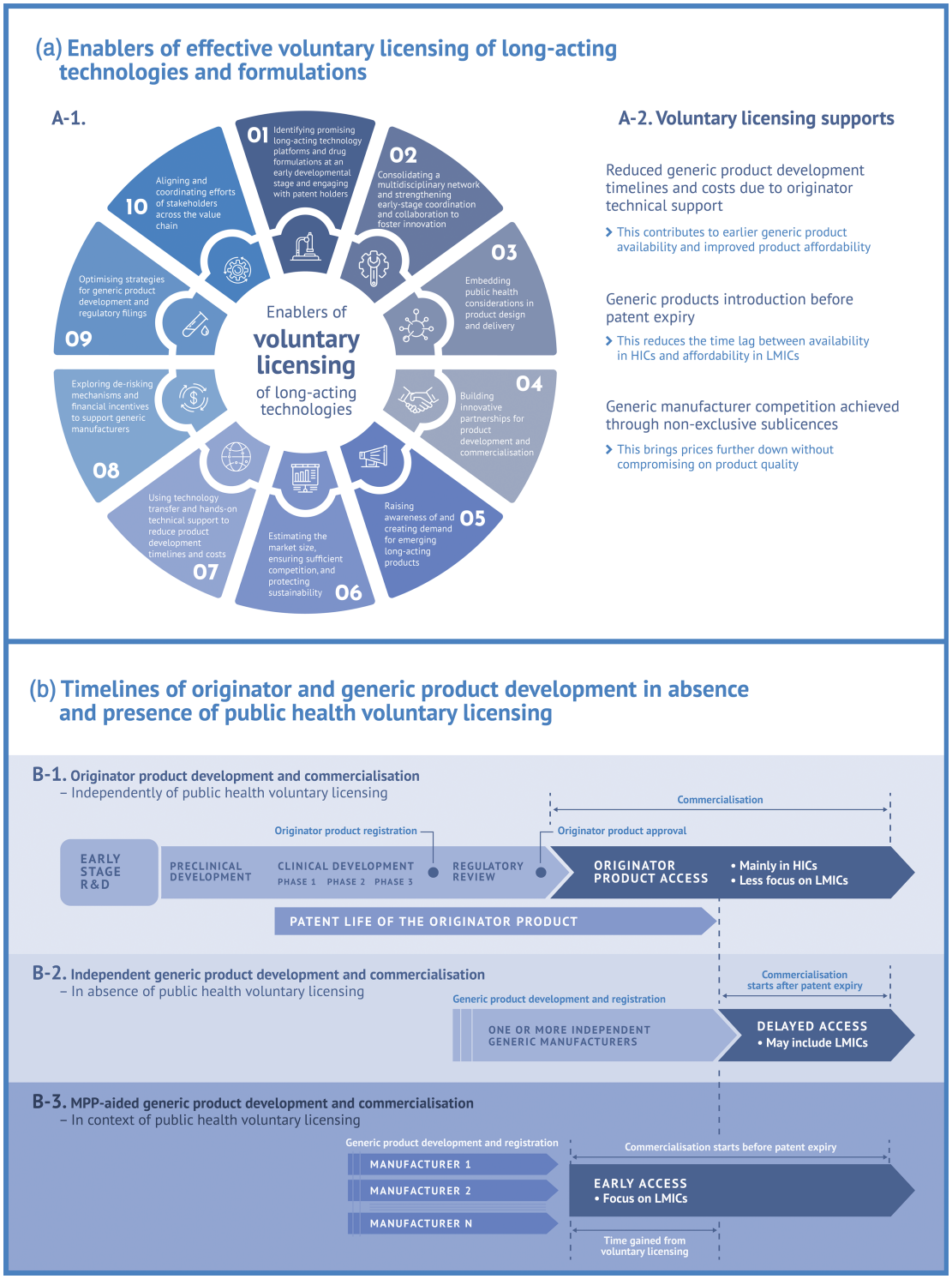

Figure 1. Enablers (a) and timeline benefits (b) of voluntary licensing of intellectual property rights as a model to rapidly expand at-scale, sustainable, quality-assured, and affordable supplies of long-acting HIV prevention and treatment products in low- and middle-income countries (LMICs). (a) Enablers of effective voluntary licensing. (A-1) The 10 key supporting enablers discussed in the paper. (A-2) The main beneficial effects of voluntary licensing—enabled by supporting elements in the wheel (A-1)—that help accelerate access to more affordable products for populations in LMICs. (b) Illustrative development and commercialization timelines for originator (B-1) and generic products: independently (following patent expiry, B-2) and through voluntary licensing (before patent expiry, B-3) compared in terms of the time gap between availability in the high-income country (HIC) markets compared to affordable access to generic versions in LMIC markets. Abbreviations: R&D, research and development; MPP, Medicines patent pool.

stay in a given market—in a sustainable manner—depends on the overall size of that market (which can be a single market, across most or all LMICs, as in the case of pooled procurement through the Global Fund) [65–69]. As such, estimating short-, mid- and long-term demand forecasts (where possible), in alignment with funding and rollout plans of governments and international procurement agencies, is key, and efforts to develop projections have long been established for HIV treatment (not HIV prevention, despite progress around CAB-LA for PrEP). Forecasting the demand and/or market size of early-stage and/or new products with the potential to modify service delivery and/or patient acceptance paradigms may be prone to large uncertainties. Nevertheless, even scenario-based projections can be useful in framing potential uptake and identifying the necessary levers for impact [70, 71].

2.7 | Enabler 7: Using technology transfer and hands-on technical support to reduce product development timelines and costs

LA products may be technologically challenging to manufacture, requiring a substantial amount of expertise and experience for successful generic version development [43, 72–76]. Inherent product characteristics, including complex manufacturing processes, often relying on specialized machinery or infrastructure—especially where LA properties of a formulation depend on niche formulation technologies—may also complicate product development [75, 77, 78]. Technology transfer (of any necessary process, together with documentation and professional expertise, between development and manufacturing sites) may help reduce generic product development timelines and lower their prices at launch [11]. In such cases, the transfer of documentation alone is often not enough to ensure smooth knowledge transfer and optimal process reproducibility, compared to a well-defined plan with hands-on technology transfer (e.g. short-term allocation of receiving party personnel at the transferrer's site). The level of technology transfer needed depends on the know-how that the originator may agree to provide and the experience and capability to adsorb the technology of the receiving unit. If sufficient technology transfer is not executed diligently, troubleshooting may lead to additional development work, and product quality and reproducibility, process efficiency, time to market and costs can all be at risk. Careful selection of manufacturers with specific expertise and equipment, as practiced through MPP's comprehensive Expression of Interest (EOI) blinded selection process followed by meticulous multi-year licence management, can ensure successful and timely product development and regulatory approval [79, 80].

2.8 | Enabler 8: Exploring de-risking mechanisms and financial incentives to support generic manufacturers

Financial and other development incentives may help de-risk infrastructure investments, such as for specialized equipment and sterile manufacturing lines. An example incentive programme that has worked as a complement to voluntary licensing is the Optimal project implemented by CHAI that has reduced "the time it takes for the medicines to get onto the market [by] finding ways to save on production costs and generating demand for the medicines" [81]. The paediatric dolutegravir formulation component of this project has included financial and technical support to two selected generic manufacturers (among MPP sub-licensees), in addition to an originator-supported technology transfer programme and regulatory work in collaboration with the US Food and Drug Administration (US FDA). This led to the fastest stringent regulatory approval of a generic HIV drug in a paediatric formulation ever [82–84].

2.9 | Enabler 9: Optimizing strategies for generic product development and regulatory filings

Strategic development approaches (including studies establishing bioequivalence) and subsequent regulatory approval, for gatekeeping "stringent" regulatory approval (e.g. US FDA, European Medicines Agency or WHO Prequalification—PQ, as required by MPP licences and international procurement agencies) and in-country registration, are critical [18–21]. The most challenging areas for generic development of LA formulations may be establishing bioequivalence (defined by WHO as: "assurance that [the product] is clinically interchangeable with, i.e., therapeutically equivalent or bioequivalent to, the innovator product") [85]. Challenges of bioequivalence studies for LA products include pharmacokinetic variability (i.e. differences among individuals being administered the product) resulting in large sample sizes, and long duration (stemming from a product's LA nature). These challenges have been acknowledged by regulatory bodies, that are now actively working on pilot projects to establish model-integrated evidence approaches for bioequivalence [86]. A licence could allow generic manufacturers' access to *in vivo* pharmacokinetic data generated by an originator, along with any *in vitro in vivo* correlation model established, thereby helping generics design their bioequivalence studies. A licence may also include originator pre-clinical and clinical data to help generics file (and possibly adopt an abridged regulatory pathway, where it exists) in countries where the product has not yet been registered. More broadly, well-defined regulatory pathways for generic LA products can ensure timely availability in LMICs. For this, the availability of regulatory guidelines (e.g. bioequivalence recommendations and product monographs) and prompt inclusion of prioritized products in a WHO PQ EOI can help guide generic manufacturers' development and regulatory strategies. Challenges at the national regulatory approval level may be addressed by strengthening regulatory systems and building the capacity of regulatory assessors relative to LA products. In some cases, reliance on or recognition of stringent regulatory approval or WHO PQ may accelerate and simplify review processes in LMICs.

2.10 | Enabler 10: Aligning and coordinating efforts of stakeholders across the value chain

Expanding at-scale, sustainable, quality-assured, and affordable supplies of LA HIV prevention and treatment regimens requires alignment and coordination of stakeholders' efforts across the value chain. This includes originator

pharmaceutical companies, generic manufacturers, funders, regulators, procurement and other global health agencies, access to medicines advocates, and, importantly, the communities of people living with, affected by, providing care for and/or at-risk of HIV. To catalyze cross-project synergies and allow the sharing of lessons learned and best practices for three early-stage products it is supporting, Unitaid is convening the Long-Acting Project Advisory Committee [18, 19, 21, 87]. Similarly, Unitaid, WHO, UNAIDS, Global Fund, PEPFAR and AVAC are co-convening the Coalition to Accelerate Access to Long-Acting PrEP [20, 71, 88]. Finally, alignment and coordination of stakeholder efforts can be aided by transparency on licensing terms (which MPP makes publicly available online) [89, 90].

3 | CONCLUSIONS

We discussed 10 enablers of voluntary licensing that can support the rapid access to emerging LA HIV prevention and treatment regimens and technologies (Figure 1A). How these enablers, with the participation of key stakeholders, can help shorten the time between originator product availability in HICs until affordable access to quality-assured generic versions in LMICs is illustrated in Figure 1B.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

SM developed the paper outline; AD, IJ, LG and SM drafted the paper; LG and SM conceptualized the figures; EB, RM and SN provided strategic guidance; all authors reviewed the full paper.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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COMMENTARY

What will it take for an injectable ARV to change the face of the HIV epidemic in high-prevalence countries? Considerations regarding drug costs and operations

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Abstract

Introduction: The proven effectiveness of injectable cabotegravir (CAB-LA) is higher than that of any other HIV prevention intervention ever trialled or implemented, surpassing medical male circumcision, condoms and combination antiretroviral treatment. Based on our own analyses and experience with the South African oral pre-exposure prophylaxis (PrEP) programme, we review the supply and demand side factors that would need to be in place for a successful rollout of CAB-LA, and delineate lessons for the launch of other long-acting and extended delivery (LAED) antiretroviral drugs.

Discussion: On the supply side, CAB-LA will have to be offered at a price that makes the drug affordable and cost-effective to low- and middle-income countries, especially those with high HIV prevalence. An important factor in lowering prices is a guaranteed market volume, which in turn necessitates the involvement of large funders, such as PEPFAR and the Global Fund, and a fairly rapid scale-up of the drug. Such a scale-up would have to involve speedy regulatory approval and WHO pre-qualification, swift integration of CAB-LA into national guidelines and planning for large enough manufacturing capacity, including the enabling of local manufacture. On the demand side, existing demand for HIV prevention products has to be harnessed and additional demand created, which will be aided by designing CAB-LA programmes at the primary healthcare or community level, and involving non-traditional outlets, such as private pharmacies and doctors' practices.

Conclusions: CAB-LA could be the game changer for HIV prevention that we have been hoping for, and serve as a useful pilot for other LAEDs. A successful rollout would involve building markets of a guaranteed size; lowering the drug's price to a level possibly below the cost of production, while also lowering the cost of production altogether; harnessing, creating and sustaining demand for the product over the long term, wherever possible, in national programmes rather than single demonstration sites; and establishing and maintaining manufacturing capacity and supply chains. For this, all parties have to work together—including originator and generic manufacturers, donor organizations and other large funders, and the governments of low- and middle-income countries, in particular those with high HIV prevalence.

Keywords: cabotegravir; LAED; PrEP; South Africa; cost; demand/supply

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1 | INTRODUCTION

Could injectable cabotegravir (CAB-LA) be the game changer for HIV prevention that the world has been waiting for—especially low- and middle-income countries (LMICs) with high HIV prevalence? And what can it teach us as we await the launch of other long-acting and extended delivery (LAED) antiretroviral preparations? CAB-LA certainly has proven the effectiveness that is higher than that of any other HIV prevention intervention ever trialled or implemented [1, 2], surpassing medical male circumcision [3, 4] and condoms [5]—at least at the current levels of use- and even higher than the prevention effect of combination antiretroviral treatment [6]. In a recent analysis for South Africa, home to a fifth of the world's people living with HIV where an estimated 200,000 additional people acquire HIV every year, we showed that, depending on uptake and duration of use, CAB-LA could prevent between 15% and 28% of HIV infections over 20 years—more than any other single intervention that we have evaluated over the 7 years that we spent re-optimizing the country's HIV programme through annual Investment Cases [7, 8]. Our findings confirm those of earlier analyses done before the full effect of CAB-LA was known [9–11]. What is important to note is that this large reduction in HIV infections would play out over a baseline of the fairly successful existing South African HIV programme, in which all other prevention

interventions are already routinely offered, and the first and third UNAIDS 90-90-90 targets have been met [12]. CAB-LA, however, comes at a significantly high price, with the only currently listed prices available being US$4,434,024 per person per year in the United States [13], and US$3801.79 in the UK [14], which point to affordability being a major factor to consider. Against this backdrop, we are painfully aware that for the exceptional benefits to materialize, CAB-LA would first need to be affordable for an LMIC, such as South Africa.

What else would be needed to be in place for a successful CAB-LA rollout? As economists and policy analysts, we think about access as the result of demand and supply side factors playing out—if possible, in a coordinated fashion. As members of the South African Department of Health's PrEP technical working group, our views are also informed by the lessons learned while advising on South Africa's oral PrEP programme.

2 | DISCUSSION

On the supply side, much attention has focussed on the price at which CAB-LA will be offered to LMIC, including South Africa, by the manufacturer of the originator drug or the three generic manufacturers that have recently been issued with voluntary licenses under a deal brokered by the Medicines Patent Pool (MPP) [15]. This price will define whether CAB-LA will be affordable to enough governments of high-burden countries to have a chance at making an impact. By the same token, the more countries that are enabled to rollout CAB-LA, the lower the price level should become. Very simply put, the total profit that can be generated by a drug (or any other commodity) is a function of the price per unit and the total volume of units sold. (Putting to one side the argument that drugs preventing severe disease should not be a commodity, or that the manufacturer, judging by its own policy guidance documents, "does not expect to profit from sales of its marketed products to public HIV programmes and international donor agency programmes in all low-income countries, least developed countries, and sub-Saharan African countries" [16].) This means that a profit can be either made from setting a higher price level—or, just as well, by enabling a larger number of clients to access the drug. History shows how well the latter can work: the same logic was employed to drive down the cost of antiretrovirals in the early 2000s to levels that allowed HIV treatment to be rolled out globally—through enabling generic competition and market shaping. This large volume was in part guaranteed by the involvement of PEPFAR, the Global Fund (GF), and, later, UNITAID—which, we argue, might need to play the same role in getting CAB-LA to the people who most need it.

But what does this lower price level need to be? The lively current discussion between the manufacturer and international organizations has resulted in estimates of a feasible minimum price of CAB-LA for HIV programmes ranging from US$16 (excluding capital expenditure) to US$270 per patient per year—assuming 6–7 injections per client per year (for more details on these estimates, see [8]). For South Africa, using the principles of threshold analysis, we established that CAB-LA would need to cost less than US$105 per patient-year to be at least as cost-effective as current oral PrEP [8]. When confronted with these findings, the manufacturer responded by pointing out that this price "significantly underestimates the cost of manufacture," which "is more expensive and much harder than for generic oral PrEP, which is a simple white tablet" [17]. If this were true, there would indeed be an argument for the involvement of a large donor to bring the price below cost, and to a level acceptable to the South African government, essentially shifting the risk of investment in a novel intervention with as yet unclear demand away from an LMIC government, many of which are experiencing significant economic challenges. Successful examples of this approach are the buy-down such as that brokered by the Bill & Melinda Gates Foundation for HIV self-test kits which single-handedly created the market for millions of self-test kits to be used by LMIC governments [18]. This would then, in a second step, enable the South African government, which funds the lion's share of the world's largest HIV programme, to commit to a large CAB-LA rollout programme and, in turn, drive down the cost for the rest of the world—something that it has done successfully for laboratory commodities, such as the MTB Rif Xpert cartridge [19] and HIV viral load tests [20]. If such commitments cannot be made, the second-best option would be for CAB-LA to be sold at a price as close as possible to the cost of production—for all LMICs, including middle-income countries outside of Africa, which are currently not included in the MPP deal but which would stand to benefit substantially [21].

South Africa's HIV budget for the next 3 years contains a sizeable budget for oral PrEP which could be re-purposed for injectable PrEP at a rate controlled by CAB-LA's final market price. For a volume large enough to substantially lower prices, however, the pace of a potential CAB-LA scale-up is crucial—as it is for the drug's benefits to be as large as estimated by us and others. This requires three elements to fall into place relatively soon: rapid regulatory approval in those countries where the drug has been filed for approval, including South Africa, Australia, Botswana, Brazil, Kenya and Malawi (following the example of Zimbabwe [22] and Uganda [23] where it has already been approved), and a speedy WHO pre-qualification which is relevant for countries without their own medicines regulatory authority; swift integration of CAB-LA into national guidelines, where appropriate, and inclusion into PEPFAR and GF drugs lists; and rapidly upscaling large enough manufacturing capacity, including the enabling of local manufacture (another commitment by the manufacturer [24]), and supporting in-country supply chain management. And while the pace of scale-up has to be gauged against concerns, such as increased INSTI resistance if routine HIV testing cannot be kept up, modelling studies suggest that even at high levels of integrase inhibitor resistance, the longer-term mortality benefits of CAB-LA are still likely to far outweigh the risks [25].

What needs to happen on the demand side? While we strongly believe that good enough health interventions manage to make a case for themselves, this is not always true for interventions whose main benefit may lie in the future or accrues to other people—COVID-19 vaccination (and its relatively low uptake even in those LMICs that had some supply) being one strong case in point. In South Africa, strong demand for CAB-LA has been documented [26]—but might be

limited to people already on oral PrEP, most of whom who would much rather access an injection once every 2 months than take pills daily, as well as others keen on adding to or changing away from their current prevention options [26]. Programmes will need thus to both harness existing demand (what we sometimes refer to as prevalent demand) and create additional demand (incident demand), including in people who might not be aware of, or have considered for themselves, PrEP even in its oral form—such as heterosexual men. This demand needs to be created and maintained into the future, learning painful lessons from the experience with oral PrEP on which, in South Africa alone, over 560,000 people have been started on PrEP—but very few return for even just a second month [27]. Finally, a strong case has been made for making CAB-LA access as easy as possible, based on the excellent experience with community-based, peer-led prevention care in parts of the world [28]. For this, CAB-LA programmes would need to be intentionally designed to be a departure from the current oral PrEP programme. In contrast to oral PrEP, CAB-LA would need to be rolled out at the primary healthcare or community level, involving the lowest staff cadre (potentially necessitating injection into the deltoid instead of gluteal muscle) and simplified monitoring. Extending the dosing interval, as is currently being discussed for both CAB-LA and other potential LAED products, will further support community rollout, by reducing the number of required injections and, thus, visits to/from a qualified healthcare provider. Additionally, non-traditional outlets, such as private pharmacies and doctors' practices, might have to be involved wherever they have a chance of bringing the product closer to clients, and at all of these outlets (including primary healthcare clinics and community programmes), conversations about PrEP initiation would need to be linked to any kind of HIV testing services, as soon as there is a negative test result.

We would be remiss if we did not mention the role of the many planned demonstration and implementation science projects. While we acknowledge that they allow everyone—donors, governments and manufacturer alike—to move ahead with *something* while awaiting cheaper prices, regulatory approval, demand to be created and one of the other parties to commit first, we believe that they could be detrimental to overall progress—by dampening enthusiasm on both the demand and supply side. Arguably, this is something that happened with oral PrEP rollout in South Africa, where an incremental approach to rolling out to successive target populations defined by HIV risk and dependence on small-scale demonstration projects funded by donors might have inhibited government's commitment to creating, and sustainably funding, a large enough programme to make a difference. (We speculate that it might also have thwarted demand in the targeted population groups who might have read government's hesitancy as proof that there was something wrong with the product proper, and the early focus on key populations might have worked to stigmatize the intervention altogether.) Additionally, the manufacturer's policy of making LMICs' access to CAB-LA contingent on their approval of implementation science protocols could reduce access in the crucial time period until generic versions are registered and available in these countries [29].

It is prudent to note that many of these issues will be the same for other injectable antiretroviral products currently still in the pipeline—whether they will be used for prevention or treatment purposes. CAB-LA will be a test case for how cheaply sterile injections can be manufactured, and how simply their distribution can be organized. While we think about CAB-LA programming, we need to keep our eye on that pipeline, ready to pivot to new products as soon as their effectiveness is confirmed.

3 | CONCLUSIONS

We believe, based on our own and the analytical work of others, that CAB-LA could be the game changer for HIV prevention that we have been hoping for—and could serve as a useful pilot for other LAEDs. Based on our experience with one country's oral PrEP programme, we know that in order for CAB-LA to realize its potential, all parties have to work together—that includes originator and generic manufacturers, donor organizations, such as PEPFAR and the GF, other funders, such as the Bill & Melinda Gates Foundation, and the governments of LMICs, in particular those with high HIV prevalence, such as South Africa. The work required to make this a reality is cut out for all of us and involves building markets of a guaranteed size; lowering the drug's price to a level possibly below the cost of production, while also lowering the cost of production altogether; harnessing, creating and sustaining demand for the product over the long term, wherever possible, in national programmes rather than single demonstration sites; and establishing and strengthening manufacturing capacity and supply chains. For now, CAB-LA, together with maintaining high uptake of HIV testing and treatment, has the singular potential to help end AIDS. We collectively have a single shot to show that we dare not waste this potential.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

First draft: GM-R and LJ; conceptualization: GM-R, LJ and YP; editing: YP. All authors have read and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to no new data generated.

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COMMENTARY

Securing accelerated access to long-acting injectable cabotegravir for HIV prevention in low- and middle-income countries

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Abstract

Introduction: Reductions in HIV acquisition have slowed, and the global community is significantly off track from global goals. Oral pre-exposure prophylaxis (PrEP) alone cannot address the diverse needs of the millions of people at risk of HIV acquisition. Long-acting injectable cabotegravir (CAB-LA) received United States Food and Drug Administration approval for HIV prevention in December 2021. When studied, CAB-LA demonstrated high effectiveness, provides months of protection versus daily use, is preferred by some users and has the potential to achieve commodity cost reduction. These factors position CAB-LA to catalyse transformation in HIV prevention. Significant work must be undertaken to ensure at-scale uptake in low- and middle-income countries. Leveraging decades of product introduction experience, Clinton Health Access Initiative (CHAI) has developed an innovative roadmap to support equitable CAB-LA introduction, comprising tightly executed market-shaping, product development, regulatory, and programmatic and implementation action.

Discussion: Proven models exist (e.g. long-acting reversible contraceptives, paediatric tuberculosis treatment and antiretrovirals (ARVs), such as paediatric dolutegravir and tenofovir disoproxil fumarate, lamivudine, and dolutegravir) for partnership-driven, accelerated, impactful product introduction. Based on learnings from these models and needs in the prevention space, CHAI developed a roadmap to maximize the near-term impact of CAB-LA and accelerate the development of, access to and impact of quality-assured, low-cost generic CAB-LA. This roadmap is intended to inform introduction planning and investment decision-making across a range of stakeholders, including donors, governments, manufacturers and other partners working in the HIV prevention space. Elements include (1) ensuring coordination and alignment across partners, and avoiding redundancy experienced during oral PrEP introduction; (2) preparing national programmes and providing support to maximize impact, including the development of national policies, guidelines and introduction plans; system strengthening; quantification and procurement; and addressing evidence needs, among other areas; (3) supporting community engagement, ensuring that demand generation and delivery approaches are person-centred and community-led; (4) incentivizing generic product development through, for example, milestone-based commercialization incentives and product development cost-sharing; and (5) expediting regulatory reviews.

Conclusions: Accelerating access to affordable, generic CAB-LA can transform progress towards HIV epidemic control. This vision of impact at scale in prevention is achievable, if informed by results-backed approaches to introduction.

Keywords: cabotegravir; long-acting; HIV prevention; access; LMICs; PrEP

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1 | INTRODUCTION

With 1.5 million new human immunodeficiency virus (HIV) acquisition in 2021, the 2020 UNAIDS target of 500,000 annual new acquisitions was missed by a million new acquisitions [1, 2]. If trends continue, the 2025 target will be missed by over a million new acquisitions [2]. High rates of HIV acquisitions persist despite significant progress increasing treatment coverage and viral suppression. Increasing access to effective prevention interventions, including condoms, voluntary medical male circumcision (VMMC) and oral pre-exposure prophylaxis (PrEP), will be critical to achieve and sustain epidemic control. However, there is an urgent need to expand the portfolio of prevention options to support person-centred services aligned with user preferences and lifestyles. As demonstrated in family planning, expanded options can also drive increased uptake and coverage [3].

Oral PrEP uptake has increased, with an estimated 2.8 million cumulative initiations as of mid-2022 and over a million new initiations in 2021 [4, 5]. However, annual initiations

remain below the 2020 target of 3 million persons accessing PrEP and off track to reach the 2025 target of 10 million initiations [6, 7]. Moreover, these data do not reflect the number currently using PrEP and most programmes are unable to quantify the duration of use. Many of those at the highest risk of HIV face challenges using oral PrEP, including stigma, pill burden and low-risk perception [8–10]. Oral PrEP alone cannot address the diverse needs of the millions at risk of HIV.

Long-acting injectable cabotegravir (CAB-LA) received United States Food and Drug Administration (US FDA) approval in December 2021 [11]. In clinical trials, CAB-LA was shown to be safe and effective at preventing HIV [12, 13]. As a bimonthly injection, CAB-LA offers a discreet, long-acting option aligned with the preferences of many at risk of HIV [14–17]. The analysis also indicates that generic manufacturer can produce CAB-LA affordably [18]. Based on these factors, CAB-LA has the potential to catalyse transformation in HIV prevention. However, barriers to access remain. Generic manufacture is expected to take several years and, while production costs are estimated to be low, without intervention, an affordable generic price is not guaranteed. Moreover, in the near-term, supply is limited in a single supplier market. Pricing from ViiV Healthcare, the originator of CAB-LA, is also expected to be substantially higher than the price of oral PrEP. Significant work is needed to enable the widespread use of CAB-LA, particularly in low- and middle-income countries (LMICs). With few countries delivering oral PrEP at scale, health systems lack experience with high-volume PrEP delivery. Oral PrEP experience also demonstrated that poorly coordinated implementation projects can lead to persistent evidence gaps, slowing adoption and scale-up. For example, in 2018, fewer than 21 LMICs had adopted the World Health Organization (WHO) oral PrEP guidelines [19].

Leveraging decades of product introduction experience, Clinton Health Access Initiative (CHAI) developed an innovative roadmap to accelerate equitable CAB-LA introduction. This roadmap was informed by ongoing collaborations, including with the Coalition to Accelerate Access to Long-Acting PrEP, convened by Unitaid, WHO, UNAIDS, Global Fund, and the US President's Emergency Plan for AIDS Relief (PEPFAR) and other PrEP planning mechanisms.

Alongside implementation considerations and research gaps outlined in WHO guidelines, partners have initiated the development of introduction plans for CAB-LA [20, 21]. This roadmap complements those plans by leveraging an evidence-based approach to systematically document successful introduction models and identify how approaches need to be adapted for CAB-LA. Previously published work has taken a similar evidence-based approach, investigating market-shaping investments needed to bring long-acting products, such as CAB-LA, to the generic marketplace [22]. However, this paper addresses a more comprehensive scope of introduction needs, from the collaborations needed to facilitate market-shaping investments to the engagement required to generate demand at the community level. It aims to inform planning and decision-making among donors, governments and other partners working to accelerate access and impact of CAB-LA.

2 | DISCUSSION

Recent HIV treatment transitions demonstrated the pace and scale of innovation possible through collaborative partnerships [23]. In 2018, a breakthrough agreement between CHAI, the UK's Foreign and Commonwealth Development Office, Unitaid, Bill & Melinda Gates Foundation, the governments of South Africa and Kenya, PEPFAR, the Global Fund, WHO, UNAIDS, United States Agency for International Development (USAID), Mylan and Aurobindo to accelerate access to the fixed-dose combination of tenofovir disoproxil fumarate, lamivudine and dolutegravir (TLD) achieved an LMIC launch price lower than the standard of care for the first time ever [24]. By 2021, TLD was included in national guidelines in over 120 countries with over 18 million patients on dolutegravir (DTG)-based regimens in LMICs at a price of under US$50 per patient per year [25, 26]. The successful transition to TLD was driven by this landmark pricing agreement alongside effective global coordination, tireless community advocacy and engagement, intensive in-country planning and targeted market-shaping interventions.

There are also important models to leverage from product introduction in sexual and reproductive health (SRH), especially given similarities with the multi-product, choice-driven landscape. In 2013, a CHAI agreement, which lowered the price of long-acting reversible contraception from US$18 to US$8.50 per implant and led to a five-fold increase in consumption shows that well-designed, timely market interventions translate into health benefits for large populations [27].

Leveraging successful product introduction experience and learnings, this roadmap outlines a pathway to maximize impact and accelerate the development and introduction of quality-assured, affordable generic CAB-LA. The roadmap addresses five thematic areas outlined in Figure 1. While we focus on CAB-LA, insights can also inform planning for other PrEP products, like the dapivirine vaginal ring.

2.1 | Partner coordination and alignment

During TLD rollout, the ART Optimization Programme Advisory Committee, led by USAID and Unitaid and co-chaired by WHO and the Global Fund, coordinated donor investments [23]. Meanwhile, mechanisms, such as the Antiretroviral Procurement Working Group, provided a platform for coordinating procurement and increasing transparency for suppliers [23].

Effectiveness of these collaborative platforms for information sharing is enabled through complementary and separate high-touch, nimble coordination using bilateral and focused convenings. This is essential with CAB-LA, as the Unitaid, WHO, UNAIDS, Global Fund and PEPFAR-convened Coalition focuses on planning for multiple PrEP products [28]. Avoiding bottlenecks for planning that involves patented or sensitive information, such as generic licensing and incentive agreements, will require focused engagement with suppliers, payers and the negotiating party. Similarly, establishing an acceptable price for ViiV's product will require streamlined partner engagement with major purchasers. Achieving an affordable price may require innovative financing mechanisms,

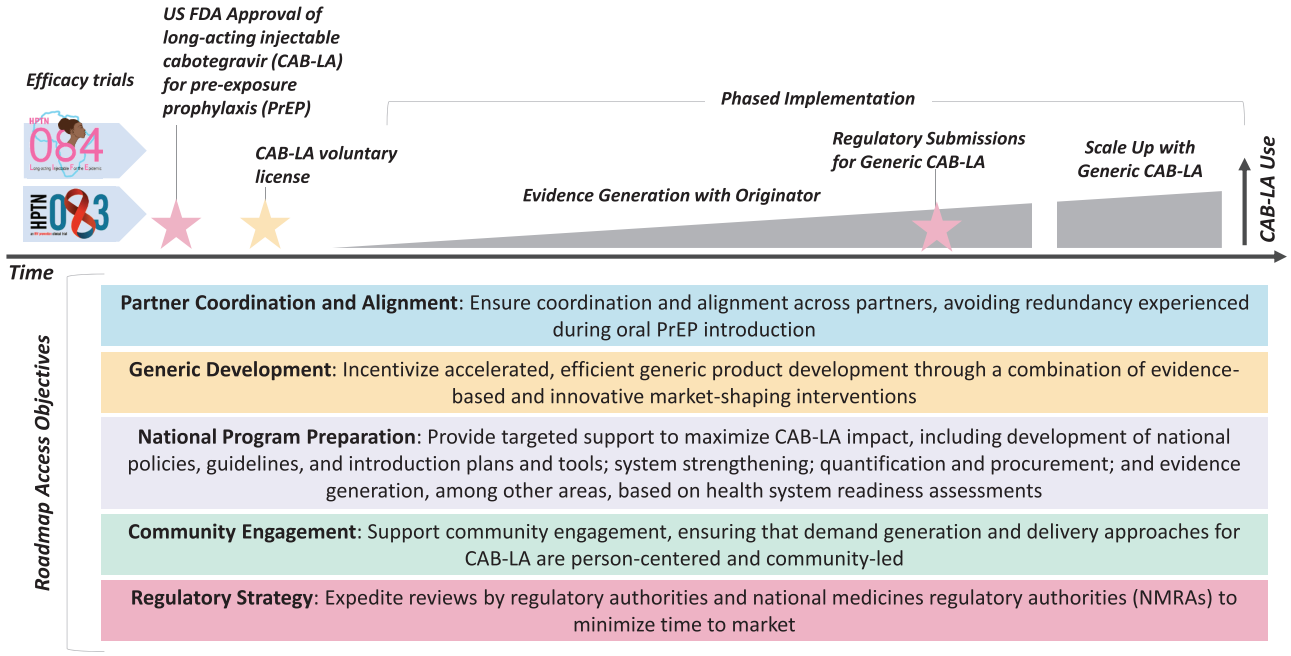

Figure 1. Long-acting injectable cabotegravir (CAB-LA) roadmap areas and access objectives.

such as donor-supported subsidies or volume guarantees. Negotiations to secure these interventions must commence immediately and be supported by demand forecasting, government engagement to understand potential introduction pathways and timelines, and cost transparency.

Governments, donors and major procurers will also need to collaborate closely to coordinate supply. During generic DTG rollout, catalytic procurement initiatives across early adopter countries provided a platform to coordinate efficient evidence generation and supply [23]. This will be essential in the early CAB-LA rollout, both due to pending research questions outlined in WHO's CAB-LA guideline [20] and ViiV's limited manufacturing capacity. In sum, effective partner coordination and alignment will require differentiated approaches, with multilateral mechanisms providing important platforms for information sharing and more targeted engagement supporting agile decision-making and negotiation.

2.2 | Generic development

CAB-LA manufacture requires additional steps versus active pharmaceutical ingredient and formulation development typical for antiretroviral tablets, including particle size reduction via nanomilling, suspension formulation, sterile vial filling and gamma irradiation sterilization. While production costs for generic companies are expected to be lower than the innovator, development costs are expected to be considerably higher than more standard dosage forms [18]. Limited demand visibility is also a barrier to progressing more resource-intensive development of a complex finished dosage form.

The Unitaid-funded STEP-TB project offers an example of addressing demand visibility to drive generic development. STEP-TB market research and modelling improved understanding of the burden of tuberculosis in children and directly informed the successful introduction of dispersible, fixed-dose combination drugs produced affordably by generic manufacturers [29]. To address similar demand visibility challenges for CAB-LA, a need-based demand forecast has been conducted through the Coalition to Accelerate Access to Long-Acting PrEP. With more information on price, this model can be refined to quantify real-life demand and inform generic production.

However, without an incentive package and appropriate market-shaping interventions, market conditions will not support generic development at the pace or price required for rapid impact. Securing a milestone-based incentive structure to share risks, provide accountability, and promote rapid development and commercialization of CAB-LA is an immediate priority following the completion of licensing agreements. Supplier selection for incentives will be needed, based on detailed articulation of CAB-LA production manufacturer capacity and capability, and potential for sustainably supporting low-cost, quality-assured supply. A well-designed incentive package will also enable ceiling price negotiations using the site and process-specific data on generic costs.

Finally, throughout development, stakeholders must support and identify the technical assistance and partnerships needed to ensure efficiency, including with ViiV, mill manufacturers and gamma irradiation suppliers.

2.3 | National programme preparation

A fragmented landscape of over 130 post-approval oral PrEP studies that were not linked to country priorities contributed to slow oral PrEP introduction, with a 4-year delay between US FDA approval and earliest adoption in LMICs [30]. For example, multiple demonstration projects were conducted among female sex workers in Benin and Senegal [31, 32].

However, as of mid-2022, neither country has continued PrEP delivery to this population [4]. In contrast, all three countries (Kenya, Nigeria and Uganda) included in the 2017 catalytic procurement initiative for DTG tablets have transitioned over 90% of adults on first-line treatment to DTG-based regimens [33]. These experiences demonstrate that early introduction mechanisms are unlikely to catalyse wider scale-up without co-ownership with government stakeholders.

To inform CAB-LA adoption, country-specific investment cases informed by opinion leaders, clinician societies and other stakeholders will be needed. Leveraging technical working groups, stakeholders will need to co-develop introduction strategies and transition plans to inform M&E system development, service delivery, training and budgeting. This should be informed by readiness assessments that identify health system adaptations, considering existing infrastructure and human resources. Technical assistance will also be needed to support formative policy and guideline development.

The early introduction must address pending research questions, such as feasible testing algorithms and delivery models. Collaboration across implementation projects, including USAID's MOSAIC project, Unitaid's research in Brazil and South Africa, and other introduction studies is needed to ensure projects efficiently inform CAB-LA scale-up [34, 35]. Once generic CAB-LA is available, stakeholders will need to adapt systems and approaches to drive a rapid transition to scale, leveraging existing PrEP infrastructure and progress towards de-medicalized services. This may include capacitating SRH delivery channels by introducing PrEP diagnostic algorithms and expanding provider training. If donors and governments do not prioritize health systems preparation in parallel to other supply-side investments, we risk another decade of small-scale PrEP demonstration projects with limited epidemic impact.

2.4 | Community engagement

Community networks have played an important role in demanding access to CAB-LA and pressuring global stakeholders to prioritize meaningful, actionable consultation [36–39]. Community leadership must be hardwired into all levels of global and national prevention programming to ensure that communities play a leading role in driving CAB-LA access and person-centred introduction planning. As seen in the early days of DTG introduction with the neural tube defect safety signal, introduction decision-making must be led by the needs and priorities of those impacted [40].

Community advisory board platforms in the treatment space, such as those led by AfroCAB, have driven transformative new product introduction efforts for first- and second-line HIV treatment options, such as TLD, paediatric DTG (pDTG) and darunavir [23]. These platforms should be adapted for prevention through engagement of populations at risk of HIV, including young people and key populations, and existing prevention advocacy networks, such as the Southern African Women Advocates. Co-developing a community engagement strategy will be essential to informing the advocacy agenda, including micro-grants to local networks.

Community engagement must also support sensitization and demand generation among healthcare workers and communities. To accelerate pDTG uptake, CHAI engaged community advisory board members to develop a comprehensive package of patient literacy materials, which have been adapted to local contexts [41]. Widespread access to these materials, alongside community-led sensitization sessions with caregivers and community leaders, equipped thousands of community members with critical information, driving uptake. CAB-LA scale-up will require generating demand among many populations who are not already in care or taking PrEP and this will require new approaches, leveraging information channels outside facilities and health systems. To maximize the impact of community engagement, donors and governments should prioritize not only directly supporting community organizations to carry out demand-side activities, but should also ensure that investment decision-making is informed by the priorities of communities through meaningful consultation and co-creation.

2.5 | Regulatory strategy

There are several challenges associated with regulatory approval of generic CAB-LA. First, PEPFAR's mandate around regulatory structures and pathways was developed in the context of HIV treatment. This mandate provides a critical pathway for accelerated review of ARVs for HIV treatment, allowing stringent regulatory authority review for products still under patent in the United States [42]. Without a pathway for prevention commodities, products that have not already been approved for a treatment indication must rely on WHO prequalification (PQ) and the Global Fund's Expert Review Panel. To address this challenge, stakeholders must advocate to secure support from PEPFAR and other US government partners for the revision of policies to include PrEP products, potentially involving a revised mandate or new agreement with the US FDA.

Second, while WHO PQ enables access to WHO's Collaborative Registration Procedure (CRP), which supports accelerated country reviews, achieving WHO PQ can be a bottleneck due to delayed submissions from manufacturers, lengthy review times and limited transparency on estimated timelines [43]. Moreover, although the target for WHO-CRP review is 90 days, review times by national regulatory authorities vary widely [44]. As of April 2022, WHO PQ has included CAB-LA on its Expression of Interest, an important first step to enable suppliers to submit for PQ [45]. Increased timeline transparency from WHO PQ will enable suppliers to prepare for commercialization and countries to prepare for procurement. An efficient, proactive strategy and coordination to secure rapid reviews and/or waivers will be required to reduce time to market in LMICs.

Finally, as a long-acting product, CAB-LA will require longer, more complex and more costly bioequivalence studies for regulatory submission. Generic manufacturers will need ongoing technical assistance to ensure alignment with requirements, including the design of bioequivalence studies agreed in advance with regulators or normative bodies. The US FDA has indicated its intention to release product-specific guidance for the generic development of CAB-LA [46]. Coordinated, proactive guidance from WHO PQ would also support efficient development by setting clear expectations for suppliers.

Addressing these complex regulatory challenges for CAB-LA will require strategic action from PEPFAR and WHO.

3 | CONCLUSIONS

Accelerating access to affordable, generic CAB-LA can transform progress towards HIV epidemic control. This vision of prevention impact at scale is achievable, if informed by results-backed approaches, including those from successful product introduction in HIV treatment and family planning. VMMC also provides an important model for delivery at scale, with nearly 18 million VMMCs performed between 2016 and 2020 in 15 high-burden African countries, driven by community engagement, innovative demand creation approaches and service delivery models (including clinic- and community-based services), and a strong focus on government ownership and sustainability [47, 48].

However, CAB-LA brings unique opportunities and challenges for HIV prevention and years of missed PrEP targets demonstrate the need to establish a new pathway, leveraging proven models from outside of HIV prevention for partnership-driven, accelerated, impactful product introduction.

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COMPETING INTERESTS

No competing interests to declare for any author.

AUTHORS' CONTRIBUTIONS

SYJ, DR, AS and CA contributed to the conceptualization and outline. SYJ, DFR, ZP, MW and CA contributed to manuscript writing. All authors provided critical feedback to shape the final manuscript.

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DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings outlined in this commentary are available within the article.

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REVIEW

Implementation and resource needs for long-acting PrEP in low- and middle-income countries: a scoping review

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Abstract

Introduction: Several low- and middle-income countries (LMICs) are preparing to introduce long-acting pre-exposure prophylaxis (LAP). Amid multiple pre-exposure prophylaxis (PrEP) options and constrained funding, decision-makers could benefit from systematic implementation planning and aligned costs. We reviewed national costed implementation plans (CIPs) to describe relevant implementation inputs and activities (domains) for informing the costed rollout of LAP. We assessed how primary costing evidence aligned with those domains.

Methods: We conducted a rapid review of CIPs for oral PrEP and family planning (FP) to develop a consensus of implementation domains, and a scoping review across nine electronic databases for publications on PrEP costing in LMICs between January 2010 and June 2022. We extracted cost data and assessed alignment with the implementation domains and the Global Health Costing Consortium principles.

Results: We identified 15 implementation domains from four national PrEP plans and FP-CIP template; only six were in all sources. We included 66 full-text manuscripts, 10 reported LAP, 13 (20%) were primary cost studies-representing seven countries, and none of the 13 included LAP. The 13 primary cost studies included PrEP commodities (n = 12), human resources (n = 11), indirect costs (n = 11), other commodities (n = 10), demand creation (n = 9) and counselling (n = 9). Few studies costed integration into non-HIV services (n = 5), above site costs (n = 3), supply chains and logistics (n = 3) or policy and planning (n = 2), and none included the costs of target setting, health information system adaptations or implementation research. Cost units and outcomes were variable (e.g. average per person-year).

Discussion: LAP planning will require updating HIV prevention policies, technical assistance for logistical and clinical support, expanding beyond HIV platforms, setting PrEP achievement targets overall and disaggregated by method, extensive supply chain and logistics planning and support, as well as updating health information systems to monitor multiple PrEP methods with different visit schedules. The 15 implementation domains were variable in reviewed studies. PrEP primary cost and budget data are necessary for new product introduction and should match implementation plans with financing.

Conclusions: As PrEP services expand to include LAP, decision-makers need a framework, tools and a process to support countries in planning the systematic rollout and costing for LAP.

Keywords: economics; healthcare costs; implementation planning; LMICs; long-acting HIV prevention; pre-exposure prophylaxis

Additional information may be found under the Supporting Information tab of this article.

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1 | INTRODUCTION

Of the nearly 1.5 million annual new HIV acquisitions globally, most occur in low- and middle-income countries (LMICs), and 70% of acquisitions occur in sub-Saharan Africa (SSA) [1–3]. In 2020, most of the 14 countries that achieved UNAIDS "Fast-Track" targets of 73% across the testing and treatment cascade were LMICs, and seven were in eastern and southern Africa (ESA) [4] In countries achieving UNAIDS Fast-Track targets, new HIV acquisitions have declined from 39% in Uganda

to 70% in Zimbabwe, but no country has achieved the projected elimination target [1, 2]. Fast-track goals for comprehensive HIV prevention, including 3 million person-years of pre-exposure prophylaxis (PrEP) by 2020, were not achieved [5]. Additionally, more than two in five oral PrEP users globally discontinue within 6 months of initiation with higher rates in LMICs and women [6]. PrEP discontinuation rates may represent individual-level changes in potential HIV exposure or it may signal a preference for products other than daily oral PrEP [7].

In July 2022, the World Health Organization (WHO) added conditional recommendations for two long-acting HIV prevention interventions: the monthly dapivirine vaginal ring (PrEP ring) and long-acting cabotegravir (CAB LA; injectable PrEP), joining oral PrEP as part of combination HIV prevention [8, 9]. The 2022 WHO Guidelines mark an unprecedented moment in HIV prevention, when multiple PrEP methods are recommended as part of biomedical prevention for all at elevated risk of HIV (Appendix S1) [8–18]. Notably, for the first time, cis-gender women can utilize three HIV PrEP methods: daily oral PrEP, PrEP ring, and injectable PrEP [10, 11, 15]. By October 2022, the monthly PrEP ring had been approved in six countries in ESA and is currently undergoing regulatory review in six additional ESA countries [19]. Long-acting cabotegravir received approval from the US Food and Drug Administration and the Australian Therapeutic Goods Administration in December 2021 [20] and August 2022, respectively. In October 2022, Zimbabwe became the first LMIC to approve injectable PrEP for use [21, 22]. Injectable PrEP has also been approved by South African Health Products and Regulatory Authority (SAPHRA) and is currently undergoing regulatory review in several LMICs [19, 21].

Evidence review of "Fast-Track" goals highlighted global challenges in implementation and widening funding gaps that reduced the impact of HIV prevention amid biomedical advancements [4]. The UNAIDS strategy 2021–2026 highlights the need to systematize HIV prevention implementation and address the widening funding gap for the HIV response, particularly financing for HIV prevention [3]. In an earlier review of daily oral PrEP costs and cost-effectiveness modelling studies, Case et al. highlighted the poor quality of PrEP cost-effectiveness and modelling studies and the lack of primary cost data collection, "real world costs," or inclusion of service delivery strategies in modelling studies [23, 24]. The introduction long-acting pre-exposure prophylaxis (LAP) marks an opportunity for choice in HIV prevention, accompanied by increased complexity in health service delivery. This opportunity should be met with plans to guide and assess implementation systematically. Further, improved cost analyses are critical to inform such plans [1, 3]. Without these, the recognized deficiencies threaten to deepen and jeopardize LAP's potential. With this scoping review, we sought to inform costed plans for LAP implementation by: (1) collating and synthesizing evidence from costed national plans of oral PrEP and family planning (FP) implementation; (2) developing a consensus on the range of key activities and inputs needed for systematic delivery of PrEP innovations, including LAP (hereafter referred to as implementation domains); (3) appraise the cost evidence that would typically inform national implementation plans using this implementation framework; and (4) provide recommendations on future considerations for improving systematic LAP delivery.

2 | METHODS

2.1 | Defining implementation domains

We reviewed publicly available national costed PrEP implementation plans to identify implementation domains that will help achieve national PrEP scale-up or impact goals and objectives. Broad searches were conducted through Google, and focused searches were conducted through websites of national ministries of health, multilateral agencies and digital repositories, like PrEPwatch.com. Implementation details were extracted and mapped to describe the real-world consensus of implementation domains. We also mapped domains from templates of FP costed implementation plans (CIPs) [25–28].

2.2 | Search strategy

We conducted a scoping review of PrEP costing and cost-effectiveness studies adhering to the Cochrane Handbook 5.1 and Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA) scoping review guidance [29] (Supporting Information S2). Between 1–30 June 2022, we searched nine databases for peer-reviewed literature: PubMed, Medline, Web of Science, Embase, PsychInfo, Africa Wide Information, Global Index Medicus, Cochrane and Econlit—using terms regarding (1) PrEP methods, (2) costing and (3) LMICs to identify potential publications (Supporting Information S3). Lastly, we solicited the International AIDS Economics Network for unpublished reports and non-peer-reviewed literature.

2.3 | Inclusion criteria

We included all studies reporting PrEP interventions currently or imminently available (e.g. daily oral, event-driven PrEP, PrEP ring, and CAB LA), or likely to make a market debut within the next 10 years (see Supporting Information S3 for full list) [30]. Additional inclusion criteria were that the study: (1) measured cost or estimated cost through primary data collection or other methods, including epidemiologic and mathematical modelling; (2) was published between 1 January 2010 and 30 June 2022; (3) reported cost data (e.g. average or incremental) or economic evaluation outcomes, such as cost-effectiveness, cost-benefit, or cost-utility; (4) was conducted in any LMIC (classified using World Bank categorizations [31]); and (5) was published in English. We compared our final study sample with other recent reviews on the modelling and cost-effectiveness of biomedical HIV prevention by Bozzani et al. and Giddings et al. [32, 33]. We chose 2010 because clinical trials for daily oral PrEP were underway, and many countries were already considering ways to incorporate PrEP into national HIV plans, pending proven safety and efficacy. We excluded publications reporting only qualitative data; assessing treatment as prevention, microbicides, vaccines, or broadly neutralizing antibodies only; examining high-income country settings only; missing full texts; and conveying aggregate (other reviews), subjective (letters to the editor,

commentaries), formative (study protocols), or theoretical (not reporting cost or cost-effectiveness) research information.

2.4 | Data screening and extraction

Two reviewers (EG and NT) independently screened titles and abstracts for eligibility using Covidence (Veritas Health Innovation, Australia), followed by a review of full-text articles. Three investigators (DC, SF and CJH) independently reviewed and resolved discrepant screenings and reviewed a sub-sample of concordant studies to validate the agreement. When needed, the broader team discussed and resolved discrepancies. Co-authors (DC, SF, CJH, NT, JW and KK) extracted relevant data from the included studies into REDCap [34]. Co-authors (FB, FTP and STR) conducted an independent review to supplement this review's findings [32, 35].

The data collection instrument included: implementation domains previously identified, author, country, year of publication, study year, study purpose, study design, population(s), intervention(s), perspective, duration of observation, period type, sampling strategies, data collection, scope, cost type, estimation method of inputs, discount and inflation rates, analytic methods and findings, transparency regarding limitations, conflicts of interest, and data availability. Data abstraction was disaggregated by geographic area, priority population, PrEP method, and service delivery platform for each cost or economic result. For articles published before 2015, we classified reports of PrEP as daily oral PrEP if the authors did not explicitly state the type of PrEP method.

2.5 | Assessment of financial and economic evidence

We utilized principles 1–17 from the Global Health Costing Consortium (GHCC) reference case, which presents principles of quality and completeness of costing studies of health interventions with qualitative and quantitative information [25–28, 36].

2.6 | Data analysis and synthesis

We assessed inter-rater reliability using Cohen's Kappa (*K*), a statistic that accounts for agreement due to random chance, at each screening stage [37, 38]. We created a PRISMA diagram to present the number of included and excluded publications [39]. Descriptive statistics were used to summarize the study characteristics from quantitative variables (i.e. frequencies and percentages for categorical variables; maximums, medians and modes for continuous variables). We synthesized extracted texts on costs and assumptions. Given the diversity of study designs included in the review, we did not conduct assessments of quality or bias.

3 | RESULTS

3.1 | National costed PrEP implementation plans

Our search for available costed national PrEP operational plans from LMICs yielded four country plans from ESA: Kenya, South Africa, Zambia and Zimbabwe [25–28]. No publicly available plans included LAP.

3.2 | Identified implementation domains

Also, we examined the GHCC and the template for developing CIPs for FP, as well as some resulting national CIPs, as source files for identifying implementation domains [36, 40, 41]. Reviewing these reports, we identified the following 15 key inputs and activities (implementation domains) in at least one document (Table 1) that represent our study team's consensus:

1. **National coordination, policy and planning**—Leadership, governance, and activities to increase ownership and coordination of the HIV PrEP response. Additional activities include implementation planning, adaptation and dissemination of guidelines and policies, community and stakeholders' engagement, and coordination to start up, scale, or sustain PrEP programme.
2. **Target setting**—Activities to define priority populations, coverage levels, the pace of introduction and scale-up, and other rollout scenarios to achieve impact.
3. **Communication/awareness raising/demand creation**—Activities to increase knowledge and awareness of PrEP services, create demand for PrEP among priority populations and PrEP advocacy at all levels.
4. **Service delivery approaches**—Includes service entry points for integrating PrEP, and feasibility of integrating PrEP into other services. We particularly focused on non-HIV services integration, such as FP, sexual and reproductive health, antenatal care, and community-based services. We also identified inclusion into HIV programmes, including self-testing.
5. **Counselling and adherence support**—Includes counselling to initiate, sustain, discontinue, and adhere to PrEP.
6. **Human resources**—Includes in-service and pre-service education and training for physicians and allied health professionals.
7. **PrEP intervention (commodities)**—Includes cost of PrEP products.
8. **Laboratory monitoring services and other commodities**—Includes baseline tests for eligibility and safety monitoring.
9. **Supply chain management and logistics**—Includes commodity inventory management, reporting, tracking, and handling procedures for distributing PrEP to service delivery points. This includes warehousing and distribution of PrEP and other necessary commodities.
10. **Health information systems**—Developing and updating information systems and registers to document and report PrEP services for quality improvement or reporting purposes.
11. **Monitoring and evaluation**—Activities to define indicators, include PrEP monitoring as part of routine HIV services, and continuous quality control and improvement to ensure that the services are of the highest possible standard.

Table 1. Mapping of key implementation domains drawn from costed national implementation plans for daily oral PrEP.

Kenya: Framework for implementation of pre-exposure prophylaxis in Kenya—2017	South Africa: NDoH PrEP implementation pack	Zambia—Implementation framework and guidance for pre-exposure prophylaxis of HIV infection 2018	Zimbabwe—Implementation plan for HIV pre-exposure prophylaxis in Zimbabwe 2018–2020	Family planning CIP template	GHCC principles	Consolidated implementation domains/content areas
Planning, leadership and governance* Leadership and governance to increase ownership and coordination. Adaptation and dissemination of guidelines and policies, capacity building and community engagements.	Clinical guideline development	Leadership and governance Sub-committee National taskforce	National coordination and advocacy for an enabling policy environment	Policy and advocacy to secure resources for plan development stewardship and governance	Start-up period versus implementation or both	National coordination, policy and planning
		Prioritizing and implementing PrEP services - Populations with high HIV incidence/prevalence by geography, population groups and risk behaviours	Target settings		Target population, coverage, time period	Target setting
Communications, advocacy and community engagement	Communication and community-based strategies	Build awareness/create demand Mobilize communities	Awareness raising, PrEP promotion	Demand, communication and outreach		Communication/ awareness raising/ demand creation
Service delivery operations* -delivered using community-based and facility-based delivery models, -prevention centres, pharmacies, stand-alone DICEs, special clinics MCH/FP/ANCs, youth-friendly centres, comprehensive care centres, outpatient departments	Quality of care Effectiveness and efficiency Integration across various entry points	Programming PrEP services Service delivery minimum standards where PrEP demand can be generated Integrated in existing services to reach populations Facilities with relevant services, (HIV and STI testing, ART, YFS, MNCH, VMMC, OPD, family planning), facility readiness	Public and private-sector facility mapping Provision of PrEP	Service delivery	Delivery mechanism	Service delivery approaches

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Table 1. (Continued)

Kenya: Framework for implementation of pre-exposure prophylaxis in Kenya—2017	South Africa: NDoH PrEP implementation pack	Zambia—Implementation framework and guidance for pre-exposure prophylaxis of HIV infection 2018	Zimbabwe—Implementation plan for HIV pre-exposure prophylaxis in Zimbabwe 2018–2020	Family planning CIP template	GHCC principles	Consolidated implementation domains/content areas
Adherences support	Quality of care: counselling, stigma reduction and adherence					Counselling and adherence support
Human resources In-service training/pre-service education Trainer of trainers (TOT)	Human resources	Human resources - integrated HIV care training	Provider sensitization and training	Salary/labour cost		Human resources
PrEP (TDF/FTC)*	PrEP (TDF/FTC)	PrEP (TDF/FTC)		Commodities	Intervention	PrEP intervention (commodities)
Laboratory (baseline tests and monitoring) forecasting and quantifying Monitoring for supply security Warehousing and distribution		Laboratory services	Laboratory monitoring services			Laboratory monitoring services and other commodities
Commodity management procedures* (ordering/handling and reporting) Commodity security Logistic management information systems (LMIS): forecasting and quantifying Monitoring for supply security Warehousing and distribution	Functioning supply chain, including drugs and commodities	Procurement and supply chain	Maintain a consistent supply of PrEP medicines	Commodity security		Supply chain management and logistics

(*Continued*)

Table 1. (Continued)

Kenya: Framework for implementation of pre-exposure prophylaxis in Kenya—2017	South Africa: NDoH PrEP implementation pack	Zambia—Implementation framework and guidance for pre-exposure prophylaxis of HIV infection 2018	Zimbabwe—Implementation plan for HIV pre-exposure prophylaxis in Zimbabwe 2018–2020	Family planning CIP template	GHCC principles	Consolidated implementation domains/content areas
Monitoring and evaluation systems (documentation and reporting)		Developing system triggers for people who cannot adhere			Supporting change	Health information systems
Monitoring and evaluation* Quality improvement Facilitate and inform scale up Improving PrEP programme efficiency Continuous quality control and improvement (CQI)	Monitoring and evaluation	Monitoring and evaluation Integrate PrEP monitoring within existing reporting services Assess adherence, retention and linkages Consider risk-based reasons for stopping	Integrated monitoring and evaluation system for PrEP	Monitoring and coordination		Monitoring and evaluation
Research and impact evaluation			Conduct research and evaluation		Research and supporting change	Implementation science and operations research
Financing and resource mobilization*	Costing and financing the PrEP and T&T policy - establish the cost of implementation of these plans at national and provincial levels		Mobilize and track resources	Financing		Budgeting, costing and financing
				Capital	Overhead costs Above-service delivery	Indirect/overhead Above-site activities

Note: Asterisks (*) indicate that the cost was estimated or budgeted within the National plan. Abbreviations: ANCs, Antenatal care; ART, antiretroviral therapy; CIP, costed implementation plans; DICEs, drop-in centres; FP, family planning; GHCC, Global Health Cost Consortium; MCH, maternal and child health; MNCH, maternal neonatal and child health; NDoH, National Department of Health; OPD, outpatient departments; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infections; TDF/FTC, tenofovir disoproxil and emtricitabine; VMMC, voluntary medical male circumcision; YFS, youth-friendly services.

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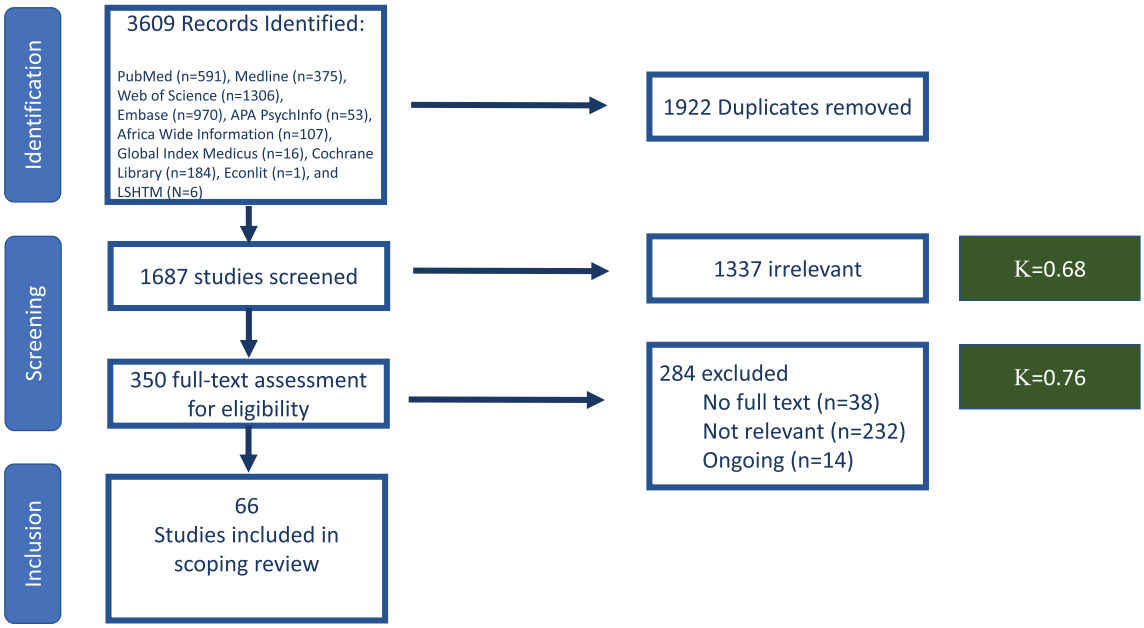

Figure 1. PRISMA diagram of identified, screened and included studies.

12. **Implementation science and operations research**—Includes planned research activities to facilitate and inform scale-up.
13. **Budgeting, costing and financing**—Budget, cost, and economic evaluations to develop cost estimates of PrEP service delivery, impact, and financing shortfalls. This includes stakeholder engagement to blend finances through public–private partnerships to support PrEP delivery.
14. **Indirect/overhead**—Includes costs that cannot be directly traced to the provision of a service, such as administration, security personnel, buildings, and general equipment.
15. **Above-site activities**—Includes various support services provided by the central administration, such as training, education and outreach, demand generation campaigns, central laboratory services, technical assistance, and capacity building.

Six of the 15 implementation domains were in five (plans and template): national coordination, policy, and planning; awareness raising and demand creation; service delivery approaches; human resources; supply chain and logistics; and monitoring and evaluation (Table 1). The other domains were included in two or three plans.

3.3 | Study characteristics

Searches of electronic databases for oral PrEP and LAP costing and cost-effectiveness literature yielded 3609 publications; of which, 1922 were duplicates, 1687 underwent title-abstract screening, 1337 were excluded and 350 underwent full-text review. We excluded ongoing studies (n = 14) and studies lacking full-text availability (n = 38) or relevancy (n = 232), such as only high-income country settings, not reporting cost data, or reporting only qualitative findings. Ultimately, 66 studies were included (Figure 1). Reviewers exhibited moderate to good agreement during title-abstract screening (K = 0.68) and better agreement in full-text review (K = 0.75).

3.4 | Populations

The 66 studies (Table 2) represented the following specific population groups: adolescent girls and young women (AGYW) (29%); men who have sex with men (MSM) (27%); sex workers (27%, majority female sex workers except for one reported male sex worker); general population (26%); women of any age (18%); men of any age (9%); and serodifferent couples (SDCs) (17%). The populations least represented (<7%) were adolescent boys and young men (ABYM), people who inject drugs, trans women, pregnant and breastfeeding women, and prisoners. Additional study details of each population group disaggregated cost and economic data are shown in S4A, and for all populations regardless of cost and economic data disaggregation in S4B.

3.5 | Geography

The 66 studies, representing 69 countries (Figure 2), and one study representing all of SSA without sufficient details to make a country assignment were included. Most studies represented a few countries: the top six countries were South Africa (44%, n = 29), Kenya (24%, n = 16), China (14%, n = 9), Zimbabwe (12%, n = 8) and Uganda & Zambia (11%, n = 7). Eleven studies were multicounty. Studies represented the following UNAIDS geographic regions: Southern and Eastern Africa (n = 47), West and Central Africa (n = 4), Asia and the Pacific (n = 12), Eastern Europe and Central Asia (n = 2), Latin America and the Caribbean (n = 5), and the Middle

Table 2. Characteristics of included studies (N=66).

Author	Year of publication	Countries	Priority population represented	Priority population costed	Primary costing	PrEP methods	Long-acting PrEP	Aims/objectives
Ying	2015	Uganda	Sero-different couples (SDC)	SDC	Yes	Daily oral PrEP	No	Estimate the additional operational costs of PrEP delivery in an open-label, prospective study and project long-term health and economic outcomes and estimate cost-effectiveness of PrEP implementation
Eakle	2017	South Africa	Sex worker	Sex worker	Yes	Daily oral PrEP	No	Support integration of oral PrEP, as part of a combination prevention approach, and early antiretroviral therapy (ART) into existing HIV services in two urban settings, with specific aims to assess uptake, retention and adherence among female sex workers and to estimate the cost of this strategy
Suraratdecha	2018	Thailand	Men who have sex with men (MSM)	MSM	Yes	Daily oral PrEP	No	Assess the cost of providing oral PrEP to MSM and estimate the epidemiological impact and cost-effectiveness of oral PrEP for this target group
Wong	2018	China (Hong Kong)	MSM	MSM	Yes	Daily oral PrEP	No	Examine the impact of PrEP in a setting with low HIV incidence with a low proportion of high-risk MSM in Asia, through developed an epidemic model and conducted cost-effectiveness analysis using empirical multicentre clinical and HIV sequence data from MSM living with HIV in Hong Kong, in conjunction with behavioural data of local MSM
Irungu	2019	Kenya	SDC	SDC	Yes	Daily oral PrEP	No	Estimate the cost of delivering antiretroviral-based HIV prevention to HIV SDC in public health facilities in Kenya and the incremental cost of providing PrEP as a component of this strategy
Roberts	2019	Kenya	Adolescent girls and young women (AGYW)	AGYW	Yes	Daily oral PrEP	No	Estimate the incremental cost of integrating PrEP delivery into routine MCH and FP services and explore the cost implications of service delivery modifications, such as timing of creatinine monitoring and prioritized delivery to women identified as having high risk for HIV acquisition

(*Continued*)

Table 2. (Continued)

Author	Year of publication	Countries	Priority population represented	Priority population costed	Primary costing	PrEP methods	Long-acting PrEP	Aims/objectives
Hughes	2020	Zimbabwe	SDC	SDC	Yes	Daily oral PrEP	No	Estimate the resources required to deliver various safer conception strategies and calculate the incremental cost per couple for "real world" scenarios for the delivery of the safer strategies in the public sector
Peebles	2021	Kenya	SDC	Other	Yes	Daily oral PrEP	No	Estimate the incremental cost of public-sector HIV-1 care clinic-based provision of PrEP in Kenya
Hendrickson	2021	Zambia	AGYW, general population, MSM, sex worker	AGYW, general population, other	Yes	Daily oral PrEP	No	Present the results of a costing study of PrEP implementation in Zambia, aiming to provide cost estimates of PrEP provision disaggregated by programme type and showcase costs per PrEP-month of effective use, using aggregate PrEP persistence data, and compare that to costs for perfect use
Wanga	2021	Kenya	AGYW	AGYW	Yes	Daily oral PrEP	No	Evaluate the cost of delivering daily oral PrEP to AGYW in two family planning clinics in Kisumu and estimate the total annual cost and average cost per client-month of PrEP dispensed as implemented in the study setting and as would be incurred by the Kenyan Ministry of Health if it were to implement PrEP delivery to the same population in the same facilities
Mudimu	2022	South Africa	AGYW	AGYW	Yes	Daily oral PrEP	No	Evaluate the cost of PrEP provision with effective use counselling offered to AGYW through community-based HIV testing platforms
Mangenah	2022	Zimbabwe	AGYW, men, women	AGYW, men, women	Yes	Daily oral PrEP	No	Provide input into cost-effectiveness modelling and data for assessing resource needs associated with scaling up PrEP delivery
Okal	2022	Kenya	AGYW	AGYW	Yes	Daily oral PrEP	No	Compare unit costs of providing DREAMS interventions to AGYW across two sites, an urban (Nyalenda A Ward) and peri-urban (Kolwa East Ward) setting, in Kisumu County, Kenya

(*Continued*)

Table 2. (Continued)

Author	Year of publication	Countries	Priority population represented	Priority population costed	Primary costing	PrEP methods	Long-acting PrEP	Aims/objectives
Smith	2016	South Africa	Sex worker, ABYM, AGYW, men, women, adolescents	General population	No	bnAbs, PrEP ring, daily oral PrEP, injectable PrEP	Yes	Construct a strategic approach to HIV prevention using limited resources to achieve the greatest possible prevention impact through the use of interventions available today and in the coming years
Stover	2016	Asia and Pacific, East and Southern Africa, Eastern Europe and Central Asia, Latin America, Middle East and North Africa, West and Central Africa, West and Central Europe and North America	AGYW, general population, MSM, people who inject drugs (PWID), prisoners, SDC, sex worker, trans women (TGW)	Other	No	Other PrEP (PrEP includes oral pills, vaginal gel, vaginal ring and injectable forms)	Yes	Describes the analysis that produced the 2020 and 2030 Fast-Track targets and the estimated resources needed to achieve them in low- and middle-income countries
Walensky	2016	South Africa	Women	Women	No	Daily oral PrEP, injectable PrEP	Yes	Anticipate the development of newer PrEP formulations, investigate the effectiveness thresholds that would justify the additional cost over existing PrEP alternatives in a population of high-risk young women in South Africa, and identify the key drivers and uncertainties behind that assessment
Glaubius	2016	South Africa	General population	General population	No	Injectable PrEP	Yes	Analyse scenarios of RPV PrEP scale-up for combination HIV prevention in comparison with a reference scenario without PrEP
Quaife	2018	South Africa	AGYW, sex worker, women	AGYW, sex worker, women	No	Daily oral PrEP, PrEP ring, other PrEP (includes multiple combinations of multi-purpose oral, vaginal ring, injectable, gels and diaphragm technologies)	Yes	Examine the cost-effectiveness of the incremental benefits and health system costs of single- and multi-purpose prevention products, compared to current practice of condom use and male circumcision prevalence and model cost-effectiveness across three female groups: younger women (aged 16–24), older women (aged 25–49) and female sex workers

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Table 2. (Continued)

Author	Year of publication	Countries	Priority population represented	Priority population costed	Primary costing	PrEP methods	Long-acting PrEP	Aims/objectives
van Vliet	2019	South Africa	Women	Women	No	Injectable PrEP	Yes	Model how many HIV infections could be averted if injectable contraceptive users started using long-acting PrEP and determine the cost at which long-acting PrEP drugs would be cost-effective
Glaubius	2019	South Africa	Women	Women	No	PrEP ring	Yes	Evaluated the potential epidemiological impact and cost-effectiveness of dapivirine vaginal ring PrEP among 22- to 45-year-old women in KwaZulu-Natal, South Africa
Reidy	2019	Kenya, South Africa, Uganda, Zimbabwe	AGYW, general population, sex worker	AGYW, general population, sex worker	No	Daily oral PrEP, PrEP ring	Yes	Explore the impact and cost-effectiveness of the PrEP ring in different implementation scenarios alongside scale-up of other HIV prevention interventions
Vogelzang	2020	South Africa	Adolescent boys and young men (ABYM), men	ABYM, men	No	Daily oral PrEP, injectable PrEP, other PrEP (oral PrEP + injectable PrEP)	Yes	Estimate 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
Adeoti	2021	Nigeria	General population	General population	No	Other PrEP (PrEP as a concept)	Yes	Evaluate the impact of PrEP/PEP using a novel artificial intelligence technology, assessing the impact on HIV burden (incidence) and service utilization in a Nigerian HIV treatment centre
Pretorius	2010	South Africa	AGYW	AGYW	No	Daily oral PrEP	No	Evaluate PrEP alongside ART and condom-use interventions by developing an age-structured model, which is contextualized to the South African epidemic, paying attention to the distribution of relative infection risks between age categories
Hallett	2011	South Africa	SDC	SDC	No	Daily oral PrEP	No	Examine impact and cost-effectiveness of different TasP and oral PrEP strategies
Gomez	2012	Peru	MSM, sex worker, TGW	MSM, sex worker, TGW	No	Daily oral PrEP	No	Investigate the impact of a feasible intervention, determine the most efficient strategies for rollout and examine the impact of coverage, adherence and prioritization on both health benefits and costs to the health system

(*Continued*)

Table 2. (Continued)

Author	Year of publication	Countries	Priority population represented	Priority population costed	Primary costing	PrEP methods	Long-acting PrEP	Aims/objectives
Long	2013	South Africa	Men, women	Men, women	No	Daily oral PrEP	No	Assess the impact of simultaneously scaling up multiple biomedical HIV prevention programmes and calculate the benefits of reduced secondary transmission among partners of programme recipients
Cremin	2013	South Africa	ABYM, AGYW	Adolescents and young adults	No	Daily oral PrEP	No	Estimate the potential impact and cost-effectiveness of antiretroviral-based HIV prevention strategies
Nichols	2013	Zambia	Other	General population	No	Daily oral PrEP	No	Explore the possibilities of daily oral PrEP optimization using realistic data collected in the rural HIV clinic at the Macha Mission Hospital in Zambia and evaluate the risk for resistance development
Verguet	2013	42 Sub-Saharan countries	General population	General population	No	Daily oral PrEP	No	Study the potential impact and incremental cost-effectiveness of providing PrEP over a 5-year period (2013–2017) to a general adult population in sub-Saharan Africa to provide insight into where and why a PrEP intervention could be best put to use for HIV prevention
Stover	2014	25 Low- and middle-income countries	Adolescents and young adults, general population, MSM, other, SDC, sex worker	Adolescents and young adults, general population, MSM, other, SDC, sex worker	No	Daily oral PrEP, HIV vaccine	No	Examine the impact of achieving high coverage of all existing HIV prevention interventions and three new approaches on the HIV epidemic in all low- and middle-income countries
Nichols	2014	Zambia	Other	General population	No	Daily oral PrEP	No	Compare the cost-effectiveness and economic affordability of antiretroviral-based prevention strategies in rural Macha, Zambia
Anderson	2014	Kenya	Sex worker, MSM, men, women	General population	No	Daily oral PrEP	No	Examine how a fixed amount of resources for HIV prevention can be used to generate reductions in the rate of new HIV infections using two forms of resource allocation: (1) the rollout of particular interventions is uniform across the country; and (2) interventions can be focused on geographic or key affected populations that contribute to HIV strongholds

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Table 2. (Continued)

Author	Year of publication	Countries	Priority population represented	Priority population costed	Primary costing	PrEP methods	Long-acting PrEP	Aims/objectives
Alistar	2014	South Africa	General population	Other	No	Daily oral PrEP	No	Study the population health outcomes and cost-effectiveness of implementing expanded ART coverage and oral PrEP in a setting with a heavy HIV burden
Alistar	2014	Ukraine	PWID	PWID	No	Daily oral PrEP	No	Evaluate the cost-effectiveness of PrEP for PWID alone or as part of a portfolio of interventions including methadone maintenance treatment for PWID and antiretroviral treatment for all individuals living with HIV and project the evolution of the epidemic under various combinations of strategies for HIV control: oral PrEP programmes for uninfected IDUs, MMT programmes for PWID and scale-up of ART programmes for eligible people living with HIV (including PWID and non-PWID)
Cremin	2015	Mozambique	Women	Women	No	Daily oral PrEP	No	Estimate the prevention impact and the cost-effectiveness of providing time-limited PrEP to partners of migrant miners in Gaza, Mozambique
Jewell	2015	South Africa	SDC	SDC	No	Daily oral PrEP	No	Estimate the cost-effectiveness of daily oral tenofovir-based PrEP, with a protective effect against HSV-2 as well as HIV-1, among HIV-1 SDC in South Africa
Cremin	2015	Kenya	General population	General population	No	Daily oral PrEP	No	Investigate the influence of potential interactions between key aspects of a PrEP intervention on projections of epidemiological impact and cost-effectiveness
Mitchell	2015	Nigeria	SDC	SDC	No	Daily oral PrEP	No	Estimate the impact and cost-effectiveness of PrEP, TasP and condom promotion for SDC in Nigeria
Price	2016	Sub-Saharan Africa/Zambia	Pregnant and breastfeeding women	Pregnant and breastfeeding women	No	Daily oral PrEP	No	Develop a decision analytic model to evaluate a strategy of daily oral PrEP during pregnancy and breastfeeding in SSA

(*Continued*)

Table 2. (Continued)

Author	Year of publication	Countries	Priority population represented	Priority population costed	Primary costing	PrEP methods	Long-acting PrEP	Aims/objectives
Moodley	2016	South Africa	Adolescents and young adults	Adolescents and young adults	No	Daily oral PrEP, HIV vaccine	No	Economically evaluate individual and combination HIV preventive strategies and compare their impact against both the current rollout of ART and a potential scaling-up of the ART programme
Meyer-Rath	2017	South Africa	AGYW, sex worker	AGYW, sex worker	No	Daily oral PrEP	No	Identify the optimal mix of HIV services under a constrained budget for the South African HIV Investment Case
Chiu	2017	South Africa	AGYW, sex worker	AGYW, sex worker	No	Daily oral PrEP	No	Describe optimization routines developed for the South African HIV Investment Case and compare its results with those generated using conventional cost-effectiveness analysis methods to examine the incremental benefit of accounting for interaction effects between interventions and non-linear effects across scale up
Cremin	2017	Kenya	MSM, sex worker	MSM, sex worker	No	Daily oral PrEP	No	Identify an optimal portfolio of interventions to reduce HIV incidence for a given budget and determine the circumstances in which PrEP could be used in Nairobi, Kenya
Akudibillah	2017	South Africa	General population, sex worker	Other	No	Daily oral PrEP	No	Inform drug-allocation policy in resource-limited settings by using a compartmental mathematical model for heterosexual transmission of HIV with treatment targeted by infection status, sexual-activity level and gender
Alsallaq	2017	Kenya	AGYW	AGYW	No	Daily oral PrEP	No	Compared the impact and costs of HIV prevention strategies focusing on youth (15- to 24-year-old persons) versus on adults (15+ year-old persons) in a high-HIV burden context of a large, generalized epidemic
Anderson	2018	Kenya	Men, MSM, sex worker, women	Men, MSM, sex worker, women	No	Daily oral PrEP	No	Quantify the cost of short-term funding arrangements on the success of future HIV prevention programmes
Li	2018	China	MSM	MSM	No	Daily oral PrEP	No	Assess the benefits of full implementation of current policies and the timely introduction of novel policies and makes recommendations for future HIV policy responses in China

(*Continued*)

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Table 2. (Continued)

Author	Year of publication	Countries	Priority population represented	Priority population costed	Primary costing	PrEP methods	Long-acting PrEP	Aims/objectives
Luz	2018	Brazil	MSM	MSM	No	Daily oral PrEP	No	Analyse daily tenofovir/emtricitabine PrEP use in MSM and TGW at high risk of HIV in Brazil using the best available epidemiological, clinical and economic data
Stopard	2019	South Africa, Tanzania	General population	General population	No	Daily oral PrEP	No	Investigate how "real-world" constraints on the allocative and technical efficiency of HIV prevention programmes affect resource allocation and number of infections averted
Zhang	2019	China	MSM	MSM	No	Daily oral PrEP	No	Evaluates the epidemiological impact and cost-effectiveness of implementing PrEP in Chinese MSM over the next two decades
Bórquez	2019	Peru	TGW	TGW	No	Daily oral PrEP	No	Investigate the status of HIV prevention and delivery of care in Peru in terms of infrastructure, staff capacity, budget allocation, activities, organization and outputs; explore perceptions of HIV risk and knowledge of, attitudes towards and intention to use diverse prevention methods among members of the MSM and transgender women communities, as well as adoption by health professionals and decision-makers; and estimate the impact and cost-effectiveness of the various interventions to identify cost-effective and feasible combinations in the Peruvian setting
Selinger	2019	South Africa	General population	General population	No	Daily oral PrEP, event-driven PrEP	No	Inform ongoing vaccine access planning elements, including priority populations for whom the pox-protein HIV vaccine would be expected to have the greatest and/or most efficient public health impact
Hu	2019	China	MSM	MSM	No	Daily oral PrEP	No	Evaluate reductions in HIV transmission that may be achieved through early initiation of ART plus partners' PrEP

(*Continued*)

Table 2. (Continued)

Author	Year of publication	Countries	Priority population represented	Priority population costed	Primary costing	PrEP methods	Long-acting PrEP	Aims/objectives
Grant	2020	Kenya, South Africa, Zimbabwe	AGYW, sex worker, women	AGYW, sex worker, women	No	Daily oral PrEP	No	Highlight key considerations to feed into policymaking, as countries consider scaling up PrEP across a more broadly defined group of women at risk in sub-Saharan Africa, and present decision-makers with a range of important considerations, including PrEP cost-effectiveness, cost and estimated number of HIV acquisitions averted on PrEP for different groups of women at population level
Kazemian	2020	India	MSM, PWID	MSM, PWID	No	Daily oral PrEP, event-driven PrEP	No	Examine the cost-effectiveness of both PrEP and HIV testing strategies for MSM and PWID in India
Pretorius	2020	Eswatini, Ethiopia, Haiti, Kenya, Lesotho, Malawi, Mozambique, Namibia, Nigeria, Tanzania, Uganda, Zambia, Zimbabwe	AGYW, SDC, sex worker	Other	No	Daily oral PrEP	No	Estimated the impact, cost and cost-effectiveness of scaling up oral PrEP in 13 countries
Jamieson	2020	South Africa	ABYM, AGYW, MSM, pregnant and breastfeeding women, sex worker	ABYM, AGYW, MSM, pregnant and breastfeeding women, sex worker	No	Daily oral PrEP	No	Analyse the epidemiological impact of PrEP provision to adolescents, young adults, pregnant women, female sex workers, and MSM and estimate the cost and cost-effectiveness of PrEP
Kazemian	2020	India	MSM	MSM	No	Daily oral PrEP	No	Develop, validate and demonstrate a novel, practical method to estimate the community benefit of HIV interventions that help prevent transmission of HIV without a dynamic transmission model

(*Continued*)

Table 2. (Continued)

Author	Year of publication	Countries	Priority population represented	Priority population costed	Primary costing	PrEP methods	Long-acting PrEP	Aims/objectives
Wu	2021	China	SDC	SDC	No	Daily oral PrEP	No	Evaluate health economics of antiretroviral-based strategies for HIV SDC in China
Phillips	2021	South Africa	AGYW, general population, sex worker	General population, other	No	Daily oral PrEP	No	Predict the impact and cost-effectiveness of PrEP with use concentrated in periods of condomless sex, accounting for effects on drug resistance
Ten Brink	2022	Cambodia, China, India, Indonesia, Myanmar, Nepal, Thailand, Vietnam	MSM	MSM	No	Daily oral PrEP	No	Estimate the impact and cost-effectiveness of daily versus event-driven dosing of PrEP for eight Asian countries and compare branded with generic PrEP in China
Kripke	2022	Lesotho, Mozambique, Uganda	General population	General population	No	Daily oral PrEP	No	Examine the role and cost-effectiveness of HIV prevention in the context of "universal test and treat" in three sub-Saharan countries with generalized HIV epidemics
Jin	2022	China	MSM	MSM	No	Daily oral PrEP	No	Evaluate the HIV epidemic under several PrEP coverages with or without expanded ART and calculate the cost-effectiveness of various PrEP scenarios
Phillips	2022	Sub-Saharan Africa/South Africa	General population	General population	No	Daily oral PrEP	No	Explore the conditions under which widely accessible PrEP could be cost-effective in sub-Saharan Africa, assuming a concentration of PrEP use during periods of risk with high adherence to daily pill-taking
Ghayoori	2022	Rwanda	Women	Women	No	Daily oral PrEP	No	Examine transmission of HIV among female sex workers, general population, sex clients and MSM to inform scaling up PrEP beyond the highest risk population is considered via an analysis of cost-effectiveness

Note: Adeoti (2021) did not refer to the route of administration or PrEP modality in their paper, only "pre-exposure prophylaxis." Given when the article was published, we assumed this conceptual mention of PrEP included long-acting methods, along with daily oral PrEP.

Abbreviations: ABYM, adolescent boys and young men; AGYW, adolescent girls and young women; ART, antiretroviral therapy; DREAMS, Determined, Resilient, Empowered, AIDS-free, Mentored, Safe; MMT, methadone maintenance treatment; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; PWID, people who inject drugs; TasP, treatment-as-prevention; TGW, trans women.

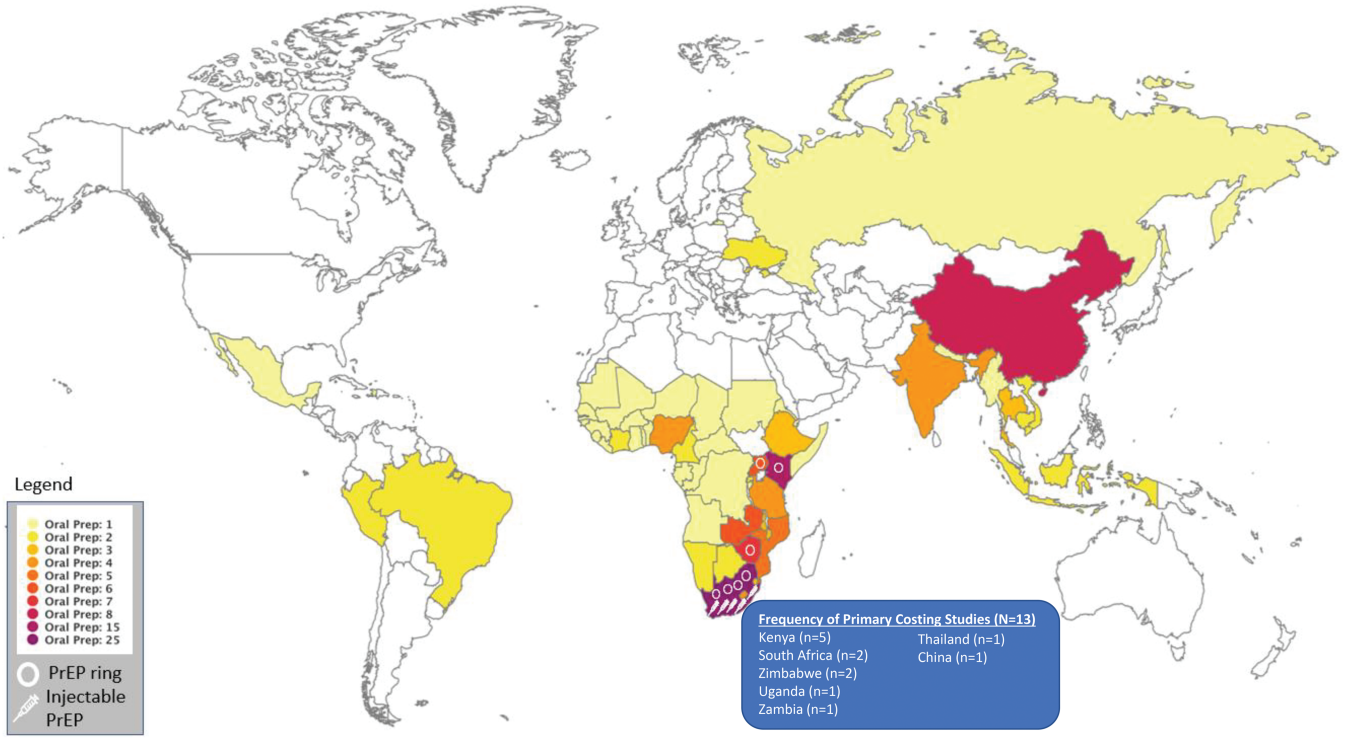

Figure 2. Distribution of countries and PrEP methods represented in sample of costing studies (*N* = 66).

East and North Africa (*n* = 1). Additional details by region and country are shown in S5A for regions or countries with disaggregated cost and economic data and S5B for all countries cited regardless of disaggregation.

3.6 | Long-acting PrEP studies

Figure 3 shows the frequency of studies by year and the PrEP method reported. Approximately 15% (*n* = 10) were specifically LAP studies (Table 2), with two reporting injectable PrEP, one reporting PrEP ring, and seven reporting multiple forms or combinations of LAP. In total, five reported injectable PrEP, four reported on the PrEP ring, and four reported combinations of methods, such as dual HIV and pregnancy prevention or without enough specificity to define the type of LAP. The LAP studies focused on general population women (5), AGYW (4) and female sex workers (3) primarily (Table 2). The 14 country results from 10 LAP studies were mainly conducted in South Africa (*n* = 8), with results from Nigeria, Zimbabwe, Kenya and Uganda. One study reported LAP data for all global regions (Figure 2).

3.7 | Description of implementation domains reported in primary cost evaluations

Table 3 displays the distribution of implementation domains among the included studies and Table 4 for LAP studies specifically. Since purpose, scope, and methods can differ by study type, we stratified these findings to discern primary cost studies from secondary or modelled evaluations. Given their direct implications for implementation, we focus our findings on the primary costing studies below.

Among the 13 primary cost studies, the most reported implementation domains were: PrEP-intervention-commodities (*n* = 12), laboratory and other commodities (*n* = 10), human resources (*n* = 11), indirect/overhead costs (*n* = 11), communication/awareness raising/demand creation (*n* = 9), counselling and adherence support (*n* = 9), and monitoring and evaluation (*n* = 7). A few studies included the cost of integration into non-HIV services (*n* = 5), above-site activities (*n* = 3), supply chain management and logistics (*n* = 3), or national coordination policy and planning (*n* = 2). No primary cost study included target setting, health information systems, or research. None of the primary costed studies included LAP. Of the 13 primary cost studies, 53.8% (*n* = 7) were conducted in government or public facilities (Table 5). Most primary studies estimated average costs (*n* = 9) and incremental costs (*n* = 7). Three studies also modelled cost-effectiveness. Most of the costing studies utilized the health system perspective (*n* = 11) and applied a discount rate (*n* = 11). Two studies did not report conflict of interest statements. Similar details for modelled studies are reported in S6.

3.8 | Implementation assumptions in primary cost evaluations

All primary cost studies reported costs in USD; 11 studies included overhead costs. All studies reporting discount rates (*N* = 11) used 3%. Considerable heterogeneity persisted in the activities described in the primary cost studies, the costs estimated, and the units defined in all other

Table 3. Frequency of key PrEP implementation domains for all studies, by biomedical HIV prevention method and costing approach

Costed implementation domains	Total			Daily oral PrEP		Event-driven PrEP		Injectable PrEP		PrEP ring		Other PrEP		Primary costing references	Secondary costing or modelling references
	All (*N* = 66)	Primary costing (*n* = 13)	Secondary costing or modelling (*n* = 53)	Primary costing (*n* = 13)	Secondary costing or modelling (*n* = 48)	Primary costing (*n* = 0)	Secondary costing or modelling (*n* = 2)	Primary costing (*n* = 0)	Secondary costing or modelling (*n* = 5)	Primary costing (*n* = 0)	Secondary costing or modelling (*n* = 4)	Primary costing (*n* = 0)	Secondary costing or modelling (*n* = 4)		
National coordination, policy and planning	3	2	1	2	1				1		1			47, 52	84
Target setting															
Human resources	30	11	19	11	16				2		2		2	42, 44, 51, 45, 50, 49, 43, 47, 52, 46, 53	96, 95, 132, 98, 84, 89, 133, 135, 114, 125, 122, 88, 109, 87, 110, 127, 128, 93, 111
Communication/ awareness raising/ demand creation	21	9	12	9	11				2		2		1	42, 44, 45, 50, 49, 43, 47, 46, 53	96, 84, 89, 133, 135, 113, 114, 122, 88, 109, 127, 128
Counselling and adherence support	25	9	16	9	15				1		1		1	42, 44, 45, 50, 49, 43, 48, 47, 46	97, 96, 89, 134, 113, 88, 109, 110, 123, 124, 94, 127, 119, 128, 111, 105
PrEP intervention (commodities)	38	12	26	12	32		1		3		4		4	42, 44, 45, 50, 49, 43, 83, 48, 47, 52, 46, 53	96, 95, 132, 98, 84, 108, 134, 135, 113, 114, 86, 125, 122, 88, 109, 123, 124, 116, 127, 91, 128
Supply chain management and logistics	6	3	3	3	2									47, 52, 53	84, 135, 125
Laboratory and other commodities	28	10	18	10	17		1		2		2		1	42, 44, 51, 45, 50, 49, 43, 48, 47, 46	96, 95, 132, 89, 108, 134, 135, 113, 114, 86, 122, 88, 123, 124, 116, 127, 91, 128
Health information systems															
Service delivery approaches	13	5	8	5	6				2		1		1	42, 44, 45, 83, 52	89, 125, 88, 87, 110, 128, 111, 105
Monitoring and evaluation	11	7	4	7	3				2				1	42, 51, 45, 49, 83, 47, 53	96, 89, 92, 128
Implementation science and operations research															
Above-site activities	5	3	2	3	2									47, 52, 46	113, 122
Indirect/overhead	20	11	9	11	6				2		1		2	42, 44, 51, 45, 50, 49, 43, 47, 52, 46, 53	98, 89, 114, 88, 87, 124, 127, 128, 93
Other costs	14	7	7	7	6								1	42, 51, 45, 50, 43, 47, 53	98, 135, 99, 116, 127, 93, 129

Note: The one PrEP-bnAbs secondary costing or modelling study (Citation 84) costed policy & planning, awareness raising & demand generation, PrEP commodities and supply chain logistics & management. Of the two PrEP-HIV vaccine secondary costing or modelling studies, one (Citation 111) costed human resources, counselling and PrEP integration into non-HIV services.

Among primary costing studies reporting integration data (*N* = 5), studies costed the integration of PrEP into sexual and reproductive health services (*n* = 4), family planning services (*n* = 3), and maternal and child health services (*n* = 1). For secondary costing or modelling studies (*N* = 6), sexual and reproductive health services was the most common (*n* = 4), followed by family planning (*n* = 1), antenatal care (*n* = 1), and HIV treatment and methadone maintenance treatment (*n* = 1).

Abbreviation: PrEP, pre-exposure prophylaxis.

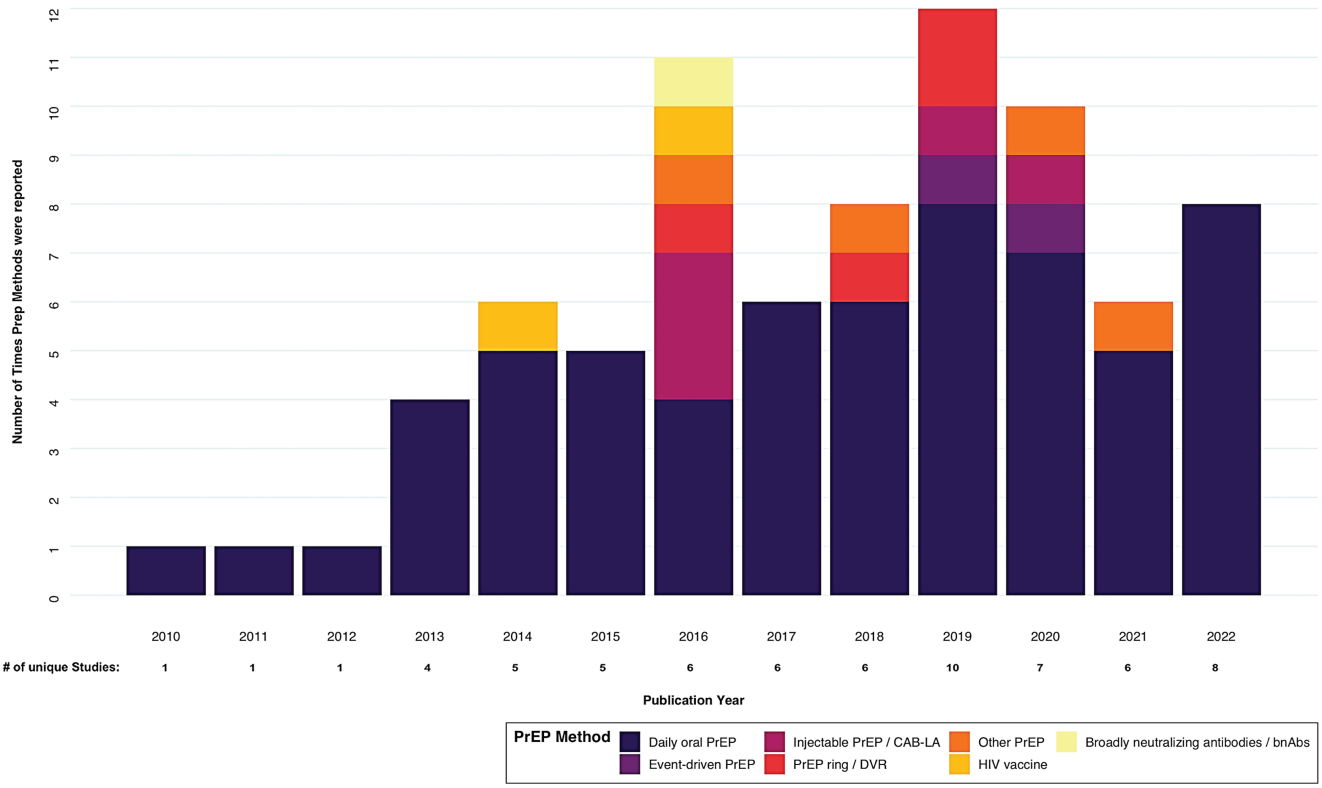

Figure 3. Frequency of reported PrEP methods, by number of unique costing studies and publication year.

Table 4. Frequency of key PrEP implementation domains for all LAP studies (*N* = 10)

Costed implementation domains	Total *N* = 10	Injectable PrEP *n* = 5	PrEP ring *n* = 4	Other PrEP *n* = 4	References
National coordination, policy and planning	1	1	1		84
Target setting					
Human resources	5	2	2	1	84, 87, 88, 89, 93
Communication/ awareness raising/ demand creation	3	2	2	1	84, 88, 89
Counselling and adherence support	2	1	1	1	88, 89
PrEP intervention (commodities)	9	3	3	4	84, 85, 86, 92, 88, 87, 90, 91, 93
Supply chain management and logistics	1				
Laboratory and other commodities	4	2	2	1	86, 88, 89, 91
Health information systems					
Service delivery approaches	3	2	1	1	87, 88, 89
Monitoring and evaluation	2	2		1	89, 92
Implementation science and operations research					
Above-site activities					
Indirect/overhead	4	2	1	2	87, 88, 89, 93
Other costs				1	93

Abbreviations: LAP, long-acting pre-exposure prophylaxis; PrEP, pre-exposure prophylaxis.

Table 5. Economic analysis features and analytic approaches of primary costing studies (N = 13).

	Total (*N* = 13)	Daily oral PrEP (*n* = 13)	Event-driven PrEP (*n* = 0)	Injectable PrEP (*n* = 0)	PrEP ring (*n* = 0)	Other PrEP (*n* = 0)	References
Facility type							
NGO & NGO facility	5	5					42, 44, 51, 45, 52
Private-for-profit & private non-profit & private facility	2	2					52, 53
Government & public facility	7	7					44, 49, 43, 48, 47, 52, 53
Type of economic analysis							
Cost-effectiveness	8	8					42, 44, 45, 50, 43, 83, 48, 47
Cost-benefit							
Cost-utility	3	3					44, 83, 48
Average costing	9	9					51, 45, 50, 49, 43, 47, 52, 46, 53
Incremental costing	7	7					42, 44, 45, 43, 83, 48, 47
Costing approach							
Guideline/normative	3	3					51, 50, 83
Real world/actual	5	5					42, 44, 49, 48, 47
Both	5	5					45, 43, 52, 46, 53
Economic v. financial costing							
Economic costing	9	9					44, 51, 45, 49, 43, 47, 52, 46, 53
Financial costing	4	4					42, 50, 83, 48
Perspective							
Health system	11	11					42, 44, 51, 45, 50, 49, 43, 48, 52, 46, 53
Societal							
Both	1	1					47
Not reported	1	1					83
Discount rate reported	11	11					42, 44, 51, 50, 49, 43, 83, 48, 47, 52, 53
Conflict of interest							
Yes	1	1					46
No	10	10					42, 44, 51, 45, 50, 49, 43, 83, 52, 53
Not reported	2	2					48, 47
Approach							
Observed	9	9					42, 44, 51, 49, 43, 47, 52, 46, 53
Observed + modelled	4	4					45, 50, 83, 48

Abbreviations: NGO, non-governmental organization; PrEP, pre-exposure prophylaxis.

implementation domains. For instance, within the commonly reported PrEP commodities domain, average drug costs were described as cost per implementation scenario [42, 43], costs across all sites and per site [44], cost per couple [43, 45], cost per client [46–48], costs per bottle [43, 49, 50], per person-year [43, 50], and per month [45, 47]. The recurrent drug costs cited ranged from $24.43 to $382.00. PrEP commodities were only included if the input costs of the drug were explicitly reported, could be disaggregated or were cited as being included in the unit cost. The human resources domain included clinicians, social workers, and counsellors staff time based on time and motion studies [42]. Other studies included the site doctor, pharmacist, peer educators [44], and administrators [51]. Merely three studies described start-up training [45, 46, 49]. For the more infrequently costed domains, policy and planning costs were estimated for stakeholder coordination required to start up and microplanning [47, 52], and supply chain costs were estimated for central storage and distribution fees and a one-time PrEP importation fee [47, 52, 53].

3.9 | Primary costing study outcomes

Table 7 summarizes average and incremental cost outcomes reported across the 13 primary cost studies and Tables 8 and 9 detail cost and cost-effectiveness outcomes of studies by

scenarios costed. The 13 studies reported 11 unique outcome indicators. Cost per person/client-month (n = 6) was the most frequently reported outcome, followed by annual costs (n = 4), cost per visit (n = 4), and cost per person/client-year (n = 3). Three primary costing studies also reported the results of cost-effectiveness analyses: one study reported an incremental cost-effectiveness ratio (ICER) without clearly defining the time horizon; one reported an ICER (cost per acquisition averted) over a 10-year horizon; and the third reported the incremental cost-effectiveness per quality-adjusted life year (QALY) gained in a 5-year time horizon. No single cost or cost-effectiveness outcome was measured by all studies utilizing the same analytic approach. The highest frequency of studies reported on oral PrEP among AGYW, followed by SDC.

3.10 | Implementation domains in secondary data or modelled studies

A lower percentage of modelled than primary costing studies included the costs of any implementation. Among the 53 modelled studies (Table 6), the cost of PrEP commodities was the most frequently included (40%, n = 21), followed by human resources (36%, n = 19). Table 6 summarizes all modelled studies. As shown in S6, most modelled studies were cost-effectiveness (N = 41), followed by cost-utility studies (N = 15). Evaluations mostly took a guidelines approach (N = 32), from the health system perspective (N = 42). About 69.8% reported discount rates (N = 37) (Tables 6).

3.11 | Implementation domains regarding long-acting PrEP

None of the 10 modelled studies of LAP included costs on target setting, supply chain logistics and management, health information systems, operations research and implementation science, or above-site domains (Table 4). Further, only PrEP commodities (N = 9) and human resources (N = 5) domains were reported >50% of the time. The other domains were reported at frequencies of 2 and 1 for the five injectable LAP studies and four studies on the PrEP ring (Table 4).

4 | DISCUSSION

This scoping review synthesized national implementation plans from four costed rollout plans (CRPs) operationalizing oral PrEP from Kenya, South Africa, Zambia, and Zimbabwe, and the FP CIP template. Few CRPs have been developed to support daily oral PrEP, and no plans included LAPs. The AVAC tracker showed that over 20 SSA countries approved PrEP, yet only four implementation plans were found. Interestingly, these four countries represent over 50% of SSA PrEP initiations between 2016 and 2022 [19]. While all countries have fallen short of HIV prevention benchmarks, the crude correlation is suggestive that CRPs reflect country-level and -led discussions about systematic planning of implementation, an indication of national commitment and political will, which may contribute to greater PrEP achievement.

Our CRP review identified 15 domains as necessary inputs and activities. Six of the 15 domains were reported in all plans reviewed; however, we cannot conclude that they are more important than domains not consistently included since plans were not based on rubrics or frameworks. We observed variations in the naming of the implementation domains and incorporated activities or inputs. Also, CRP domains lacked any prioritized order or hierarchy, highlighting the need for a framework for developing CRPs and a consensus process for composing activities and inputs. We surmised that all domains were method agnostic and relevant for implementing LAP (Table 4). CRPs will be important because of LAPs complexity of choice, variation in logistics ,and likely cost.

Further, most (80%) of the 66 studies published between January 2010 and 30 June 2022 were secondary data or modelled evaluations, and few (19.6%) reported primary costing. The 15 implementation domains were included inconsistently. None of the 13 primary costing studies included all 15 domains, but most included: PrEP commodities, human resources, indirect cost, and other associated commodities. Few primary costing studies included policy and planning, supply chain and logistics, or above-site costs, which include technical assistance and domains that were present in all implementation plans. Modelled or cost-effectiveness studies, many of which applied a guideline costing approach to inform policy and planning, included fewer domains than primary costing studies. We observed that most studies did not meet GHCC criteria, including variable cost and cost-effectiveness outcomes and units of measure. The lower quality, inconsistencies, and lack of transparency in cost and cost-effectiveness studies have been raised by others, but to our knowledge, this is the first study to examine the cost and cost-effectiveness literature against real-world operational plans and assess implementation inputs and activities with such specificity [32].

The unsystematic delivery of HIV services has been highlighted as a persistent structural impediment that diminishes the impact of HIV prevention interventions [1, 3]. LAPs will undoubtedly increase the complexity of HIV prevention delivery at all levels of the health system. LAPs vary in reported efficacy and effectiveness, user preferences, laboratory requirements to initiate and sustain use, supply chain needs to deliver a safe and effective product, and monitoring and evaluation for continuous quality improvement, among others [54–57]. Terris-Prestholt et al. previously stated that plans outlining systematic introduction and delivery of PrEP, including impact on efficiency, uptake, and equity, are needed to manage scarce human and financial resources. We need user-tailored messaging and optimized delivery channels to reach high-need groups given resource constraints [58]. CIPs, multi-year actionable roadmaps designed to help governments achieve their FP goals by facilitating systematic implementation, scale-up, and financing, have facilitated many programmatic achievements owing to streamlined planning, implementation and stakeholder consultation, and systematic costing [41, 59]. Amid the scarcity of costed plans for operationalizing HIV PrEP delivery [25–28], CIPs and national costed HIV plans serve as a model for LAP rollout in countries and settings not currently applying this approach.

As noted above, plans did not mention a rubric guiding which implementation domains to include and the rationale for including some domains over others. A lack of specificity on what is needed to implement LAP will further stymy implementation given the current concerns about the cost of LAP.

Table 6. Economic analysis features and analytic approaches of secondary costing or modelling studies (N = 53).

	Total (*N* = 53)	Daily oral PrEP (*n* = 48)	Event-driven PrEP (*n* = 2)	Injectable PrEP (*n* = 5)	PrEP Ring (*n* = 4)	Other PrEP (*n* = 4)	References
Facility type							
NGO & NGO facility	4	4					125, 122, 99, 116
Private-for-profit & private non-profit & private facility	1	1					125
Government & public facility	3	3					95, 113, 122
Type of economic analysis							
Cost-effectiveness	41	40	1	3	1	2	97, 96, 95, 132, 98, 120, 130, 89, 106, 107, 108, 101, 133, 135, 136, 113, 117, 114, 86, 118, 125, 121, 122, 92, 102, 88, 109, 99, 123, 124, 94, 116, 103, 127, 91, 119, 100, 128, 111, 129, 105
Cost-benefit							
Cost-utility	15	14	1	2		1	96, 130, 89, 107, 108, 101, 133, 113, 117, 118, 92, 123, 124, 100, 105
Average costing	12	11			2	1	97, 98, 135, 125, 122, 115, 88, 124, 94, 127, 91, 128
Incremental costing	8	7				1	97, 98, 130, 88, 116, 91, 128, 105
Costing approach							
Guideline/normative	32	28	2	2	3	2	97, 96, 95, 98, 120, 89, 107, 117, 125, 121, 122, 102, 126, 115, 88, 87, 110, 131, 99, 123, 94, 116, 103, 104, 90, 127, 91, 100, 128, 93, 111, 105
Real world/actual	1	1					124
Both	14	13		3	1	2	132, 130, 84, 106, 108, 101, 133, 112, 85, 113, 114, 86, 118, 92
Not reported	6	6					134, 135, 136, 109, 119, 129
Economic v. financial costing							
Economic costing	32	29	1	3	4	2	96, 95, 132, 98, 84, 89, 107, 101, 133, 134, 85, 113, 114, 86, 118, 125, 122, 115, 88, 99, 123, 124, 94, 116, 103, 104, 90, 127, 91, 119, 100, 105
Financial costing	15	14	1	2		1	97, 120, 130, 106, 108, 112, 117, 92, 102, 126, 87, 110, 131, 128, 111
Not reported	6	5				1	135, 136, 121, 109, 93, 129
Full v. incremental costing							
Full (Average)	11	11	1	1	2		120, 84, 115, 131, 123, 124, 94, 103, 91, 119, 129

(*Continued*)

Table 6. (Continued)

	Total (*N* = 53)	Daily oral PrEP (*n* = 48)	Event-driven PrEP (*n* = 2)	Injectable PrEP (*n* = 5)	PrEP Ring (*n* = 4)	Other PrEP (*n* = 4)	References
Incremental	5	4			1		134, 136, 104, 90, 127
Both	34	31	1	4	1	3	97, 96, 95, 132, 98, 130, 89, 106, 107, 108, 101, 133, 112, 85, 113, 117, 114, 86, 118, 125, 121, 122, 92, 102, 126, 88, 109, 87, 110, 99, 116, 100, 111, 105
Not reported	3	2				1	135, 128, 93
Perspective							
Health system	42	39	1	4	4	3	97, 96, 95, 132, 98, 84, 89, 106, 107, 108, 101, 133, 135, 112, 85, 113, 117, 114, 86, 118, 125, 122, 92, 88, 109, 110, 131, 99, 123, 94, 116, 103, 104, 90, 127, 91, 119, 100, 128, 111, 129, 105
Societal	5	4	1	1			130, 126, 115, 87, 124
Both							
Not reported	6	5				1	120, 134, 136, 121, 102, 93
Discount rate reported	37	34	2	5	3	2	97, 95, 132, 98, 130, 84, 89, 106, 107, 108, 101, 133, 134, 135, 86, 118, 121, 122, 92, 102, 126, 88, 109, 87, 110, 131, 99, 123, 124, 116, 104, 90, 119, 100, 111, 129, 105
Conflict of interest							
Yes	12	10	1	3			89, 106, 133, 135, 117, 114, 86, 118, 121, 126, 87, 131
No	27	26	1	2	2	3	97, 132, 98, 120, 130, 84, 108, 101, 134, 112, 85, 113, 125, 122, 92, 102, 115, 88, 109, 110, 99, 123, 116, 119, 100, 128, 129
Not reported	14	12			2	1	96, 95, 107, 136, 124, 94, 103, 104, 90, 127, 91, 93, 111, 105
Approach							
Observed	8	5	1		1	1	120, 126, 115, 88, 103, 104, 90, 91
Modelled	49	44	1	5	3	4	97, 96, 95, 132, 98, 120, 130, 84, 89, 106, 107, 108, 101, 133, 134, 135, 136, 112, 85, 113, 117, 114, 86, 118, 125, 121, 122, 92, 102, 126, 88, 109, 87, 110, 131, 99, 123, 124, 94, 116, 127, 91, 119, 100, 128, 93, 111, 129, 105

Abbreviations: NGO, non-governmental organization; PrEP, pre-exposure prophylaxis.

Table 7. Economic analysis features and analytic approaches of secondary costing or modelling studies

Author	Year	Country	PrEP method	Population	Total costs	Annual costs	Total 5-year	Total 10-year	Cost per person/ client	Cost per person/ client-month	Cost per person/ client-year	Cost per couple	Cost per couple-year	Cost per visit (initiation, follow-up, any visit)	Total recurrent cost per PrEP-client per year	Discounted incremental cost of PrEP strategies over 5-year	Incremental cost of PrEP per couple	Annual incremental cost
Suraratdecha	2018	Thailand	Daily oral PrEP	MSM		✓	✓			✓								
Wong	2018	China (Hong Kong)	Daily oral PrEP	MSM												✓		
Ying	2015	Uganda	Daily oral PrEP	SDC				✓									✓	
Eakle	2017	South Africa	Daily oral PrEP	Sex worker							✓			✓				
Roberts	2019	Kenya	Daily oral PrEP	AGYW		✓				✓				✓				
Irungu	2019	Kenya	Daily oral PrEP	SDC		✓							✓				✓	✓
Hughes	2020	Zimbabwe	Daily oral PrEP	SDC								✓						
Peebles	2021	Kenya	Daily oral PrEP	Other (see below)	✓				✓	✓								
Wanga	2021	Kenya	Daily oral PrEP	AGYW		✓				✓				✓				
Hendrickson	2021	Zambia	Daily oral PrEP	AGYW/GP/other (FSW & MSM together)						✓	✓				✓			
Okal	2022	Kenya	Daily oral PrEP	AGYW	✓				✓									
Mudimu	2022	South Africa	Daily oral PrEP	AGYW						✓								✓
Mangenah	2022	Zimbabwe	Daily oral PrEP	AGYW/men/women							✓			✓				
Total					2	4	1	1	2	6	3	1	1	4	1	1	2	2

Note: When studies listed costs as "Total annual," we recorded them as Annual costs and only noted Total costs if they were framed exactly as such (i.e. "Total costs").
Abbreviations: AGYW, adolescent girls and young women; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; SDC, sero-different couples.

Table 8. Cost outcomes of primary costing studies

Author	Population(s)	Scenarios	Findings	Sensitivity analysis performed
Suraratdecha	MSM	Cohort study (includes MOPH and project staff), which presented two implementation options: Option 1: one visit for initial PrEP counselling and recruitment, four additional HIV tests, two tests for creatinine, one HBs Ag test, 12 months TDF/FTC combination, six visits for maintenance support (counselling) Option 2: option 1 package plus two times upgraded STIs screening (chlamydia, gonorrhoea, syphilis rapid test, nucleic acid amplification test)	Cohort study total annual costs associated with PrEP initiation and clinic visits Personnel: $1452, Lab supplies: $1406, PrEP drugs: $14,106, Other supplies: $242 Total: $17,206 Option 1: Unit cost of PrEP recommended package (per person per year) Personnel: $24.66, Supplies: $10.36, Tenofovir/Entricitabine (12 bottles: 1 pill/day): $186.33 Total unit cost: $221.34 Total unit cost with 0.7% overhead: $222.89 Total unit cost with 0.7% overhead and 22% demand generation activities: $271.59 Option 2: Unit cost of PrEP recommended package (per person per year) Personnel: $25.63, Supplies: $41.41, Tenofovir/Entricitabine (12 bottles: 1 pill/day): $186.33 Total unit cost: $253.37 Total unit cost with 0.7% overhead: $255.14 Total unit cost with 0.7% overhead and 22% demand generation activities: $310.88	No (Cost-effectiveness only)
		Providing PrEP to only high-risk MSM (defined as having engaged in condomless sex with casual or known HIV-positive partners) versus all MSM, regardless of risk	TOTAL 5-YEAR PROGRAMME COST: PrEP provided to High-risk MSM $41.99 (M) PrEP provided to All MSM $147.14 (M)	

(*Continued*)

Table 8. (Continued)

Author	Population(s)	Scenarios	Findings	Sensitivity analysis performed
Wong	MSM	Basecase with 10%, 30% and 90% coverage of PrEP involving low-risk and high-risk MSM (i.e. non-targeting approach) with low or high adherence usage and high-risk MSM only (i.e. targeting approach) with low or high adherence usage Plans (apply to both scenarios) Plan A: PrEP priced at the market rate: $7880/year Plan B: PrEP priced at the generic rate: $519/year Plan C: PrEP is free	DISCOUNTED INCREMENTAL COST OF PrEP STRATEGIES OVER 5-YEAR TIME HORIZON Plan A Respective costs of Non-targeting 10%; 30%; and 90% are $123,458,936; $370,266,861; and $1,113,780,354 Respective costs of Targeting 10%; 30%; and 90% are $52,571,166; $157,200,505; and $472,011,282 Plan B Respective costs of Non-targeting 10%; 30%; and 90% are $17,294,670; $51,648,582; and $157,156,635 Respective costs of Targeting 10%; 30%; and 90% are $7,459,389; $21,831,597; and $65,661,580 Plan C Respective costs of Non-targeting 10%; 30%; and 90% are $9,806,914; $29,176,464; and $89,686,050. Respective costs of Targeting 10%; 30%; and 90% are $4,277,659; $12,284,040; and $37,001,772	Yes
		Test-and-Treat included a high rate of diagnosis and treatment initiation (minimum 90% from 2017) with 10%, 30% and 90% coverage of PrEP involving low-risk and high-risk MSM (i.e. non-targeting approach) with low or high adherence usage and high-risk MSM only (i.e. targeting approach) with low or high adherence usage	DISCOUNTED INCREMENTAL COST OF PrEP STRATEGIES OVER 5-YEAR TIME HORIZON Plan A Respective costs of Non-targeting 10%; 30%; and 90% are $158,411,503; $398,568,822; and $1,127,434,311 Respective costs of Targeting 10%; 30%; and 90% are $89,432,361; $190,572,365; and $496,573,340 Plan B Respective costs of Non-targeting 10%; 30%; and 90% are $ 52,137,608; $79,665,459; and $170,226,003 Respective costs of Targeting 10%; 30%; and 90% are $44,267,840; $55,056,540; and $89,865,774 Plan C Respective costs of Non-targeting 10%; 30%; and 90% are $44,642,119; $57,173,233; and $102,714,188 Respective costs of Targeting 10%; 30%; and 90% are $41,082,391; $45,498,622; and $ 61,180,726	

(*Continued*)

Table 8. (Continued)

Author	Population(s)	Scenarios	Findings	Sensitivity analysis performed
Ying	SDC	As-studied	INCREMENTAL COSTS (PER COUPLE) As-studied (total clinical HIV treatment + PrEP): $1058, As-studied SoC (HIV treatment without PrEP): $650, As-studied PrEP: $408	No (Cost-effectiveness only)
		MoH	INCREMENTAL COSTS (PER COUPLE) MoH total clinical: (HIV treatment + PrEP) $453, MoH standard of care (i.e. HIV treatment without PrEP): $361, MoH PREP: $92 MoH Assumptions showcasing reduction in as-studied to MoH PrEP price As-studied with PrEP with public-sector staff salaries: $370, and reduced medication costs: $254, and fewer lab tests: $101, and PrEP task-shifting: $92	
		MoH adds PrEP programme for all high-risk SDC (i.e. when the HIV-negative partner is aged < = 25 years and both partners are in the top 15th percentile in number of casual sexual partners). Scenario also assumes 40% baseline ART coverage, 80% of high-risk couples are without CD4/VL criteria and 80% PrEP coverage among high-risk couples	$219 million over 10 years	
Eakle	Sex worker	N/A	PrEP PER PERSON-YEAR, Y1 Average: $126.60 (Johannesburg: $146.60, Pretoria: $106.60) COST PER VISIT Outreach contact visit—Average: $2.80 (Johannesburg: $3.00, Pretoria: $2.60) VCT Session—Average: $18.10 (Johannesburg: $21.2, Pretoria: $15.10) PrEP Enrolment Visit —Average: $34.70 (Johannesburg: $40.40, Pretoria: $29.00) PrEP Monitoring Visit —Average: $35.20 (Johannesburg: $37.40, Pretoria: $33.00) PrEP Refill Visit —Average: $6.80 (Johannesburg: $7.40, Pretoria: $6.20)	No

(*Continued*)

Table 8. (Continued)

Author	Population(s)	Scenarios	Findings	Sensitivity analysis performed
Roberts	AGYW	As-implemented	Total annual programme cost: $204,253 Average cost of per client-month of PrEP dispensed: $26.52 UNIT COST BY CLINICAL ACTIVITY PrEP screening —Total annual cost: $69,876; Total unit cost (variable + fixed): $2.91 PrEP initiation —Total annual cost: $80,525; Total unit cost (variable + fixed): $19.18 PrEP follow-up -Total annual cost: $53,852; Total unit cost (variable + fixed): $12.16	Yes
		Service delivery modification: Postponed creatine testing to first follow-up visit	Total annual cost: $188,932 Cost per client-month of PrEP dispensed: $24.53	
		Service delivery modification: Prioritized delivery to clients at high risk for HIV infection	Total annual cost: $175,793 Cost per client-month of PrEP dispensed: $31.88	
		As-implemented scenario with public-sector clinical staff salaries	Total annual cost: $199,613 Cost per client-month of PrEP dispensed: $25.92	
		As-implemented scenario with MOH supervision and public-sector clinical staff salaries	Total annual cost: $138,609 Cost per client-month of PrEP dispensed: $18.00	
		As-implemented scenario with facility creatinine testing, MOH supervision and public-sector clinical staff salaries	Total annual cost: $127,421 Cost per client-month of PrEP dispensed: $16.54	
Irungu	SDC	As-studied	ANNUAL COST OF DELIVERING INTEGRATED PrEP AND ART TO SDC Total cost: $757,483.58; Cost per couple: $1.454.87 ANNUAL INCREMENTAL COST OF ADDING PREP TO CURRENT ART PROGRAMME Total cost: $441,555.40; Cost per couple: $305.75	Yes
		Current care and PrEP with MoH costs	ANNUAL COST OF DELIVERING INTEGRATED PrEP AND ART TO SDC Total cost: $361,304.58; Cost per couple: $250.19 ANNUAL INCREMENTAL COST OF ADDING PREP TO CURRENT ART PROGRAMME Total cost: $125,338.15; Cost per couple: $86.79 per couple	
		Current care & PrEP costs (removing research costs)	ANNUAL COST OF DELIVERING INTEGRATED PrEP AND ART TO SDC Total cost: $962,032.84; Cost per couple: $66.16	

(*Continued*)

Table 8. (Continued)

Author	Population(s)	Scenarios	Findings	Sensitivity analysis performed
Hughes	SDC	SAFER	Individual strategy—PrEP: $1229 per couple Multiple strategies: ART-VL + PrEP: $1709 per couple; PrEP + SW: $1659 per couple; PrEP + AVI: $1242 per couple	Yes
		High intensity (study-level) with real-world prices	Individual strategy—PrEP: $403 per couple Multiple strategies: ART-VL + PrEP: $517 per couple; PrEP + SW: $771 per couple; PrEP + AVI: $408 per couple	
		Target intensity, incremental cost added to CP	Individual strategy—PrEP: $266 per couple Multiple strategies: ART-VL + PrEP: $483 per couple; PrEP + SW: $563 per couple; PrEP + AVI: $291 per couple	
		Target intensity, incremental cost added to SOC	Individual strategy—PrEP: $88 per couple Multiple strategies: ART-VL + PrEP: $166 per couple; PrEP + SW: $387 per couple; PrEP + AVI: $114 per couple	
Peebles	Other (see below)	N/A	FINANCIAL COSTS Total: $91,175; Cost per PrEP Client: $35.52; Cost per person-month of PrEP: $10.31 ECONOMIC COSTS Total: $188,584; Cost per PrEP Client: $73.46; Cost per person-month of PrEP: $21.32	No
Wanga	AGYW	POWER Study scenario	Estimated Total (variable + fixed) economic costs Annual cost: $44,933; Cost per client-month of PrEP: $28.92 Estimated Total (variable + fixed) economic costs by visit type Initiation—Annual cost: $23,520; Cost per client-month of PrEP: $47.09 Follow-up—Annual cost: $20,896; Cost per client-month of PrEP: $20.99	No
		MoH scenario	Estimated Total (variable + fixed) economic costs Annual cost: $22,566; Cost per client-month of PrEP: $14.52 Estimated Total (variable + fixed) economic costs by visit type Initiation—Annual cost: $10,156; Cost per client-month of PrEP: $20.33 Follow-up—Annual cost: $11,997; Cost per client-month of PrEP: $12.05	

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Table 8. (Continued)

Author	Population(s)	Scenarios	Findings	Sensitivity analysis performed
		Scaled-MoH scenario	Estimated Total (variable + fixed) economic costs Annual cost: $83,196; Cost per client-month of PrEP: $10.88 Estimated Total (variable + fixed) economic costs by visit type Initiation—Annual cost: $38,352; Cost per client-month of PrEP: $11.84 Follow-up—Annual cost: $43,213; Cost per client-month of PrEP: $9.81	
Hendrickson	AGYW	Integrated into DREAMS, including community sensitization and demand creation through short-term mobilizers	Total recurrent cost per PrEP-client per year: $320 Total average cost per PrEP-client per year: $394 Total cost per person-month: $33	No
	GP	Integration Model 1: Outreach using trained CHW to sensitize community about PrEP and refer interested people to nearest clinic	Total recurrent cost per PrEP-client per year: $530 Total average cost per PrEP-client per year: $760 Total cost per person-month: $63	
		Integration Model 2: Site readiness through preliminary site assessments, trainings, community consultations and global technical assistance	Total recurrent cost per PrEP-client per year: $381 Total average cost per PrEP-client per year: $406 Total cost per person-month: $34	
		Integration Model 3: Community HIV Epidemic Model of care, focused on community education, mobilization, PrEP sensitization, and training CHW on key population sensitivity and PrEP services	Total recurrent cost per PrEP-client per year: $586 Total average cost per PrEP-client per year: $659 Total cost per person-month: $55	
	Other (FSW & MSM together)	Targeted community-based demand creation with referrals to local facilities for PrEP initiation and follow-up	Total recurrent cost per PrEP-client per year: $350 Total average cost per PrEP-client per year: $425 Total cost per person-month: $35	
Okal	AGYW	N/A	Costs of delivering dreams interventions Urban Total: $215,440; Cost of providing DREAMS interventions to 1 AGYW: $67 Peri-urban Total: $408,884; Cost of providing DREAMS interventions to 1 AGYW: $129	Yes
Mudimu	AGYW	As-implemented	Incremental cost of community-based prep provision Standard of Care Annual cost: $135,314; Cost per person month of PrEP: $105.74 Club Annual cost: $135,143.42; Cost per person month of PrEP: $105.61 Individual Annual cost: $135,791.40; Cost per person month of PrEP: $106.09	No

(*Continued*)

Table 8. (Continued)

Author	Population(s)	Scenarios	Findings	Sensitivity analysis performed
		DoH scenario	Incremental cost of community-based prep provision Standard of Care Annual cost: $70,944.44; Cost per person month of PrEP: $55.46 Club Annual cost: $70,811.93; Cost per person month of PrEP: $55.32 Individual Annual cost: $71,227.59; Cost per person month of PrEP: $55.65	
		Scaled-DoH scenario	Incremental cost of community-based prep provision Standard of Care Annual cost: $142,342.77; Cost per person month of PrEP $13.99 Club Annual cost: $144,881.73; Cost per person month of PrEP: $15.48 Individual Annual cost: $133,822.61; Cost per person month of PrEP: $26.40	
Mangenah	AGYW	N/A	Cost per person-year of receiving oral PrEP: $839 Average costs by visit type Initiation: $240 per client initiated, Month 3 follow-up: $434 per client continued to 3 months, Month 6 follow-up: $844 per client continued to 6 months	Yes
	Men	N/A	Cost per person-year of receiving oral PrEP: $1219 Average costs by visit type Initiation: $215 per client initiated, Month 3 follow-up: $712 per client continued to 3 months, Month 6 follow-up: $1363 per client continued to 6 months	
	Women	N/A	Cost per person-year of receiving oral PrEP: $857 Average costs by visit type Initiation: $243 per client initiated, Month 3 follow-up: $480 per client continued to 3 months, Month 6 follow-up: $828 per client continued to 6 months	

Abbreviations: AGYW, adolescent girls and young women; ART-VL, antiretroviral therapy with frequent viral load testing; AVI, manual artificial vaginal insemination; CP, Current Practice; DoH, Department of Health; FSW, female sex workers; GP, general population; MoH, Ministry of Health; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; SDC, sero-different couples; SOC, Standard of Care; SW, semen washing; TDF/FTC, tenofovir disoproxil and emtricitabine.

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Table 9. Cost-effectiveness outcomes of primary costing studies

Author	Population(s)	Scenarios	Findings	Sensitivity analysis performed
Suraratdecha	MSM	Providing PrEP to only high-risk MSM (defined as having engaged in condomless sex with casual or known HIV-positive partners) versus all MSM, regardless of risk	Cost-Effectiveness: PrEP provided to High-risk MSM: $3.99 (M) lifetime treatment costs averted PrEP provided to All MSM: $9.84 (M) lifetime treatment costs averted ICER OVER 5-YEAR TIME HORIZON PrEP provided to High-risk MSM: $4836 per DALY averted; $68,468 per HIV infection averted PrEP provided to All MSM: $7089 per DALY averted; $100,367 per HIV infection averted	Yes
Wong	MSM	Basecase with 10%, 30% and 90% coverage of PrEP involving low-risk and high-risk MSM (i.e. non-targeting approach) with low or high adherence usage and high-risk MSM only (i.e. targeting approach) with low or high adherence usage Plans (apply to both scenarios) Plan A: PrEP priced at the market rate: $7880/year Plan B: PrEP priced at the generic rate: $519/year Plan C: PrEP is free	DISCOUNTED INCREMENTAL COST-EFFECTIVENESS (INCREMENTAL $/QALY GAINED) OF PrEP STRATEGIES OVER 5-YEAR TIME HORIZON Plan A Respective incremental cost-effectiveness of Non-targeting 10%; 30%; and 90% are $1,842,204; $1,745,524; and $2,115,619 Respective incremental cost-effectiveness of Targeting 10%; 30%; and 90% are $2,162,072; $1,583,136; and $1,642,874 Plan B Respective incremental cost-effectiveness of Non-targeting 10%; 30%; and 90% are $258,064; $243,483; and $298,518 Respective incremental cost-effectiveness of Targeting 10%; 30%; and 90% are $306,779; $219,862; and $228,540 Plan C Respective incremental cost-effectiveness of Non-targeting 10%; 30%; and 90% are $146,335; $137,545; and $170,358 Respective incremental cost-effectiveness of Targeting 10%; 30%; and 90% are $175,926; $123,710; and $128,788	Yes

(*Continued*)

Table 9. (Continued)

Author	Population(s)	Scenarios	Findings	Sensitivity analysis performed
		Test-and-Treat included a high rate of diagnosis and treatment initiation (minimum 90% from 2017) with 10%, 30% and 90% coverage of PrEP involving low-risk and high-risk MSM (i.e. non-targeting approach) with low or high adherence usage and high-risk MSM only (i.e. targeting approach) with low or high adherence usage	DISCOUNTED INCREMENTAL COST-EFFECTIVENESS (INCREMENTAL $/QALY GAINED) OF PrEP STRATEGIES OVER 5-YEAR TIME HORIZON Plan A Respective incremental cost-effectiveness of Non-targeting 10%; 30%; and 90% are $929,125; $1,345,390; and $1,985,645 Respective incremental cost-effectiveness of Targeting 10%; 30%; and 90% are $668,940; $956,132; and $1,366,821 Plan B Respective incremental cost-effectiveness of Non-targeting 10%; 30%; and 90% are $305,830; $268,915; and $299,803 Respective incremental cost-effectiveness of Targeting 10%; 30%; and 90% are $331,116; $276,227; and $247,356 Plan C Respective incremental cost-effectiveness of Non-targeting 10%; 30%; and 90% are $261,863; $192,991; and $180,901 Respective incremental cost-effectiveness of Targeting 10%; 30%; and 90% are $307,290; $228,274; and $168,400	
Ying	SDC	MoH adds PrEP programme for all high-risk SDC (i.e. when the HIV-negative partner is aged < = 25 years and both partners are in the top 15th percentile in number of casual sexual partners). This scenario also assumes 40% baseline ART coverage, 80% of high-risk couples are without CD4/VL criteria and 80% PrEP coverage among high-risk couples	ICER OVER 10-YEAR HORIZON $1340 per HIV infection averted $5354 per DALYs averted	Yes

Abbreviations: ART, antiretroviral therapy; DALYs, disability-adjusted life year; ICER, incremental cost-effectiveness ratio; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QALY, quality-adjusted life year; SDC, sero-different couples; VL, viral load.

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LAP options are being introduced in the context of static prevention funding. The costs of LAPs are considered a major determinant and threat to their implementation [60]. Stakeholders debate the lack of transparency in injectable PrEP and alternative pricing. For instance—stating that success will require cabotegravir to be offered at an affordable price is all the more concerning when injectable PrEP's threshold for cost-effectiveness in South Africa is <$100 per person-year [61, 62]. Moreover, due to COVID-19 and ongoing global economic instability, some policymakers and other stakeholders call for strategies to improve efficiencies in HIV investments [63]. Understanding the current oral PrEP and LAP rollout, full and incremental costs can inform programme efficiencies and financing innovations. This dearth of primary cost data across the full implementation process, concern about transparent LAP pricing, and nascent understanding of the evolving implementation landscape with the introduction of LAPs elevate the importance of systematic real-world delivery accompanied by primary cost data.

We described how implementation domains included in studies were operationalized in the current context of PrEP delivery. This serial scoping review identified and addressed several literature gaps. First, our rapid review of implementation plans revealed: (1) the rarity of national costed PrEP rollout plans despite expanded PrEP delivery in resource-constrained settings; and (2) the variability of plans' composition and costed domains. Additionally, our scoping review of primary costing and model-based evaluations highlighted (1) a preliminary understanding of real-world PrEP costs due to a preponderance of model-based studies; (2) primary costed studies only explored 12 of the 15 implementation domains, overlooking target setting, health information systems, and implementation science research; and (3) costing units and assumptions varied greatly across primary costing studies, precluding comparison. Together, our reviews highlight the need to further refine and prioritize: (1) content areas for PrEP implementation plans in LMICs; and (2) templates and resources to systematically develop CRPs for approved LAP methods.

No study costed all implementation domains. PrEP costs will need to be more appropriately estimated on a case-by-case basis according to the scope of required activities in each country. For instance, how will countries establish targets for PrEP overall and disaggregated by PrEP methods, including LAP? What technical resources will be needed to estimate initial targets and use various data to update targets as implementation progresses? Health information systems will need to be updated to include multiple methods with different frequencies of use, routes of administration, and means of monitoring. Implementation research is also critical to identify ways that complex interventions could be bundled together and identify implementation strategies that facilitate uptake and effective use of LAP. Investments in supply chain and logistics may also require consideration of the unique needs of injectable Cab PrEP or the push to de-medicalize the PrEP ring. Many studies that cost human resources included costs for training and supportive supervision, both of which will be critical for LAP. Implementers grapple with setting metrics to monitor and evaluate LAP use in programmes, requiring alterations in the health information systems [64]. PrEP metrics need to measure LAP delivery and uptake in service points like FP, where LAP could be integrated [65]. However, no studies accounted for costs associated with updating information systems. Since only 20% of PrEP studies included primary cost data collection, this suggests that most economic evaluations use historical estimates that may no longer represent the current implementation landscape.

PrEP commodities and human resources were the domains most included in modelled evaluations. As with primary cost studies, activities like implementation research to inform decision-making, target setting, awareness raising, technical assistance, and health information system strengthening—vital and catalytic investments in the early phase of introducing new products into the public health system—were not included. Our findings corroborate other reviews examining PrEP cost and cost-effectiveness in mathematical modelling studies [23, 66–79]. Case et al. highlighted in a 2019 review the outdated assumptions in the modelling literature, the lack of "real-world costing" and the limitation of the modelling studies to include programme implementation, among other factors [23]. To our knowledge, our paper is the first analysis that examined the intersection of implementation plans and costing or economic evaluations explicitly.

The wide variation in cost outcomes poses a synthesis challenge identified in this review and previously [32]. Standardized costing instruments should be created, including guidance on costing attributes for inclusion and the process of costing PrEP. Appropriate costing units can help establish higher-quality, consistent cost data to inform planning for LAP. One example can be found on Prepwatch [80]. Around 2016, we observed an increased frequency and diversity of PrEP methods in the cost and economic literature, 1 year after daily oral PrEP was recommended for all by the WHO [14]. With WHO's recommendation, country-level approval and the imminent introduction of LAP, priority should be placed on primary costing studies of LAPs that align with real-world implementation needs [81]. This is an important time for costing experts and decision-makers to ensure that standards are in place for the comprehensive primary costing of LAP. Health economic studies are instrumental to policy and programme planning and should broaden the scope of costed activities to better reflect the real-world implementation, as also noted by Torres-Rueda et al. [35].

4.1 | Limitations

Our scoping review focused on peer-reviewed English-language literature only. We tried to overcome this limitation by utilizing nine electronic databases, including several databases that index work in SSA, which allowed us to cross-reference extensively. Additionally, we reached out through professional networks to identify grey literature. This effort yielded additional peer-reviewed literature through collaborators (authors FTP, FB and STR). We identified implementation domains through a rapid review of four country plans and conducted the thematic analysis inductively. These domains have not been vetted beyond our study team. Other countries may have plans that were not publicly or easily accessed. As a result, we may classify activities differently. Further work is needed to develop a stakeholder-informed con-

sensus template for key domains to consider when planning implementation. Implementation frameworks (e.g. AGREE-II or GLIA) may provide some additional structure that is validated, but based on our assessment, these frameworks would need to be modified to fulfil the purpose of the implementation plan review and evaluation [82, 83]. The GHCC reference case provided methodological principles for evaluating the studies. However, operationalizing the components of the principles in this evaluation revealed that the principles are complex and multidimensional, and the categories are not often mutually exclusive. These factors make it difficult to apply the principles quantitatively.

We note the significant lack of primary data collection related to the cost of delivering PrEP (particularly LAP). For those not reliant on primary data collection, or when the report was unclear, the research team could not analyse how unit cost data were obtained (e.g. budgetary figures, modelling cost estimates, imputation from neighbouring countries, etc.). Further analysis of these studies should allow for a more in-depth review of what figures are currently being used and their comparability. As a result, the studies differed in the scope of interventions offered, and in that sense, mixed-cost data are not comparable. As an example, some PrEP interventions spend significantly on client retention, while other interventions do not. Meaningful conclusions can, therefore, not be drawn from head-to-head comparisons of studies.

This synthesis included studies with different analytic approaches, populations, and assumptions that will result in very different cost estimates. For instance, some studies focused on financial costs, while others focused on economic costs. As a result, it needed to be clarified if or how studies dealt with costing in-kind resources. Differences in interventions (PrEP as part of an integrated HIV prevention or other health programmes), staff time and burden (time-and-motion analysis vs. provider interviews), and targeting (details about specific populations vs. cost estimates per person reached) also existed. The inherent heterogeneity of these studies is both a limitation and a strength in ascertaining assumptions.

5 | CONCLUSIONS

The successful integration and scale-up of new LAP methods into existing service delivery will depend on robust implementation built on sound logistical and financial planning. Based on these observations, we recommend: (1) a framework and tools to support countries in developing CRPs for LAP; (2) a process to ensure that there is global consensus on the composition of domains, defining activities and inputs, and a process for developing costed plans and determining essential and optional components; (3) further examination of implementation considerations for LAP and for supporting a method mix of biomedical HIV prevention; and (4) we echo the call for improved quality, consistency, and transparency in cost and cost-effectiveness studies developed to inform national planning.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

DC, CJH and SF conceptualized the manuscript. EG and NVT performed independent title and abstract screening for eligibility and initial full-text review articles. DC, SF and CJH independently reviewed all articles with discrepant reviews and a subset of initially concordant reviews. DC, SF, CJH, NVT, JW and KKu extracted relevant data from the included studies into REDCap. DC, SF and CJH cross-validated data entry. FB, FT-P and STR performed an independent review that supplemented the search and review. DC and CJH prepared the first draft of the manuscript. All authors edited and commented on the drafts of the manuscript. All authors have read and approved the final manuscript.

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DISCLAIMER

The content is solely the responsibility of the authors. It does not necessarily reflect the views of PEPFAR, USAID, NIH or the U.S. Government and also does not represent the official views of the United States Agency for International Development, the National Institutes of Health or the Global Fund for AIDS, Tuberculosis and Malaria (GFATM).

DATA AVAILABILITY STATEMENT

Data are made available upon request to the primary author.

REFERENCES OF INCLUDED STUDIES

Author	Year of publication	Reference
Ying	2015	[48]
Eakle	2017	[49]
Suraratdecha	2018	[50]
Wong	2018	[84]
Irungu	2019	[43]
Roberts	2019	[52]

(*Continued*)

Author	Year of publication	Reference
Hughes	2020	[45]
Peebles	2021	[47]
Hendrickson	2021	[46]
Wanga	2021	[53]
Mudimu	2022	[42]
Mangenah	2022	[44]
Okal	2022	[51]
Smith	2016	[85]
Stover	2016	[86]
Walensky	2016	[87]
Glaubius	2016	[88]
Quaife	2018	[89]
van Vliet	2019	[90]
Glaubius	2019	[91]
Reidy	2019	[92]
Vogelzang	2020	[93]
Adeoti	2021	[94]
Pretorius	2010	[95]
Hallett	2011	[96]
Gomez	2012	[97]
Long	2013	[98]
Cremin	2013	[99]
Nichols	2013	[100]
Verguet	2013	[101]
Stover	2014	[102]
Nichols	2014	[103]
Anderson	2014	[104]
Alistar	2014	[105]
Alistar	2014	[106]
Cremin	2015	[107]
Jewell	2015	[108]
Cremin	2015	[109]
Mitchell	2015	[110]
Price	2016	[111]
Moodley	2016	[112]
Meyer-Rath	2017	[113]
Chiu	2017	[114]
Cremin	2017	[115]
Akudibillah	2017	[116]
Alsallaq	2017	[117]
Anderson	2018	[118]
Li	2018	[119]
Luz	2018	[120]
Stopard	2019	[121]
Zhang	2019	[122]
Bórquez	2019	[123]
Selinger	2019	[124]
Hu	2019	[125]
Grant	2020	[126]
Kazemian	2020	[127]
Pretorius	2020	[128]
Jamieson	2020	[129]
Kazemian	2020	[130]
Wu	2021	[131]
Phillips	2021	[132]
Ten Brink	2022	[133]
Kripke	2022	[134]
Jin	2022	[135]
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SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article:

Supporting Information 1: Timeline and populations of World Health Organization Guidance for Biomedical HIV Prevention Strategies.

Supporting Information 2: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

Supporting Information 3: Search queries used for electronic database searches

Supporting Information 4A: Frequency of Populations Costed within Included Studies

Supporting Information 4B: Frequency of Populations Represented within Included Studies

Supporting Information 5A: Frequency of Geographies with Regional, National, or Sub-National Costing Data within Included Studies

Supporting Information 5B: Frequency of Countries and Regions Represented within Included Studies

Supporting Information 6: Economic Analysis Features and Analytic Approaches of Secondary Costing or Modeling Studies (Inclusive of bnAbs and HIV Vaccine columns)

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COMMENTARY

Shaping and coordinating the implementation science agenda for injectable cabotegravir for PrEP: the role of the Biomedical Prevention Implementation Collaborative (BioPIC)

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Abstract

Introduction: Data from two randomized controlled trials (RCTs) showed that injectable cabotegravir (CAB) for pre-exposure prophylaxis (PrEP) was efficacious in reducing HIV acquisition. The US Food and Drug Administration approved CAB for PrEP in December 2021; Australia in August 2022; Zimbabwe in October 2022; South Africa in November 2022; Malawi in March 2023; and regulatory approvals are being sought in additional countries. The World Health Organization (WHO) recommended CAB be offered to people at substantial risk of HIV in July 2022. However, implementation experience beyond RCTs is limited. As countries consider CAB implementation, questions remain regarding delivery and involvement of populations excluded from the trials. A coordinated approach is needed to ensure these are addressed and CAB can be introduced in low- and middle-income countries in timely, acceptable and effective ways.

Discussion: Beginning in 2018, the Biomedical Prevention Implementation Collaborative (BioPIC) convened over 100 global health experts to develop a comprehensive introduction strategy for CAB. Using this roadmap, country landscaping for CAB introduction and lessons from oral PrEP implementation, AVAC and WHO co-convened 50 researchers, donors, implementers and civil society in September 2021 to: (1) identify questions and evidence gaps related to CAB across contexts and partners; (2) define the implementation science agenda; and (3) agree on mechanism(s) for future coordination. As a result, CAB-related questions were identified, including: defining optimal and feasible HIV testing strategies that expand access; delivery models; integration with a range of services, including family planning and antenatal care; and embedding CAB in demand generation for HIV prevention choices. Through convenings and mapping of implementation research, BioPIC identified gaps in populations, geographies and delivery approaches.

Conclusions: The introduction strategy refined by BioPIC lays the groundwork for future HIV prevention products. Ongoing policy and implementation dialogue is critical to accelerate the design of CAB implementation studies that adequately address priority knowledge gaps. Additional long-acting HIV prevention products may be available over the next 5 years, increasing choice, but potentially making delivery and stakeholder engagement more complex. Ongoing coordination with WHO will accelerate the adoption of evidence-based policies and wide-scale implementation, and lessons from BioPIC can inform introduction processes for long-acting HIV prevention products.

Keywords: cabotegravir; HIV; implementation science; PrEP; prevention; product introduction

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1 | INTRODUCTION

Injectable cabotegravir (CAB) is an integrase strand-transfer inhibitor (INSTI) class antiretroviral. For use as HIV pre-exposure prophylaxis (PrEP), it is administered to people who do not have HIV at a dose of 600 mg, intramuscularly, 4 weeks apart for the first two injections and every 8 weeks thereafter.

Data from the HIV Prevention Trials Network (HPTN) 083 and 084 randomized controlled trials (RCTs) in 2020 indicated that CAB for PrEP is safe and efficacious in reducing the risk of HIV acquisition in multiple populations. HPTN 083 results suggest an estimated 66% relative reduction in HIV acquisition risk among cisgender men and transgender women who have sex with men [1] and HPTN 084 results suggest an 88% reduction among cisgender women compared with oral PrEP [2]. These trials have now transitioned from

blinded to open-label studies in which all trial participants are offered the choice between injectable and oral PrEP.

US regulatory approval in December 2021 paves the way for introduction in the United States. Australia approved the product in August 2022, the Zimbabwean regulatory agency approved it in October 2022, while South Africa approved it in November 2022 and Malawi in March 2023. Additional regulatory approvals are being sought in a range of countries, including several low- and middle-income countries (LMICs) [3]. In July 2022, the World Health Organization (WHO) recommended that injectable CAB may be offered as an additional HIV prevention option to people at substantial HIV risk [4].

However, implementation experience beyond the RCTs is limited. The approvals and guidelines have brought increasing momentum, discussion and concern around what is happening to ensure the introduction of CAB for PrEP maximizes its prevention potential, including whether the initial implementation science projects will answer critical remaining questions. The experiences of the first decade of oral PrEP implementation show the impact of delays in delivery and inequity in access [5]. As countries consider CAB introduction, there remain important implementation science questions regarding the delivery of CAB—notably regarding HIV testing and HIV drug resistance—and the involvement of populations not included in the trials [6, 7] that need to be answered in order to translate the strong efficacy seen in the clinical trials into public health impact. A coordinated implementation science approach is needed to ensure these are addressed and that CAB can be introduced at scale and with equity, especially in LMICs, in timely, acceptable and effective ways.

With an accelerated timeline for planning and preparing to introduce CAB prompted by the early, positive results of the two pivotal RCTs, and the progress of other long-acting HIV prevention products through the pipeline, AVAC and WHO, through the Biomedical Prevention Implementation Collaborative (BioPIC), jointly convened key stakeholders to strategize about implementation projects and other planning for product introduction.

Established in 2018 by AVAC and the Clinton Health Access Initiative (CHAI) with funding from the Bill and Melinda Gates Foundation, the BioPIC takes an innovative, collaborative approach to support rapid, successful introduction of HIV prevention products to ensure activities are well-designed, well-timed and well-funded to meet the needs of global and country decision-makers. It is made up of over 100 HIV prevention experts, including civil society representatives, donors, researchers, policymakers, normative agencies and implementers from over 20 countries, and is now serving as the secretariat of the Coalition to Accelerate Access to Long-Acting PrEP.

2 | DISCUSSION

Identifying feasible, affordable and acceptable strategies for delivering injectable CAB for PrEP is critical to ensuring that it—and other emerging HIV prevention tools—offer greater options to individuals who may benefit from using antiretroviral drugs for prevention and can have an impact on the epidemic.

Beginning in 2018, BioPIC convened over 100 global health experts to develop a comprehensive introduction strategy for CAB, including an adaptable framework for HIV prevention product introduction [8]. Using this framework alongside country-specific landscape analyses of demand and supply issues for CAB introduction and lessons from oral PrEP implementation [5], AVAC and WHO co-convened researchers, donors, implementers and civil society through a series of virtual thinks tanks to: (1) identify common questions and evidence gaps related to CAB across contexts and partners; (2) define the implementation science agenda for CAB that can help inform and, hopefully, accelerate programme scale; and (3) agree on mechanism(s) for future coordination. Think Tank topics have included: Product Introduction/Implementation Project Planning for Next-Generation PrEP (22–23 September 2021); HIV Testing and Injectable CAB for PrEP Introduction: What are the implications for HIV prevention scale-up and the HIV response? (3 December 2021); Modelling the Impact of Injectable CAB for PrEP on Drug Resistance (7 March 2022); Coordinating Implementation Science for CAB for PrEP (21 April 2022); Generating Demand for HIV Biomedical Prevention in the Era of Choice (7–8 June 2022); Coordinating Implementation Science for CAB for PrEP: Focus on Delivery Models (23 June 2022); Coordinating Implementation Science for CAB for PrEP: Focus on Research and Surveillance during Pregnancy and Breastfeeding (2 November 2022); Shaping and Strengthening Markets for a New Era of Choice-based HIV/SRH Programming: Lessons from HIV & FP Product Introduction (1 March 2023); and Bridging from the HPTN 083 and 084 Open Label Extensions to Implementation (14 March 2023) [9].

As a result, CAB-related research and implementation questions were identified, which fell into four primary categories: populations, demand creation, delivery and data. Specifically, identified research questions included: defining optimal and feasible HIV testing strategies that balance the need for affordable and feasible testing with the need to detect infections early to prevent potential INSTI resistance; delivery models; integration with a range of services, including for family planning and antenatal care; and how to embed CAB in overall demand generation for HIV prevention choices.

Through convenings and mapping of proposed implementation science projects, BioPIC identified and encouraged researchers to fill gaps in these issues. This process began by identifying priority implementation science planning issues to ensure robust, strategic and informative demonstration and introduction projects of injectable CAB for PrEP.

2.1 | Populations

Future studies need to generate information for implementation among diverse populations and geographies, looking especially beyond adolescent girls and young women in sub-Saharan Africa, the focus of many PrEP programmes to date and need to explore concerns, questions, service preferences and other issues through implementation projects when feasible or other research and community-based approaches. There is a need to ensure that all regions and "missing populations" from the RCTs, such as trans and gender-diverse people, people who inject drugs, sex workers and adolescents

are included in some aspects of this implementation research. There are also remaining questions regarding the safety of CAB during pregnancy and breastfeeding as well as potential interactions between CAB and gender-affirming hormones (although recent data suggest that there is limited impact of oestradiol-based gender-affirming hormones on CAB concentrations) [10]. These projects will need to balance messaging and services tailored to specific users and user groups with normalizing use and avoiding stigma.

2.2 | Demand creation—for CAB, for PrEP and for HIV prevention generally

As projects are designed, potential users and user groups should be defined by behaviours rather than risk, reframing injectable CAB—and other PrEP products—affirmatively by stressing benefits, such as the potential for reduced anxiety, increased connection with partners and enjoyment rather than "risk reduction." Implementation projects should invest in robust partnerships with community and potential users early and continuously, using multiple approaches—advisory groups, paid support to community-based organizations, media engagement, creation and dissemination of resource and marketing materials—to involve civil society from the beginning as experts in designing services, communications strategies and materials, and outreach. While injectable CAB is the newest option, it is not the only one, and projects should ensure that messaging emphasizes HIV prevention choices (including also the dapivirine vaginal ring) and does not play one PrEP product against another.

2.3 | Delivery

Implementation projects should be designed to explore and anticipate a range of models and approaches, such as the role of HIV testing at initiation and on an ongoing basis, integration with other services, community delivery (including through pharmacies), task sharing and involvement of peer and lay providers in delivery. These projects can be located within existing services for HIV prevention, family planning, primary healthcare and others to explore how people choose and potentially switch among different options like oral PrEP, CAB, the dapivirine vaginal ring and condoms, what typical patterns of use look like and how to best support effective adherence. There are important lessons and examples from a range of health services and systems beyond PrEP. For example, contraceptive programmes have long experience with offering clients a choice of methods and in managing switching and "discontinuation," and injectable contraception has clear parallels with CAB. Now that multiple antiretroviral (ARV)-based prevention options may be available, projects need to monitor, understand and support use across the product spectrum, including initial product uptake, continuation and possible switching between methods for the first time. Also, these projects should be designed from the outset to be scalable, pragmatic and sustainable.

2.4 | Data

Upcoming projects should include specific outcome measures that explore how people choose among different prevention options, as well as patterns of starting/stopping and switching, and their reasons for doing so. This will require agile monitoring and evaluation systems and indicators that can accurately monitor use patterns in programmes, differences across service delivery and demand creation models, and costs. Given concerns for potential HIV drug resistance, it is essential to establish robust, feasible monitoring systems for resistance in PrEP programmes. Effective surveillance systems for pregnancy outcomes will also be critical to generate evidence on the safety of CAB for PrEP during pregnancy and breastfeeding. Coordinating and sharing information among projects will be needed to develop an evidence base and clear strategy to actively cultivate interest and address questions from governments that may have limited capacity for and/or interest in investing in new products, including cost and cost-effectiveness.

Research approaches and outcomes will likely vary by context, population and other factors, so it will be important that implementation science is seamlessly part of scale-up rather than a separate step. In the context of oral PrEP programmes, there was a reluctance to initiate large-scale programmes before the implementation science projects were completed. Given the epidemiologic need and the potential of this new prevention option, it is possible to use real-time data to inform and drive accelerated scale-up with efforts to identify effective strategies for specific populations and geographies, planning in parallel to answer questions and build programmes, rather than seeing implementation science and scaled programmes as sequential. Implementation research will need to be adapted to various contexts, but for the most part drive towards similar outcomes (Table 1). These outcomes would evaluate the overall effectiveness and impact of both individual and cumulative HIV prevention products on the epidemic, document actual acceptability, use patterns and challenges in "real world" conditions and compare the effectiveness of different delivery, demand creation and community engagement models. Standardizing outcome measures across projects and partners can help to produce more comparative and generalizable data to drive decision-making and identify what strategies can and should be taken to scale.

Through this process, a CAB for PrEP Implementation Study Tracker [11] was established to track all currently known partner activities relating to landscaping, product introduction, introduction studies and implementation research. These studies are mapped against the Implementation Science Questions for CAB for PrEP framework in Table 1 [12] to monitor for any gaps, overlaps and/or opportunities for collaboration, and BioPIC and WHO continue to convene researchers to facilitate sharing implementation plans and information, to drive innovation and collaboration, and to coordinate among projects for different geographies, populations and donors.

3 | CONCLUSIONS

With over 25 implementation research studies for injectable CAB for PrEP already being at different stages of planning and preparation [8] and as programmes shift towards choice-based models for HIV prevention, this is a critical time to

Table 1. Potential outcome measures for implementation science research on injectable cabotegravir (CAB) for pre-exposure prophylaxis (PrEP)

Category	Outcomes
Uptake, use and impact	Where feasible, disaggregate outcomes by population, age and gender: • Proportion of eligible individuals initiating CAB • Proportion of new PrEP (PrEP naïve) CAB enrolments versus switches from other PrEP products to CAB • Proportion of individuals who seroconvert while using CAB • Proportion of individuals who acquire drug-resistant HIV infections due to PrEP exposure versus those who acquire transmitted drug resistance • Proportion of individuals who are initiated on CAB after acquiring HIV • Proportion of individuals who stop using CAB and switch to another prevention method, who stop and use another prevention method to cover the tail, who stop without using another HIV prevention method; reasons for doing so • Reduction in HIV incidence among CAB users; number of HIV infections averted
Cost-effectiveness	• Delivery and commodity costs of CAB • Cost of PrEP delivery by model typology • Feasibility and health facility readiness for CAB implementation • Cost-effectiveness and cost-utility of CAB in different implementation scenarios, including when CAB is prioritized to "high-risk" individuals or all individuals who could benefit from PrEP and comparisons to other PrEP options. • Cost-effectiveness of different HIV testing approaches • Cost of preparing health facilities for CAB implementation
Collateral impacts	• Impact of delivering CAB within family planning clinics on contraceptive uptake and adherence • Impact of use of CAB on sexual behaviour and sexually transmitted infections (STI) incidence • Impact of CAB availability and use on overall HIV prevention coverage • Impact of delivery of CAB on uptake of a range of primary healthcare services, including ante-natal and postnatal care attendance and uptake of sexual and reproductive health services • Changes in reported quality of life, depression or anxiety and self-efficacy/empowerment
Community and end-user engagement	• Increased community awareness and education of CAB as a prevention option • Increased end-user and community participation in CAB implementation research, delivery, monitoring and demand generation

correct for missed opportunities with oral PrEP rollout, and ensure more effective coordination across geographies, populations and projects. This work needs to run in parallel with ongoing advocacy related to accelerate access to the product and reduce the cost of the product, both significant barriers to scale and impact.

Oral PrEP was first shown to be safe and effective in 2010 and first approved for use in the United States in 2012, but the field moved slowly—and now 10 years later, only approximately 3 million people have initiated the use of this option and approximately 1.6 million current users by the end of 2021, far slower than the 2020 target of 3 million, far short of the new 2025 target of 10 million PrEP users and a tiny fraction of the estimated number of people who need it and could benefit from it. There are significant questions about how to deliver injectable CAB for PrEP, therefore, coordinated partnerships and bold action are needed urgently.

The implementation science agenda refined by BioPIC lays the groundwork for future HIV prevention products. Ongoing policy and implementation dialogue, including with civil society, is critical to accelerate the design of CAB implementation studies that adequately address priority knowledge gaps. Additional long-acting products may be available over the next 5 years, increasing choice, but potentially making delivery and

stakeholder engagement more complex. Ongoing coordination with WHO will also accelerate the adoption of evidence-based policies and wide-scale implementation. While any one project may or may not be a success on its own, systematically monitoring and analysing how the introduction and delivery of CAB for PrEP across the evolving ecosystem affects key individual-level and public health-level questions identified in this process can contribute to building a sustainable platform for HIV prevention. The need for enhanced coordination has never been greater and lessons from BioPIC can inform introduction processes not only for CAB but also for other products.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

MW drafted the initial version of the manuscript. All authors reviewed and revised the manuscript. All authors approved the final version of the manuscript.

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DISCLAIMER

The authors alone are responsible for the views expressed in this article and they do not necessarily represent the views, decisions or policies of the institutions with which they are affiliated.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

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RESEARCH ARTICLE

Population-level impact of expanding PrEP coverage by offering long-acting injectable PrEP to MSM in three high-resource settings: a model comparison analysis

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Abstract

Introduction: Long-acting injectable cabotegravir (CAB-LA) demonstrated superiority to daily tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) for HIV pre-exposure prophylaxis (PrEP) in the HPTN 083/084 trials. We compared the potential impact of expanding PrEP coverage by offering CAB-LA to men who have sex with men (MSM) in Atlanta (US), Montreal (Canada) and the Netherlands, settings with different HIV epidemics.

Methods: Three risk-stratified HIV transmission models were independently parameterized and calibrated to local data. In Atlanta, Montreal and the Netherlands, the models, respectively, estimated mean TDF/FTC coverage starting at 29%, 7% and 4% in 2022, and projected HIV incidence per 100 person-years (PY), respectively, decreasing from 2.06 to 1.62, 0.08 to 0.03 and 0.07 to 0.001 by 2042. Expansion of PrEP coverage was simulated by recruiting new CAB-LA users and by switching different proportions of TDF/FTC users to CAB-LA. Population effectiveness and efficiency of PrEP expansions were evaluated over 20 years in comparison to baseline scenarios with TDF/FTC only.

Results: Increasing PrEP coverage by 11 percentage points (pp) from 29% to 40% by 2032 was expected to avert a median 36% of new HIV acquisitions in Atlanta. Substantially larger increases (by 33 or 26 pp) in PrEP coverage (to 40% or 30%) were needed to achieve comparable reductions in Montreal and the Netherlands, respectively. A median 17 additional PYs on PrEP were needed to prevent one acquisition in Atlanta with 40% PrEP coverage, compared to 1000+ in Montreal and 4000+ in the Netherlands. Reaching 50% PrEP coverage by 2032 by recruiting CAB-LA users among PrEP-eligible MSM could avert >45% of new HIV acquisitions in all settings. Achieving targeted coverage 5 years earlier increased the impact by 5–10 pp. In the Atlanta model, PrEP expansions achieving 40% and 50% coverage reduced differences in PrEP access between PrEP-indicated White and Black MSM from 23 to 9 pp and 4 pp, respectively.

Conclusions: Achieving high PrEP coverage by offering CAB-LA can impact the HIV epidemic substantially if rolled out without delays. These PrEP expansions may be efficient in settings with high HIV incidence (like Atlanta) but not in settings with low HIV incidence (like Montreal and the Netherlands).

Keywords: HIV prevention; men who have sex with men; modelling; PrEP; North America; Europe

Additional information may be found under the Supporting Information tab of this article.

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1 | INTRODUCTION

Two clinical studies (HPTN 083 and HPTN 084) have shown that long-acting injectable cabotegravir (CAB-LA) pre-exposure prophylaxis (PrEP) given every 8 weeks is highly efficacious at preventing HIV among cisgender men who have sex with men (MSM) and transgender and cisgender women in several countries [1, 2]. This new HIV prevention option may help increase PrEP coverage as it may be more appealing to people at risk who do not want or are unable to use daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) PrEP. In trial settings, participants have found CAB-LA to be acceptable, with many participants interested in continuing injections [3–5]. Currently, CAB-LA is approved for use in the United States, though not yet in Canada or the Netherlands [6], and the World Health Organization (WHO) has recently

recommended CAB-LA as an additional prevention choice for people at substantial risk of HIV acquisition [7, 8].

Many factors need to be considered to determine how to optimize the use of CAB-LA after its approval by regulatory authorities. Given that CAB-LA will be offered alongside other HIV prevention options, including daily TDF/FTC [9, 10], it is important to determine who will have access to CAB-LA based on local eligibility criteria [11–13] to predict what proportion of current TDF/FTC users may decide to switch to CAB-LA [14] and how many additional PrEP users may need to be recruited to more substantially impact HIV incidence after CAB-LA becomes available. It is critical that the introduction of CAB-LA does not result in decreases in PrEP coverage by creating additional barriers to service access or by negatively affecting integration with existing HIV prevention options [15].

Aiming to address questions about the impact of PrEP scale-up by offering CAB-LA alongside TDF/FTC, the HPTN Modelling Centre (https://hptnmodelling.org/) and the HIV Modelling Consortium collaborated to conduct a model-based comparison of the expected population-level impact of introducing CAB-LA in different geographic areas with different HIV incidence and current PrEP coverage levels and in selected risk populations. The goal of this project is to use existing, well-calibrated, transmission-dynamic models of HIV to predict and compare the population-level effectiveness and efficiency of expanding overall PrEP coverage by adding CAB-LA to the HIV prevention portfolio under prioritized and access-to-all strategies. The results of this study were used to inform current WHO recommendations [16] and could provide the basis for regional, national and local HIV prevention policy recommendations as well as support strategic planning and allocation to key population programmes.

In this paper, we estimate the potential impact of expanding PrEP coverage by offering CAB-LA to MSM populations in high-income countries based on models from three groups that accepted the invitation to participate in this model comparison project. We compared results from risk-stratified HIV transmission dynamic models among MSM which were independently parameterized and calibrated to local data from Atlanta in the United States [17], Montreal in Canada [18] and in the Netherlands [19, 20], populations with HIV epidemics dominated by MSM transmission. Population-level effectiveness and efficiency were estimated over 20 years and the feasibility of different PrEP expansion strategies for each epidemic setting is discussed.

2 | METHODS

We present results from three models of the HIV epidemic in MSM populations (parameterized and calibrated for Atlanta, USA, Montreal, Canada, and the Netherlands) that simulated a set of pre-designated PrEP expansion scenarios over 20 years (2022–2042) and provided inputs and results in the requested forms. Modelling teams were expected to employ estimates of TDF/FTC PrEP efficacy and adherence representative of the populations they simulated. The goal was to present a spectrum of potential outcomes associated with the expansion of PrEP coverage by increasing CAB-LA usage and/or switching existing TDF/FTC PrEP users to CAB-LA [17–20]. CAB-LA efficacy (91%, range 82%–96%) and retention rates (16.8% discontinuation over 12 months) from the HPTN 083 trial were standardized across the models [1], while TDF/FTC effectiveness (incorporating adherence), population access and propensity to use PrEP, and other parameters, were specific to each model and its geographic setting. All models reported results with at least 100 calibrated parameter sets which best represent the HIV epidemic in their setting. The modelling assignment provided to the participating teams is included in the Supporting Information.

2.1 | Participating teams and settings

The Atlanta model developed by the HPTN Modelling Centre [17] was used to assess the impact of interventions in an MSM population with high HIV prevalence. The Montreal [18] and Netherlands [19, 20] models, developed by the McGill University and Erasmus Medical Centre/Maastricht University teams, respectively, reflected settings with lower HIV prevalence among MSM. Table 1 summarizes key characteristics of each model and Figure 1 shows baseline population characteristics and risk configurations assumed in each model. More details and parameter tables for each model are included in the Supporting Information.

2.2 | Baseline scenarios with TDF/FTC use only

Baseline scenarios were simulated to project TDF/FTC use and the HIV care continuum in each setting in the absence of CAB-LA and serve as counterfactual estimates when evaluating CAB-LA expansion scenarios. Parameters related to antiretroviral therapy (ART) use, including initiation and discontinuation rates, and rates of achieving viral suppression (VS) were based on local data in the simulated communities between 2022 and 2042. Model projections of TDF/FTC use, initiated in accordance with local PrEP eligibility criteria, used availability and acceptability measures set to reflect current and expected future use.

A comparison of the predicted epidemic under the baseline scenario across models is presented in Figure 1 and Table S1. The predicted HIV prevalence and incidence in 2022 were significantly higher in the Atlanta model (26% and 2.1 per 100 PYs) than in the Montreal model (6% and 0.1 per 100 PYs) or the Netherlands model (9% and 0.1 per 100 PYs). HIV incidence was predicted to decrease by 21% (Atlanta), 63% (Montreal) and 98% (Netherlands) from 2022 to 2042 even without offering CAB-LA. The estimated HIV treatment cascade in 2022 was better in Montreal and the Netherlands than in Atlanta with 95% (Montreal), 94% (Netherlands) and 56% (Atlanta) of MSM living with HIV on ART and 90% (Montreal) and 51% (Atlanta) of MSM living with HIV virally suppressed. VS in the Netherlands is very high (96% [24]) and was not included explicitly in that model. The proportions of MSM living with HIV on ART and virally suppressed were expected to improve slightly over time in all settings. The Netherlands model assumed the fewest PrEP-eligible MSM in 2022 (26% of MSM not living with HIV [12]) compared to Atlanta (47% of MSM not living with HIV) or Montreal

Table 1. Model characteristics

Model characteristics	Atlanta	Montreal	Netherlands
Model description	Deterministic compartmental	Stochastic agent-based	Deterministic compartmental
Population stratification	Age (18–24, 25+ years old), race (Black, White), sexual activity group (PrEP indication)	Age (15–24, 25–34, 35–44, 45–54, ≥ 55), sexual activity group (≤5, 6–10, ≥11 anal sex partners per year)	Sexual activity group (IQR[a] <1, 2–4, 8–12, 35–55 new partners every 2 years)
Age range	18+	15+	15+
TDF/FTC effectiveness	82% (range: 75%–87%) [9, 21]	86% [22]	85% [10]
TDF/FTC discontinuation rate	0.33/year [21]	0.90/year [23] (0.84–0.96 IQR)[b]	0.62/year (0.48–0.79 IQR)[b]
CAB-LA effectiveness*	91% (82%–96% range) [1]		
CAB-LA discontinuation rate*	0.168/year [1]		
Proportion in each sexual activity group[c]	53% high 47% low	40% high 19% medium 41% low	11% (11%–12% IQR) high 14% (12%–16% IQR) medium high 19% (14%–23% IQR) medium 56% (49%–61% IQR) low[b]
HIV incidence ratio between sexual activity groups[d]	High sexual activity group 3.3x risk of low sexual activity group	High sexual activity group 5–7x that of lower sexual activity group (after 1985)	High sexual activity group 80x risk of low sexual activity group (58–116 IQR) Medium high sexual activity group 17x risk of low sexual activity group (12–28 IQR) Medium sexual activity group 5x risk of low sexual activity group (3–7 IQR)[b]
Median HIV incidence in each sexual activity group[d]	High: 3.7/100 person-years (PYs) Low: 1.1/100 PYs	High: 0.16/100 PYs Medium: 0.05/100 PYs Low: 0.03/100 PYs	High: 0.46/100 PYs Medium-high: 0.10/100 PYs Medium: 0.03/100 PYs Low: 0.006/100 PYs
PrEP allocation by sexual activity group (PrEP-eligible model scenario)	Cover 90% of high sexual activity group, then offer to low sexual activity group	Each individual was assessed for eligibility and a binomial distribution with a probability of uptake determined if those eligible initiated PrEP[e]	Cover the two highest sexual activity groups, then offer to lower sexual activity groups

[a]Interquartile range.
[b]Following model calibration.
[c]On 1 January 2022.
[d]Annual HIV incidence between groups in the absence of PrEP.
[e]Coverage by risk group 1 January 2022: 4% (IQR: 3%–5%) low activity group; 7% (IQR: 5%–9%) medium activity group; 9% (IQR: 7%–12%) high activity group.
*Constant between all models.
[a]Abbreviations: TDF/FTC, tenofovir disoproxil fumarate/emtricitabine; CAB-LA, long-acting injectable cabotegravir; PrEP, pre-exposure prophylaxis.

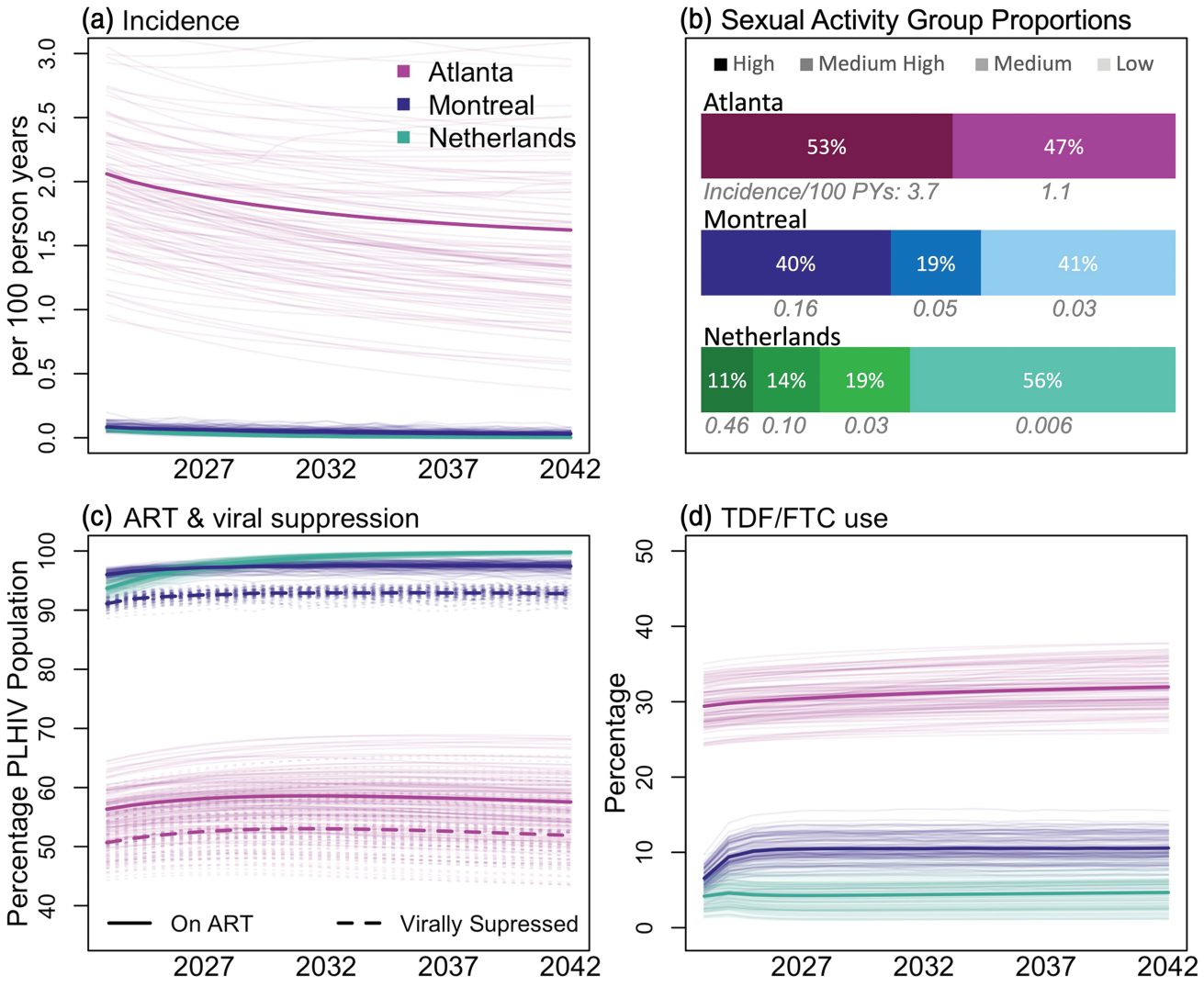

Figure 1. Baseline model characteristics in Atlanta, Montreal and the Netherlands. (A) HIV incidence. (B) Proportion of the population and estimated HIV incidence in each sexual activity group in 2022. (C) Antiretroviral therapy (ART) and viral suppression in the PLHIV population (viral suppression was not simulated in the Netherlands model). (D) Projected tenofovir disoproxil and emtricitabine (TDF/FTC) use among MSM not living with HIV. Bold lines show means of all scenario replicates. Thin lines show individual simulations. Variation shown in the range of simulation lines comes from parameter variability in the deterministic compartmental models and stochastic variability in the agent-based model. Abbreviations: PLHIV, people living with HIV; MSM, men who have sey with men

(59% of MSM not living with HIV). The Atlanta model had substantially higher TDF/FTC use among MSM not living with HIV (29%) in 2022 compared to 6% in Montreal and 4% in the Netherlands. Sexual activity groups varied between models; 53% (Atlanta), 40% (Montreal) and 25% (the Netherlands) of MSM were in the high or medium-high sexual activity groups.

2.3 | PrEP expansion scenarios

CAB-LA expansion was initiated in 2022 and increased the overall PrEP coverage (including both TDF/FTC and CAB-LA users) to between 15% and 50% of the total population of MSM not living with HIV (Table 2 and Figure 2). Two potential PrEP coverage timelines were included, one in which coverage targets were expected to be reached by 1 January 2027 (5-year target) and one by 1 January 2032 (10-year target). PrEP coverage could not exceed the targeted coverage by more than 1 percentage point (pp). The analysis was restricted to scenarios where the targeted coverage following CAB-LA expansion exceeded the projected PrEP coverage in the baseline scenario. Different proportions (0%–100%, Table 2) of TDF/FTC users were assumed to switch to CAB-LA at the start of the simulation (1 January 2022) and the same proportion of baseline TDF/FTC users were assumed to initiate CAB-LA instead of TDF/FTC throughout the simulation (Figure 1). Recruitment of new CAB-LA users (in addition to those projected to switch from TDF/FTC) was modelled in two different ways: (i) preferentially from groups of PrEP-eligible MSM at higher risk as defined in each model

Table 2. PrEP expansion intervention details

Intervention components	Scenarios simulated
PrEP coverage of MSM not living with HIV (TDF/FTC + CAB-LA PrEP users combined)	15%, 30%, 40% and 50%
Time to achieve targeted PrEP coverage	5 and 10 years (by 2027 and by 2032)
Proportion of current/projected TDF/FTC users switching to CAB-LA	0%, 15%, 30%, 50% and 100%
Recruitment of new CAB-LA users (users in addition to those on TDF/FTC PrEP at baseline)	Based on current PrEP eligibility criteria: those in higher sexual activity groups prioritized for PrEP coverage Proportionally distributed: distributed across risk and age groups to all MSM not living with HIV

[a]Abbreviations: PrEP, pre-exposure prophylaxis; MSM, men who have sex with men; TDF/FTC, tenofovir disoproxil and emtricitabine; CAB-LA, long-acting cabotegravir.

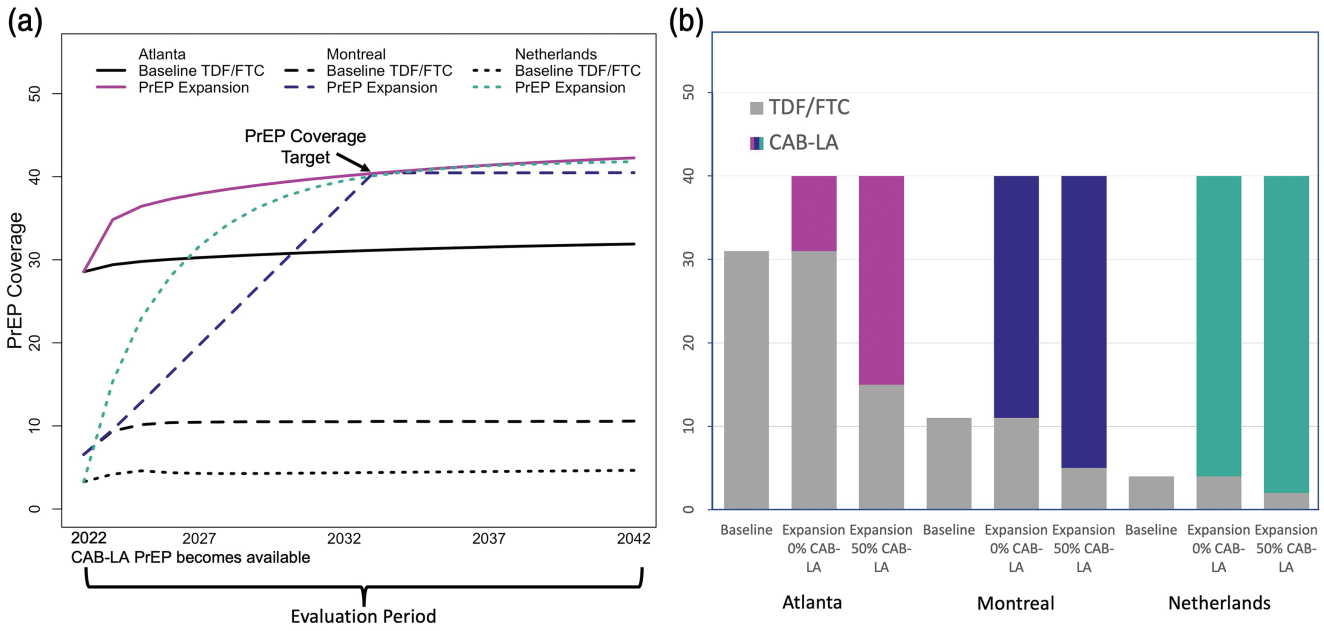

Figure 2. Pre-exposure prophylaxis (PrEP) expansion scenario structure. (A) The baseline (counterfactual) scenario projected that tenofovir disoproxil and emtricitabine (TDF/FTC) usage will increase slightly over time from its current level in 2022 (29% Atlanta, 6% Montreal and 4% Netherlands) to 2042 (32% Atlanta, 10% Montreal and 5% Netherlands, black lines). Reaching a targeted coverage (40%) in 10 years (by 2032) required initiating new long-acting cabotegravir (CAB-LA) users (coloured lines). (B) The distribution of CAB-LA and TDF/FTC use in each scenario depended on the prevalence of TDF/FTC use in the baseline scenario. Expansion with 0% CAB-LA use caused only those in the expansion group to use CAB-LA. Expansion with 50% CAB-LA caused 50% of the baseline TDF/FTC users to instead use CAB-LA, in addition to those in the expansion group who always use CAB-LA.

and (ii) proportionally across the population assuming universal access to CAB-LA.

2.4 | Metrics of impact

Population-level effectiveness was assessed by two metrics: (i) the *cumulative fraction of new HIV acquisitions averted over 20 years* (calculated as the complement of the cumulative number of new HIV acquisitions between 2022 and 2042 in each PrEP expansion scenario divided by the cumulative number of HIV acquisitions in the baseline scenario) and (ii) the *relative reduction in annual HIV incidence after 10 years* (calculated as one minus the incidence in 2032 divided by the baseline HIV incidence in 2022). To better understand the projected impact of PrEP expansions, we calculated the *"effective risk coverage"* based on the proportion of MSM in each sexual activity group, HIV incidence ratio between groups and PrEP coverage achieved in each group as reported in Table 1. This measured the proportion of HIV risk covered when targeted coverage is reached in 2032 calculated from PrEP coverage of each sexual activity group weighted by the proportion of new acquisitions expected to occur in that group. Sexual activity group size and incidence were calculated from group proportions and incidence at baseline on

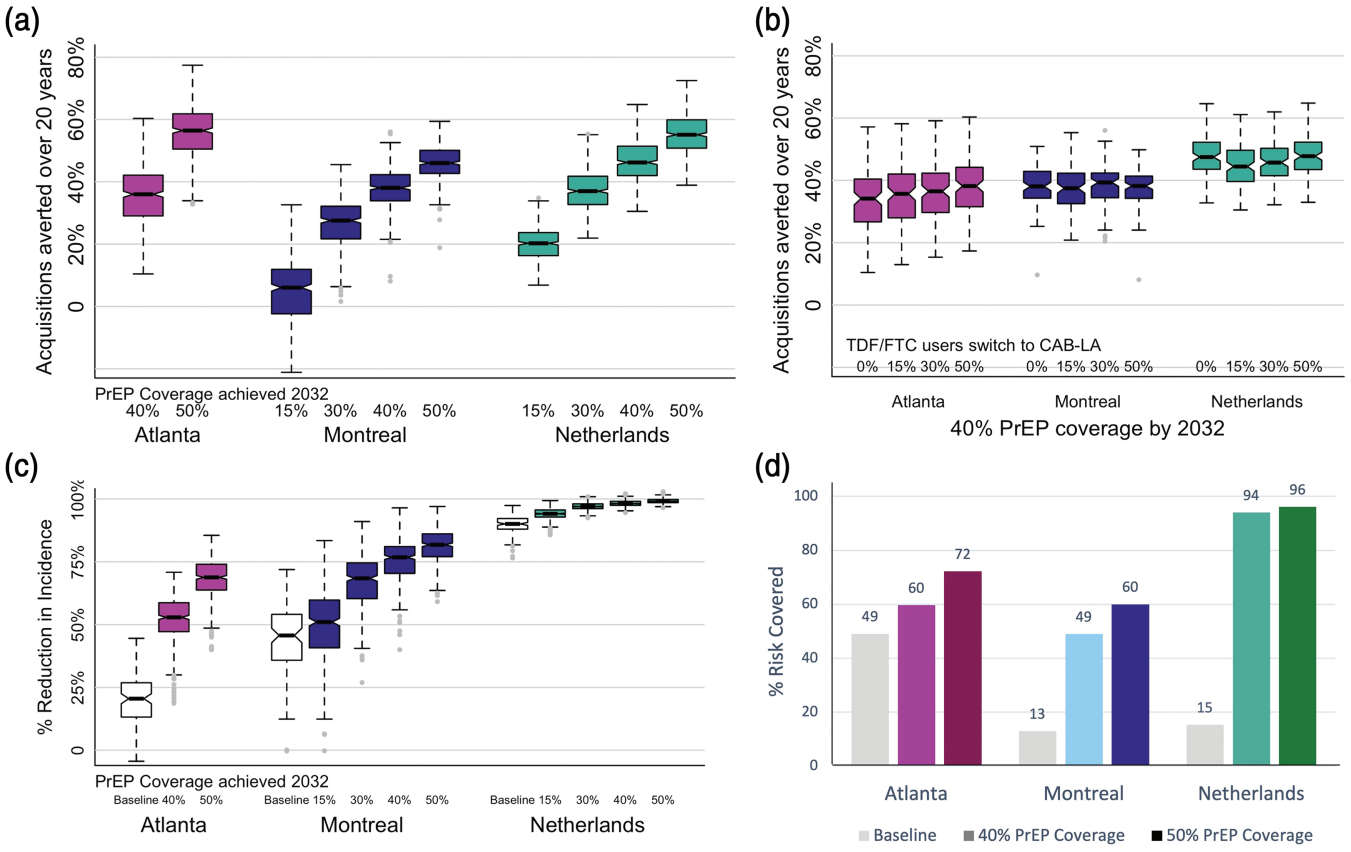

Figure 3. Population effectiveness. (A) Acquisitions averted over 20 years (2022–2024) with pre-exposure prophylaxis (PrEP) coverage achieved by 2032. Fifteen percent and 30% PrEP coverage levels were not modelled in Atlanta as baseline PrEP coverage was 29%. (B) Acquisitions averted with 40% PrEP coverage achieved by 2032 for different proportions of tenofovir disoproxil and emtricitabine (TDF/FTC) users switching to long-acting cabotegravir (CAB-LA). (C) Projected reductions in HIV incidence in 2032 relative to 2022 incidence in the baseline (white) and expanded PrEP coverage (colours) scenarios. A and C cumulate all TDF/FTC to long-acting cabotegravir (CAB-LA) switching scenarios. (D) Proportion of risk covered for different PrEP expansions, estimated by the proportion of PrEP coverage of each sexual activity group weighted by the proportion of new acquisitions expected to occur in that group. Notches in boxplot show 95% credible interval for the median. Dotted lines show full results range without outliers.

1 January 2022. Population-level efficiency was measured as the *number needed to treat (NNT)* to prevent one HIV acquisition calculated as the number of additional PYs on PrEP in each PrEP expansion scenario (compared to baseline) divided by the number of acquisitions averted (difference from baseline) between 2022 and 2042. Unless otherwise stated, all metrics are the medians over the full range of switching scenarios for each PrEP expansion level.

3 | RESULTS

3.1 | Expanding PrEP coverage with CAB-LA among MSM at higher risk

Increasing overall PrEP coverage by 11 pp to 40% by 2032 in Atlanta was expected to avert median 36% of new acquisitions over 20 years when higher sexual activity groups were prioritized (Figure 3A). Substantially larger increases in PrEP coverage (33 and 26 pp to achieve 40% and 30% coverage in Montreal and the Netherlands, respectively) were needed to avert a similar fraction of new acquisitions (38% in Montreal and 37% in the Netherlands). Increasing overall PrEP coverage by an additional 10 pp by 2032 to 50% in Atlanta and Montreal and 40% in the Netherlands resulted in an additional 20 pp acquisitions averted in Atlanta, 8 pp in Montreal and 9 pp in the Netherlands. Meeting coverage targets 5 years earlier (by 2027) resulted in averting 2–5 pp more acquisitions in Atlanta across expansion scenarios compared to 3–10 pp more in Montreal and 5–6 pp more in the Netherlands (full 5-year coverage results shown in Figures S1–S3).

Increasing the proportion of TDF/FTC users switching to CAB-LA (Figure 3B and Figures S4–S7) had only a small positive effect in Atlanta (4 pp) and almost no effect in Montreal and the Netherlands, provided that the same overall PrEP coverage is reached. The proportions of TDF/FTC users who could potentially switch to CAB-LA depended on the proportion of current and projected PrEP users in the baseline, which varied across models as baseline PrEP use ranged from 29% in Atlanta to 7% in Montreal and 4% in the Netherlands.

Population effectiveness, measured as a relative reduction in annual HIV incidence, strongly depended on the expected incidence reduction in baseline scenarios. In Atlanta and

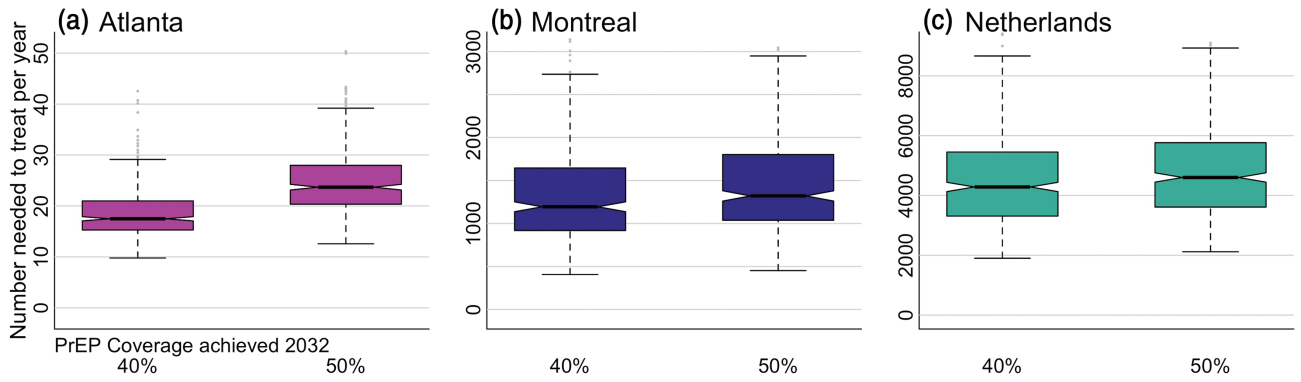

Figure 4. Population efficiency. Additional years on pre-exposure prophylaxis (PrEP) needed to prevent one HIV acquisition with PrEP coverage achieved by 2032 in (A) Atlanta, (B) Montreal and (C) the Netherlands. Includes all tenofovir disoproxil and emtricitabine (TDF/FTC) to long-acting cabotegravir (CAB-LA) switching scenarios. Note different y-axes. Notches in boxplot show 95% credible interval for the median. Dotted lines show full results range without outliers.

Montreal, where the projected baseline reduction in incidence was low or moderate, expansions to 40% PrEP coverage were expected to reduce HIV incidence by an additional 32 and 31 pp, respectively (Figure 3C). In the Netherlands, where the projected baseline reduction in incidence was high, reaching 40% PrEP coverage was only expected to reduce HIV incidence by an additional 8 pp.

The expected coverage of HIV risk at each PrEP coverage level varied greatly between models (Figure 3D). In Atlanta, baseline risk coverage was high at 49% while reaching 40% PrEP coverage by 2032 covered 60% of the risk. At baseline, Montreal and the Netherlands both had comparably low-risk coverage, (13% and 15%, respectively), but expansion to 40% PrEP coverage by 2032 resulted in significantly lower risk covered in Montreal (49%) compared to the Netherlands (94%).

Projected population efficiency strongly depended on the HIV incidence over the 2022–2042 period (Figure 4). The PrEP expansion in Atlanta, where HIV incidence in the baseline scenario remained high (between 1.5% and 2%), was highly efficient with an estimated NNT of 17 and 24 with 40% and 50% PrEP coverage achieved by 2032, respectively. In comparison, the projected NNT in Montreal, where annual HIV incidence was below 0.1% in the baseline scenario, was substantially higher at 1194 (40% PrEP coverage by 2032) and 1320 (50% PrEP coverage by 2032). The corresponding NNT was estimated to be greater than 4000 for the Netherlands where the existing HIV prevention programmes were expected to practically eliminate HIV transmission by 2042 in the baseline.

3.2 | Impact of PrEP expansion on racial disparities

PrEP expansion with CAB-LA represents an opportunity to begin to rectify the racial disparities that have thus far existed in the distribution of TDF/FTC PrEP [11]. The Atlanta model was the only model in this comparison to include race; here, 62% of modelled individuals were Black MSM and 38% were White MSM. Fifty-three percent of modelled Black MSM and 55% of modelled White MSM had a PrEP indication. Baseline PrEP coverage reflected current disparities in PrEP access as PrEP-indicated White MSM had 23 pp higher PrEP coverage than PrEP-indicated Black MSM. In comparison, PrEP expansion with 40% and 50% coverage by 2032 significantly reduced this difference to 9 and 4 pp, respectively (Figure 5A). Distributing additional PrEP coverage in these expansions to previously uncovered MSM with PrEP indications is expected to narrow the PrEP usage gap by race due to substantially higher proportions of acquisitions averted in PrEP-indicated Black MSM (50% and 75%) with 40% and 50% overall PrEP coverage by 2032, respectively (Figure 5B). The NNT was significantly lower in PrEP-indicated Black MSM than PrEP-indicated White MSM, with NNT of 17 and 70, respectively, with 40% overall PrEP coverage by 2032 (Figure S8).

3.3 | Expanding PrEP coverage with CAB-LA available to all MSM

Providing universal access to CAB-LA was modelled by expanding PrEP coverage proportionally throughout the entire population, instead of offering it preferentially to MSM at higher risk, as a hypothetical comparison to reflect when PrEP programmes are not well prioritized to those at risk. Such an intervention was projected to have a lower impact in terms of percent of acquisitions averted with 40% PrEP coverage by 2032 by a median 16 pp in Atlanta, 10 pp in Montreal and 15 pp in the Netherlands (Figures 6A and S9). This also made PrEP expansions in the Atlanta model less equitable. Significantly larger disparities in PrEP coverage by race (16 and 14 pp) remained as coverage increased to 40% and 50%, respectively, in the proportional expansion compared to the expansion prioritizing those in higher sexual activity groups, with 28 and 43 pp fewer acquisitions averted among PrEP-indicated Black MSM (Figure S10).

3.4 | Importance of adherence in who is choosing CAB-LA over TDF/FTC

In all simulations thus far, the models assumed that the group who switched to CAB-LA was representative of all TDF/FTC users. Further analyses were performed with the Atlanta

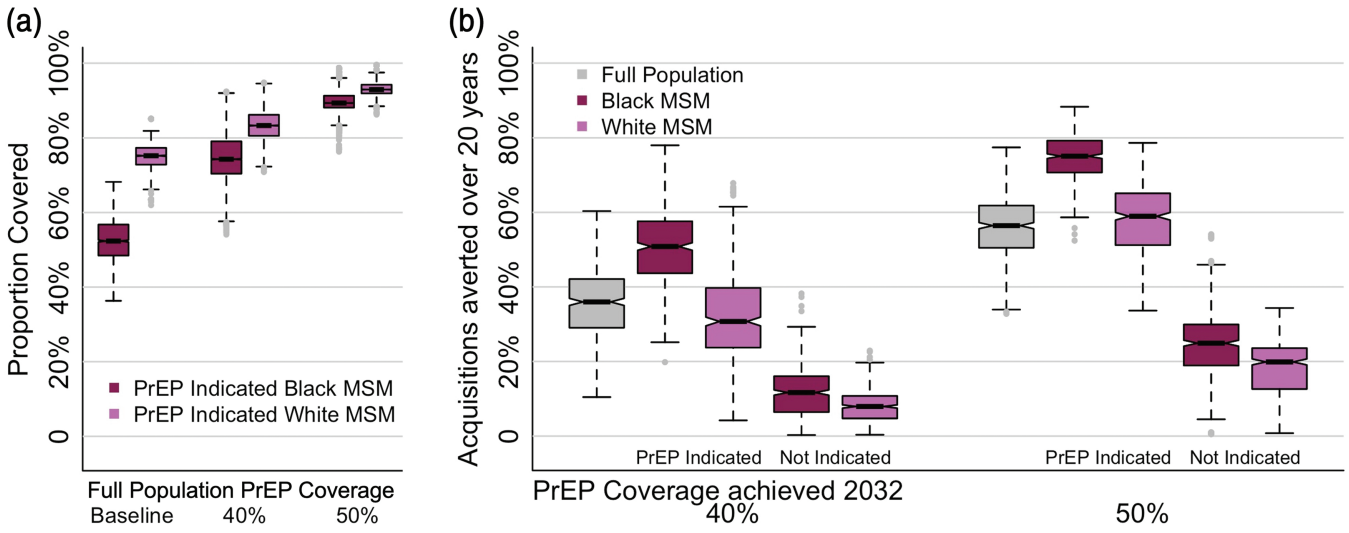

Figure 5. Effects of pre-exposure prophylaxis (PrEP) expansion on racial disparities in the Atlanta model. (A) Racial differences in the proportion of men who have sex with men (MSM) with PrEP indications on PrEP with baseline and expanded PrEP coverage. Median PrEP coverage of MSM with no PrEP indication was 0% in all scenarios. (B) Acquisitions averted over 20 years in Black and White MSM with and without a PrEP indication. Notches in boxplot show 95% credible interval for the median. Dotted lines show full results range without outliers.

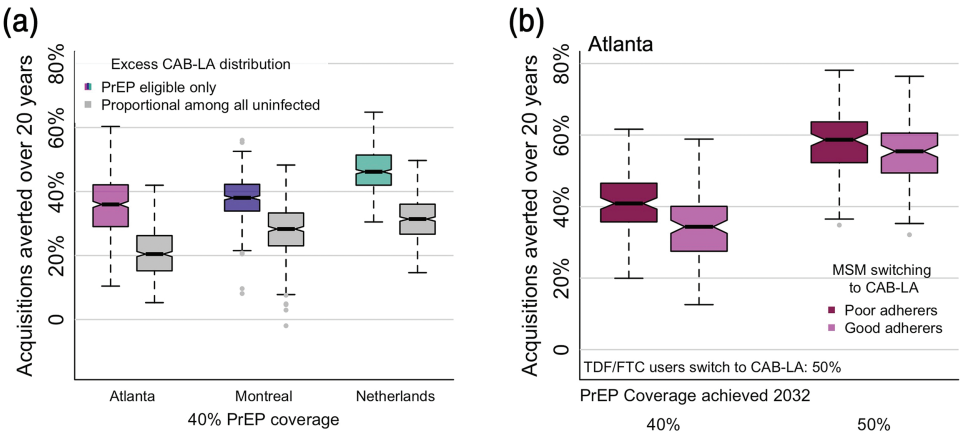

Figure 6. Additional pre-exposure prophylaxis (PrEP) expansion scenarios. (A) PrEP expansion among PrEP-eligible men who have sex with men (MSM) versus proportionally among all MSM not living with HIV. Acquisitions averted when PrEP expansion is only to those PrEP-eligible (colours) or proportionally among all MSM not living with HIV (grey) with 40% PrEP coverage, including all tenofovir disoproxil and emtricitabine (TDF/FTC) to long-acting cabotegravir (CAB-LA) switching scenarios. (B) Prioritized interventions based on adherence to TDF/FTC in the Atlanta model. Poor TDF/FTC adherers switching to CAB-LA (darker colours) and good TDF/FTC adherers switching to CAB-LA (lighter colours) with 40% and 50% PrEP coverage achieved by 2032. Notches in boxplot show 95% credible interval for the median. Dotted lines show full results range without outliers.

model, in which CAB-LA expansion was either (i) successfully prioritized to poor TDF/FTC adherers, which resulted in improved PrEP effectiveness (90%) in those who remained on TDF/FTC or (ii) alternatively, prioritized to good TDF/FTC adherers, which resulted in reduced PrEP effectiveness (60%) among those who remained on TDF/FTC (Figure 6B). When 50% of TDF/FTC users switched to CAB-LA, adherence prioritizing improved impact by 7 pp with 40% PrEP coverage. The importance of adherence prioritizing decreased with higher PrEP coverage levels.

4 | DISCUSSION

Our analysis focused on the expected benefits of adding CAB-LA to the HIV prevention portfolio in populations with HIV epidemics dominated by MSM transmission assuming that PrEP expansion with CAB-LA will improve both overall PrEP coverage and PrEP adherence. Our findings suggest that expanding CAB-LA may avert a significant proportion (36%) of expected new HIV acquisitions over the next 20 years in a setting where TDF/FTC coverage and HIV incidence

are both high (like Atlanta) if the expansion increases the current PrEP coverage in the MSM population by a third. However, a substantially larger increase in overall PrEP coverage (double or triple the current coverage) would be needed to achieve a comparable reduction of acquisitions averted in settings with low current PrEP use and HIV incidence (like Montreal and the Netherlands). The Netherlands model was able to cover nearly all HIV risk with 50% PrEP coverage leading to an almost 100% reduction in incidence. Notably, all models predicted that the number of expected HIV acquisitions over 20 years will be reduced by close to 60% if 50% population PrEP coverage is reached by 2027. However, this result might not be generalizable to other settings given this metric's dependence on multiple factors, such as differences in PrEP eligibility, initial PrEP coverage and expected PrEP use in the baseline scenarios in which only TDF/FTC is available. On the other hand, all PrEP expansion scenarios included in this analysis may still present quite reasonable approximations of the expected intervention impact, even if the increased PrEP coverage is achieved with the addition of other, even slightly better PrEP products (as PrEP efficacy cannot improve greatly above the 91% assumed here) over the 20-year period.

We found that expanding the PrEP toolbox with CAB-LA is projected to be a highly efficient intervention in places with high HIV incidence (like Atlanta) where the estimated additional years on PrEP needed to prevent one acquisition (NNT) were expected to be comparable to TDF/FTC interventions among adult MSM [25] and among Black adolescent sexual minority males [26], and significantly more efficient than the daily TDF/FTC interventions tested in the iPrEx study [27]. In contrast, the estimated efficiency of PrEP expansions was low in Montreal and the Netherlands, mainly due to the low and decreasing HIV incidence in these populations—even in the baseline scenario—leaving few acquisitions to be prevented by any new intervention.

The Atlanta model showed that CAB-LA PrEP expansions that manage to reach the majority of MSM with PrEP indications could lead to more equitable outcomes. Baseline PrEP coverage reflected current PrEP disparities [11], while increased overall PrEP coverage led to both much higher PrEP coverage and to high proportions of acquisitions averted among Black MSM. Addressing this unmet need for PrEP by expanding CAB-LA coverage in Black MSM could help address the continuing racial disparities in HIV incidence. However, the success of such interventions depends on the ability to reach and engage MSM who face barriers to PrEP access or currently do not consider PrEP as a viable prevention option.

Recruiting new CAB-LA PrEP users had a larger impact than switching existing PrEP users from TDF/FTC to CAB-LA. With 40% PrEP coverage, adding PrEP users from the high sexual activity groups increased acquisitions averted substantially in each model but the proportion of baseline PrEP users switching to CAB-LA did not, due to the high effectiveness (combining efficacy and adherence) to TDF/FTC assumed in the models. This finding agrees with the results from another model of CAB-LA use by MSM in the southeastern United States [28]. This study found that increasing PrEP coverage with CAB-LA would avert more acquisitions than switching existing users with 17% of acquisitions averted over 10 years if CAB-LA caused the PrEP initiation rate to double, compared to only 4% if half of the existing TDF/FTC users switched to CAB-LA.

Other published models of CAB-LA in MSM populations have focused on scenarios in which only TDF/FTC or CAB-LA was available. This precludes these models from estimating the effects of switching between regimens or the population impacts when multiple regimens are in use. One analysis of offering PrEP to MSM and transgender women at very high risk of HIV acquisition in the United States showed relatively small differences in acquisitions averted if all individuals used CAB-LA (68%) versus TDF/FTC (60%) [29]. A larger difference in the reduction in new HIV acquisitions (11 pp) achieved with 35% PrEP coverage of CAB-LA, compared to TDF/FTC was projected with an agent-based model of MSM in Atlanta as a result of larger difference in the products' assumed effectiveness [30].

This analysis has several limitations. The effectiveness (which incorporates both efficacy and adherence) of TDF/FTC, informed by local data in all three models, was assumed to be high, which may underestimate the advantage of CAB-LA over TDF/FTC. Therefore, these results are not generalizable to populations with lower TDF/FTC adherence. Conservatively, the Atlanta and Netherlands models assumed no protection in the cabotegravir tail phase after CAB-LA discontinuation. This assumption should be reassessed after the completion of ongoing open-label extensions of the CAB-LA trials [1, 2]. While one model incorporated race, modelled CAB-LA expansions used current local guidance to recommend PrEP based on sexual behaviour only. Models assumed different discontinuation rates for TDF/FTC and CAB-LA, which may not reflect true behaviour, as discontinuation rates were similar for both TDF/FTC and CAB-LA in the HPTN 083 trial (although all trial participants received both oral tablets and injections) [1]. ART use and VS levels were not varied between simulations, precluding insights into the effect of changing ART coverage with rising PrEP coverage.

Adding long-acting injectable PrEP as an HIV prevention option for MSM has several important implications. First, the effectiveness of CAB-LA was demonstrated against a highly effective competitor (TDF/TFC) in clinical trials [1, 2], suggesting that it is reasonable to associate it with improved adherence. Second, offering a completely different and less frequent delivery route may appeal to new users and result in higher overall PrEP coverage. In preference surveys, 73% of MSM reported they would be interested in long-acting injectable PrEP [31]; young adults [32], young adult Black MSM [33] and MSM with higher self-perception of risk [34] have also expressed preference for long-acting injectable PrEP options. It is unclear if and how this preference will shape the future rollout of CAB-LA and other long-acting PrEP products but data from contraception studies have shown that more options lead to more users [35]. Thirty-one percent of MSM currently taking oral TDF/FTC expressed preference for a long-acting injectable in one survey, pointing to the likelihood of some users switching PrEP regimens when new options become available [14]. Third, offering new PrEP options to MSM with PrEP indications may help reduce HIV disparities if it leads to a significant increase in PrEP coverage in this group. When given a choice, the vast majority of MSM

(over 95%) in the ongoing HPTN 083 open-label extension decided to continue on CAB-LA [36]. Finally, CAB-LA serves as a proof of concept that long-acting prevention solutions against HIV are possible, which should encourage the development of more products with different delivery routes and decreased frequency of use.

5 | CONCLUSIONS

Our analysis suggested that expanding PrEP coverage with CAB-LA can help progress towards ending the HIV epidemic, provided that it increases PrEP coverage and supports better adherence. However, PrEP expansion needs to occur equitably across all groups impacted by HIV. In the United States, Black and Hispanic MSM have lower rates of PrEP initiation than White MSM, despite their higher HIV burden [11] and PrEP persistence was lower in PrEP recipients who were younger or Black [37]. Fewer days with pills taken and high discontinuation of oral PrEP in younger and more economically disadvantaged MSM [38] makes them good candidates for CAB-LA expansion. Our analysis shows that engaging and offering CAB-LA to current and prospective oral PrEP users who struggle to adhere to daily oral PrEP could noticeably increase the impact of the intervention. This could help reduce, not widen, equity gaps when CAB-LA becomes widely available.

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COMPETING INTERESTS

The authors have no competing interests to declare.

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Conception of the research question: SES, DTD and M-CB. Model development, parameterization, coding and simulation: KMM, M-CB, MM and DTD (Atlanta model); CMD, RMM, YX and MM-G (Montreal model); DvdV and HW (Netherlands model). Model comparison analysis, statistical analysis, figure & table creation: SES and BH. Drafting of the manuscript: SES, JH and DTD. Critical input into draft manuscript: all authors. Read and approved the final manuscript: all authors.

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DATA AVAILABILITY STATEMENT

The model results that support the findings of this study are available from the corresponding author upon reasonable request.

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VIEWPOINT

Ensuring impact of long-acting HIV therapeutics through multi-level treatment research: a view from NIH

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Long-acting and extended delivery (LAED) HIV therapeutic regimens represent a revolutionary advance in HIV treatment. However, to fully benefit from this promising advance, LAED regimens must be paired with care delivery innovations that facilitate their access and use. These integrative approaches will require a multi-disciplinary research agenda that generates additional long-acting treatment options as well as strategies that support the effective and equitable use of these novel therapeutics.

HIV treatment regimens that require lifetime daily administration present challenges, including treatment fatigue, privacy concerns and suboptimal adherence [1]. LAED regimens can mitigate these challenges for people with HIV (PWH). The first long-acting injectable (LAI) HIV treatment regimen for maintenance of viral suppression (Cabenuva) entered the US market 2 years ago, and consumer feedback has been overwhelmingly positive [2, 3]. LAI regimens administered on a monthly or bi-monthly basis may reduce adherence burdens, HIV-related stigma and privacy concerns that are often associated with daily oral HIV treatment. During a 2022 US Conference on HIV/AIDS session organized by NIAID, NIMH and the Office of HIV/AIDS Network Coordination (HANC), consumer panelists reported that LAI regimens offered them "freedom;" one panelist described LAI treatment as "a dream come true."

Multiple LAED therapeutics and drug delivery systems are being developed, and some have regulatory approvals for select populations with HIV. The possibilities of LAED regimens can be glimpsed in lenacapavir, a first-in-class capsid inhibitor approved for heavily treatment-experienced patients with multi-drug resistant HIV-1 that can be administered subcutaneously every 6 months [4]. Beyond small molecules, broadly neutralizing antibodies (bnAbs) against HIV-1 are another class of treatments that may offer a LAED treatment option. While still in early development, clinical trials have shown that bnAbs can affect viral suppression with the potential for prolonged treatment durations [5, 6]. Further research is needed to define how to best utilize this new technology for the treatment of PWH, including a better understanding of viral susceptibility and resistance, how to combine bnAbs with anti-HIV small molecule drugs and/or other bnAbs for best anti-viral efficacy, and development of assays to predict clinical efficacy among PWH. As these technologies advance, once-a-year treatments for HIV may be possible in the future. Continued research to discover and develop promising LAED therapeutic agents will be critical to realizing this aspirational goal.

These new therapeutic options also drive a need for innovations in HIV clinical practice and monitoring. Clinical strategies to enable treatment experienced PWH to benefit from LAEDs, including LAED treatment initiation without prior viral suppression using oral regimens, would have a profound impact on the health outcomes of many PWH, and research towards this end is urgently needed. Research can additionally improve clinical care through the development of tools that facilitate mutual decision-making between patients and providers on LAED treatment options. Rapid point-of-care assays to measure LAED drug levels and HIV viral load would be valuable for monitoring periods of LAED treatment discontinuation or interruption, when drug levels may be sub-therapeutic and risks for developing HIV drug resistance increase [7]. The pharmacokinetic "long-tail" that follows the interruption or discontinuation of current LAI regimens will require clinical strategies and oral medication adherence support to prevent the development of drug resistance.

While LAIs open new possibilities for patient care, they have also challenged the operational and workforce models of many HIV clinics. Strategies to overcome these challenges and associated infrastructural hurdles must be developed, tested and applied, including strategies to manage cold-chain requirements for drug shipping and storage, intensified staffing needs for treatment injection administration and scheduling, and complex billing and reimbursement processes for LAIs [8]. Early experiences with LAI implementation underscore the importance of a multi-disciplinary, multi-level research agenda that looks beyond the need for improved therapeutics to

focus on supporting people, health systems and communities who need and use these new treatment options.

New LAED therapeutic options should leverage and spur innovations in HIV treatment and service delivery to fully realize their potential impact. Models of healthcare delivery that provide low-barrier care and integrated services for HIV, chronic conditions and unmet basic needs have improved HIV care engagement and clinical outcomes in populations that experience complex adherence challenges [9, 10]. These person-centred care models, together with innovations like telehealth that were widely used during the COVID-19 pandemic, should be leveraged to support equitable access to and delivery of LAED regimens. Demonstration projects in San Francisco and other communities have shown that multidisciplinary HIV medical care can be delivered through non-traditional venues, such as digital tools and mobile medical units [11, 12]. LAED treatment regimens will provide further opportunities for advancing models of community-based care, including the potential use of pharmacies, mobile vans and home nurse visits to administer LAED regimens to populations with adherence challenges.

Advancing the equitable impact of long-acting therapeutics will require concurrent consideration of broader social determinants of health, such as intersectional HIV stigma and discrimination, that can impede HIV treatment adherence, retention and viral suppression [13, 14]. Further research is necessary to better understand the mechanisms through which intersectional stigma and other social factors may affect long-acting antiretroviral therapy access, use and outcomes, which will lead to effective multi-level interventions to address these issues [15].

LAEDs are a technological advance with the ability to significantly improve patient outcomes for all PWH. However, research is still needed to realize the full potential of this technology. The research needs span the research pipeline from the discovery and development of new therapeutic entities and diagnostic assays to the elucidation of novel clinical strategies that address the many interacting levels of healthcare delivery and patient care. NIAID and NIMH have called for research on these fronts, including innovations in long-acting regimen development (NOT-AI-22-042), clinical monitoring (PAR-21-070), behavioural support interventions (PAR-23-060, -061 and -062) and implementation science (RFA-AI-21-024). Given the need for multi-sectoral work, academic and commercial partnerships through small business research grants (PA-22-176, -177, -178 and -179) could additionally develop and test innovations that may facilitate LAED uptake. Advancing a robust and multi-level LAED research agenda will better capacitate our ability to overcome inequities in HIV care access and outcomes and bring the HIV pandemic to an end.

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COMMENTARY

The importance of the "how": the case for differentiated service delivery of long-acting and extended delivery regimens for HIV prevention and treatment

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Abstract

Introduction: Long-acting and extended delivery (LAED) regimens for HIV treatment and prevention offer unique benefits to expand uptake, effective use and adherence. To date, research has focused on basic and clinical science around the safety and efficacy of these products. This commentary outlines opportunities in HIV prevention and treatment programmes, both for the health system and clients, that could be addressed through the inclusion of LAED regimens and the vital role of differentiated service delivery (DSD) in ensuring efficient and equitable access.

Discussion: The realities and challenges within HIV treatment and prevention programmes are different. Globally, more than 28 million people are accessing HIV treatment—the vast majority on a daily fixed-dose combination oral pill that is largely available, affordable and well-tolerated. Many people collect extended refills outside of health facilities with clinical consultations once or twice a year. Conversely, uptake of daily oral pre-exposure prophylaxis (PrEP) has consistently missed global targets due to limited access with high individual cost and lack of choice contributing to substantial unmet PrEP need. Recent trends in demedicalization, simplification, additional method options and DSD for PrEP have led to accelerated uptake as its availability has become more aligned with user preferences. How people currently receive HIV treatment and prevention services and their barriers to adherence must be considered for the introduction of LAED regimens to achieve the expected improvements in access and outcomes. Important considerations include the building blocks of DSD: who (provider), where (location), when (frequency) and what (package of services). Ideally, all LAED regimens will leverage DSD models that emphasize access at the community level and self-management. For treatment, LAED regimens may address challenges with adherence but their delivery should provide clear advantages over existing oral products to be scaled. For prevention, LAED regimens expand a potential PrEP user's choice of methods, but like other methods, need to be delivered in a manner that can facilitate frequent re-initiation.

Conclusions: To ensure that innovative LAED HIV treatment and prevention products reach those who most stand to benefit, service delivery and client considerations during development, trial and early implementation are critical.

Keywords: differentiated service delivery; long-acting extended delivery; HIV prevention; HIV treatment; ARV; health systems

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1 | INTRODUCTION

Successes in the HIV response can be attributed to parallel innovations both in the development of antiretroviral drugs for treatment and prevention, the "what," as well as in the delivery of these commodities, the "who," "where" and "when." In HIV treatment, the development of oral dolutegravir-based regimens [1] has been so well-received that more than 80% of people globally now take the same one-pill-a-day regimen (tenofovir-lamivudine-dolutegravir or TLD) regardless of where they live. Similarly, ground-breaking was the discovery of effective biomedical solutions for preventing HIV acquisition in the form of pre-exposure prophylaxis (PrEP), which has seen delays in reaching similar uptake [2–5].

Beyond progress in the development of antiretroviral drugs and their formulations, the HIV response has pioneered innovations in service delivery. Since 2015, the World Health Organization (WHO) has recommended a differentiated service delivery (DSD) approach—acknowledging the diverse needs of people living with and vulnerable to HIV [6, 7]. A DSD approach considers the "building blocks" or the "who," "where," "when" and "what" of service delivery and adapts

these to meet the needs and expectations of clients while acknowledging the resource constraints of the public health system [8, 9].

Daily oral pills have been the primary formulation of antiretroviral therapy (ART) for both HIV prevention and treatment. There is growing recognition of the potential role of long-acting and extended delivery (LAED) regimens [10–12] with recent approvals for a long-acting injectable antiretroviral combination for treatment [13] and a long-acting vaginal ring and a long-acting injectable [14] for prevention. LAEDs offer unique benefits to expand uptake, effective use and adherence. LAEDs should follow the example of TLD by tying product development to the creation of target product profiles that address critical service delivery and adherence challenges. Beyond clinical science outcomes, implementation research to address programmatic considerations will be essential [15]. A safe and efficacious LAED will only be impactful if it can be delivered with DSD approaches that balance system constraints against client needs, often defined by the outcomes of acceptability, feasibility, effectiveness, cost and appropriateness [16, 17]. In particular, consideration of whether a LAED may address some of the behavioural challenges to adherence (e.g. combatting stigma and challenges to disclose) should be considered.

Future LAED products for HIV treatment and prevention include a number of potential delivery mechanisms or modalities: longer-acting oral tablets; intra-muscular, sub-cutaneous and self-injections; implants and different types of patches. In this commentary, we outline the role of DSD in the provision of these future and diverse LAED products for HIV treatment and prevention.

2 | DISCUSSION

The realities and challenges within HIV treatment and prevention programmes are distinctive, with marked differences in access and scale-up of ART compared to the limited scale-up seen for PrEP. As a result, the future positioning of LAED products and their integration into DSD models is likely to differ as they address these distinct challenges. Table 1 outlines suggested building blocks of DSD for both treatment and prevention considering DSD models with daily oral tablets, DSD with current LAED and ideal service delivery with future available long-acting formulations.

2.1 | Considerations for future positioning and integration into DSD of LAED products for HIV treatment

Globally, an estimated 28.7 million people were accessing HIV treatment by the end of 2021 [18]. In low- and middle-income countries, upwards of 90% of these people are on a daily fixed-dose combination oral pill that is largely available, affordable and well-tolerated [19], and are virally suppressed [18].

Accelerated by the availability of TLD, HIV treatment programmes have adopted and implemented DSD [20–22]. Rather than a "one-size-fits-all" approach, those who are clinically suppressed, or "established on ART," are eligible for DSD models where the building blocks of their ART refills are separated from their clinical consultations [7]. ART refills have been extended to 3–6 monthly and are available through the four DSD models described in the WHO 2021 consolidated guidelines [7]. Particularly in eastern and southern Africa, a DSD approach to HIV treatment has been widely adopted within national guidance following recommendations from WHO and support from global funders [7, 23, 24]. Implementation data highlight that more than 4.5 million people supported by PEPFAR in 2021 received 6-month ART refills with an additional 5.7 million on 3- to 5-month ART refills [25]. In South Africa, a cohort of approximately 1.45 million people living with HIV receive their ART refills outside of health facilities and closer to home [26].

Given the high levels of uptake of TLD delivered through DSD models, the target audience and formulation of a future LAED treatment product will require careful consideration. LAED products may be targeted as possible treatment options to specific individuals or populations for whom adherence on daily oral ART is a challenge. Intra- and interpersonal challenges affecting adherence and viral suppression include struggles with daily pill taking, fear of disclosure (driven by both external and internalized stigma) and different stages of the life course (e.g. adolescents, during pregnancy and breastfeeding, elderly) [27, 28]. In addition, lower rates of viral suppression are consistently observed in specific populations, such as children and adolescents [18], despite advances in regimens and innovations in service delivery. LAED products could directly address some of these challenges and support improved outcomes in these specific populations, including decreased rates of perinatal transmission.

There is also increasing evidence of the challenges faced among those living with HIV who are highly mobile and may not be able to carry large supplies of ART or reliably adhere to therapy, collect refills or attend appointments even if they intend to do so, all of which is associated with risk of poor outcomes and development of drug resistance whether using daily or long-acting therapies [29–31]. LAED products that support increased self-management—longer oral tablet regimens, patches or self-injections—and have some forgiveness in their dosing schedules could offer a better alternative to daily oral tablets for this vulnerable population.

For people living with HIV who are established on treatment, DSD using daily oral pills has enabled less frequent clinic visits with some settings providing an annual clinical visit and 6-monthly refills. Currently available LAED treatment products are delivered by intra-muscular injections. These require private and confidential space, the ability to safely discard needles and syringes, and additionally must be staffed by trained and qualified administrators of the injection. In addition, the cabotegravir/rilpivirine long-acting formulation has a cold-chain requirement further complicating its administration. It is also a non-nucleoside reverse transcriptase inhibitor associated with increased risk of both pre-existing drug resistance among likely clients, including adolescents, and of acquired drug resistance if clients are not adherent to the repeat injection schedule that will necessitate a frequent interaction with the health system. Until such LAED products are available that can match the current frequency of clinical visits (long-acting (LA) oral pills, implants or patches), DSD programmes must innovate to maximize the benefits of available injectable LAED options for treatment. This may include adapted

Table 1. Ideal differentiated service delivery models with future long-acting extended delivery antiretrovirals for HIV treatment and prevention

	HIV antiretroviral treatment			HIV antiretroviral prevention		
Building blocks of service delivery	**Current DSD model with daily oral tablets**	**DSD with current LAED[a]**	**Ideal with future LAEDs (including oral tablets, injections, implants and patches)**	**Current DSD model with daily oral tablets**	**DSD with current LAED[b]**	**Ideal with future LAEDs (including oral tablets, injections, implants and patches)**
WHEN Service frequency (frequency of refills and clinical consultations)	3- to 6-monthly drug pickup 6- to 12-monthly clinical visits	1- to 2-monthly IM injections with 6- to 12-monthly clinical visits,[c] 6-monthly SC injection with 6- to 12-monthly clinical review[d]	6- to 12-monthly delivery system (LA oral tablets, longer IM injections, SC self-injections, implants and patches) 6- to 12-monthly clinical visits Alignment with visits for other medical needs	3-monthly PrEP refills (moving towards 6 monthly) 3- to 6-monthly clinical visits	2-monthly IM injections and clinical visits	6- to 12-monthly delivery system (LA oral tablets, longer IM injections, SC self-injections, implants and patches) 6- to 12-monthly clinical visits Alignment with visits for other medical needs
WHERE Service location	ART refills through fast-track in PHC or decentralized to community settings Clinical visits at primary healthcare	PHC/hospital (with infrastructure for IM injection, cold chain for RPV, management of syringes and needles)	Decentralized—fast track collection at facilities or outside of PHC and hospitals and into communities (e.g. pharmacies, community-based organizations, mobile vans, home delivery, etc.)	PrEP refills decentralized to community settings Clinical visits at primary healthcare or via telemedicine	PHC/hospital (with infrastructure for IM injection, management of syringes and needles)	Decentralized—fast track delivery at facilities or outside of PHC and into communities (e.g. pharmacies, community-based organizations, mobile vans, etc.) supported by telemedicine
WHO Service provider (e.g. clinician, nurse, pharmacist, HCW, CHW and peer)	ART refills distributed by lay providers, including peers, pharmacists, CHWs Clinical visits by trained nurses	Trained HCW for IM injections and ART prescribing	Treatment options supporting self-management: choice of, for example, 6- to 12-month implant; 6 × monthly oral tablets; 6–12 months of a self-managed SC self-injection or patch Trained nurse for prescription, implant insertion and monitoring	PrEP refills distributed by lay providers, peers, pharmacists, CHWs and courier Clinical visits by trained HCWs or lay providers supported by clinicians (prescriptions by clinicians)	Trained HCW for IM injections and PrEP prescribing and monitoring	Treatment options supporting self-management: choice of, for example, 6- to 12-month implant; 6 × monthly oral tablets; 6–12 months of a self-managed SC or patch Clinical visits by trained HCWs or lay providers supported by clinicians (prescriptions by clinicians)

(*Continued*)

Table 1. (Continued)

	HIV antiretroviral treatment			HIV antiretroviral prevention		
Building blocks of service delivery	**Current DSD model with daily oral tablets**	**DSD with current LAED[a]**	**Ideal with future LAEDs (including oral tablets, injections, implants and patches)**	**Current DSD model with daily oral tablets**	**DSD with current LAED[b]**	**Ideal with future LAEDs (including oral tablets, injections, implants and patches)**
WHAT Package of services provided	ART refills (& psychosocial support) And at clinical consultations prescriptions, clinical and lab monitoring, OI and other management	Same as current DSD	Same as current DSD + site for implant insertion + product and service integration for other health needs, including STIs, contraception, NCDs and GAHT	PrEP refills, other prevention commodities, HIV self-test kits, HIV risk and PrEP effective use counselling, PrEP clinical management and monitoring	Same as current DSD	Stipulated minimum package of services (supporting demedicalization) + product and service integration for other health needs, including STIs, contraception, NCDs and GAHT

Abbreviations: ART, antiretroviral therapy; CAB, cabotegravir; CAB/RPV, cabotegravir/rilpivirine; CHW, community-health worker; DSD, differentiated service delivery; GAHT, gender-affirming hormonal therapy; HCW, healthcare worker; IM, intramuscular injection; LA, long-acting; NCDs, non-communicable diseases; OI, opportunistic infection; PHC, primary health centre; SC, subcutaneous.
[a]CAB/RPV, lenacapvir.
[b]CAB-LA.
[c]Oral lead in and specifics on loading doses also to be considered.
[d]Could also consider 6-monthly SC injection with 6- to 12-monthly clinical review for the treatment of HIV-1 infection in heavily treatment-experienced adults with multidrug resistant HIV-1 infection and not currently available in low- and middle-income countries (initiation oral dosing also to be considered).

policies supporting task sharing and decentralization of intramuscular injections, including training of community and potentially lay cadres, and delivery via fixed outreach or mobile clinics. For countries already leveraging private pharmacy networks for the distribution of oral ART tablets [32, 33], expansion of the partnerships to include the distribution of other formulations and injection administration of injectables could be considered.

Costs, acceptability and feasibility—for the health system, healthcare providers and clients—need to be considered along with the challenges and cost implications of the supply chain (including cold chain if required). The benefits of co-formulations, especially with contraception, are increasingly critical. Reducing the frequency of health facility visits has increased the risk of reducing contraceptive coverage and increased unintended pregnancies among those on short-acting intramuscular injectable contraception, requiring focused co-formulation product development to ensure both ART and contraceptive coverage.

2.2 | Considerations for future positioning and integration into DSD of LAED products for HIV prevention

PrEP for people at substantial risk of acquiring HIV has been recommended by WHO since 2015 [6]. Compared to the successful scale-up of HIV treatment, access to PrEP has fallen far below global targets [34, 35]. The majority of PrEP scale-up has been in high-income countries, predominately among gay men and other men who have sex with men [18]. Until recently, the only PrEP option was oral PrEP, which is known to be associated with mild and self-limiting side effects that can result in early discontinuation [36]. In low- and middle-income countries, progress towards improving PrEP uptake has been challenged by poor access, the limited choice of PrEP method and considerable costs, including to the client. Further, effective use of PrEP has been limited with high rates of discontinuation [37–39]. Stigma and challenges with disclosure of PrEP use to partners and family has been cited as an underlying reason for the poor uptake and continuation of PrEP services [40, 41].

In response to COVID-19, adaptations to PrEP service delivery resulted in increased flexibility with trends towards demedicalization, simplification and integration within other health services [42], provision of virtual support and DSD for PrEP aligning with client preferences [35, 43–45]. As a result, the number of people on oral PrEP doubled between 2020 and 2021 from 800,000 to 1.6 million [18]. This suggests that DSD models have the potential to increase PrEP access. New technical considerations released by WHO in 2022 provide guidance on differentiated PrEP service delivery, including community-based and virtual support, longer durations of

PrEP refills, reduced clinical visits for PrEP users with support provided by peers and increased use of HIV self-testing to enable PrEP continuation [46].

To support the scale-up of PrEP, LAED products could be offered to all PrEP clients as part of a PrEP menu aimed at overcoming specific individual and health system barriers by optimizing DSD features, such as access to services outside of the facility and minimal engagement with health professionals [47]. This differs from the approach discussed for treatment, where LAED products may be more appropriate for specific populations. Offering an informed choice of PrEP products, including LAED, must be presented to reflect relative efficacy but also take into consideration user preferences that may impact on stigma, changing risk exposures, challenges to travel to a facility and longer-term adherence.

Key considerations for the choice of PrEP agent could include the discreteness of LAED products that may overcome the stigma faced by people taking daily pills [48, 49] as well as adherence challenges. Results from the HIV Prevention Trials Network studies 083 and 084 of comparing injectable cabotegravir and daily oral tablets illustrate that adherence to LAED dosing may be easier than daily pill taking in populations at substantial risk of HIV acquisition [50, 51]. LAED products that enable increased self-management, such as self-injectables, long-acting oral tablets or patches or 6- to 12-monthly intramuscular injectables, will also address challenges of frequent clinical visits and daily adherence.

The duration of HIV risk or vulnerability will also impact the choice of PrEP product and DSD model to deliver it. HIV risk is not a constant and this variability is an important factor in determining PrEP method choice and the ideal duration of PrEP needed and wanted. For some who have longer-term more continual HIV acquisition risk, a longer-acting (6–12 monthly) injection may be preferable. For others, who experience periods of vulnerability, a self-managed long-acting oral pill or patch that provides prophylaxis for a month may be sufficient to cover the period of vulnerability and, therefore, be preferable to a longer-acting injectable that requires administration by a healthcare provider. Counselling needs to be framed around reasons for stopping PrEP relative to ongoing risk, empowering self-managed PrEP use and ensuring that users understand the risks associated with missed doses with respect to emergent infection and theoretical risk for resistance during this period. Capacity building for healthcare workers to adequately assess this risk and offer choice based not only on efficacy but also on user preferences in terms of formulation and how that impacts on the where and when of PrEP delivery will be essential.

Considering integration into DSD for PrEP services of currently available long-acting products, the DPV-VR could already be provided as a multi-month refill as it does not require a cold chain for storage and is self-administered. However, as for treatment, currently available long-acting injectable PrEP requires a 2-monthly intra-muscular injection. Therefore, the same innovations will be needed, including adapted policies supporting task sharing and decentralization of intramuscular injections.

In addition to considering the changes in risk, other essential components of the service package—such as HIV self-testing, contraception commodities, gender-affirming hormonal treatment and possibly other self-test products such as those for sexually transmitted infections (STIs) and viral hepatitis—should be optimized to enable increased and virtual delivery and re-initiation of PrEP [52]. There is an opportunity to consider how best to integrate other sexual and reproductive health services in this self-care model, and it is likely PrEP users will place a premium on comprehensive sexual health services, not just a reduced risk of HIV acquisition. There is also a research need to better understand self-testing in the context of LAED given the challenges in diagnosis.

As LAED PrEP products are introduced, the choice remains a priority. The recent increase in the rate of PrEP users that has coincided with DSD approaches to PrEP implementation suggests that there is still considerable potential growth with daily oral PrEP if the DSD approach is more broadly supported in policy and implementation scaled. Introduction of the combined PrEP and contraceptive products is under investigation, including a dual prevention pill [53], with a 2024 anticipated approval [54, 55], and co-formulated vaginal ring products [56]. It may be that developing a user base for any HIV prevention product will smooth the path for future LAED products that may have more optimal characteristics [57]. As LAED products are introduced, it will be important that they are offered as part of a menu of PrEP options and not deemed preferential just because they are long-acting. Shared decision-making with the client reflecting the relative efficacy of the product alongside issues of stigma and confidentiality will continue to be critical to scaling up of PrEP services.

Finally, and critically, prevention programming requires finances and resources—funding PrEP is challenging within the HIV and global health space [18]. New LAED products have the potential to expand the PrEP market for both daily oral PrEP and future LAED products with longer durations that are more easily administered and difficult trade-offs may have to be made.

3 | CONCLUSIONS

There are exciting new options for LAED products for HIV treatment and prevention, both in the pipeline and receiving regulatory approval. The success of future LAED products will be determined by "how" their delivery improves on what is currently offered by daily oral therapies recognizing the balance between some clients preferring reduced facility visits versus those who will accept additional clinic visits for the benefits of reduced pill burden and possible reduction of stigma. For HIV treatment, daily oral therapies already offer a high standard of care on metrics, such as acceptability, effectiveness, feasibility and cost, all of which have been further optimized through the use of DSD. However, there are specific populations for whom the current regimen presents challenges that may be overcome with future LAED products. For HIV prevention, however, where method choice is a priority and delivery of oral PrEP to date has been overmedicalized, LAED products that better align with the concepts of DSD may prove to be very acceptable to all stakeholders. Funding for the future integration of LAEDs and ongoing advocacy for a sustainable and affordable supply compared to existing treatment and prevention options will be essential. For any

LAED product, it is critical to emphasize the use of implementation science metrics to define and prioritize the challenges that a new product seeks to address from the perspective of the client, the provider and the health system.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

AG, LW and HB conceived of the manuscript. SD-M, PE, KG, MM, KN, NJO, MP, WV and MV provided inputs on the initial outline. MV drafted the initial table and AG drafted the initial manuscript. All authors provided inputs on the draft manuscript and approved the final submission.

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DATA AVAILABILITY STATEMENT

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COMMENTARY

Preparing for long-acting PrEP delivery: building on lessons from oral PrEP

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Abstract

Introduction: With recent approvals of long-acting (LA) HIV pre-exposure prophylaxis (PrEP) in the form of injectable cabotegravir and the dapivirine ring, programmes need to consider how to optimize the delivery of PrEP methods, including by leveraging lessons from the past decade of oral PrEP delivery.

Discussion: Framed around differentiated service delivery building blocks, the major considerations for the delivery of LA PrEP are how to reach the populations who would most benefit from PrEP, where to locate PrEP services, how to reduce the user burden of accessing and continuing with PrEP, and how to integrate PrEP with other services. Demand creation for LA PrEP and education about new LA PrEP options should be co-developed with communities and be positively framed. Client-facing clinical decision support tools provide information about HIV prevention and PrEP options in non-technical ways and can support their informed decision-making about PrEP. Training for providers is needed to increase their ability to ask about sexual and drug use behaviours in a non-judgmental and comfortable manner as part of risk assessment, discuss harm reduction strategies and counsel about available PrEP options that fit clients' circumstances and needs. PrEP adherence support should include supportive counselling and be tailored to address an individual's particular barriers and needs. Reminders through text messaging or calls can foster PrEP persistence, given the narrow the window around dosing for injectable cabotegravir. Strategies are needed to expand PrEP delivery options, including telePrEP, pharmacy-based PrEP, key population-led services and mobile venues. Integrated delivery models are needed which include sexually transmitted infection testing and treatment, contraception for cis-women not desiring to become pregnant, PrEP for pregnant women in high HIV prevalence settings, and gender-affirming hormones and support for transgender persons.

Conclusions: The outcome of expanding PrEP options through LA PrEP formulations is to increase PrEP coverage, adherence, persistence and effectiveness by offering a choice of PrEP that meets the needs of persons who would benefit from PrEP. The lessons learned from the delivery of oral PrEP about demand creation, informed client decision-making, provider training, adherence support and service delivery model are relevant to the delivery of LA PrEP and integration with other services.

Keywords: adherence; delivery; HIV pre-exposure prophylaxis; lessons; long-acting; persistence

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1 | INTRODUCTION

In planning for the implementation of long-acting (LA) options for HIV pre-exposure prophylaxis (PrEP), it is important to consider the progress and lessons from the implementation of oral tenofovir-based PrEP since the U.S. Food and Drug Administration (FDA) approval in 2012. High efficacy was observed in randomized placebo-controlled trials among men and women who took oral PrEP consistently [1–6]. Event-driven oral PrEP has also been demonstrated to have comparable effectiveness to daily oral PrEP among men who have sex with men (MSM), providing an alternative to daily PrEP for this population [7]. Population benefits of oral PrEP have been demonstrated in several settings, including in Australia where following the transition from PrEP delivery from the research context to publicly subsidized care, HIV incidence among MSM remained low over 3 years [8]. In addition, in the context of universal community-based testing and HIV treatment in the SEARCH trial in Kenya and Uganda, PrEP was offered to persons at elevated risk, one-third of whom initiated PrEP. Notably, the population HIV incidence in SEARCH communities was reduced by 74%, which demonstrates the population impact of primary HIV prevention in the setting of universal antiretroviral therapy (ART) [9].

Despite impressive levels of protection at an individual and population level, the first decade of PrEP implementation was marked by slow and fragmented implementation with insufficient demand creation, PrEP access, provider training

and efforts to reach marginalized key populations. Oral PrEP was not feasible for some users, as healthy persons need to develop the habit of pill-taking and some have concerns about disclosure and stigma from taking a pill that looks identical to antiretrovirals for HIV treatment. These issues are manifested in the large gap between global targets and the number of people on PrEP. UNAIDs set the target of 3 million PrEP users by 2020, but the estimated number of PrEP users by the end of 2020 was only 1 million, increasing to 2.8 million by mid-2022 [10]. There is substantial geographic disparity with the majority of PrEP users in North America, Europe and Australia. In 2022, UNAIDS announced a new goal for PrEP of 10 million persons [11]. To achieve a population-level impact, it will be necessary to improve PrEP persistence and effective use, which are harder to measure than PrEP initiation.

To maximize PrEP impact, innovative solutions are needed that address barriers to PrEP delivery, use, adherence and persistence. Some user barriers to oral PrEP will be addressed by more discrete LA PrEP formulations, specifically bimonthly injectable LA cabotegravir (CAB-LA) and the monthly dapivirine vaginal ring (DVR), but longer-acting PrEP formulations alone will not overcome all user barriers. To support LA PrEP implementation, it is useful to review lessons and successful strategies from oral PrEP delivery and consider which strategies are applicable to the delivery of LA PrEP with specific considerations for implementation of DVR and CAB-LA (Table 1).

2 | DISCUSSION

2.1 | Reaching populations who would benefit from PrEP

One of the biggest challenges with oral PrEP has been reaching populations at greatest need and tailoring PrEP delivery to their circumstances and needs, as manifested in drop-offs in the PrEP cascade in achieving sufficient uptake, adherence and persistence in order to achieve prevention benefits [12]. A global systematic review found that 41% discontinued with PrEP by 6 months, 47% reinitiated PrEP within 1 year, and with lower discontinuation rates among PrEP projects that included adherence interventions [13]. Those who have a higher risk of not initiating PrEP or premature discontinuation include youth, racial and ethnic minorities, and those without a healthcare provider or without health insurance. The HIV prevention cascade must be strengthened with interventions to stimulate demand from those who would benefit from PrEP, support users in their PrEP adherence and persistence, and reduce health systems barriers [14]. Demand stimulation needs to be motivational and gain-framed rather than loss-framed, and co-developed with communities to find images and messages that motivate potential PrEP users [15]. Although low-risk perception is cited as a reason why people decline PrEP, using risk calculators and risk-targeting can themselves increase stigma and be counter-productive [16]. Other barriers include uncertainty about where to access PrEP, lack of insurance or a provider, costs of PrEP medications and associated testing, concerns about side effects, daily pill-taking, stigma and competing life priorities [17].

A client-centred approach to HIV prevention is centred on effectively communicating information about HIV prevention, including the advantages and disadvantages of available HIV prevention methods to facilitate informed decision-making. The contraceptive field has pioneered patient-facing decision support tools which have helped facilitate contraceptive choices and increase satisfaction by providing women with an opportunity to compare options and consider their needs and preferences [18]. A PrEP decision support tool needs to include information in non-technical terms about available PrEP formulations and their effectiveness, safety and user experience in order to facilitate decision-making about short versus LA PrEP and contraception. A PrEP decision support tool for young African women was modelled after a client-facing decision support tool for contraception and showed two-fold higher PrEP persistence at 1 month among women who were randomized to use the tool [19]. Research is needed on how to support integrated PrEP and contraceptive decision-making and understand the major factors that influence product choices, including side effects, efficacy, convenience and discrete use. More research is needed about whether prospective PrEP users understand the concept of reversibility and whether it is a significant consideration in different populations in their preferences for different PrEP products.

Provider training and engagement are also important, and should include how to ask about sexual and drug use behaviour in an open and non-judgemental manner, individual's circumstances, need and motivation for PrEP, and specific needs of transgender persons [20]. Providers need to be familiar with available PrEP formulations, counselling about side effects, stopping and restarting PrEP, switching to another PrEP method and HIV testing, including the interpretation and management of atypical HIV test results and HIV RNA screening as part of CAB-LA delivery [21]. For women, providers need to assess fertility intentions, offer contraceptive options for women who do not want to become pregnant, and counsel about PrEP use and safety during pregnancy and lactation for women.

2.2 | Expanding PrEP delivery to increase access and acceptability

PrEP implementation for MSM and transgender women (TGW) in Latin America and Asia and adolescent girls and young women (AGYW) in Africa has highlighted the feasibility and benefits of same-day PrEP delivery and differentiated PrEP service delivery models. Same-day oral PrEP start was feasible in the ImPrEP study in Brazil, Mexico and Peru [22, 23], which also demonstrated the importance of assessing early adherence to PrEP given that it is associated with PrEP persistence and a lower likelihood of seroconversion [24]. Early follow-up after PrEP initiation is an opportunity to counsel about side effects, and encourage PrEP adherence and continuation [25]. Additional PrEP adherence support may be beneficial for younger persons, those with less formal education, and those who have experienced discrimination and stigma from healthcare providers. The PrEPARADAS study in Brazil found lower PrEP adherence and persistence among TGW with less education and of black race and higher

Table 1. Implementation barriers and strategies to facilitate the delivery of oral and long-acting PrEP

Barriers to PrEP access, uptake, adherence and persistence	Strategies from oral PrEP that address barriers	Specific considerations for the delivery of dapivirine vaginal ring (DVR)	Specific considerations for the delivery of injectable cabotegravir (CAB-LA)
Challenges in reaching populations who could benefit from PrEP: limited awareness, low perceived risk of HIV, concerns about side effects and use	• Demand creation with community input • Positive, gain-framing messages about benefits of PrEP in terms of empowerment and greater intimacy • Client-centred decision support tools • Provider training in risk assessment and counselling • User and provider PrEP champions to increase knowledge and motivation	• Education campaigns about DVR, including safety of DVR during pregnancy and breastfeeding • Expand client-facing tools to describe new PrEP formulations in non-technical terms in order to provide more informed PrEP decision-making • FAQs about DVR and counselling for providers	• Education campaigns about high efficacy and convenience of CAB-LA, as introduced • Expand client-facing tools to describe new PrEP formulations in non-technical terms in order to provide more informed PrEP decision-making • FAQs for providers about CAB-LA dosing, tail and, possible LEVI syndrome
PrEP delivery: availability of providers, frequency of visits, stigma from bottles of pills	• Reduce frequency of visits through multi-month dispensing and HIV self-testing without compromising retention [46]. • TelePrEP • Pharmacy PrEP programmes • Peer PrEP programmes • Peer navigators in clinic-based programmes • Reduce out of pocket costs • Discrete storage containers • Assess substance use, IPV and mental health needs and provide referrals	• DVR users would benefit from WhatsApp or text messages for appointment reminders administration • Oral fluid HIVST enables less frequent clinic visits • Counsel women about discrete storage of DVR and disposal	• CAB-LA is administered every 2 months, with more frequent visits than every 3 months oral PrEP • Users would benefit from WhatsApp or text messages for appointment reminders in order to stay in 14-day window around injections • Provider training in giving gluteal injections and private area for administration • Oral fluid HIVST may not be sensitive for detecting infections with low antibody levels or during CAB-LA PK "tail"
PrEP integration with sexual and reproductive health services	• "One stop services" • For women, integration with contraceptive and STI services • For TGW, integration with provision of gender-affirming hormones • STI screening and treatment	• Counsel women about safety of use of DVR during menses • STI screening and treatment	• STI screening and treatment • Can co-administer hormonal contraception or gender-affirming hormones with CAB-LA • Limited drug–drug interactions
PrEP adherence and persistence	• Menu of adherence support options • PrEP support clubs • SMS reminders for visits	• Reminders for women to replace DVR monthly	• Reminders for CAB-LA injections which are sometimes used for DMPA and NET-EN could reduce missed visits and the need to restart with a loading dose

Abbreviations: DMPA, depot-medroxyprogesterone acetate; FAQs, frequently asked questions; HIVST, HIV self-testing; IPV, intimate partner violence; LEVI syndrome, Long-acting Early Viral inhibition Syndrom; NET-EN, norethisterone enanthate: PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection; TGW, transgender women.

adherence among TGW receiving gender-affirming hormones from the study [26].

Community-based, peer-led PrEP services for MSM and TGW have been successful. A large number of MSM and TGW were reached through the Princess PrEP programme in Thailand [27], which includes community-based screening, risk assessment, HIV and transmitted infection STI testing, and PrEP initiation [28]. When CAB-LA becomes available in national PrEP programmes, peers could offer CAB-LA or oral PrEP, although the gluteal CAB-LA injection would need to be administered by a healthcare professional, requiring close linkages with healthcare facilities. Task-shifting of PrEP prescribing from physicians to nurses has significantly increased PrEP prescribing in Brazil [29]. Providers who are PrEP champions are very effective in motivating and supporting other providers during PrEP implementation.

Diversification of PrEP delivery points and task shifting are also needed to expand PrEP coverage in Africa. PrEP was initially delivered in HIV clinics, which worked well to increase PrEP uptake among HIV-uninfected partners in HIV serodifferent couples through integrated care programmes delivering both ART and PrEP [30, 31]. Increasingly, PrEP is being integrated into other service points to cater for different populations, such as in antenatal clinics [32, 33], family planning clinics [33], post-abortion care [34] and STI clinics [35].

One population that has lagged behind in PrEP effective use is African AGYW due to low adherence and persistence; multiple PrEP demonstration projects have shown encouragingly high PrEP uptake among African AGYW but lower adherence and persistence than MSM [36]. Mobile adolescent-friendly health services have successfully reached South African AGYW for PrEP, contraception, and sexually transmitted infection (STI) testing and treatment [37]. The high efficacy and bimonthly dosing of CAB-LA could address challenges with adherence and persistence of oral PrEP among African AGYW, many of whom use injectable contraception, but will involve bimonthly instead of quarterly visits, which need to occur within a 14-day window to maintain sufficient cabotegravir levels.

Pharmacy-based PrEP delivery is another innovation to bring PrEP closer to potential users and to avoid clinic waits and other barriers, which could and expand to include the delivery of LA PrEP [38–41]. In Vietnam, differentiated PrEP delivery has supported increased scale-up; one-third of clients initiated PrEP at clinics led by community health workers who are MSM or TGW and PrEP is now being rolled out in pharmacies [42]. Characteristics of PrEP initiators and data about PrEP persistence from different service points and providers will provide useful insights for LA PrEP delivery.

Another method to increase PrEP persistence is to improve efficiency during clinic visits. The promising "one stop" PrEP delivery model could be expanded to include LA PrEP as another PrEP option [43]. Laboratory screening for PrEP should be streamlined. Many PrEP programmes have shifted to offering same-day PrEP after a negative HIV test, given the rarity of renal insufficiency in young populations [44]. Same-day PrEP starts are feasible with the DVR but will be more challenging with injectable PrEP, given the turnaround time for viral load testing, and the need for prior authorization for insurance approvals in settings such as the U.S. Laboratory monitoring can be a cost and logistic barrier to PrEP implementation and should be carefully considered. Notably, Kenyan guidelines for oral PrEP include optional renal monitoring given the rarity of nephrotoxicity [45]. After PrEP initiation, quarterly HIV testing is recommended, which typically necessitates clinic visits. Encouragingly, a recent study in Kenya demonstrated that HIV self-testing is acceptable to PrEP users and reduced the frequency of clinic visits from every 3 to every 6 months without compromising PrEP retention, adherence and HIV testing [46]. Secondary distribution of HIV self-test kits could also increase partner testing and identify prospective PrEP users [47]. However, CAB-LA PrEP requires every 2-month visits for injections, and may require viral load monitoring to detect seronegative early HIV infection [48]; the more frequent visit schedule could be burdensome for users and viral load testing adds to the costs of CAB-LA [49].

2.3 | Achieving adherence with PrEP

Adherence to oral PrEP has been challenging for some populations, such as African AGYW, in part due to stigma from tablets and bottles that look identical to antiretrovirals for treatment, the need to establish pill-taking habits, and the dynamic nature of sexual behaviour and perceived HIV risk. Strategies to support oral PrEP adherence include retrospective drug-level feedback based on intracellular tenofovir diphosphate levels; however, the testing is costly and complex to implement and did not increase PrEP adherence among African AGYW [50, 51]. Low-cost, same-day point-of-care urine assays that measure tenofovir use in the past 5 days are promising for adherence counselling [52]. Peer support, more frequent visits and flexible adherence support interventions may address challenges for African AGYW [49]. Given low adherence to oral PrEP and DVR among African AGYW, the REACH crossover study of oral PrEP and the DVR among late adolescent girls ages 16–21 had encouraging findings with over half having high adherence to both oral PrEP and DVR in the context of monthly visits and a menu of adherence support options [53].

The goal is for high PrEP adherence during periods when an individual has a greater risk of HIV exposure ("prevention-effective adherence") [54, 55], which highlights the need for periodic reassessment of risk after PrEP initiation. A PrEP demonstration project among AGYW in southern Africa found evidence of prevention-effective adherence and higher PrEP adherence during periods of higher risk [56]. Providers need to be aware that although cycling on and off PrEP is expected, the high HIV incidence observed after PrEP discontinuation indicates the need for ongoing risk assessment to identify individuals who have ongoing risk and for whom stopping PrEP can be premature [57].

2.4 | Integrating PrEP with other reproductive and sexual health services

Given that the populations who have the highest HIV incidence rates and the greatest need for PrEP often are also at risk for bacterial STIs, PrEP delivery should include STI testing and treatment. STI rates are very high with a pooled incidence

of chlamydia, gonorrhoea and early syphilis of 72.2 per 100 person-years across diverse geographies and populations taking PrEP [58]. In 2022, the WHO provided guidance on the integration of STI services into PrEP programmes [59].

Sexual and reproductive health services need to be integrated into PrEP delivery for cis-gender women, with an assessment of fertility intentions, provision of contraception options for women who desire to not become pregnant, and screening and referral for intimate partner violence (IPV) [60]. Studies have reported that IPV interferences with women's interest and willingness to use PrEP, and is associated with interruptions in PrEP use, and poor adherence [60]. Symptoms of depression have been prevalent among African AGYW in PrEP demonstration projects with persistent depressive symptoms associated with lower PrEP adherence and persistence [61]. LA PrEP products that do not require daily adherence may be a good option for persons experiencing depression or IPV.

For transgender populations, PrEP provision in gender-affirming environments improves uptake and adherence and enhances the effectiveness of PrEP delivery [62, 63]. Gender-affirming hormone therapy (GAHT) is a key aspect of the standard of care for TGW to induce secondary female sex characteristics while reducing male sex characteristics. Key components of gender-affirming and HIV prevention primary care include providing adequate information for TGW on the lack of drug–drug interactions between PrEP and GAHT which may increase PrEP adherence, capacity building and training for key population-led clinics, one-stop primary healthcare for transgender populations, and national HIV and transgender healthcare guidelines. Thigh injections of CAB-LA are feasible, well-tolerated and provide an injection option for persons with gluteal implants [64]. Lastly, stimulant use and chemsex is prevalent among MSM and transgender populations in PrEP programmes [65, 66], and presents additional challenges with PrEP adherence and persistence. If PrEP programmes are not able to provide substance use interventions, referrals should be provided.

3 | CONCLUSIONS

Experiences from oral PrEP implementation have identified strategies to mitigate user and provider barriers which have relevance to the introduction of new LA PrEP formulations, namely DVR and CAB-LA, which reduce user burden associated with oral PrEP, and could improve coverage through increasing choice to allow users to identify which PrEP option best fits their needs. However, new products have costs and programmatic demands, such as supply chain management that will impact their introduction. Demonstration projects are useful to identify the best practices of how to implement new PrEP products, and it may be beneficial to stagger the introduction of new PrEP products in order to support uptake (e.g. through decision support tools for clients and training of providers) and digital tools for visit reminders in order to foster PrEP persistence. In addition, structural factors, such as poverty, stigma and access barriers to HIV prevention, disproportionately impact vulnerable and often marginalized populations. Strategies to address these inequities need to be a focus of LA PrEP implementation, so that access gaps to these exciting new PrEP formulations do not widen. The past decade of oral PrEP implementation highlights the need to move from facility-based, medicalized models of HIV prevention, to provide non-stigmatizing and supportive counselling, and to deliver PrEP as part of an integrated service package. Programmes need to partner with communities in demand creation and delivery models, learn from users about what they need to support them in PrEP choice and continuation, and support providers to ensure that the second decade delivers the promise of LA PrEP, in part by building on lessons from the first decade of implementing oral PrEP.

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COMPETING INTERESTS

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CC prepared the initial draft of the manuscript, and BG and KN revised the manuscript. All authors have read and approved the final manuscript.

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VIEWPOINT

What will it take to bring LAED medication regimens to young people?

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Two long-acting extended delivery (LAED) antiretrovirals for HIV (cabotegravir/rilpivirine for treatment and cabotegravir alone for prevention) were recently licensed in adolescents around the same time as adults (Table 1). We commend the early inclusion of minors in product development trials, reflecting many years of advocacy and evolving ethical standards. However, regulatory approval allowing new product use in adolescents is a necessary but insufficient condition for equitable implementation. Interventions aimed at the socio-ecological barriers to engaging with HIV treatment and prevention services (e.g. stigma, parental disclosure, medical mistrust and healthcare access) must first be deployed to fulfil expectations that LAED products will be a gamechanger, transforming HIV outcomes in young key populations.

Young people bear a disproportionate burden of HIV globally yet continue to have the worst outcomes in both treatment and prevention cascades [1]. Compared to all populations living with HIV, adolescents aged 13–24 are the age group most likely to not know their status or access antiretroviral treatment (ART), have higher levels of skipped medication doses and missed medical visits, and demonstrate the lowest rates of viral suppression even in the context of widespread access to ART [2, 3].

Addressing the slow rate of decline in new HIV infections among key populations of youth remains critical to controlling the HIV pandemic, especially in adolescent girls and young women in Africa and sexual and gender minority youth globally. Despite global guidelines recommending tenofovir-based oral pre-exposure prophylaxis (PrEP) for adolescents at substantial risk, HIV prevention efforts are severely undermined by profound inequalities in PrEP access for key youth populations [4]. For example, only 11% of youth with a PrEP indication in the United States are taking it [2]. A significant proportion of youth do not persist with oral PrEP, and strategies are needed to help youth assess their ongoing risk of acquiring HIV, remain motivated and overcome adherence challenges for daily oral PrEP [5].

LAED products offer tremendous promise to curb the challenges of medication adherence by simplifying regimens and decreasing daily pill burdens. LAED products also provide an increased level of privacy that can ameliorate concerns regarding stigma and unintentional disclosure associated with sexual activity and/or sexual identity for PrEP users. The availability of safe, efficacious LAED options for youth continues to grow and expands the choices youth have for products that fit their needs and circumstances (see Table 1). Unfortunately, significant barriers exist that interfere with the proper implementation and subsequent access to these products.

Worldwide, access to quality sexual and reproductive health, including HIV testing, treatment and prevention, is a challenge for youth. Less than optimal HIV testing rates can be attributed, in part, to the stigmatization of HIV as well as biased perceptions of sexual activity. Stigma and discrimination can have profound negative impacts on the health of young key populations. For example, people living with HIV are twice as likely to significantly delay engagement in care if they perceive high levels of stigma and discrimination regarding their HIV status [6]. To reduce HIV-related stigma and encourage the uptake of new LAED HIV prevention tools, a status-neutral approach is needed in which HIV testing is the natural first step towards engagement with HIV services, for either prevention or treatment [7]. Routinization of HIV testing in schools, communities and households can decrease stigma and discrimination towards key populations living with and at risk for HIV.

Adolescent sexual activity remains taboo in some communities, affecting service providers' attitudes towards providing sexual and reproductive health services, including PrEP, to sexually active adolescents. In the case of sexual and gender minority youth, overt hostility directed towards the community blocks access to HIV prevention, treatment and other health services [8, 9]. The provision of effective resources to community-led advocacy and health organizations is critical for engaging key populations in essential prevention and treatment research and services and overcoming barriers [10].

Worldwide, laws that inhibit the autonomy and decision-making abilities of youth (including young pregnant women) make it increasingly difficult if not impossible to access essential sexual and reproductive health services. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reports that among 141 countries with available data, 75% require adolescents to obtain parental/guardian consent for HIV test-

Table 1. Long-acting and extended delivery products for HIV prevention and treatment

Product	Regimen	Regulatory timeline
HIV TREATMENT		
Cabotegravir/rilpivirine	Intramuscular injections either monthly or every 2 months after a loading dose	October 2020—EMA: recommended rilpivirine and cabotegravir to be used together for the treatment of HIV in adults. January 2021—FDA: approved in adults as a complete regimen for the treatment of HIV. March 2022—FDA: approved in adolescents aged 12 years and over weighing at least 35 kg.
HIV PREVENTION		
Dapivirine vaginal ring	Monthly insertion	July 2020—EMA: provided a positive benefit–risk opinion for use in adult women as a complementary prevention approach in addition to safer sex practices when women cannot use or do not have access to oral oral PrEP. January 2021—WHO: adolescent use approved simultaneously with adults; may be offered as an additional HIV prevention choice for women at substantial risk of HIV infection as part of a combination of prevention approaches. From July 2021—various country drug regulatory authorities: approved for use in adult women. Some countries allow use in adolescents.
Cabotegravir	Intramuscular injections every 2 months after a loading dose	December 2021—FDA: approved simultaneously in adolescents and adults weighing at least 35 kg. July 2022—WHO: adolescent use approved simultaneously with adults; may be offered as an additional HIV prevention option for people at substantial risk of HIV infection as part of combination prevention approaches.
Lenacapavir	Subcutaneous injections every 6 months	Phase 3 trials ongoing (NCT: 04925752 & 04994509)

Abbreviations: EMA, European Medicines Agency; FDA, US Food and Drug Administration; PrEP, pre-exposure prophylaxis; WHO, World Health Organization.

ing [11]. Similar rates of restrictions related to contraception are evident, meaning that in many of these countries, adolescent girls can legally engage in sex but not access HIV testing or contraceptive services. The debate also swirls around the autonomy of pregnant women to make decisions about their health and safety as well as that of the developing foetus [12, 13]. Whether it is the ability to consent for trial participation, to make choices regarding medications during pregnancy or to make decisions about pregnancy termination, young women's autonomy continues to be questioned by policymakers and regulatory authorities. Finally, attacks on the autonomy of medical providers in countries like the United States to make decisions with their patients around sexual and reproductive health threaten to upend HIV prevention progress among key populations. Whether it is abortion prohibition or legal interference with the provision of gender-affirming care, healthcare providers are at risk of losing their autonomy to practice without fear of legal ramifications [14]. To reach the full potential of LAED regimens, respect for the decision-making autonomy of patients and providers is essential.

In sum, the implementation of wholistic HIV prevention and treatment services is much more than administering a biomedical product, *regardless of whether the product is LAED or not*. Integrated strategies must incorporate social and structural components to provide the support young people (and their parents/guardians) need for effective and sustained sexual and reproductive health. Almost 20 years ago, the World Health Organization issued recommendations for HIV services to be based around five adolescent-friendly principles: accessible, acceptable, equitable, appropriate and effective [15]. However, the persistent disparities in HIV outcomes among youth indicate these principles must be broadly applied to support the development, effective implementation and equitable delivery of LAED products for HIV prevention and treatment.

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COMPETING INTERESTS

LS-C received travel support from ViiV to attend the International Workshop on HIV and Adolescence 2022, Cape Town, South Africa. SH has no conflicts to declare.

AUTHORS' CONTRIBUTIONS

SH and LSC contributed equally to researching, writing and editing this manuscript.

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VIEWPOINT

Including pregnant and breastfeeding people in trials of novel LAED PrEP agents: perspectives from sub-Saharan Africa community stakeholders

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In 2022, the World Health Organization (WHO) recommended long-acting injectable cabotegravir (CAB) for use as pre-exposure prophylaxis (PrEP) [1]. This recommendation was supported by data from two large randomized controlled trials that demonstrated the safety and efficacy of CAB compared to tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) for HIV prevention [2, 3]. CAB is one of the first in a pipeline of long-acting or extended delivery (LAED) agents that have the potential to have a significant impact on high HIV incidence rates in women in sub-Saharan Africa [4]. However, as countries plan for CAB introduction, data on the safety and pharmacology of CAB in pregnant and lactating people (PLP) are limited, presenting a challenge for programmes.

Participants of child-bearing potential in HPTN 084, the trial that enrolled individuals assigned female at birth, were required to use long-acting reversible contraceptives (LARCs) with a failure rate of <1%. This stringent requirement was in response to a safety signal associated with peri-conception dolutegravir (DTG) use in women living with HIV [5]. CAB injections were discontinued in participants who declined a LARC, wished to conceive or had a positive pregnancy test, and participants were offered open-label TDF/FTC. These actions were taken out of an abundance of caution but reinforced traditional concerns about the potential harms of including PLP in pre-licensure trials. By contrast, there is growing support for a paradigm shift that recognizes PLP as a complex population better served through inclusion in research with adequate protection and monitoring, to generate data on safety, efficacy and pharmacology in pregnancy, thus avoiding delays in access to effective medications for PLP who also experience risk for HIV [6]. Community stakeholders, however, need to understand and support this paradigm shift before this aspiration can be fully realized.

Good participatory practice (GPP) recommends that community stakeholders contribute to protocol development to ensure locally appropriate and acceptable trial procedures [7]. Following the HPTN 084 efficacy results, all participants were unblinded, while the protocol was amended to offer access to CAB. Prior to the implementation of protocol changes, HPTN 084 community working group members hosted a stakeholder consultation to gather community perspectives on proposed pregnancy-related amendments, including relaxation of contraceptive requirements and active CAB dosing during pregnancy and lactation. Due to COVID-19 restrictions, a 2-hour consultation (14:00–16:00 Central Africa Time) was held virtually. Zoom polls were used to gauge the strength of feelings around preference-sensitive issues, to stimulate conversation and to create space to hear opposing views, and for investigators to respond to information gaps.

Overall, (N = 101) stakeholders from HPTN 084 countries (n = 82) and the United States (n = 19) attended the consultation, with most representing community (86%), global (7%) and other (7%) stakeholder groups as defined by GPP guidelines [7]. Despite the virtual meeting limitations, the consultation provided an opportunity to (1) provide updates on peri-conception DTG use and the diminishing evidence for a neural tube defect association; (2) socialize the ethical framework that reframes PLP as a complex population in need of protection through research and fair inclusion in trials; and (3) understand the acceptability of protocol amendments to community stakeholders in participant communities. An average of (n = 50) (range 43–52) stakeholders from sub-Saharan Africa responded to polling questions (Figure 1). While qualitative in nature, the Zoom polls confirmed that the greatest concerns related to CAB safety during pregnancy (as opposed to lactation despite virtually no available data on CAB in breast milk), and that partners were likely to be extremely influential in participants' decisions to use CAB in pregnancy. Subsequent discussions affirmed that the DTG experience had a negative impact on community confidence in CAB safety. This impact cannot be underestimated and will likely linger in the public consciousness. Trialists will need to provide regular communication about the evidence for risks and benefits as data evolve, but ultimately robust surveillance systems will be needed to re-build public confidence. Despite concerns, stakeholders recognized the importance of the inclusion of PLP in research. With adequate information, stakeholders acknowledged that inclusion of PLP in trials could lead to earlier access to effective products for PLP, and avoid the

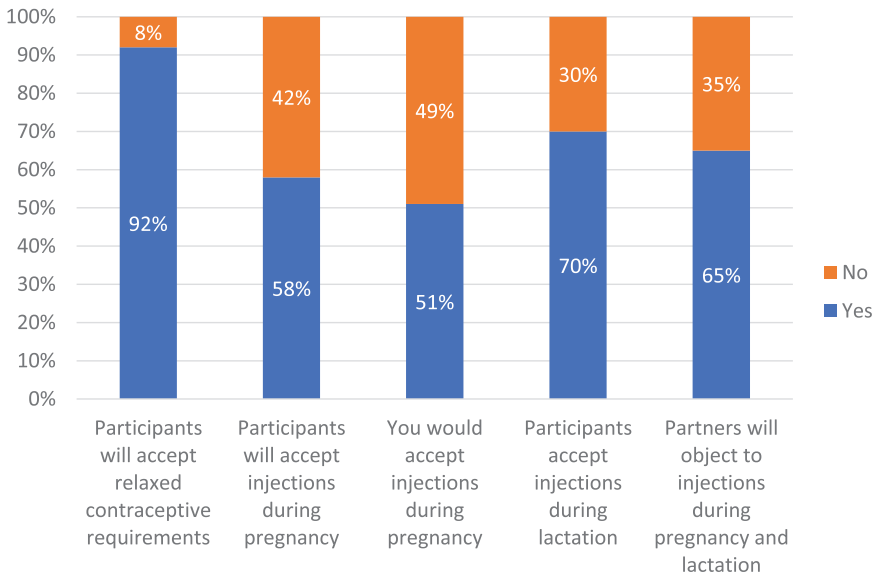

Figure 1. Sub-Saharan African stakeholders' consultation polling results.

harms associated with off-label use of drugs in PLP where robust data on safety, efficacy and pharmacology are missing. While the views presented were community stakeholder views, the polls coupled with the subsequent discussions highlighted the multiplicity of strongly held opinions that a participant might have to navigate when making decisions about PrEP use in pregnancy, especially in communities where gender and social roles may limit women's autonomy and where partners place a premium on a positive pregnancy outcome. Without the consultation, it is possible that the study team could have underestimated the importance of this issue to study communities. In response, the study team developed a shareable video that showed a participant having conversations with influential members of her social network, for example partner, family members and a healthcare provider. Counselling job aids that individualize risk–benefit discussions between counsellors and participants were also developed. Tools like these may be useful in providing information to participants and their significant others about study product use in pregnancy, thus supporting choices that align with participant values while acknowledging participant autonomy and ensuring enhanced engagement in the study. While trial considerations may be unique, these tools are likely to have benefit for product introduction and programmes.

The 2021 WHO call to action to accelerate the study of new drugs for HIV in PLP invites civil society to engage as partners in the research process, to take the lead in building community literacy and to partner with researchers to develop tools to aid communication on the need for trials in pregnancy [8]. Despite limitations, the HPTN 084 community consultation gave substance to this call and gained insights that are valuable for both trial and programme implementation. While there are unique reasons for the initial exclusion of PLP from CAB trials, the lessons from HPTN 084 are relevant for current CAB implementation and future LAED development in PLP. Safe pregnancy outcomes are a concern in many communities. Opportunities to solicit feedback, respond to concerns and build community trust in the scientific process should not be underestimated. Community stakeholders are central to efforts to include PLP in pre-licensure trials by communicating these paradigm shifts. Over time, these engagements strengthen trial conduct, ensure support for PLP and their choices, build community confidence in LAED products and the science that confirms their effectiveness, and leading ultimately to high uptake and coverage in those at greatest need, including PLP and those that wish to conceive.

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RW, MD, SD-M and MH designed the consultation and developed the viewpoint. SD-M and MH also presented and addressedstakeholders' questions and comments. RW wrote first draft, and all authors contributedto revisions and approval of the final draft.

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VIEWPOINT

Benefits and limitations of different study designs for long-acting antiretroviral therapy among people living with HIV with viremia

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Although there are highly effective options for once-daily oral antiretroviral therapy (ART) to treat HIV, not all patients living with HIV on ART are virologically suppressed. Adherence barriers to oral regimens are common and span individual and structural factors, including stigma, forgetting, unstable housing, food insecurity, insurance lapses or prohibitive co-pays, mental illness, substance use, transportation challenges and stock-outs. Long-acting (LA) injectable agents administered monthly or less frequently could circumvent some of these barriers.

LA agents have been developed for contraception and other disease states like psychiatric illness. For HIV infection, LA treatment is relatively new. The U.S. Food and Drug Administration (FDA) approved a combination of two injectable antiretroviral medications, cabotegravir (CAB) and rilpivirine (RPV), for administration every 4 weeks in both ART-naïve and ART-experienced patients in January 2021; a higher dose of each given every 8 weeks was approved in March 2022. The approvals were based on registrational trials of LA CAB/RPV in treatment-naïve and experienced participants who were first virologically suppressed on oral regimens [1–3]. In an updated analysis of the registrational trials out to 152 weeks, the confirmed virologic failure rate was low (1.4%) [4]. A recently presented study confirmed low rates of virologic failure (0.4%) and high treatment satisfaction at 12 months with a switch to LA CAB/RPV from bictegravir/tenofovir alafenamide/emtricitabine (BIC/TAF/FTC) [5]. Two demonstration projects in Europe found high rates of maintenance of virologic suppression and treatment satisfaction when switched to injectable agents [6, 7].

All of these studies started LA CAB/RPV in virologically suppressed patients. However, given the difficulties with adherence in multiple contexts worldwide, studies using LA-ART in adherence-challenged patients are needed. A demonstration project conducted at the Ward 86 HIV Clinic at San Francisco General Hospital, which serves a publicly insured or uninsured population of people with HIV (PWH) in San Francisco, provides the most extensive experience to date: 133 patients received LA CAB/RPV; 76 (57%) of whom were virologic suppressed on oral ART and 57 (43%) with viremia off of ART due to adherence challenges [8]. The cohort was diverse: 68% non-White; 88 (66%) unstably housed; and 44 (33%) endorsed substance use. All patients started on injectable ART who had achieved virologic suppression on an oral regimen remained suppressed. All but two of the viraemic patients were suppressed on LA CAB/RPV over a median of 26 weeks (2–42), providing an overall virologic suppression rate in the cohort of 98.5%, similar to that in registrational clinical trials. The rate of suppression among initially viraemic patients was 96.5%. Of note, the Ward 86 demonstration project included frequent outreach and treatment support services. While these results are not directly comparable to data from randomized clinical trials, they are encouraging in demonstrating that administration of LA CAB/RPV *can* lead to virologic suppression in unsuppressed patients.

Discussions around the use of LA CAB/RPV before and after its approval have centred around the idea of equity and extending the use of this combination treatment to adherence-challenged and hard-to-reach populations, including those with marginal housing, individuals experiencing incarceration and adolescents [9–11]. However, a randomized controlled trial (RCT) comparing LA CAB/RPV in patients with viremia on oral ART has never been performed. The AIDS Clinical Trials Group (ACTG) is studying LA CAB/RPV among adherence-challenged patients who have demonstrated difficulty achieving virologic suppression on oral ART. In this RCT (A5359), participants are being randomized to a standard-of-care oral ART arm versus an arm using LA CAB/RPV after the achievement of virologic suppression on oral ART with adherence interventions and incentives. Although this study will reveal important insights into treating adherence-challenged populations who are able to first suppress on oral therapy (with incentives), the utility of treating viraemic patients with LA CAB/RPV cannot be defined by the A5359 study design.

The U.S. FDA usually approves medications based on evidence from randomized trials. However, patients with ongoing viremia are often not able to suppress on an oral ART regimen, which can make an RCT difficult to enrol and a likely set-up for failure in the oral ART arm. A recent modelling study showed that only 22% of patients with long-standing adherence challenges and viremia are likely to suppress on oral ART, even with wrap-around services [12]. Therefore,

examining the question of using LA CAB/RPV via an RCT design does not meet the criteria for equipoise, is not likely to be feasible and may even be unethical for those randomized to oral ART.

In the case of a "rare condition," the U.S. FDA allows single-arm trials to determine the efficacy of a medication in the population [13]. For instance, the prevalence of multidrug-resistant (MDR) HIV-1 in the United States is low and the disease state is, therefore, rare. The entry inhibitor, ibalizumab, was approved by the FDA for use in MDR HIV based on the results of a single-group, open-label study with a total of 31 participants enrolled [14]. Although adherence difficulties are common, the population who cannot take oral ART and will only agree to be on ART if prescribed as monthly or bimonthly injectables is relatively rare. Therefore, we would argue that a single-arm trial to show the effectiveness of LA CAB/RPV among viraemic patients who will not take oral ART is not only justifiable, but the most feasible and ethical design.

Although important for market introduction, the drug label is not the only source of evidence for clinical practice and reimbursement. Treatment guidelines from reputable sources can influence which medications are reimbursed. In HIV, the Department of Health and Human Services Panel on Antiretroviral Treatment Guidelines for Adults and Adolescents in the United States [15] serves this purpose. In contrast to the stringent requirements for regulatory approval and indication as stated on the drug label, treatment guideline panels review and grade all available evidence. A larger, multicentre, single-arm trial for LA CAB/RPV in viraemic patients than what has been presented to date from Ward 86 could lead to this addition to the guidelines, which will help prescribing providers garner insurance approval in the United States. The trial design could involve examining feasibility and acceptability, in addition to effectiveness and safety, which would aid in implementation in real-world settings.

We thereby recommend the consideration of a well-conducted, multi-centre, single-arm trial examining LA CAB/RPV in viraemic participants. The details of the study design should involve intensive consultation with the community as well as clinicians with expertise in serving these communities to examine safety, efficacy, acceptability and feasibility.

Whether or not LA-ART will change population health outcomes depends on the willingness of the HIV community to test this strategy in viraemic patients in order to generate data for treatment guideline panels and regulatory authorities. To truly reach the U.S. End the HIV Epidemic (EHE) goals, we need a way to harness innovative strategies to help patients with viremia achieve virologic suppression. LA ART can be the "game changer" to help achieve EHE goals, and innovative study designs to rapidly evaluate this important new strategy among viraemic patients are indicated.

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