



Published in final edited form as:

*Curr Opin HIV AIDS*. 2025 January 01; 20(1): 48–53. doi:10.1097/COH.0000000000000899.

## Why is roll-out of long-acting PrEP agents so slow?

Rupa R. Patel<sup>a</sup>, Kenneth H. Mayer<sup>b,c</sup>

<sup>a</sup>Division of HIV Prevention, Centers for Disease Control and Prevention, Atlanta, Georgia

<sup>b</sup>The Fenway Institute, Boston, Massachusetts, USA

<sup>c</sup>Harvard Medical School, Boston, Massachusetts, USA

### Abstract

**Purpose of review**—Injectable cabotegravir for HIV preexposure prophylaxis (PrEP) is effective, yet global implementation has been slow. We review factors which have contributed to the delayed roll-out of this medication.

**Recent findings**—Fifty-three countries have approved cabotegravir for HIV prevention yet roll-out has been slow. Cabotegravir made up 2.5% of all U.S. PrEP prescriptions in 2023 and is very slowly increasing after FDA approval in 2021. Medication has not been available outside of implementation science studies in Africa and Asia. There is a lengthy process for generic medication production despite agreements signed in 2021; the first available generic dose is not anticipated until 2027. In the United States, where some of the cabotegravir medication costs can be covered under individual insurance plans, high costs and medication acquisition pathways for health centers have been complex, contributing to national implementation delays. The intensity of the staffing required for medication acquisition, insurance paperwork filing, process documentation, billing, injection administration, appointment scheduling, missed appointment monitoring and client follow up has burdened healthcare organizations.

**Summary**—Injectable cabotegravir PrEP has not reaped its potential to be an alternative in those for whom adherence to a daily PrEP pill is challenging. Lessons learned regarding cabotegravir medication acquisition pathways and clinical delivery strategies can inform the rollout of future HIV prevention long-acting agents.

### Keywords

cabotegravir; HIV preexposure prophylaxis; long-acting antiretrovirals

## INTRODUCTION

As of the latest UNAIDS update for 2023, there are 1.3 million new infections every year, globally, and HIV preexposure prophylaxis (PrEP) holds promise to reduce HIV incidence [1]. There are an estimated 7.48 million people who have started any form

Correspondence to Rupa R. Patel, CDC: Centers for Disease Control and Prevention, Atlanta, GA 30333, USA. ntw4@cdc.gov.  
Financial support and sponsorship  
None.

of PrEP worldwide since 2012, of which 7.46 million initiations are with oral PrEP [2]. Long-acting injectable cabotegravir was FDA approved in the United States for HIV prevention in December 2021 after the results of the HPTN 083 and 084 trials that included cisgender MSM, transgender women who have sex with men (TGW) and cisgender women. Cabotegravir, injected in the intramuscular ventrogluteal area every 2 months, was found to be 66% and 89% efficacious when compared to daily oral TDF/FTC PrEP in HPTN083 and 084, respectively [3,4]. Global cabotegravir PrEP rollout has been slow. This article will review the reasons for implementation delays which are largely driven by the lack of medication availability and access.

### Slow cabotegravir preexposure prophylaxis implementation globally

There are 53 countries with cabotegravir regulatory approval while nine countries have approvals pending [2]. In contrast to daily oral TDF/FTC, the regulatory approval timeline worldwide has been faster for cabotegravir by an average of 3 years. Seven African countries had their cabotegravir approvals within 2 years of U.S. FDA approval, in contrast to the over 3 years that passed before any African nation approved oral TDF/FTC. Projects in low-and-middle-income-countries (LMICs) have received noncommercial cabotegravir supplies 3 years earlier than receiving oral TDF/FTC [5]. The Biomedical Prevention Implementation Collaborative spearheaded the Coalition to Accelerate Access to Long-Acting PrEP to advocate for product availability [6,7–9], while the WHO and several countries developed clinical cabotegravir guidance and trainings [10–12]. Despite these milestones, an estimated 15 500 people started injectable cabotegravir PrEP worldwide since December 2021, with 11 000–14 000 of those individuals residing in the United States [2].

As of this writing, there are 1685 people who started cabotegravir in South Africa, 1290 in Zambia, 895 in Zimbabwe, 650 in Brazil, and 40 in Malawi [2]. These absolute numbers and the rate of growth are relatively slower than expected given that efficacy results for long-acting cabotegravir were available by 2020 and given the context that, worldwide, PrEP clinics, staff, clinical protocols, and beyond have been in existence since 2012. The United States is the only country that has integrated cabotegravir PrEP into their healthcare system with a funded mechanism through public and private insurance coverage. From January 2023 to December 2023, there were a total of 505,730 people prescribed PrEP, of which 2.5% were cabotegravir prescriptions [13]. The annual U.S. cabotegravir cost is \$22,200–\$25,900 per person [14]. High costs and complex insurance and manufacturer-related medication acquisition pathways drive product inaccessibility despite product availability in the United States.

In contrast to the United States where cabotegravir PrEP is available but not consistently accessible, there is little product availability in the rest of the world. In countries that have centralized public health systems, high costs have delayed cabotegravir's integration into national health systems. Over 1 million medication doses will be supplied to LMICs for the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and Global Fund financed cabotegravir programs, continued access for HPTN trials, and 36 implementation projects in Africa, Asia, and Ukraine from 2023 to 2025 [5]. The PEPFAR negotiated cabotegravir price is \$30 per person 2-month dose, or \$180 per year [15,16].

Generic cabotegravir production is anticipated in 2027 despite licensing agreements having been signed between Medicine Patent Pool and ViiV Healthcare in July 2022 and three companies having signed agreements to manufacture the medication in May 2023. Production is nearly 7 years after cabotegravir trial efficacy results were published and is similar to the timeline of oral TDF/FTC [17,18]. This lengthy medication production timeline is due to the steps needed to validate generic medication production, including bioequivalence evaluations [16■,19,20]. A critical step after validating medication production will be to create a generics commercial market to ensure sustained medication availability, which ensures equitable global access to injectable cabotegravir for individuals at risk for HIV [20].

## DEMONSTRATION AND IMPLEMENTATION SCIENCE PROJECTS

When cabotegravir is available and delivered without the barriers that drive inaccessibility (e.g., insurance gaps), global programs have demonstrated high cabotegravir uptake and feasibility of differentiated service delivery. In the HPTN 083 and 084 open-label extension (OLE) studies, 96 and 78% of participants chose cabotegravir over oral daily TDF/FTC, respectively [21,22].

Similarly, in SEARCH, a cluster randomized trial in Uganda and Kenya provided PrEP choice (i.e., ring, injection, or daily pills) to men and women with sexual risk for HIV in the dynamic choice prevention arm (DCP) ( $n = 487$ ) compared to standard of care ( $n = 497$ ) in three settings (outpatient and antenatal clinics and door-to-door community health workers). In the DCP, there was 56% cabotegravir uptake, zero infections, and 76.5% had biomedical HIV prevention coverage during self-reported periods of risk for HIV (vs. 16.2% in the standard of care arm where only oral TDF/FTC was available) [23]. Most (98%) opted to take cabotegravir after 48 weeks in the study revealing that if barriers to access are minimized then there is a high uptake with improved health outcomes [24].

The PrePare to Choose study in Cape Town had high injectable cabotegravir PrEP uptake during the project's first few weeks in March 2023 among adolescent cisgender men and women who were offered oral or injectable PrEP. Eighty initiations occurred within a week and occurred on a mobile unit [25]. PrEP is being offered in the trial at mobile clinic vans, youth clubs, clinics, courier service, and schools to at least 900 participants over 18 months [26]. The five African country, USAID-funded CATALYST trial plans to offer PrEP choices (i.e., ring, injection, oral pill) to 4225 adolescent girls and young women, which can shed more light on cabotegravir use when barriers to access are removed [27].

## UNITED STATES BASED REAL-WORLD EXPERIENCES

In the United States where cabotegravir as PrEP is available, there are issues related to access through the elaborate, often changing, and complicated system of injectable cabotegravir medication acquisition [28]. This complex system coupled with high medication and healthcare costs (i.e., provider visit, laboratory tests) and the heterogeneity (i.e., uninsured, underinsured, and having meaningful insurance coverage) and dynamism, or “insurance churning,” of individuals' having insurance coverage can lead to significant

challenges. Little data exist on the cabotegravir PrEP users' out-of-pocket (OOP) costs, but recent studies have shown that despite the Affordable Care Act (ACA) PrEP financial protections established in 2021, over 70% of oral PrEP users have had OOP costs for ancillary services of over \$200 per year in 2023. Fifty percent of these OOP ancillary service costs have been charged for the provider visit—the crucial first step in PrEP care where individuals receive a clinical evaluation and prescription [29]. High OOP costs are known to lead to oral PrEP discontinuation [30] and are impeding cabotegravir use [31]. There has been a nationwide initiative to standardize PrEP medical coding to minimize PrEP user OOP charges related to ACA and other insurance procedures [32].

In addition to the individual-level barriers to cabotegravir PrEP access with high OOP costs, medication acquisition poses a barrier at the organization-level. Injectable cabotegravir can be obtained by either pharmacy distribution or buy-and-bill, which is determined by the PrEP user's insurance and whether charges will be a medical or pharmacy benefit. Unlike oral PrEP, cabotegravir is viewed as a medical service since a provider is required to perform an injection and the medication must be delivered to the provider's clinic. Related to this, the buy-and-bill process requires organizations to first "buy" or pay for the medications with existing clinic funds, then bill individual PrEP users' insurance companies after injection administration, and, only then, receive monetary reimbursement [14].

Several issues have arisen from this medical benefit process which contribute to stagnant, and potentially inequitable, national cabotegravir PrEP scale up. Since each PrEP injection is roughly \$3000, organizations are required to have a substantial amount of money upfront to buy several medications doses before being reimbursed. This requirement selects for certain organizations that can afford such financial risk to both start and maintain cabotegravir injection PrEP care programs. Buy-and-bill has been observed to be largely required by commercial insurances and many organizations who are not equipped with the staffing and finances needed to engage in buy-and-bill medication acquisition will not offer cabotegravir to those with commercial insurance. Furthermore, full reimbursement is not always guaranteed due to medical chart and billing documentation or other paperwork errors, which have led organizations to implement staff training for buy-and-bill reimbursement. Another reason for non-reimbursement is because of PrEP user appointment no shows, where medication cannot be redirected to another individual since the medication was billed and obtained under a unique person's insurance plan. Reimbursement amounts can vary by insurance type and can take months; thus, organizations have been in the "red" well over \$100 000 while waiting for medication cost reimbursement. This entire process has led to small volume clinics such as community-based organizations, public sexual health clinics, and academic centers, especially in less populous Midwestern and Southern states, to either begin and then stop offering cabotegravir, not initiate implementation at all, minimize care to certain insurances, and/or limit the total number of persons ever offered PrEP cabotegravir care. While long-acting injectables can offer an effective alternative to those who cannot take a pill everyday, the medication acquisition process has fostered and has potentially widened inequitable access to care [28].

Similarly, nonresearch program documentation has not only demonstrated prior authorizations and insurance denials becoming a barrier to access PrEP cabotegravir but

can also play a role in continuing PrEP if insurance coverage changes during care [28]. The median time from cabotegravir prescription to first injection, at a Chicago safety-net primary care center in a cohort of 270 individuals, was 24 days (IQR 11–51 days); 41.9% of PrEP users had delays of more than 30 days; 60% of PrEP users were commercially-insured. First-time injection delays were more likely with having to pay out of pocket [aOR 1.97; 95% confidence interval (95% CI): 1.04–4.80] and less likely with public insurance (aOR 0.60; 95% CI: 0.36–0.81). Eighteen percent of the 27 discontinuations were due to loss of insurance coverage [33]. Commercial insurance may require prior authorizations and paperwork which may contribute to delays in obtaining the first injection. In contrast, public insurance, which commonly uses pharmacy benefit, may minimize time to obtaining the first injection. A rapid-start program in San Francisco was able to deliver cabotegravir PrEP to 30 individuals; they served persons with homelessness (20%), unstable housing (23%), and substance use (67%); 93% had public insurance. The time from cabotegravir care referral to receipt of the first injection was a median of 14 days [34].

Cabotegravir discontinuations have been attributed to insurance coverage gaps in several studies [31,33,35,36]. Among 164 individuals seen at an HIV clinic in San Diego, insurance coverage evaluation was often the limiting step to obtain cabotegravir; discontinuations were more likely when individuals did not receive cabotegravir through the state's PrEP medication assistance program [odds ratio (OR), 12.5; 95% CI, 1.49–111.11] but instead through private insurance or out of pocket [36]. In a study of 293 persons eligible for cabotegravir across 26 outpatient clinics in 6 states as part of a large community-based clinic network (CAN Community Health), only 52.9% went on to receive the first injection and 24.1% of discontinuations after the first injection were caused by insurance gaps or cost [31].

Once medication acquisition is successful, delivering cabotegravir to a PrEP user encompasses several additional steps and real-time communication and coordination between six key organizational systems: clinical care, laboratory, pharmacy, scheduling, billing, and monitoring and evaluation or quality improvement (Fig. 1). For example, once a prescription is written after a clinician evaluation, it is processed through insurance checks and travels down the correct medication acquisition pathway. Once the medication is received, an appointment needs to be scheduled; if it is a follow-up appointment, then it should be scheduled within the window period of within 7 days of the target injection date. Before injection administration and/or on the same day, laboratories need to be obtained to ensure the PrEP user is HIV uninfected. Medical documentation occurs by the clinician so that billing can be processed, especially in the situation of buy-and-bill mediation acquisition. If the PrEP user misses an appointment, this needs to be detected in a timely fashion and the individual rescheduled, thus there needing to be available appointment openings so target injection windows are not missed. If target windows are missed (unplanned or planned), individuals need to have biomedical HIV protection with oral cabotegravir or TDF/FTC or TAF/FTC. Discontinuations need to be detected and persons reached to offer another form of PrEP.

Despite challenges in medication access and injection workflows, organizations have been able to implement cabotegravir PrEP programs; there are similar barriers and approaches

to cabotegravir HIV treatment implementation [37■,38■,39,40]. Important organizational-level implementation facilitators include long pre-implementation planning phases (i.e., 6–12 months) with dedicated cabotegravir implementation workgroups [35,41], having an injectable PrEP coordinator [35,37■,41], staff task shifting for injection administration [35,42], scheduling injection clinics or specific injection days [41], simultaneously rolling out long-acting injection HIV treatment programs [35,41], having 340B medication and staff financing mechanisms [35], having specific staff training on medication acquisition processes and PrEP billing [42], and having separate real-time communication channels between medication acquisition staff, providers, and schedulers [35]. Howard Brown Health, a community health center in Chicago, implemented injection clinics or hubs at each site for seamless referral and scheduling of missed appointments. Similarly, Whitman-Walker Health in Washington, D.C., has engaged lay worker PrEP specialists to administer cabotegravir injections within designated PrEP injection clinic days, while Legacy Community Health in Houston, Texas, has pharmacist injection clinic days and Philadelphia FIGHT engages medical assistants to deliver injections [25,35].

The implementation of cabotegravir for prevention, the first long-acting agent to come to market, has implications for how future agents are rolled out. A capsid inhibitor, lenacapavir, administered every 6 months for HIV prevention showed 100% and 96% efficacy in the PURPOSE 1 and 2 studies, respectively, and is slated for FDA approval in mid-2025 [43,44]. The rollout of cabotegravir has many lessons for lenacapavir's soon-to-come implementation and other promising agents in the pipeline. Lenacapavir shows promise to have a faster timeline than cabotegravir with the announcement of generic voluntary licensing prior to regulatory approval [45]. For lenacapavir, this seems to be the first critical step to ensure realistic product pricing with timely generic production to provide global product availability and access.

## CONCLUSION

Injectable cabotegravir PrEP has not reaped its potential to be an alternative for individuals who cannot adhere to daily oral PrEP. The lack of medication availability and access with long timelines for generic production and complex medication acquisition pathways are the main drivers for the delays in cabotegravir PrEP scale up. The frequency of injections can re-medicalize care and foster discontinuation. Future studies on client-centered delivery strategies such as at home, in pharmacies or on mobile units are needed, worldwide. Several ongoing implementation studies that remove barriers to access and incorporate differentiated service delivery will shed light on consumer PrEP choice, switches, discontinuation, and re-engagement. Lessons learned regarding cabotegravir generic production timelines, medication acquisition pathways, and clinical delivery strategies can inform the roll-out of near future long-acting HIV prevention agents. We need to create better mechanisms to rapidly optimize the power of long-acting agents' potential in curbing new HIV infections globally.

## Acknowledgements

The findings and conclusions are solely those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the U.S. Department of Health and Human Services.

### Conflicts of interest

R.R.P. reports no reported conflicts of interest. K.H.M. reports participating in scientific advisory boards for Gilead Sciences, Merck, Inc, and ViiV Healthcare, and his institution has received unrestricted research grants from all three companies.

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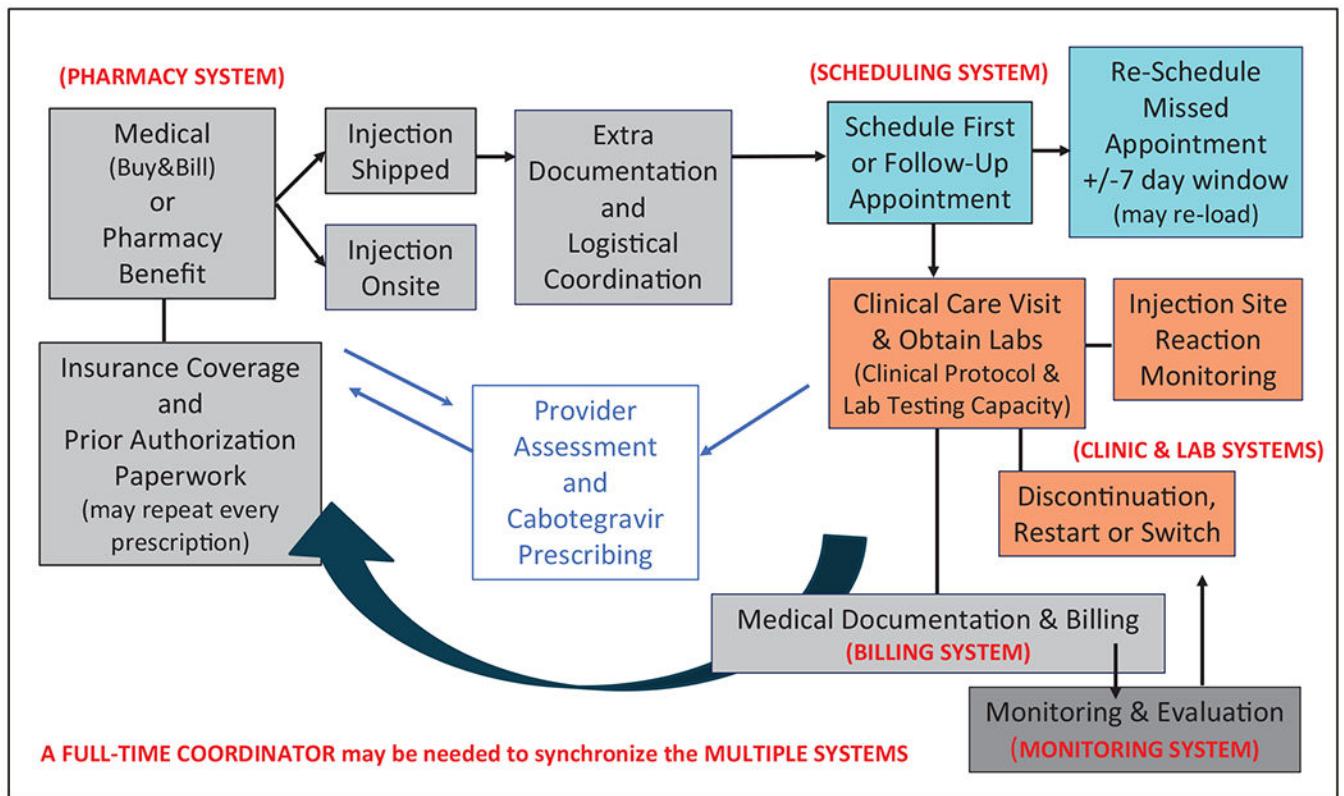
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**KEY POINTS**

- Global cabotegravir PrEP implementation delays are largely driven by a lack of medication availability and access.
- High costs and complex medication acquisition pathways in the United States drive product inaccessibility.
- Lengthy processes for generic medication approval and production have delayed worldwide rollout. Some medications have been procured for implementation science studies in Asia and Africa.
- The intensity of the staffing required for medication acquisition, insurance paperwork filing, process documentation, billing, injection administration, appointment scheduling, missed appointment monitoring and PrEP user follow up has burdened healthcare organizations.
- Lessons learned regarding cabotegravir medication acquisition pathways and clinical delivery strategies can inform the rollout of future long-acting HIV prevention agents.



**FIGURE 1.**  
Long-acting injectable cabotegravir preexposure prophylaxis workflow in the United States.