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Barriers to Pre-Exposure Prophylaxis Uptake Among High-Risk Populations

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Abstract

Pre-exposure prophylaxis (PrEP) has been shown, across successive oral and long-acting injectable formulations, to reduce HIV acquisition risk by well over 90% when used as directed, yet uptake among the populations it was developed for remains far below eligibility in the United States and globally. This article synthesizes the literature on why that gap persists, tracing PrEP's efficacy evidence from the foundational oral trials through the cabotegravir and lenacapavir injectable trials, then examining the individual, interpersonal, and structural barriers documented across Black men who have sex with men, transgender communities, people who inject drugs, cisgender women, and adolescents. We find that only around a quarter of PrEP-eligible people in the United States have been prescribed it, that stigma and medical mistrust operate as distinct but compounding barriers separate from cost and geographic access, and that these barrier categories combine differently across subpopulations rather than applying uniformly. Long-acting injectable formulations meaningfully address daily-adherence burden but leave most other documented barriers, including provider readiness, clinic-visit dependency, and population-specific access constraints, substantially unresolved. Closing the uptake gap, on this evidence, requires differentiated, population-specific intervention rather than a single structural or biomedical fix.

Keywords: pre-exposure prophylaxis; HIV prevention; PrEP stigma; healthcare access disparities; high-risk populations

1. Introduction

Pre-exposure prophylaxis has, in the space of about fifteen years, gone from an experimental hypothesis to a licensed, guideline-recommended, and in one formulation twice-yearly injectable intervention that reduces the risk of acquiring HIV through sex by well over 90% when used as directed [1,2,3]. That is, by the standards of infectious-disease prevention, an extraordinary tool. And yet HIV incidence in the populations PrEP was built for -- Black and Latino men who have sex with men in the U.S. South, transgender women, people who inject drugs, adolescent girls and young women in sub-Saharan Africa -- has not fallen anywhere near as fast as the biomedical evidence would predict. The U.S. Centers for Disease Control and Prevention estimates that only around a quarter of the roughly 1.2 million people in the United States who could benefit from PrEP have actually been prescribed one of the three approved regimens, and that gap is not evenly distributed: awareness, prescription, and persistence all run substantially lower among Black and Hispanic/Latino men who have sex with men and among Black and Hispanic/Latino transgender and cisgender women, the very groups carrying the highest share of new HIV diagnoses [4]. The problem, in other words, is not that PrEP fails to work. It is that the systems, relationships, and social conditions surrounding PrEP delivery routinely fail the people who need it most.

This article is a literature synthesis, not a report of new data. Its aim is to pull together what the trial literature established about PrEP's efficacy, what the implementation and behavioral-science literature has documented about why uptake lags so far behind eligibility, and what the more recent long-acting-formulation literature suggests about which barriers a new drug delivery mechanism can plausibly fix and which barriers it cannot. We organize the discussion around five themes: the trial evidence establishing PrEP's efficacy across the populations it has been tested in; the scale and distribution of the uptake gap nationally and globally; individual- and interpersonal-level barriers, principally stigma, disclosure risk, and medical mistrust; structural and health-system barriers, principally cost, geographic access, and provider readiness; and barriers specific to particular high-risk subpopulations -- cisgender women, transgender communities, people who inject drugs, and

adolescents and young adults -- whose relationship to PrEP delivery differs in ways that a single undifferentiated account of "barriers to uptake" tends to flatten.

It is worth being explicit about what kind of claim this synthesis is making. We are not arguing that any single barrier, once removed, would close the uptake gap; the literature is fairly consistent that these barriers are layered and interacting rather than additive, and that a person can clear a structural barrier (insurance coverage, a nearby clinic) and still not initiate PrEP because of a psychosocial one (anticipated stigma, distrust of the prescribing clinician), or vice versa [5]. What we can say with some confidence, because it recurs across studies conducted in different U.S. regions, different countries, and different risk populations using different methods, is that the barriers cluster into a fairly stable set of categories, and that most PrEP-eligible people who are not on PrEP are not refusing it out of indifference to HIV risk -- they are running into one or more of those categories.

2. The Biomedical Case for PrEP: Efficacy Across Trial Populations

The efficacy evidence for oral PrEP was established across a handful of large randomized trials conducted in different populations between roughly 2010 and 2015, and it is worth recalling how population-specific that evidence base originally was, because the uptake barriers discussed later in this article map fairly closely onto which populations were, and were not, centered in that original evidence. The iPrEx trial, led by Grant and colleagues, randomized men and transgender women who have sex with men across six countries to daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) or placebo and found a 44% reduction in HIV incidence in the intent-to-treat analysis, with efficacy rising sharply among participants whose drug levels indicated consistent adherence [1]. The Partners PrEP study, conducted in HIV-serodiscordant heterosexual couples in Kenya and Uganda, found a 75% reduction in HIV acquisition with TDF/FTC and a similar effect with tenofovir alone, among the first direct evidence that PrEP worked in heterosexual transmission, not only in men who have sex with men [2]. The TDF2 trial, conducted among heterosexual men and women in Botswana, independently found a 62% reduction in HIV incidence with daily TDF/FTC, reinforcing that the

heterosexual efficacy signal from Partners PrEP was not a fluke of that particular cohort [6].

Not every trial in this era found an effect, and the negative results turned out to matter as much as the positive ones for understanding uptake. The VOICE trial, which tested oral TDF, oral TDF/FTC, and a tenofovir vaginal gel in women in South Africa, Uganda, and Zimbabwe, found no protective effect for any arm, and post-hoc pharmacokinetic analysis showed this was overwhelmingly attributable to low adherence rather than biological failure of the drug -- most participants simply were not taking the product as directed, for reasons the trial itself was not designed to fully explain [7]. VOICE is, in retrospect, one of the earliest and clearest pieces of evidence that PrEP's real-world effectiveness is gated by an adherence and acceptability problem sitting on top of, not instead of, a biomedical efficacy question, and it foreshadows almost everything the subsequent uptake-barriers literature would go on to document in more qualitative detail.

The long-acting injectable formulations that followed oral PrEP were developed substantially in response to this adherence problem, and their trial results speak directly to how much of the "PrEP doesn't work for me" experience is actually a daily-pill-adherence experience rather than an intrinsic property of PrEP as a prevention strategy. HPTN 083 compared injectable cabotegravir, dosed every eight weeks after an oral lead-in, against daily oral TDF/FTC in cisgender men and transgender women who have sex with men, and found cabotegravir superior, with a 66% relative reduction in incident HIV infections compared to the oral arm [8]. HPTN 084 tested the same injectable regimen in cisgender women in seven African countries and found an even larger relative advantage over oral PrEP, a 89% relative reduction, driven in substantial part by the fact that many women in the oral arm were, as in VOICE, not reliably taking a daily pill, whereas an injection administered by a clinician every two months does not depend on daily self-administration at all [9]. Most recently, the twice-yearly injectable lenacapavir moved this logic further still: the PURPOSE 1 trial in cisgender women in South Africa and Uganda found zero infections among more than 2,000 participants receiving lenacapavir, a result strong enough that the trial's data safety monitoring board recommended unblinding it early, and PURPOSE 2, conducted in cisgender men,

transgender men, transgender women, and gender-nonbinary people who have sex with men across multiple countries, found a 96% reduction in incident HIV relative to background incidence, leading to lenacapavir's 2025 approval and a formal CDC clinical recommendation for its use as PrEP [3,10,11]. We discuss what these long-acting formulations can and cannot be expected to fix later in this article; for now, the point is simply that the efficacy question, across three successive drug-delivery generations, has been answered about as decisively as an efficacy question in HIV prevention gets answered. The open question this article is about is a different one.

3. The Scale and Distribution of the Uptake Gap

The gap between who could benefit from PrEP and who is actually using it is large, well documented, and unevenly distributed along lines that track the broader racial and gender disparities in HIV incidence itself. Jackson, McCoy, and White's review of a decade of U.S. PrEP delivery puts a number on the aggregate gap: roughly 25% of the estimated 1.2 million people in the United States who could benefit from PrEP have been prescribed one of the three approved regimens, well short of the national target of 50% coverage by 2030, and the review is explicit that "rates of PrEP use and PrEP awareness among Black/African American and Hispanic/Latino/a/x men who have sex with men as well as Black/African American and Hispanic/Latino/a/x transgender and cisgender women are disproportionately low, while new cases of HIV are disproportionately high in these groups" [4]. That sentence is, in a fairly compact form, the entire disparity this article is trying to explain: the populations with the least PrEP coverage are systematically the populations with the most HIV incidence, which is close to the opposite of what an equitably distributed prevention tool would look like.

The gap is not simply an awareness gap, though awareness gaps are real and well documented in specific subpopulations. Among people who inject drugs surveyed in Portland, Oregon, only 15% of the sample was aware of PrEP at all, a strikingly low figure given how squarely injection drug use sits within CDC PrEP eligibility criteria [12]. A follow-up comparison of the same population surveyed again several years later found that awareness had more than doubled, from 17% in 2018 to 33% in 2022, but that PrEP access and actual

use had not meaningfully changed over the same period and remained rare in both years -- awareness moved, uptake did not [13]. That dissociation between awareness and use recurs, in a different form, among Black men who have sex with men, where the gap is not primarily an awareness problem at all. Adeagbo and colleagues, synthesizing surveillance data on Black men who have sex with men in the Southern United States, report that 78.3% of Black men who have sex with men surveyed in 2017 were aware of PrEP, yet only 18.8% had ever used it, and that in one state-level snapshot, of 9,040 adults meeting PrEP indications, only 590 -- 6.5% -- had actually received a prescription [14]. Sullivan and Eaton's Atlanta-based study of Black men who have sex with men finds an almost identical pattern with an even wider gap: 88.7% awareness against only 10.1% who had ever used PrEP [5]. Read together, these figures make a specific point: for Black men who have sex with men in the U.S. South, the uptake problem is overwhelmingly a conversion problem -- turning awareness into an actual initiated, sustained prescription -- rather than an information-deficit problem, which has direct implications for where intervention resources should be aimed.

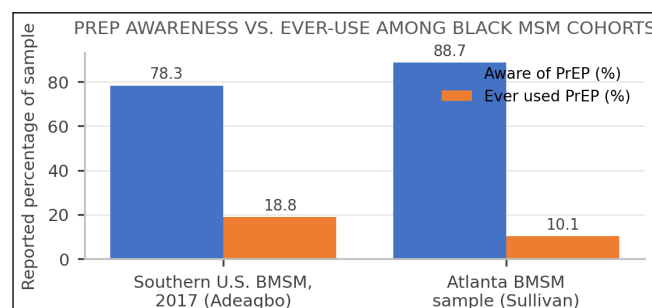


Figure 1: PrEP awareness versus ever-use among two U.S. Black men-who-have-sex-with-men cohorts, illustrating that the uptake gap in this population is overwhelmingly a conversion problem rather than an information-deficit problem -- most surveyed men already know PrEP exists, but very few have ever used it [14,5].

4. Individual and Interpersonal Barriers: Stigma, Disclosure, and Medical Mistrust

Stigma is the barrier most consistently named across the qualitative and mixed-methods PrEP literature, and it operates on at least two distinct levels that the field has found useful to distinguish empirically. Algarin and colleagues developed and validated the Community PrEP-Related Stigma Scale specifically to capture the first of these: stigma an individual anticipates or perceives from their broader community -- family, neighbors, sexual partners -- as a consequence of being

seen taking or requesting PrEP, independent of any stigma encountered inside a clinical encounter [15]. Siegler and colleagues took a complementary approach, validating an HIV PrEP-specific stigma scale using both Likert and semantic-differential item formats and demonstrating that PrEP stigma is measurable, internally consistent, and behaviorally consequential rather than a vague background sentiment too diffuse to study rigorously [16]. The existence of two independently developed, psychometrically validated PrEP stigma instruments within roughly a year of each other is itself a signal of how central the construct had become to the field's understanding of uptake by the early 2020s.

What these stigma measures pick up on in practice is a fairly specific and recurring set of anxieties: that carrying PrEP, filling a PrEP prescription at a local pharmacy, or being seen at a clinic associated with sexual health services will be read by others as an admission of behavior the person does not want disclosed, whether that is same-sex sexual activity, non-monogamy, or injection drug use. Sullivan and Eaton frame this explicitly as a syndemic phenomenon among Black men who have sex with men in Atlanta: PrEP stigma rarely occurs in isolation, but co-occurs with and compounds other psychosocial stressors -- depression, substance use, experiences of racial discrimination, and internalized homophobia -- such that participants carrying a higher burden of these co-occurring conditions were significantly less likely to have ever used PrEP, even though awareness of PrEP did not differ much by syndemic burden [5]. That finding matters for intervention design because it implies that stigma-reduction messaging aimed only at PrEP itself, without addressing the broader psychosocial context PrEP-related stigma is embedded in, is likely to under-perform relative to interventions that treat PrEP uptake as one outcome among several connected to a person's overall psychosocial burden.

A second, distinct interpersonal barrier is medical mistrust, which is conceptually related to stigma but analytically separable from it: stigma concerns what other people will think of a person for using PrEP, while mistrust concerns whether a person believes the healthcare system offering PrEP has their interests at heart in the first place. Powell and colleagues, studying African American men's preventive health screening

behavior more broadly, found that medical mistrust -- shaped by historical experiences of medical racism, including but not limited to the Tuskegee syphilis study's long shadow, along with more recent personal experiences of discrimination in clinical encounters -- was independently associated with delayed engagement with preventive health services, a pattern the PrEP-specific literature has repeatedly found applies to PrEP initiation as well [17]. Adeagbo and colleagues name "mistrust of healthcare systems" and "negative attitudes from healthcare providers" explicitly among the barriers obstructing PrEP uptake among Black men who have sex with men in the Southern United States, alongside stigma and homophobia [14]. The practical upshot is that a clinic can address every structural barrier -- free PrEP, walk-in availability, a location on a bus line -- and a patient can still decline to initiate or persist on PrEP if the interaction with the prescribing clinician itself feels adversarial, judgmental, or unsafe to disclose sexual or drug-use history within, which is precisely the mechanism several qualitative studies of transgender PrEP experience describe as well [18].

5. Structural and Health-System Barriers: Cost, Access Deserts, and Provider Readiness

Structural barriers are, in one sense, more tractable than stigma and mistrust, because they are policy-addressable in a fairly direct way -- and the recent trend data bear that out to some degree, even as significant gaps remain. D'Angelo and colleagues, tracking self-reported cost and insurance barriers to PrEP among a U.S. cohort surveyed in both 2019 and 2021, found a substantial decline in the proportion reporting difficulty paying for PrEP medication itself, from 20.8% in 2019 to 6.4% in 2021, a period that coincides with expanded insurance mandates and manufacturer copay-assistance programs for PrEP [19]. That is genuine progress, and it is a useful demonstration that policy levers aimed narrowly at drug cost can move the needle on a specific, well-defined barrier relatively quickly. But the same study found that people who had discontinued PrEP within the past year were significantly more likely than continuing users to report having experienced most categories of PrEP-related cost and insurance challenges, which suggests that even a declining aggregate cost-barrier rate can still be concentrated enough among the people at highest risk of discontinuation to matter clinically [19].

Table 1: Representative structural and health-system barrier indicators reported in the PrEP uptake literature, with the direction and magnitude of change each cited study reports. [4,19,20,21].

Indicator	Source	Reported Baseline / Comparator	Reported Change or Current Level
National PrEP-to-need ratio (prescribed vs. eligible)	Jackson et al. [4]	Est. 1.2 million eligible in the U.S.	~25% prescribed; national target is 50% coverage by 2030
Self-reported difficulty paying for PrEP medication	D'Angelo et al. [19]	20.8% reported difficulty in 2019	Fell to 6.4% reporting difficulty in 2021
U.S. population living in a "PrEP desert" county	Kane [20]	~191.1 million residents in 2020	Fell to ~73.1 million residents in 2023
U.S. population in highest-need PrEP deserts	Kane [20]	~10.5 million residents in 2020	Fell to ~2.2 million residents in 2023; 5 states still worsened
Late-adopter primary care providers reporting PrEP knowledge/comfort gaps	Sell et al. [21]	Rural and suburban late-adopter clinicians surveyed	Persistent knowledge and comfort gaps directly predicted lower prescribing

Geographic access to a PrEP-prescribing clinician is a second structural barrier with its own, more uneven trajectory. Kane's analysis of "PrEP deserts" -- U.S. counties with high need but limited or no nearby PrEP-prescribing capacity -- documents real aggregate improvement: the population living in a PrEP desert fell from roughly 191.1 million in 2020 to about 73.1 million in 2023, and the population in the highest-need deserts fell from roughly 10.5 million to 2.2 million over the same period, driven substantially by more than five million residents in Ending the HIV Epidemic priority jurisdictions gaining geographic access to a PrEP provider [20]. Yet the same analysis found the improvement was not universal: five states -- Alaska, Alabama, Kentucky, Maine, and Montana -- saw their PrEP-desert populations increase rather than decrease over the study period, certain rural areas developed new access gaps even within states that improved overall, and communities of color in some states saw access decline even as state-level averages improved, meaning the aggregate trend line can mask a widening, rather than narrowing, disparity for the specific populations bearing the highest HIV incidence [20]. This is a recurring pattern across the structural-barriers literature: national or state-level averages improve while

the subpopulations the intervention was most needed for see slower gains or, in some cases, none at all.

Table 1 summarizes several of these structural and access-related findings side by side, because the individual figures are easy to lose track of in isolation but form a coherent pattern when placed next to one another: cost barriers falling, geographic deserts shrinking in aggregate but not universally, and a persistent prescription-to-need gap that none of the cost or geography improvements have yet closed.

Provider-side readiness is the third structural barrier, and arguably the one most directly under a health system's own control, since it concerns clinician knowledge, comfort, and behavior rather than patient-side cost or geography. Sell and colleagues surveyed primary care providers identified as comparatively late adopters of PrEP prescribing, concentrated in rural and suburban practice, and found persistent gaps in PrEP-specific knowledge and comfort discussing sexual history and drug use with patients, gaps that directly predicted lower rates of PrEP prescribing even among providers who reported general awareness that PrEP existed and was recommended by guidelines [21]. This provider-level finding dovetails with the patient-reported "negative attitudes from healthcare providers" that Adeagbo and colleagues identify as a barrier from the patient side [14]: a provider who is uncertain how to open a nonjudgmental conversation about a patient's sexual practices or drug use is, functionally, producing the same chilling effect on disclosure and PrEP discussion that an openly stigmatizing provider would, even without any hostile intent. Expanding PrEP-prescribing capacity into primary care, rather than concentrating it in specialty sexual-health clinics, is frequently proposed as a structural fix for geographic and stigma barriers simultaneously -- a patient can see a familiar primary care provider rather than a specialist whose clinic itself signals what the visit is about -- but that fix only works to the extent primary care providers are actually equipped and comfortable prescribing, which the evidence suggests is not yet reliably the case outside of PrEP-experienced practices [21].

6. Barriers Specific to Priority Subpopulations

The barriers described so far recur across populations, but they combine differently, and in some cases entirely different additional barriers appear, once the population

in question shifts away from the cisgender men who have sex with men on whom much of the earliest U.S. PrEP-delivery literature concentrated. Four subpopulations illustrate this well: transgender communities, people who inject drugs, cisgender women, and young people.

For transgender and gender-diverse patients, Bruxvoort and colleagues, studying PrEP barriers and facilitators within an integrated U.S. health system, found that gender-affirming care and PrEP care were frequently experienced as competing priorities rather than complementary ones -- patients reported concern that a PrEP-related visit could crowd out limited clinical time better spent on gender-affirming hormone therapy, and separately reported concern, grounded in real prior experience for some, that clinicians insufficiently trained in transgender health would misgender them or otherwise handle the encounter poorly, a concern that functions as its own distinct barrier layered on top of general PrEP stigma [18]. A systematic review of the PrEP continuum of care among Latinx sexual-minoritized men and transgender women finds a structurally similar pattern, with immigration status, language-concordant care availability, and family-of-origin attitudes toward sexuality forming an additional, culturally specific layer of barriers on top of the cost, stigma, and provider-trust barriers already documented in the broader literature [22]. A broader systematic review of PrEP uptake barriers among men who have sex with men and transgender women in the United States similarly finds that intersecting stigma -- around sexual orientation or gender identity, HIV risk, and in many cases race simultaneously -- combines with these access and provider-trust barriers in ways that are not simply additive; a transgender woman of color, for instance, may face separate independent barriers related to each of those three intersecting identities rather than a single generic "PrEP barrier" that a single intervention could address [23].

For people who inject drugs, the barriers literature diverges further still, because for this population, unlike men who have sex with men, awareness itself remains a genuine bottleneck rather than a solved problem sitting upstream of a conversion failure. Spencer and colleagues' Portland studies, discussed above, found only 15% awareness of PrEP among people who inject drugs in an initial survey and, in a later comparison,

awareness that had risen to only 33% even after several years of expanded outreach, with actual access and use remaining rare and statistically unchanged across the study period [12,13]. This population also faces a barrier largely absent from the men-who-have-sex-with-men literature: many syringe-service and harm-reduction programs, which are often the point of greatest engagement people who inject drugs have with any health service at all, have historically been structured around syringe access and overdose prevention rather than sexual-health or PrEP referral, meaning the population most reachable through harm-reduction infrastructure is often not being reached with PrEP-specific messaging through that same infrastructure, a gap several of the studies synthesized here explicitly flag as an underused opportunity for co-located service delivery [13].

Cisgender women, both in the U.S. and in the high-incidence settings of sub-Saharan Africa where the original heterosexual efficacy trials were conducted, face a version of the uptake gap shaped heavily by how HIV risk itself is perceived and discussed. The VOICE trial's near-total adherence failure despite genuine HIV risk in its participant population remains, more than a decade later, one of the field's clearest illustrations that a woman's stated willingness to use PrEP in a trial-enrollment conversation does not reliably predict sustained daily use once she is back in a household and relationship context where a visible pill bottle, or a request to a partner for support attending a clinic appointment, can itself become a source of the same disclosure risk and interpersonal stigma discussed earlier in this article, now inflected by gendered power dynamics within a relationship rather than by the community-level stigma more central to the men-who-have-sex-with-men literature [7]. This is part of why HPTN 084's finding, that injectable cabotegravir delivered at a clinic visit produced a far larger relative benefit over oral PrEP in women specifically than the equivalent injectable-versus-oral comparison produced in men and transgender women in HPTN 083, is read by much of the field as evidence about adherence barriers specific to women's daily-pill circumstances rather than as evidence about any difference in the drug's biological performance by sex [9,8].

Adolescents and young adults, finally, face a barrier category that is largely structural rather than

psychosocial in a narrow sense: in many U.S. states, minor consent law for sexual-health services does not clearly or consistently extend to PrEP prescribing and dispensing without parental involvement, which means a sexually active adolescent at substantial HIV risk may be unable to access PrEP confidentially even where clinical guidelines fully support prescribing it to them, and even where every other barrier discussed in this article -- cost, geography, provider willingness -- has otherwise been addressed. The global synthesis by Ngwoke and colleagues, reviewing barriers and facilitators of oral PrEP uptake across priority populations worldwide, identifies consent and confidentiality requirements as a recurring structural barrier specific to adolescents and young people across multiple national contexts, distinct from the cost and stigma barriers dominating the adult literature [24].

7. Long-Acting Formulations as a Partial Structural Fix

It is tempting to read the long-acting injectable trial results -- cabotegravir's superiority over oral PrEP in both HPTN 083 and HPTN 084, and lenacapavir's essentially complete protection in PURPOSE 1 and PURPOSE 2 -- as evidence that the uptake-barriers problem this article has been describing is now substantially solved by drug delivery engineering rather than requiring the harder, slower work of addressing stigma, mistrust, and structural access directly [8,9,3,10]. That reading is too optimistic, though it is not entirely wrong either. A twice-yearly injection genuinely does eliminate the daily-adherence burden that VOICE showed was catastrophic for oral PrEP's real-world effectiveness in some populations, and it plausibly reduces one specific stigma vector -- a visible pill bottle at home, a daily reminder alarm on a phone -- that several qualitative studies name as a source of disclosure risk [7]. The CDC's 2025 clinical recommendation for injectable lenacapavir explicitly frames reduced dosing frequency as an equity-relevant feature of the drug, not merely a convenience one, precisely because it is expected to help patients for whom daily-pill logistics were the dominant barrier [11].

But a twice-yearly injection does not, on its own, address medical mistrust of the clinician administering it; if anything, it may deepen the dependence on a trusted, accessible clinical relationship, since a patient can no longer simply refill a prescription at a pharmacy without

a clinic visit, and instead must return to a clinical setting for the injection itself twice a year, at minimum. It does not address geographic PrEP deserts, since the injection still requires a clinician licensed and willing to administer it, quite possibly the same subset of providers already identified as insufficiently PrEP-comfortable in the oral-PrEP prescribing literature [21,20]. And it does nothing at all to resolve the confidential-access problem facing adolescents, or the syringe-service co-location gap facing people who inject drugs. The honest reading of the long-acting-formulation evidence, in other words, is that it removes one real and well-documented barrier -- daily adherence burden -- while leaving essentially every other barrier this article has surveyed in place, and in the case of clinic-visit dependency, potentially making the health-system-access barrier somewhat more, rather than less, load-bearing for overall uptake.

8. Open Challenges

Several gaps recur across the literature synthesized here and are worth naming directly. First, most of the barriers literature is descriptive and cross-sectional -- it documents what stops people from initiating or persisting on PrEP with real rigor, but comparatively few studies test interventions designed to remove a specific named barrier and then measure the resulting change in uptake, which means the field can say with confidence what the barriers are but with considerably less confidence which interventions reliably move the needle on any given one at scale. Second, syndemic and intersectional barriers are conceptually well established in this literature -- Sullivan and Eaton's Atlanta findings and the intersectional analysis in the men-who-have-sex-with-men-and-transgender-women systematic review both make this point explicitly [5,23] -- but intervention design in practice still tends to target one barrier category at a time (a cost-reduction program, a stigma-reduction media campaign, a provider training module), rather than the combined, co-occurring barrier profile most PrEP-eligible people who are not on PrEP actually present with.

Third, the PrEP-desert and cost-barrier trend data reviewed here show genuine national improvement alongside real, documented pockets of worsening access for specific states and specific racial and ethnic groups within otherwise-improving states [20,19]; national aggregate statistics are, on this evidence, an unreliable

proxy for whether the highest-need populations are actually being reached, and future evaluation of PrEP-access policy should weight subgroup and geographic disaggregation more heavily than it currently does. Fourth, the evidence base for people who inject drugs remains comparatively thin relative to the men-who-have-sex-with-men literature, with awareness itself still the binding constraint in the most recent available data rather than a solved precondition, and with harm-reduction-service co-location as a delivery model still more discussed as a promising direction than established as an evaluated one [12,13]. Fifth, and specific to the newest long-acting formulations, real-world uptake and equity data for injectable lenacapavir barely exist yet given how recently it was approved; the trial populations were large and multinational, but whether the same disparities documented for oral PrEP over the past decade will simply re-emerge for the injectable formulations, or whether the reduced dosing burden will meaningfully narrow them, is an empirical question the field will only be able to answer once several more years of real-world prescribing data accumulate.

Sixth, much of the barriers literature synthesized here is U.S.-centric, reflecting where the largest share of qualitative and survey-based PrEP-uptake research has been conducted; the global synthesis by Ngwoke and colleagues is a useful corrective, but there remains comparatively little barrier-specific evidence from the countries and regions carrying the largest share of the global HIV epidemic outside the trial contexts themselves, and generalizing U.S.-derived barrier categories, particularly around insurance and cost, to health systems structured entirely differently risks importing an analytic frame that does not transfer cleanly [24].

9. Conclusion

The literature reviewed here supports a fairly specific claim: PrEP's efficacy problem has been solved, repeatedly and decisively, across successive drug formulations and across the men who have sex with men, heterosexual, and transgender populations in which it has been tested [1,2,6,8,9,3,10]. What remains substantially unsolved is the uptake problem, and the uptake problem is not one barrier but a small, recurring, and well-documented set of them -- anticipated community and provider stigma, medical mistrust

rooted in real historical and ongoing experience, direct and indirect costs that have improved but not disappeared, geographic access that has improved in aggregate while worsening for specific communities, and provider-side knowledge and comfort gaps that are arguably the most directly fixable of the group and yet remain persistently under-addressed [4,15,17,19,20,21].

These barriers combine differently for different populations rather than applying uniformly, which is the central reason a synthesis organized only around "barriers to PrEP" in the abstract, without attention to how those barriers manifest specifically for Black men who have sex with men in the U.S. South, for transgender patients balancing PrEP against gender-affirming care priorities, for people who inject drugs whose awareness gap remains the binding constraint, for women navigating disclosure risk within relationships, and for adolescents facing confidentiality-law barriers regardless of clinical eligibility, risks producing recommendations too generic to actually close the gap for any one of them [18,13,7,24]. Long-acting injectable formulations, cabotegravir and now lenacapavir, represent genuine progress against exactly one of these barriers -- daily adherence burden -- and deserve to be read as such, but the evidence surveyed here does not support treating a better drug-delivery mechanism as a substitute for the harder, slower, and more differentiated work of addressing stigma, mistrust, cost, geography, and provider readiness directly, population by population, rather than assuming a single fix will close a gap this literature has shown, repeatedly, to be layered rather than singular.

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Conflict of Interest

The authors declare that they have no competing interests relevant to this work.

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This article is a literature synthesis and did not generate new primary data; all findings discussed are drawn from the cited published sources, which should be consulted directly for their own underlying data and code collection of primary clinical or behavioral data.

Ethical Approval

Not applicable. As a literature synthesis, this article did not involve human participants, animal subjects, or the collection of primary clinical or behavioral data.

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