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Promises and Challenges: Cabotegravir for PrEP

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Abstract

Purpose of Review: Tenofovir-based oral PrEP has been effective in reducing population-level HIV incidence in multiple settings, although disparities remain. Injectable cabotegravir-based PrEP is an alternative that may be attractive to individuals with adherence challenges or who do not desire to take a daily medication. We review promises and challenges of cabotegravir-based PrEP.

Recent Findings: Cabotegravir has demonstrated higher effectiveness than oral PrEP in two randomized trials, with a hazard ratio of 0.31 for HIV incidence among men who have sex with men and transgender women across multiple settings (95% confidence interval (CI)=0.18–0.62) and 0.11 for cisgender women in sub-Saharan Africa (95% CI=0.04–0.32). Cabotegravir was also highly effective among populations with disproportionate HIV incidence. Although cabotegravir breakthrough was rare, diagnosis was delayed with use of antigen/antibody-based HIV tests, and resistance occurred with breakthrough infections. Implementation will need to overcome several challenges, including HIV RNA laboratory monitoring not being widely available, requirement for additional staff time and clinic space, and need to provide oral medication during interruptions in dosing.

Summary: Cabotegravir-based PrEP is a highly effective additional PrEP option that will expand HIV prevention options. For successful roll-out, strategies for streamlined and accessible delivery of cabotegravir in real-world settings will need to be developed.

Keywords

long-acting cabotegravir; injectable PrEP; real-world implementation

Introduction

Tenofovir-based oral pre-exposure prophylaxis (PrEP) has been effective in dramatically reducing population-level HIV incidence in multiple districts, including London,[1] San

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Francisco,[2] New South Wales,[3, 4] and in rural Kenya and Uganda.[5] Despite these successes, PrEP has not decreased HIV incidence equally, with youth, cisgender women, and Black populations continuing to experience a disproportionate number of both incident and prevalent HIV infections.[6–9] To realize PrEP's benefits, individuals need to both initiate PrEP and remain on PrEP during periods at-risk.[10, 11] In multiple studies, reasons for stopping or never initiating PrEP include, in addition to challenges accessing the medication, low self-perceived risk, concerns about medication side effects or a desire not to take a daily pill, stigma, or competing life events.[11–14] Long-acting PrEP agents have the potential to address some of these concerns by providing consistent protection through infrequent, discrete administration, avoiding the need to take a daily medication.[15, 16] This review will discuss the promises and challenges of real-world cabotegravir implementation.

Review: Results from Phase 3 Trials of Injectable PrEP

Two large randomized controlled trials (RCTs) have demonstrated the effectiveness of injectable cabotegravir when compared to oral tenofovir-disoproxil-fumarate/emtricitabine (TDF/FTC) PrEP: HIV Prevention Trials Network (HPTN) Study 083 and HPTN Study 084. HPTN 083 is a double-blind double-dummy RCT which assessed the effectiveness of every-8-week cabotegravir for PrEP compared to oral TDF/FTC PrEP among cisgender men and transgender women at 43 sites in the United States, Latin America, Asia, and Africa using a non-inferiority study design.[17] Overall, 4,566 participants, of whom 12.5% were transgender women, were assigned 1:1 to injectable cabotegravir given every 8 weeks or daily oral TDF/FTC PrEP, and were followed for 153 weeks during the blinded phase of the study. Among the 1698 participants enrolled in the United States, 49.8% were Black. The blinded portion of the study was stopped early for efficacy, with injectable cabotegravir demonstrating superiority over TDF/FTC with a hazard ratio of 0.34 for HIV incidence when compared to TDF/FTC [95% confidence interval (CI)=0.18–0.62], with an incidence of 0.41 and 1.22 per 100 person-years in the cabotegravir and TDF/FTC arms respectively in the pre-specified analysis.[17] HIV infection was identified after enrollment in 51 participants, with only 12 occurring in the cabotegravir group.[18] When examining sub-groups, the magnitude and direction of the effectiveness of cabotegravir was preserved among populations who have historically experienced greater adherence challenges with TDF/FTC PrEP, including among youth, transgender women, and U.S. Black participants. In the open label phase, the HIV incidence increased in both the cabotegravir and TDF/FTC arms (0.54 vs. 1.57 per 100 person-years), related at least in part to lower adherence in both arms, although the hazard ratio remained the same when comparing both arms (0.34 95% CI:0.22–0.53).[20]

HPTN 084 is a similarly designed study among cisgender women in Eastern and Southern Africa, that used a superiority study design. Overall, 3,223 cisgender women were enrolled, with 57% of participants 18–25 years old. Of the 38 incident infections occurring in the study, only 4 occurred in the cabotegravir arm, providing a hazard ratio of 0.11 for HIV infection compared to TDF/FTC (95% CI=0.04–0.32), also demonstrating superiority of cabotegravir compared to TDF/FTC.[19] There were no differences in treatment effect among younger participants (age<26).

Potential Advantages of Injectable Cabotegravir

Given injectable cabotegravir's high effectiveness in these two phase 3 clinical trials, cabotegravir's roll-out is expected to contribute significantly to expanding HIV prevention options. Although TDF/FTC can achieve near-perfect efficacy for prevention of HIV sexual transmission with high adherence, significant adherence challenges have been documented among populations at highest risk of HIV infection.[6, 7, 9] Injectable cabotegravir obviates the need for daily, potentially-stigmatizing adherence behavior (daily pill-taking) but requires that the participant to present every-8-weeks to receive the injection. While some PrEP users will prefer to continue or start oral PrEP, some PrEP users will prefer an injectable option. Participants have reported equal or higher acceptability for a hypothetical injectable PrEP option; including among sub-Saharan African men and women,[16, 21–23] and U.S.-based cisgender women;[24] while 74% of U.S.-based men who have sex with men (MSM) reported a high likelihood of using injectable PrEP.[25] There was particularly high interest among individuals not willing to take oral PrEP due to desire to avoid taking a daily pill, or those with concerns about stigma from daily pill-taking.[26–28] Data from the contraceptive literature have suggested that the availability of choice of contraceptive options leads to higher overall uptake,[29] which is hypothesized to hold true for HIV prevention strategies given varying preferences for oral vs. injectable PrEP among populations at-risk for HIV.[30]

Several innovations in cabotegravir delivery are likely to enhance acceptability, including the ability to bypass an oral lead-in phase, which although part of the original randomized studies, is now being offered as optional in the open-label extensions of HPTN 083 and 084.[31] "Direct to inject" cabotegravir appears viable because, aside from injection site reactions (ISRs), injectable cabotegravir has a very low rate of adverse events and excellent tolerability, as evidenced by the low rate of injection discontinuations in HPTN 083/084.[17, 19] Weight gain was initially a concern with integrase inhibitor-based PrEP given dramatic increases in post-treatment body weight among people living with HIV who initiated dolutegravir-based antiretroviral therapy (ART).[32] However, in HPTN 083, body weight increased only 1.23 kg/year (95% CI=1.05–1.42) as compared to 0.37 kg/year in the TDF/FTC group (95% CI=0.18–0.55), with no difference in weight gain after week 40. In HPTN 084, there were weight increases of 2.4kg/year on cabotegravir and 2.2kg/year on TDF/FTC, which was not significantly different (p=0.12).[19] As differences in weight gain were not seen in a phase 2 study comparing cabotegravir and placebo (HPTN 077),[33] differences in weight gain may be driven by weight suppressive effects of TDF, rather than the weight gain being driven by cabotegravir.[34]

Given disproportionately low uptake and adherence with oral PrEP for youth, Black MSM, and transgender women, these populations have experienced worsening disparities in HIV diagnoses in the PrEP era.[6–8, 35–37] It is therefore reassuring that injectable cabotegravir has demonstrated comparable effectiveness among youth, Black MSM, and transgender women in clinical trials. The high effectiveness of injectable cabotegravir in HPTN 084 supports it as a particularly exciting option for women in sub-Saharan at-risk of HIV given prior documented adherence challenges among cisgender women in non-serodiscordant partnerships.[38–40] However, advantages in bypassing daily adherence behavior may not be

realized if individuals cannot access injectable PrEP or do not return for repeat injections. Additional data from delivery of injectable PrEP in real-world settings will be needed to support roll-out and national program decisions to include injectable PrEP as part of prevention services.

Potential Challenges of Injectable Cabotegravir as PrEP: HIV Diagnosis, Delivery, the Pharmacokinetic "Tail"

A key challenge with the implementation of injectable cabotegravir as PrEP is its impact on diagnosis of breakthrough HIV infections. In HPTN 083, in 21 of 58 cases of HIV infection, study sites did not detect HIV infection at least one study visit using an HIV screening algorithm that included fourth generation antigen/antibody testing.[18] All 4 baseline infections and 7 of 12 incident cases were missed for at least one visit, with those experiencing a delay having a median delay of 98 days (range 35–185) and a median delay of 34 days (range 14–36) in the TDF/FTC arm. It should be noted that the delay in TDF/FTC arm detection likely was significantly shorter than 34 days, but an administrative bias from the interval of testing provided the result of 34 days. This source of bias is critical to the interpretation of this finding, as it has been occasionally misinterpreted. In the TDF/FTC arm only 7 of 39 incident infections were missed using the same testing algorithm, in addition to the 3 baseline infections.[18] Nearly all of these cases would have been detected at an earlier visit through use of an HIV RNA assay for screening, which could have permitted more immediate initiation of ART. As a result of these findings, the 2021 update of the CDC PrEP guidelines recommends HIV RNA testing at cabotegravir initiation and at every 8-week follow-up visit; indeed the US FDA prescribing information also recommends the use of an HIV RNA assay that is US FDA cleared for diagnostic use. Currently, the only assays that are so-cleared are the Hologic Aptima assay, and the Roche Cobas HIV-1/HIV-2 Qualitative Test. The use of every 8-weeks HIV RNA testing at each clinical visit is being further evaluated in the HPTN 083 and 084 open-label extensions.[18] Both quantitative and qualitative viral load testing is expensive and could cause implementation of cabotegravir-based PrEP to remain limited in low- and middle-income countries (LMICs) should these testing requirements be also adopted by other regulatory agencies and guideline panels. Although pooling of HIV viral load specimens, with individual confirmatory testing performed only when the pooled specimen is positive, can help to reduce these costs,[41] this approach may reduce sensitivity and may not be feasible in lower volume PrEP programs or those that perform high volume HIV RNA testing for HIV treatment, or in regions where such assays are unavailable. In order to determine if the additional resource investment required to implement more sensitive diagnostics is cost-effective in these settings, additional data are needed–which include insights into the timing and tempo of evolution of INSTI resistance, considerations of risk for occult transmission to others, and implications for personal health. Importantly, the number of HIV infections that could be averted using cabotegravir PrEP compared to oral PrEP is likely to favor leveraging of the most sensitive HIV testing routinely available for screening when using cabotegravir, even when RNA-based assays are not available or practical.

In addition to the potential need for HIV RNA testing, there are other implementation challenges that will need to be addressed with the roll-out of cabotegravir as PrEP. The implementation of cabotegravir/rilpivirine as HIV treatment in U.S. settings provides an important example of the barriers facing the implementation of LAI PrEP.[42, 43] The need for prior-authorization in most contexts, as opposed to a “buy-and-bill mechanism,” that would allow the drug to be stocked in clinics for easy use, has increased administrative staff burden, cumbersome prior authorization processes, and delays in access. Injectable cabotegravir requires gluteal administration by a licensed provider, and is not approved currently to be self-administered by the patient. This has additional impact on clinic flow, space, and staffing, given the need for additional exam rooms for injections and more frequent in-person clinic visits for patients. As a result of these implementation challenges, uptake of injectable cabotegravir/rilpivirine as ART has been slower than expected, and has not been incorporated into the ART programs for LMICs.[43] Successful streamlining of clinic visits and recruitment of patients motivated to switch to long-acting ART have been key factors in success of cabotegravir/rilpivirine implementation,[44] and will likely need to be replicated with cabotegravir PrEP implementation.

Providers will also need to review contraindications of cabotegravir use, including the use of rifampin and rifapentine, some anticonvulsants including carbamazepine, oxcarbazepine, or phenytoin, as well as coadministration of drugs which could impact metabolism via uridine diphosphate-glucuronosyltransferase (UGT)1A1. Individuals with fillers and buttock implants were excluded from the HPTN registrational studies out of safety concerns, although injection into the thigh is being studied within the FLAIR cabotegravir/rilpivirine treatment study–results of safety and pharmacokinetic equivalence of these anterior thigh injections are eagerly anticipated. ISRs are common with injectable cabotegravir, with 81.4% vs. 31.3% of the TDF/FTC group who received at least one injection experiencing an ISR, although most of these ISRs were mild and were described as pain or tenderness at the injection site and were mostly of 1–2 days duration and self-limited. Of the 2,117 participants who received at least one active cabotegravir injection, only 2.4% discontinued the injections due to an injection-related adverse event. Nevertheless, providers will need to become comfortable with the management of ISRs during cabotegravir implementation. Lastly, there is potential for additional costs accrued by patients and delivery programs when compared to TDF/FTC oral PrEP, which is now available generically. Benefit navigators, administrative staff, and/or pharmacists therefore have important roles in the delivery of injectable cabotegravir PrEP.

The pharmacologic “tail” of injectable cabotegravir is often cited as an additional concern for cabotegravir roll-out.[45] In the phase 2 HPTN 077 study, 13% of cisgender male and 42% of cisgender females had detectable cabotegravir concentrations 76 weeks following the last injection.[46] While the long pharmacologic tail of cabotegravir provides forgiveness for delayed doses and could even potentially support quarterly dosing among cisgender women, the persistence of detectable drug at low concentrations could increase chances of development of resistance if HIV acquisitions were to occur during that period of decay. Reassuringly, in HPTN 083, there was no evidence of integrase resistance in any of the 3 individuals who were diagnosed with incident HIV infection during the “tail” phase.[18] However, additional data from the HPTN 083/084 open-label extensions, and

real-world cohorts will be needed to confirm that significant integrase inhibitor resistance does not occur during HIV acquisition during the cabotegravir tail phase. Provision of oral "bridging" during periods in which access to injectable cabotegravir is interrupted and best available HIV prevention services after cabotegravir discontinuation, is expected to prevent development of cabotegravir resistance in the setting of PrEP failure, and should be emphasized in roll-out efforts. In the registrational studies, 48 weeks of oral TDF/FTC was used to "cover the tail" beginning 8 weeks after the final injection of cabotegravir. A significant challenge will occur among individuals who stop cabotegravir PrEP due to decreased self-perceived risk of HIV infection as motivation to continue oral PrEP could wane; further, those challenged historically by daily oral pill taking may not succeed when asked to use daily oral interventions either as "bridging" or as "tail" coverage.

Although cabotegravir failure is rare, integrase inhibitor resistance can occur with PrEP breakthrough, with 1 of 4 individuals demonstrating evidence of integrase resistance who initiated cabotegravir in the setting of acute HIV infection; 2 of 3 individuals who HIV-seroconverted during the oral lead-in period; and all 4 individuals who HIV-seroconverted despite on time cabotegravir injections.[18] No data are yet available on the ability to achieve virologic suppression using second-generation integrase inhibitor based ART (i.e. dolutegravir or bictegravir) following cabotegravir breakthrough. The cause of breakthrough in the 4 cases despite on time injections remains unclear. Possible explanations include the comparatively lower tissue drug levels in the rectum as compared to the plasma (cabotegravir partitions in rectal tissue at 8–10% of plasma concentrations),[47] inflammation related to rectal sexually transmitted infections, large exposure innocula, or other factors. Use of more sensitive HIV RNA testing could have potentially prevented development of HIV resistance in most of these cases, by identifying incident infection prior to the development of integrase resistance. This is an important concern given the transition to dolutegravir-based regimens as first-line ART regimens worldwide. In the setting of limited access to HIV viral load and resistance testing in some LMICs, it will be important to monitor cases of cabotegravir PrEP breakthrough carefully during roll-out to ensure that integrase resistance dose not increase significantly at a population level, particularly if the rate of on-time injections is lower in real-world settings or if HIV monitoring adherence is not perfect.[48] In LMICs, treatment of individuals who experience breakthrough on cabotegravir will likely require protease inhibitor-based regimen usage given limited access to genotyping, or NNRTI-based regimens if NNRTI resistance can be excluded.

Conclusion:

Several ongoing studies will facilitate cabotegravir's implementation and are eagerly anticipated, including bridging trials in adolescents, and of alternate injection sites such as the thigh (being examined in FLAIR), as well as pregnancy data from the 084 open-label extension. The implementation lifecycle will also require study of strategies that could potentially facilitate its uptake, including new care delivery models such as integrated care with contraception and/or gender-affirming hormone therapy, mobile or more convenient administration through drop-in clinics, pharmacy and other non-traditional venue administration, and mHealth technologies to facilitate on-time injections. As roll-out continues, cabotegravir-based PrEP is expected to contribute significantly to global efforts

to end the HIV epidemic due to its ability to avoid daily consumer-initiated dosing, while providing protection through discrete administration, potentially reducing stigma, with high efficacy and tolerability.

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Key Points:

- Oral tenofovir-based PrEP is highly effective, but disparities remain due to lower PrEP uptake and adherence among populations disproportionately impacted by the HIV epidemic
- Injectable cabotegravir-based PrEP has demonstrated higher effectiveness than oral tenofovir-based PrEP in two randomized clinical trials among men who have sex with men and transgender women, as well as cisgender women in sub-Saharan Africa
- Expansion of HIV prevention options is likely to increase overall uptake of PrEP, with most populations surveyed expressing a strong willingness to try injectable PrEP
- Cabotegravir implementation will need to overcome challenges regarding delayed HIV diagnosis, access to HIV RNA testing, and streamlining of clinic procedures
- Additional data on breakthrough infections despite on time cabotegravir injections and resistance in real-world settings, as well as strategies for successful implementation and treatment monitoring is needed