The Journal for Nurse Practitioners 18 (2022) 947–950

Contents lists available at ScienceDirect

The Journal for Nurse Practitioners

journal homepage: www.npjournal.org

Injectable Cabotegravir: A New Approach to HIV Pre-exposure Prophylaxis

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Keywords:
AIDS
cabotegravir
HIV
HIV prevention
injectable
pre-exposure prophylaxis

A B S T R A C T

Pre-exposure prophylaxis (PrEP) involves use of antiretroviral medications to prevent HIV infection in higher-risk adolescent and adult populations. PrEP regimens conventionally used daily oral emtricitabine/tenofivir fumarate (FTC/TDF) or emtricitabine/tenofivir alafenamide (FTC/TAF). However, on December 20, 2021, the United States Food and Drug Administration approved use of injectable cabotegravir for PrEP in adolescents and adults. This article discusses indications and contraindications of injectable cabotegravir as PrEP, provides an overview of injectable cabotegravir's safety, efficacy, and regimen, contrasts traditional oral PrEP regimens with the injectable cabotegravir regimen, and examines cost and accessibility.

Introduction

This article (1) discusses indications and contraindications of injectable cabotegravir as pre-exposure prophylaxis (PrEP), (2) provides an overview of injectable cabotegravir's safety, efficacy, and regimen, (3) contrasts traditional oral PrEP regimens with the injectable cabotegravir regimen, and (4) examines issues surrounding cost and accessibility.

Impacts of Preventing HIV Through Pr-EP

PrEP consists of an antiretroviral agent that, in combination with safer sex practices, aims to reduce the risk of infection with type 1 HIV in adults and adolescents weighting at least 35 kg (77 lbs) and who are at increased risk of HIV infection.[1,2] Use of PrEP to prevent HIV infection is making notable advances in the United States (US).[3] Preliminary data from the Centers for Disease Control and Prevention indicate that by 2020, ~20% of the 1.2 million individuals with indications for PrEP were prescribed it.[4] This is a sharp increase from 2015, when the Centers for Disease Control and Prevention suggested just 3% of patients in which PrEP was indicated were prescribed it.[4] In concert with improved access to HIV treatment and screening, PrEP is attributed to the 8% decrease in new HIV infections seen in the US between 2015 and 2019, a drop from 37,800 to 34,800 new infections.[4] Use of PrEP is a major constituent of ending the HIV pandemic in the US, with a projected goal to increase its use to 50% in adults and adolescents at increased risk by 2030.[4]

Traditional PrEP Regimens

Until very recently, the pharmacologic regimen for PrEP consisted solely of use of 1 of 2 combination antiretroviral agents administered orally daily.[5] These agents were emtricitabine/tenofovir fumarate (FTC/TDF) 200 mg/300 mg (Truvada, Gilead Sciences, Inc) and emtricitabine/tenofovir alafenamide (FTC/TAF) 200 mg/25 mg (Descovy, Gilead Sciences, Inc).[5] Although firm adherence to the pharmacologic regimen is paramount,[6] engaging in safer sex practices, such as consistent use of condoms, has always been an important component of the PrEP regimen.[7] Clinical trials examining the efficacy of PrEP have supported it as highly effective in prevention of HIV infection.[8]

With strict adherence, data estimates show that both traditional oral forms of daily PrEP are ~99% effective at preventing sexually transmitted HIV infection.[8] Rates of efficacy in people who inject drugs (PWIDs) vary, with estimates ranging from 74% to 84%.[8] However, some of the data examining efficacy in PWIDs were derived from samples that included participants using tenofovir alone and also included participants for whom drug compliance was uncertain.[8] Efficacy in PWIDs may be improved with use of a daily 2-drug combination oral regimen, such as daily use of FTC/TDF or FTC/TAF. Very few breakthrough cases of HIV infection in those who were verifiably adherent to PrEP have been recorded, with these occurring solely in men who have sex with men (MSM).[8]

Research supports oral PrEP as reaching maximum serum concentration associated with protection from receptive anal intercourse at ~7 days; for receptive vaginal intercourse and injection drug use, maximum serum concentration for protection is found at 21 days.[8] An extended-release, injectable cabotegravir 600 mg suspension (Apretude, ViiV Healthcare) is a novel pharmacologic agent recently approved for PrEP.[9]

Evolution of Necessity of a Longer-Acting Injectable Agent for PrEP

Because efficacy of HIV prevention is so closely correlated to adherence to the traditional agents used in PrEP regimens (and

https://doi.org/10.1016/j.nurpra.2022.08.007
1555-4155/

Table 1
Points of Significance Regarding United States Food and Drug Administration Breakthrough Therapy Designation[9]

- Drug manufacturer requests Breakthrough Therapy designation
- Intent is to expedite the development and review of drugs used to treat a serious condition that preliminary clinical data suggests may demonstrate substantial improvement over available therapy on a clinically significant end point measuring effect on irreversible morbidity or mortality
  - Substantial improvement must be demonstrated as a "clear advantage" over available therapy
- Benefits of Breakthrough Therapy designation include:
  - All fast-track designation features
  - Intensive guidance on an efficient drug development program, beginning as early as Phase 1
  - Organizational commitment involving senior managers

because these regimens require daily oral administration), the need for a longer-acting agent for use as PrEP has been identified as important. Although young MSM are less likely to adhere to daily medication,[9] other interpersonal factors have also been identified as barriers to daily adherence including, but not limited to, substance abuse disorders, poverty, depression, and engagement in behaviors designed to conceal use of PrEP.[9]

Consequently, use of a medication capable of maintaining antiretroviral serum concentrations without requiring frequent administration could potentially improve adherence in these individuals.[9] In December 2021, the US Food and Drug Administration (FDA) approved cabotegravir extended-release, injectable 600-mg suspension as PrEP for adults and adolescents weighing >35 kg (77 lbs) at risk for sexually acquired HIV.[2,9] This approval came after cabotegravir was granted priority review by the FDA and was given the designation as a breakthrough therapy (Table 1).[2,9,10]

Clinical Pharmacology, Indications, Contraindications, and Interactions of Injectable Cabotegravir as PrEP

Cabotegravir is an HIV-1 integrase strand transfer inhibitor. Its mechanism of action consists of blocking the HIV enzyme integrase, which is vital to insertion of viral DNA into the DNA of the host cluster of differentiation 4-positive cell.[11] Injectable cabotegravir is indicated for PrEP in adults and adolescents who weigh at least 35 kg and who are at increased risk of HIV infection.[2,9,10,12] A thorough health history inclusive of a sexual history can help the nurse practitioner (NP) identify individual patient risk factors to determine which patients could benefit from PrEP (Table 2).[13] Before initiation of any PrEP regimen, including injectable cabotegravir, patients must have a documented negative HIV screening result.[11,12]

Cabotegravir is metabolized hepatically and excreted renally. No dosage adjustment is necessary for patients with mild (creatinine clearance [CrCl] >60 and <90 mL/min) or moderate renal impairment (CrCl >30 and <60 mL/min).[11] However, increased monitoring for adverse events is necessary in patients with severe renal impairment (CrCl between 15 and <30 mL/min) or end-stage renal disease (CrCl <15 mL/min). Cabotegravir is mostly (>99%) protein bound. Thus, dialysis is not expected to alter cabotegravir.[12]

Dosage adjustment of cabotegravir is unwarranted in patients with mild to moderate hepatic disease (Child-Pugh A or B).[12] However, the effect of severe hepatic impairment (Child-Pugh C) on it is unknown.[12]

Contraindications to prescribing injectable cabotegravir include prior hypersensitivity reactions to the drug or use of medications that induce uridine diphosphate glucuronosyltransferase 1A1—the sole enzyme responsible for the glucuronidation of bilirubin, allowing for its excretion—and other drug classes.[12] Concomitant use of these drugs may result in reduced plasma concentrations of cabotegravir.[12] Common examples of drugs that induce uridine diphosphate glucuronosyltransferase 1A1 include anticonvulants (carbamazepine, oxcarbazepine, phenobarbital, and phenytoin) and antimycobacterials (rifampin, rifapentine).[12]

Table 2
Behavioral Risk Factors for HIV Infection (Ranked by Risk)[12]

- Receptive anal intercourse (138 of 10,000 exposures)
- Needle sharing during injection drug use (63 of 10,000 exposures)
- Insertive anal intercourse (11 of 10,000 exposures)
- Receptive penile-vaginal intercourse (8 of 10,000 exposures)
- Insertive penile-vaginal intercourse (4 of 10,000 exposures)
- Receptive oral intercourse (low)
- Insertive oral intercourse (low)
- Sharing sex toys, throwing body fluids (eg, semen or saliva), spitting, or biting (negligible)

Injectable Cabotegravir: Regimen, Safety, and Efficacy

The cabotegravir regimen consists of initiation administration of two 600-mg intramuscular gluteal injections, given 30-days apart and then one 600-mg intramuscular gluteal injection every 2 months thereafter.[9] To ensure patient tolerability to cabotegravir, initiation of the regimen is achieved directly with use of injectable cabotegravir or first by administering cabotegravir 30-mg orally for 28 days, referred to as an oral lead-in dose (Table 3).[9,12] Differences in safety and efficacy have not been found between initiating the regimen directly with the injectable regimen or using the oral lead-in approach.[12] Clinicians should weigh the risks and benefits of each initiation approach with each individual patient to help decide the optimal approach. Patients can be given a subsequent dose of cabotegravir up to 7 days before or after their scheduled 2-month dose.[12]

Clinical trials from the HIV Prevention Trials Network (HPTN) investigating the safety and efficacy of injectable cabotegravir compared it with oral FTC/TDF. In both treatment groups (n = 2,281 in HPTN 083 trial; n = 1,614 in HPTN 084 trial), 1% of participants discontinued the drug due to adverse events, with increased alanine aminotransferase (<1%) being the main reason for discontinuation.[12] Incidence of other more common reported events with injectable cabotegravir included injection site reactions (ISRs), diarrhea, headache, pyrexia, and fatigue.[12] Table 4 reports overall adverse event incidence data.[11]

ISRs were common in clinical trials (1,740 of 2,117 [82%]). Among the 2,117 participants, 713 (41%) reported mild (grade 1), 1,185 (56%) reported moderate (grade 2), and 64 (3%) reported severe (grade 3) reactions.[12] The median duration of ISR symptoms was 4 days, with a decrease in the number of reported ISRs and their severity over

Table 3
Cabotegravir Dosing and Administration Regimen[11]

Oral Lead-In	Month 2 and 3	Continuation Injection
(at least 28 days)		(Month 5 and Every 2 Months Onward)
Cabotegravir 30 mg Oral	Cabotegravir 600 mg[a] Intramuscular gluteal	Cabotegravir 600 mg[a] Oral Intramuscular gluteal

[a] 600 mg/3 mL.

Table 4
Incidence of Adverse Events of Injectable Cabotegravir Compared With Oral Emtricitabine/Tenofovir Fumarate[11]

Adverse Event	Injectable Cabotegravir Incidence[a]	Oral FTC/TDF Incidence[b]
	(%)	(%)
Injection site reaction	82	Not applicable
Diarrhea	4	5
Headache	4	3
Pyrexia	4	<1
Fatigue	4	2
Sleep disorders	3	3
Nausea	3	5
Dizziness	2	3
Flatulence	1	1
Abdominal pain	1	1
Vomiting	<1	1
Myalgia	<1	<1
Rash	<1	<1
Anorexia	<1	<1
Somnolence	<1	<1
Back pain	<1	<1
Upper respiratory tract infection	0	1
ALT (>5 times upper normal limit)	2	2
AST (>5 times upper normal limit)	3	3
Creatinine phosphokinase (>10 times upper normal limit)	15	14
Lipase (>3 times upper normal limit)	3	3
Creatinine (>1.8 times upper normal limit or >1.5 times baseline)	3	3

ALT = alanine aminotransferase; AST = aspartate aminotransferase; FTC/TDF = emtricitabine/tenofivir fumarate
[a] Data reported are from the HIV Prevention Trials Network (HPTN) 083 clinical trial (n = 2,281).
[b] Placebo.

time.[12] In this trial, just 3% of participants discontinued their use of injectable cabotegravir due to an ISR.[12] ISR-associated adverse events included pain/tenderness, nodules, induration, swelling, bruising, erythema, pruritus, warmth, anesthesia, abscess, and discoloration. Incidence data from clinical trial HTPN 083 (n = 1,740) are reported in Table 5. Unlike oral PrEP regimens, which require less frequent HIV screening, patients taking injectable cabotegravir should be screened for HIV infection before each injection.[12] This is because of the risk of developing HIV resistance due to incomplete antiretroviral coverage in the event a patient becomes infected with HIV while using injectable cabotegravir for PrEP.[12]

In addition, it is vital to continue educating patients to engage in safer sex practices (ie, consistent and correct use of condoms, limiting the number of sex partners, and ascertaining sex partners' HIV serostatus and HIV RNA level [viral load]) with any PrEP regimen and for prevention of other sexually transmitted infections (STIs).[12] In addition to ensuring patients are HIV-seronegative before initiating PrEP, patients receiving injectable cabotegravir should also be screened for other STIs at baseline, including hepatitis B virus (HBV), chlamydia, gonorrhea, and syphilis.[14] Screening for HBV is essential, because PrEP regimens significantly suppress HBV, which could lead to a flare-up with abrupt discontinuation.[14] Screening for HBV can be done through HBV surface antigen, surface antibody (anti-HBV surface antigen), and antibody to the hepatitis B core antigen. Hepatitis C screening should be conducted in MSM and PWIDs starting PrEP.[14]

Although overall efficacy of all PrEP regimens is high,[8] data suggest use of cabotegravir as PrEP could have even greater efficacy, with clinical trials showing a 69% lower incidence of breakthrough HIV infections (12 of 3,211 person-years; 0.37%) compared with

Table 5
Cabotegravir Injection Site Reaction Adverse Event Symptom Incidence[11]

Symptom[a]	Incidence[a] (%)
	(N = 1,740)
Pain/tenderness	98
Nodules	15
Induration	15
Swelling	12
Bruising	4
Erythema	4
Pruritus	3
Warmth	3
Anesthesia	1
Abscess	<1
Discoloration	<1

[a] Data reported are from the HIV Prevention Trials Network (HPTN) 083 clinical trial.

daily oral FTC/TDF (39 of 3,193; 1.22%) PrEP regimens.[12,15] As with all PrEP regimens, however, adherence is paramount.

Cost and Accessibility

The cost for injectable cabotegravir could be considered substantial. The cost of a single dose is $3,700, or $22,200 per year.[16] Estimates suggest this is ~50 to 60 times the cost of generic FTC/TDF.[16] Accessibility could also be perceived as an issue for some individuals who might have to arrange for transportation to a clinic, take time off from work, or secure child care every other month.[16] Because of the higher costs associated with injectable cabotegravir, it is also possible that insurance companies have higher co-pays for the regimen compared with traditional oral forms of PrEP.[16] Increased frequency in the need to screen for HIV (every 2 months with injectable cabotegravir compared with every 3 months with FTC/TDF or FTC/TAF) and consequently a shortened interval between required clinic visits could also affect cost.

Despite cost and access concerns, NPs and other providers should be aware of the assistance programs offered by the manufacturer of injectable cabotegravir. Information about patient assistance programs and eligibility criteria can be found on the drug manufacturer's website.[17] Clinicians should also have knowledge regarding the various paths that exist to implement the regimen in their practices (eg, providing a prescription to receive the drug through a specialty pharmacy or independently managing administration of the regimen).[18]

Summary and Conclusion

HIV remains a global issue worldwide. However, because PrEP has emerged as a novel approach to prevention, significant impacts are being made in reducing new infections.[4] Traditional daily oral PrEP regimens have been associated with efficacy rates up to 99%; however, data suggest use of every other month injectable cabotegravir as PrEP could be even more efficacious.[8,12] NPs should be familiar with the various forms of traditional oral daily PrEP regimens in addition to the newer injectable regimen. Injectable cabotegravir may be a viable option for patients with difficulties adhering to a daily oral regimen, and it is safe.[15] Obtaining baseline STI screening test results—including HIV and HBV—before starting PrEP is crucial, and ensuring patients receiving injectable cabotegravir are HIV-seronegative by screening before each injection is essential.[14]

NPs and other health care providers serve as frontline clinicians in helping to reach public health goals[4] in reducing health

disparities in vulnerable populations. Use of PrEP regimens as a means of lowering the incidence of new HIV infections is a directive for NPs. Consequently, they should have a strong working knowledge of how to prescribe PrEP, monitor patients for adverse events that may occur with PrEP regimens, and continue to implement surveillance for HIV and other STIs during treatment. Provider services for PrEP are billable[19]; and NPs and other clinicians should use novel outreach strategies (eg, telehealth[20]) to reach patients who might benefit from PrEP. Obtaining a thorough health history on every patient to identify risk factors is also paramount.

Acknowledgment

The authors would like to acknowledge Andrew Todd, MLIS, BSN, RN, for his major contributions to the literature review used for this article.

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In compliance with standard ethical guidelines, the authors report no relationships with business or industry that would pose a conflict of interest.