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# Is injectable PrEP superior to oral therapy for HIV protection?

An RCT of HIV preexposure prophylaxis compared long-acting injectable cabotegravir with traditional daily oral tenofovir-emtricitabine—with clear results.

## PRACTICE CHANGER

Consider intramuscular (IM) injectable cabotegravir every 8 weeks for HIV preexposure prophylaxis (PrEP) in cisgender men who have sex with men (MSM) and in transgender women.

## STRENGTH OF RECOMMENDATION

**B:** Based on a single randomized controlled trial.<sup>1</sup>

Landovitz RJ, Donnell D, Clement ME, et al; HPTN 083 Study Team. Cabotegravir for HIV prevention in cisgender men and transgender women. *N Engl J Med*. 2021;385:595-608. doi: 10.1056/NEJMoa2101016

## ILLUSTRATIVE CASE

A 24-year-old cisgender man with no significant past medical history comes to your office requesting PrEP after starting a new sexual relationship. His partner is a 26-year-old cisgender man with known HIV. The patient reports that balancing graduate school and work has made him very forgetful, and he worries that he won't remember to take a daily pill. Are there any other PrEP methods you can offer?

**T**he efficacy of PrEP to reduce HIV acquisition has been established across varying populations at high risk for transmission.<sup>1</sup> PrEP has been found to reduce the risk for sexual acquisition of HIV by nearly 99%.<sup>2</sup>

Although the use of PrEP in the United States has increased steadily since 2012, adherence to an oral formulation remains a significant issue. One study of > 13,000 people

found that daily oral PrEP was discontinued by 52% of participants, only 60% of whom reinitiated the therapy after discontinuation.<sup>2</sup> Although the federal government has required Medicaid and other insurance providers to cover PrEP in an effort to increase access to the medication, this does not necessarily increase adherence to a daily medication in an often otherwise healthy population.

Long-acting injectable forms of PrEP, which have a reduced dosing frequency that may support adherence, have been studied to potentially replace daily oral pills. This latest study compared cabotegravir (CAB-LA), a long-acting IM injection given every 8 weeks, to daily oral PrEP with tenofovir disoproxil fumarate-emtricitabine (TDF-FTC).<sup>1</sup>

## STUDY SUMMARY

### Decreased seroconversion without daily pills

This randomized, double-blind, double-dummy, noninferiority trial compared long-acting injectable vs daily oral PrEP formulations for the prevention of HIV across an international population. Patients were randomized to receive either CAB-LA 600 mg IM every 8 weeks or TDF-FTC 300/200 mg orally daily. The double-dummy methodology meant that those patients receiving active CAB-LA also received a daily oral placebo, while those patients receiving active TDF-FTC also received a placebo injection every 8 weeks.

Study participants were cisgender MSM or transgender women who have sex with men; ages 18 years and older; and in good health but considered to be at high risk for HIV infection. To be included, participants had to have a negative HIV serologic test at enrollment, undetectable blood HIV RNA viral load within 14 days of enrollment, and creatinine clearance  $\geq$  60 mL/min. Exclusion criteria included intravenous (IV) drug use within 90 days of enrollment, coagulopathy, buttock implants or fillers, a seizure disorder, or a QTc interval  $>$  500 ms.<sup>1</sup>

The intention-to-treat population included 4566 patients: 2282 in the CAB-LA group and 2284 in the TDF-FTC group. Demographic characteristics—including age, race, geographic region, and cohort (MSM vs transgender women)—were not significantly different between groups at baseline. The study lasted 153 weeks, and  $>$  86% of patients were retained at 1 year (median follow-up, 1.4 years; interquartile range, 0.8-1.9).

The primary efficacy and safety outcomes of interest were HIV infection and occurrence of a grade  $\geq$  2 adverse drug reaction, respectively. HIV seroconversion occurred in 13 of 2282 (0.57%) patients in the CAB-LA group and 39 of 2284 (1.7%) patients in the TDF-FTC group (hazard ratio = 0.34; 95% CI, 0.18-0.62). The rate of severe adverse drug reactions was similar between groups. The study was stopped early due to the superiority of CAB-LA.

#### WHAT'S NEW

### Demonstrated superiority of injectable vs oral PrEP

The results of this study could have a monumental impact on the spread of HIV. Since adherence is a known limitation of daily oral PrEP, a long-acting injectable is an intriguing option. The 8-week period between injections offers convenience, allowing primary care physicians (PCPs) to schedule their patients in advance. And because every injection is administered in the office, this option would help PCPs track adherence. Witnessed adherence to the medication, and its demonstrated superiority, could have a significant effect on HIV prevention.

The limited serious adverse effects reported by both groups may ease some PCPs' hesitation to prescribe CAB-LA.

#### CAVEATS

### More injection-site reactions (but little impact on adherence)

Notably, 81.4% of patients in the CAB-LA group had injection-site reactions vs 31.3% in the TDF-FTC group. However, only 2.4% of patients in the CAB-LA group opted to stop receiving the injections because of these reactions.

Standard PrEP reduces the risk for HIV acquisition from IV drug use by 74%.<sup>2</sup> However, because IV drug use was an exclusion criterion in this study, future research will need to assess CAB-LA's effectiveness in that population.

#### CHALLENGES TO IMPLEMENTATION

### Price and storage requirements of CAB-LA may create issues

CAB-LA is expensive, costing more than \$25,000 per year—significantly outpricing TDF-FTC, which costs approximately \$8300 per year.<sup>3</sup> Insurance coverage for PrEP, including CAB-LA, varies widely. Given the superiority reflected in this study, more efforts should be made to lower the cost of the medication.

Another hurdle for CAB-LA is that it requires refrigeration for storage. Although likely not an issue in most of the United States, it will make adoption of this method difficult in other parts of the world. **JFP**

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#### References

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HIV seroconversion occurred in 0.57% of patients receiving long-acting injectable PrEP vs 1.7% of patients receiving daily oral PrEP.