Is Long-acting Cabotegravir a Pre-exposure Prophylaxis Option for Women of Childbearing Potential?

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Long-acting cabotegravir (CAB-LA) provides an exciting new option for pre-exposure prophylaxis (PrEP) in multiple populations. In this Perspective, we consider the unique pharmacokinetics of CAB-LA and the potential impact on the prescribing of CAB-LA, specifically in cis-women of reproductive potential.

Keywords. cabotegravir; HIV; pre-exposure prophylaxis; women.
The extensive half-life presents distinct challenges when using CAB-LA as PrEP in women of childbearing potential. Women who conceive up to 1 year or more after discontinuation of PrEP with CAB-LA may have significant CAB levels at the time of conception and during the first trimester. Without appropriate preconception counseling, many women may not be aware of this information, and CAB-LA is not currently recommended in women who are pregnant. Overall, the data describing the use of integrase inhibitors for treatment of HIV in women during pregnancy are positive [7], and early reports of potential safety issues with dolutegravir use in pregnancy appear to have been a false alarm [8]. Initial reports from the Tsepamo study out of Africa reported safety concerns with dolutegravir in pregnant women exposed at conception or during the first trimester, with 4 cases of neural tube defects (NTDs) in 426 women exposed to dolutegravir while pregnant [8], but the analysis of additional pregnancy data revealed an NTD rate of 0.19% (7 NTDs in 3591 deliveries), which was not statistically higher than the 0.11% rate (21 NTDs in 19361 deliveries) of NTDs reported with other antiretroviral therapy [9]. Current evidence supports the positive safety profile of dolutegravir in the second and third trimester of pregnancy [10,11]. The Tsepamo experience serves to highlight an important consideration. When safety signals related to fetal outcomes are identified in agents with protracted half-lives, the exposure may continue long after the offending agent is discontinued—and in the case of an agent with an extended half-life such as CAB-LA, the exposure is likely to occur for the duration of the pregnancy. Ongoing studies evaluating CAB-LA for PrEP in men and women (HPTN 077) and women of reproductive potential (HPTN 084) reported outcomes on only 2 pregnancies and 29 pregnancies after potential CAB-LA exposure, respectively (Table 2) [6, 12, 13]. No cases of NTDs or other adverse effects have been reported to date with the use of CAB-LA during pregnancy, but pregnancy and fetal outcomes will need to be monitored closely for women with CAB-LA exposure within the year before conception [6, 10]. Ongoing research, including an open-label extension of HPTN 084, may include women of childbearing potential not using contraception, which would provide additional information regarding use of CAB-LA and pregnancy outcomes.

For women who desire a long-acting injectable form of PrEP, an additional consideration is the logistics of the concurrent use of long-acting injectable forms of contraceptive agents such as medroxyprogesterone acetate. Both CAB-LA and

### Table 1. Preexposure Prophylaxis Options

| Drug Dose | Route | Approved Populations/Indication | Pregnancy* |
|-----------|-------|---------------------------------|------------|
| TDF/FTC (Truvada) 1 tablet daily | PO | All at-risk adults and adolescents ≥ 35 kg | Preferred |
| TAF/FTC (Descovy) 1 tablet daily | PO | All at-risk adults and adolescents ≥ 35 kg, excluding individuals at risk from receptive vaginal intercourse | Preferred |
| CAB-LA (Apretude) 1-mo oral lead in® followed by 600 mg IM monthly × 2 mo, then 600 mg every 2 mo | PO | All at-risk adults and adolescents ≥ 35 kg | Not recommended due to limited data |

Abbreviations: CAB-LA, cabotegravir; FTC, emtricitabine; IM, intramuscular; PO, by mouth; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

*Department of Health and Human Services recommendation for pregnant individuals or those attempting to conceive.

®Use of oral lead in is at discretion of provider.

### Table 2. Pregnancy Outcomes in HPTN 077 and HPTN 084

| Study | Outcomes |
|-------|----------|
| HPTN 077 [6] | • 2 pregnancies in CAB-LA group  
Patient 1: received 5 doses of CAB-LA; pregnancy estimate at 32 wk after final injection; late pregnancy preeclampsia; near-full-term healthy baby  
Patient 2: ~108 wk after last injection of CAB-LA; uncomplicated pregnancy; healthy baby |
| HPTN 084 [10] | • 29 confirmed pregnancies in CAB-LA arm (1614 subjects); 20 in TDF (1639)  
• CAB-LA  
  • 2 unknown outcomes  
  • 22 live births  
  • Pregnancy loss: 20–36 wk = 1; <20 wk = 4  
  • Congenital anomalies: 0; 3 unknown  
  • TDF  
  • 2 unknown outcomes  
  • 14 live births  
  • Pregnancy loss: 20–36 wk = 3; <20 wk = 1  
  • Congenital anomalies: 0; 1 unknown |
| | Abbreviations: CAB-LA, cabotegravir; TDF, tenofovir disoproxil fumarate. |
medroxyprogesterone acetate require IM administration via a visit to a clinic; however, the syncing of administration of these 2 medications is not currently possible due to every-2-months vs 3-month requirements, respectively. The logistical issues of asynchronous timing of injections may create adherence difficulties for some patients. Drug–drug interactions between antiretrovirals and contraceptive agents could decrease effectiveness and lead to the potential for contraceptive failure, but current data suggest that there are no drug interactions between CAB-LA and common agents used for contraception [14,15].

Ultimately, the approval of CAB-LA for PrEP adds an exciting option for the prevention of HIV and makes the goals of EHE more attainable. The availability of a long-acting injectable option for individuals seeking PrEP is a great opportunity to improve adherence and minimize barriers associated with current oral alternatives. The impressive reduction in infection rates (88%) and improved adherence related to CAB-LA compared with oral TDF/FTC in cisgender women in HPTN 084 cannot be overstated [13]. That being said, studies of CAB-LA have highlighted an unusually prolonged medication half-life, a more pronounced pharmacokinetic tail-phase in cisgender women, and limited data on pregnancy outcomes. One of the challenges facing clinicians is highlighting the significant benefit of CAB-LA in HIV prevention, specifically in women of childbearing potential, while also providing accurate information regarding the potential for prolonged exposure and the yet to be determined impact of CAB-LA in pregnancy. Women with HIV who are seeking PrEP and are of childbearing potential should be informed of these issues and included in the decision-making process during preconception counseling. If CAB-LA is determined to be the most appropriate option for HIV prevention, the concomitant use of reliable contraception should be advocated. Until additional data are accumulated regarding the safety of CAB-LA in pregnancy, providers may want to proceed with caution when using CAB-LA in women of reproductive potential. The use of TDF/FTC continues to be a safe and effective HIV prevention option in this population while additional data accumulate.

Acknowledgments

Potential conflicts of interest. All authors: no reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. E.G.S. performed the initial literature search, compilation of findings, and manuscript preparation. N.H. and J.M.D. performed manuscript preparation. K.B. performed initial literature searches.

Patient consent. This manuscript does not include factors necessitating patient consent.

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