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PERSPECTIVES

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.

Pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), and treatment as prevention (TaP) are key parts of the Ending the HIV Epidemic (EHE) initiative in the United States [1]. Bimonthly intramuscular cabotegravir (CAB-LA) has recently been approved for PrEP and treatment of HIV infection. Other long-acting injectable antivirals, such as lenacapavir (dosed every 6 months), are currently being evaluated for use in PrEP. These exciting options provide the opportunity to move the United States closer to EHE goals by improving accessibility and adherence to antiretrovirals for treatment and prevention and decreasing barriers associated with the use of daily oral medications. Updated Centers for Disease Control and Prevention guidelines list multiple options for PrEP for men who have sex with men (MSM) and transgender women (TGW) including once-daily tenofovir alafenamide/emtricitabine (TAF/FTC), daily and "on-demand" tenofovir disoproxil/emtricitabine (TDF/FTC), and now CAB-LA (Table 1) [2]. Cisgender women have 2 Food and Drug Administration (FDA)–approved options for PrEP: once-daily oral TDF/FTC or CAB-LA. TAF/FTC is currently being evaluated for PrEP in patients at risk for HIV infection due to receptive vaginal intercourse but is not currently approved for that indication. It is, however, currently approved for treatment in cisgender women with HIV when used in combination with other antiretrovirals regardless of pregnancy or childbearing status [3]. Although the FDA approval for PrEP and treatment of HIV includes women of childbearing potential or women actively trying to conceive, the use of CAB-LA in these settings presents distinct challenges of which providers should be aware.

Limited safety information is currently available regarding the use of CAB-LA for PrEP in women who become pregnant while receiving CAB-LA. The unique pharmacokinetics of CAB-LA should be considered in preconception counseling during the PrEP assessment. A review of CAB LA pharmacokinetics highlights the potential for extended exposure to CAB at therapeutic levels even after discontinuation of the injections. Several studies have shown a terminal half-life of the CAB-LA formulation ranging from 25 to 40 hours with a tail phase extending beyond 1 year [4, 5]. Landovitz and colleagues evaluated the pharmacokinetics for CAB in subjects enrolled in HPTN 077 [6]. Almost a quarter of male subjects (9/40) and >60% of female subjects (52/82) had detectable CAB concentrations in blood (>25 ng/mL) at 52 and 60 weeks after the last injection of CAB-LA. Interestingly, 42% of women (27/64) had measurable CAB concentrations at 76 weeks post–last injection. The median time for CAB to decrease to below the lower limit of detection (interquartile range) was significantly longer for women than men (63.7 [17.7–225.5] weeks vs 43.2 [20.4–152.5] weeks; $P = .003$). Additionally, in women at week 52 or 60 and week 76, 23% (19/82) and 11% (7/64), respectively, CAB concentrations ranged from 1 to 4 times greater than the protein-binding-adjusted 90% inhibitory concentration (166–664 ng/mL). The geometric mean half-life was longer for women than men (60.4 days; 95% CI, 52.9–69.0 days; vs 45.3 days; 95% CI, 37.6–54.5 days; geometric mean fold change, 1.33; 95% CI, 1.06–1.68; $P = .014$) [6]. These data illustrate the potential for extended exposure to CAB at clinically significant levels long after administration of the last dose.

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Table 1. Preexposure Prophylaxis Options

Drug	Dose	Route	Approved Populations/Indication	Pregnancy[a]
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[b] followed by 600 mg IM monthly × 2 mo, then 600 mg every 2 mo	PO IM	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.

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

[b]Use of oral lead in is at discretion of provider.

Table 2. Pregnancy Outcomes in HPTN 077 and HPTN 084

Study	
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.

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 19 361 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

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.

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