Use of Gender-Affirming Hormone Therapy with *Apretude* in Transgender Women and Transgender Men

Summary

- There are limited data on the use of *Apretude* (long-acting cabotegravir [CAB LA]) with medicines expected to be used to affirm the gender identity of transgender women and transgender men.
- Cabotegravir (CAB) is a substrate of UGT1A1 and UGT1A9.[1] Drugs that are strong inducers of UGT1A1 are expected to decrease plasma concentrations of CAB.
- CAB is not a clinically significant inhibitor or inducer of any drug metabolizing enzymes and therefore is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes.[1]
- An analysis of data collected as part HPTN 083 suggests that among transgender women taking gender-affirming hormone therapy (GAHT) there is no effect on the pharmacokinetics of long-acting cabotegravir.[12]
- Important Safety Information and Boxed Warning can be found in the Prescribing Information and can also be accessed from Our HIV Medicines.

To access additional scientific information related to ViiV Healthcare medicines, visit the ViiV US Medical Portal at viivhcmedinfo.com.

No prospective drug interaction studies have been conducted with CAB LA.[1] Since the pathways of metabolism and elimination are independent of formulation type, the data from oral CAB have been extrapolated to identify drugs with which use of CAB LA may cause an interaction.[2-9]

CAB is primarily metabolized by UGT1A1 with some contribution from UGT1A9.[1] Drugs that are strong inducers of UGT1A1 or 1A9 are expected to decrease CAB plasma concentrations.

In vivo, CAB did not have an effect on midazolam, a CYP3A4 probe.[1] CAB is not a clinically relevant inhibitor of the following enzymes and transporters: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7, UGT2B15, and UGT2B17, P-gp, breast cancer resistance protein (BCRP), Bile salt export pump (BSEP), organic cation transporter (OCT)1, OCT2, OATP1B1, OATP1B3, multidrug and toxin extrusion transporter (MATE) 1, MATE 2-K, multidrug resistance protein (MRP) 2 or MRP4.

CAB inhibited the organic anion transporters (OAT)1 (IC_{50} = 0.81 µM) and OAT3 (IC_{50} = 0.41 µM) in vitro, however, based on physiologically based pharmacokinetic (PBPK) modelling no interaction with OAT substrates is expected at clinically relevant concentrations.[1]

In vitro, CAB did not induce CYP1A2, CYP2B6, or CYP3A4.[1]

Based on these data and the results of drug interaction studies, CAB is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.[1]

TRANSGENDER WOMEN

The goal of GAHT in transgender women is to regress as much adult male sexual development as possible while inducing as much female sexual development as possible.[10]

The medicines used to accomplish these goals are as follows:[10]

- Estrogens - estradiol

- Antiandrogens and androgen suppressors – spironolactone, 5α reductase inhibitors (finasteride and dutasteride), androgen receptor blockers (bicalutamide)
- Gonadotropin-releasing hormone agonists or antagonists – leuprolide, nafarelin, goserelin, triptorelin, buserelin, and histrelin
- Progestins – progesterone, medroxyprogesterone

Data on the use of the above medicines or medicine classes with cabotegravir is limited. To date, only 1 prospective pharmacokinetic study has been conducted to assess the effect of concomitant administration of oral cabotegravir with the contraceptives ethinyl estradiol and levonorgestrel in 20 participants who were female at birth.[6]

This study showed that there was no effect of cabotegravir on the pharmacokinetics of ethinyl estradiol and levonorgestrel and vice versa.[6] Likewise, there was no effect of concomitant administration on luteinizing hormone, follicle-stimulating hormone, and progesterone concentrations.

An analysis of data from HPTN 077 showed there was no clinically significant effect of the use of hormonal contraception overall, or by route of administration (oral, injectable, vaginal ring, implant, or other), on cabotegravir pharmacokinetics when administered as a long-acting intramuscular injection to HIV-uninfected subjects who were female at birth.[11]

Using data collected from HPTN 083, an analysis was undertaken to determine if there was an effect of GAHT on the pharmacokinetics of CAB LA.[12] Table 1 shows the self-reported GAHT used in conjunction with CAB LA.

Table 1. Most Common Self-Reported GAHT Used by Transgender Women in HPTN 083[12]

GAHT	Overall (n = 330)	Reported Use of GAHT at Baseline (n = 249)	Reported GAHT Initiation Post-Enrollment (n = 81)
Cyproterone acetate and ethinyl estradiol	88 (27)	74 (30)	14 (17)
Estradiol valerate	147 (45)	110 (44)	37 (46)
Estradiol	94 (29)	79 (32)	15 (19)
Spironolactone	107 (32)	79 (32)	28 (35)

All values are n (%)
GAHT = gender-affirming hormone therapy

CAB pharmacokinetics were compared in a subset of transgender women who were either taking (n = 30) or not taking GAHT (n = 23).[12] All participants received all CAB LA doses on-time through Week 53.

CAB concentrations were comparable between the groups suggesting a lack of an interaction between GAHT and CAB LA.[12]

There are limited or no data available on the impact of cabotegravir on the pharmacokinetics of the antiandrogens and androgen suppressors, gonadotropin releasing hormone agonists/antagonists, or progestins (other than levonorgestrel).

TRANSGENDER MEN

The goal of GAHT in transgender men is to induce the secondary sex characteristics more typical of males while diminishing female secondary sex characteristics.[13]

The medicine classes used to accomplish these goals are as follows:[13]

- Androgens – testosterone
- Gonadotropin-releasing hormone agonists or antagonists
- Progestins – progesterone, medroxyprogesterone

There are no data available with the concomitant use of the above medicines or medicine classes in transgender men with cabotegravir.

This information is scientific and non-promotional in nature and is not intended for further distribution.

This information is not intended to offer recommendations for using this product in a manner inconsistent with its approved labeling. Please consult the Prescribing Information. For ViiV Healthcare to monitor the safety of our products, we encourage healthcare professionals to report adverse events or suspected overdoses to the company at 877-844-8872.

Selection of references follows principles of evidence-based medicine and, therefore, references may not be all inclusive.

REFERENCES

1. ViiV Healthcare. Global Data Sheet for Cabotegravir (PrEP). Version 05. February 19, 2024.
2. Bowers GD, Culp A, Reese MJ, et al. Disposition and metabolism of cabotegravir: a comparison of biotransformation and excretion between different species and routes of administration in humans. *Xenobiotica*. 2016;46(2):147-162. doi:http://dx.doi.org/10.3109/00498254.2015.1060372.
3. Ford SL, Gould E, Chen S, et al. Effects of etravirine on the pharmacokinetics of the integrase inhibitor S/GSK1265744. *Antimicrobial agents and chemotherapy*. 2013;57(1):277-280. doi:http://dx.doi.org/10.1128/AAC.01685-12.
4. Reese MJ, Bowers GD, Humphreys JE, et al. Drug interaction profile of the HIV integrase inhibitor cabotegravir: assessment from in vitro studies and a clinical investigation with midazolam. *Xenobiotica*. 2016;46(5):445-456. doi:http://dx.doi.org/10.3109/00498254.2015.1081993.
5. Trezza C, Ford SL, Spreen W, Pan R, Piscitelli S. Formulation and pharmacology of long-acting cabotegravir. *Curr Opin HIV AIDS*. 2015;10(4):239-245. doi:http://dx.doi.org/10.1097/coh.0000000000000168.
6. Trezza C, Ford SL, Gould E, et al. Lack of effect of oral cabotegravir on the pharmacokinetics of a levonorgestrel/ethinyl oestradiol-containing oral contraceptive in healthy adult women. *Br J Clin Pharmacol*. 2017;83(7):1499-1505. doi:http://dx.doi.org/10.1111/bcp.13236.
7. Blair CS LS, Chau G, et al. Blair CS, Li S, Chau G, et al. Hormonal Contraceptives Do Not Alter Cabotegravir PK in HIV Uninfected Women. Presented at CROI 2019; March 4-7, 2019; Seattle, WA. Poster 1791.
8. Ford SL, Sutton K, Lou Y, et al. Effect of Rifampin on the Single-Dose Pharmacokinetics of Oral Cabotegravir in Healthy Subjects. *Antimicrob Agents Chemother*. 2017;61(10). doi:http://dx.doi.org/10.1128/aac.00487-17.
9. Ford SL, Lou Y, Lewis N, et al. Effect of rifabutin on the pharmacokinetics of oral cabotegravir in healthy subjects. *Antivir Ther*. 2019. doi:http://dx.doi.org/10.3851/imp3306.
10. Randolph JF, Jr. Gender-Affirming Hormone Therapy for Transgender Females. *Clin Obstet Gynecol*. 2018;61(4):705-721. doi:http://dx.doi.org/10.1097/GRF.0000000000000396.
11. Blair CS, Li S, Chau G, et al. Brief Report: Hormonal Contraception Use and Cabotegravir Pharmacokinetics in HIV-Uninfected Women Enrolled in HPTN 077. *J Acquir Immune Defic Syndr*. 2020;85(1):93-97. doi:http://dx.doi.org/10.1097/QAI.0000000000002409.
12. Grinsztejn B, et al. Transgender Women (TGW) in HPTN 083: An Evaluation of Safety, Efficacy, and Gender Affirming Hormonal Therapy (GAHT) Interactions with Long-acting Cabotegravir (CAB-LA). Presented at AIDS 2022, July 29-August 2, 2022, Montreal, Canada, and virtually. E-poster. EPLBC04.
13. Moravek MB. Gender-Affirming Hormone Therapy for Transgender Men. *Clin Obstet Gynecol*. 2018;61(4):687-704. doi:http://dx.doi.org/10.1097/GRF.0000000000000398.