FOSTEMSAVIR AND ETHINYL ESTRADIOL DRUG INTERACTION: CLINICAL APPLICATION FOR CO-ADMINISTRATION

Nneka Nwokolo,[1] Elana Post,[2] Mindy Magee,[3] Peter Ackerman,[4] Cyril Llamoso,[4] Katy Moore[2]

[1]ViiV Healthcare, Brentford, UK; [2]ViiV Healthcare, Research Triangle Park, NC, USA; [3]GlaxoSmithKline, Upper Providence, PA, USA; [4]ViiV Healthcare, Branford, CT, USA

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Introduction

- Fostemsavir (FTR) is a first-in-class attachment inhibitor indicated for heavily treatment-experienced (HTE) people living with human immunodeficiency virus-1 (HIV-1) (PLWH)
- FTR is a prodrug of temsavir (TMR), which binds viral gp120 and prevents viral attachment and entry into host CD4+ T cells
- FTR is used with other antiretrovirals (ARVs) in PLWH who are failing on their current treatment regimen and who have limited remaining treatment options due to resistance, intolerance, or other safety concerns

Methods

- FTR-Oral Contraceptive (OC) Study with ethinyl estradiol (EE) and norethindrone (NE) (Figure 1), relevant ARV-contraceptive interaction studies, and guideline recommendations were reviewed, and data applied to other contraceptive methods and hormone-based therapies to predict the impact of FTR co-administration
- Recommendations were based on minimizing risk associated with estrogen exposure (Figure 2) and ensuring adequate hormonal concentrations to maintain targeted effect by anticipating EE concentrations with co-administration of FTR with different estrogen-based therapies and concomitant ARV therapy
- Proposals for co-administering FTR with an ARV regimen with estrogen-based therapies (contraception, menopausal hormone therapy [MHT], and feminizing gender-affirming hormone therapy [GAHT]) are provided

Figure 1. FTR-OC Study (Study 206279) EE: ↑ 40%; No Impact on NE[1]

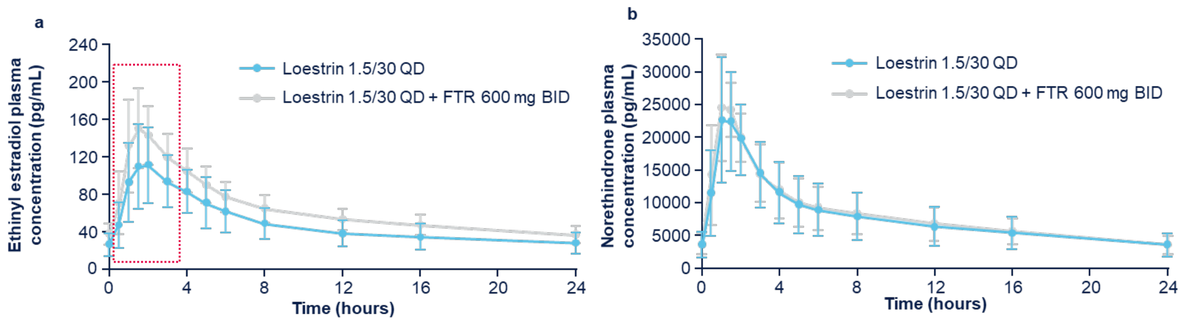
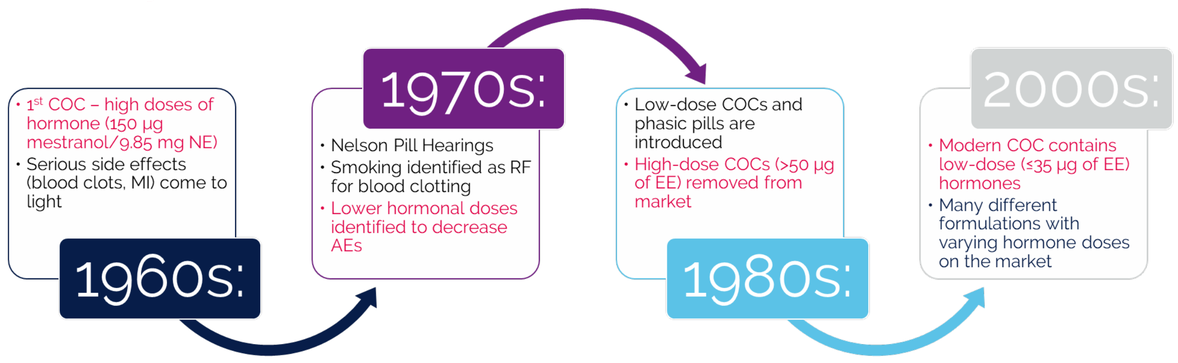


Figure 2. History of Combined Oral Contraception (COC), Estrogen Dose, and Safety



Results

Table 1. FTR and MHT and GAHT Co-administration

Data and Guideline Recommendation[2]	FTR Co-administration
Menopausal Hormone Therapy (MHT)	
INSTIs • BIC, DTG, RAL: ↔ estrogen expected with estradiol or conjugated estrogen – *No dose adjustment needed* **Boosted PIs** • All PIs: ↓ or ↑ estrogen possible with estradiol or conjugated estrogen – *Adjust estrogen dose as needed based on clinical effects* **NNRTIs** • DOR, RPV: ↔ hormonal concentrations – *No dose adjustment needed* • EFV, ETR, NVP: ↓ estrogen possible with estradiol or conjugated estrogen – *Monitor menopausal symptoms. Titrate to the dose of hormonal therapy that achieves menopausal symptom relief*	**Start estrogen dose low and titrate according to clinical effect.**
Feminizing Gender-Affirming Hormone Therapy (GAHT)	
INSTIs • BIC, DTG, RAL: ↔ estrogen expected – *No dose adjustment needed* **Boosted PIs** • PI/r: ↓ estradiol possible – *Adjust estradiol dose as needed based on clinical effects and endogenous hormone concentrations* • PI/c: ↓ or ↑ estradiol possible – *Adjust estradiol dose as needed based on clinical effects and endogenous hormone concentrations* **NNRTIs** • DOR, RPV: ↔ hormonal concentrations – *No dose adjustment needed* • EFV, ETR, NVP: ↓ estradiol possible – *Monitor feminizing effects of estrogen and antiandrogen therapy and titrate dose as necessary to achieve therapeutic goals*	**FTR and estradiol for GAHT can be co-administered with routine monitoring of hormone concentrations and clinical effects, titrating estradiol dose in line with guidelines.**

Table 2. FTR and Contraceptive Co-administration

Delivery	Data and Guideline Recommendation[2]	FTR Co-administration
Combined Hormonal Contraceptives		
Combined oral contra-ception (COC)	**INSTIs** • BIC, DTG, RAL: EE ↔, norgestimate ↔; *No dose adjustment needed for COC or ARV* **Boosted PIs** • ATV/r: EE AUC ↓ 19%, norgestimate AUC ↑ 85%; *Maintain EE ≥35 µg/day* • ATV/c: EE AUC ↓ 22%, drospirenone ↑ 2.3-fold; *Contraindicated with drospirenone-containing products, use alternative ARV or contraceptive method* • DRV/r, LPV/r, TPV/r: EE AUC ↓ 37%-55%, NE ↓ 14%-34%; *Use alternative ARV or contraceptive method* **NNRTIs** • DOR: EE ↔, levonorgestrel ↔; *No dose adjustment needed for COC or ARV* • RPV: EE ↔, NE ↔; *No dose adjustment needed for COC or ARV* • ETR: EE AUC ↑ 22%, NE ↔; *No dose adjustment needed for COC or ARV* • NVP: EE AUC ↓ 29%, NE AUC ↓ 18%; *No dose adjustment needed for COC or ARV* • EFV: EE ↔, levonorgestrel AUC ↓ 83%, norelgestromin ↓ 64%; *Use alternative ARV or contraceptive method*	**INSTIs + FTR + COC:** **Maintain EE ≤30 µg/day** **Boosted PIs + FTR + COC:** **Consider alternative ARV or additional contraceptive methods, guided by PI prescribing recommendations** **NNRTIs + FTR + COC:** • **DOR, RPV – Maintain EE ≤30 µg/day** • **ETR, NVP, EFV – Consider alternative ARV or additional contraceptive methods**
Combined hormonal patch (CHP)	**INSTIs** • No guideline recommendation available **Boosted PIs** • LPV/r: EE AUC ↓ 45%, norelgestromin ↑ 83%; *No dose adjustment needed for CHP or ARV* • All PIs: no data; *No dose adjustment needed* **NNRTIs** • No guideline recommendation available	**INSTIs + FTR + CHP:** **No expected impact** **Boosted PIs + FTR + CHP:** **Consider alternative ARV or additional contraceptive methods** **NNRTIs + FTR + CHP:** **Insufficient data for a recommendation**
Combined vaginal ring (CVR)	**INSTIs** • No guideline recommendation available **Boosted PIs** • ATV/r: EE AUC ↓ 26%, etonogestrel AUC ↑ 79%; *No dose adjustment needed for CVR or ARV* • All PIs: no data; *No dose adjustment needed* **NNRTIs** • DOR, RPV: EE ↔, etonogestrel ↔; *No dose adjustment needed for CVR or ARV* • ETR, NVP: EE and etonogestrel ↓ possible; *No data for recommendation* • EFV: EE AUC ↓ 56%, etonogestrel AUC ↓ 81%; *Consider alternative ARV or contraceptive method*	**INSTIs + FTR + CVR:** **No expected impact** **Boosted PIs + FTR + CVR:** **Consider alternative ARV or additional contraceptive methods** **NNRTIs + FTR + CVR:** • **DOR, RPV – No expected impact** • **ETR, NVP, EFV – Insufficient data for a recommendation**
Progestin-only Contraceptives		
Progestin-only implant; DMPA; Progestin-only pill		**No impact with FTR**
Barrier Contraceptive Methods		
Condoms; Spermicides; Diaphragm with spermicide or cervical cap		**No impact with FTR**

Conclusions

FTR co-administration with hormone therapy is not expected to impact hormone treatment efficacy

Contraception

- When FTR is co-administered with oral contraceptives, EE dose should be ≤30 µg/day to minimize risk
- FTR did not impact progestin. Therefore, progestin-only and non-hormonal contraceptives will not be impacted by FTR
- When FTR, ARVs, and COC are co-administered, reference guidelines[2]

MHT and GAHT

- Estrogen-containing MHT and GAHT can be co-administered with FTR, with monitoring of estrogen concentrations and dose adjustment as needed
  - With MHT, starting estradiol low and titrating according to clinical effect will enable prescription of the lowest effective dose of estrogen
  - Feminizing GAHT regimens target serum estradiol concentrations in the physiologic cisgender female range of 100 to 200 pg/mL. Routine monitoring of concentrations will allow dose adjustments to achieve goal concentrations

Please join us on Thursday, 8th October, for one of the two live Meet the Experts Q&A sessions with our senior medical experts around our most recent data presented at HIV Glasgow 2020.

Abbreviations: INSTI, integrase strand transfer inhibitor; BIC, bictegravir; DTG, dolutegravir; RAL, raltegravir; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; DOR, doravirine; RPV, rilpivirine; EFV, efavirenz; ETR, etravirine; NVP, nevirapine; r, ritonavir; c, cobicistat; ATV, atazanavir; DRV, darunavir; LPV, lopinavir; TPV, tipranavir; DMPA, depot medroxyprogesterone acetate.

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References: 1. Magee et al. IAS 2017; Paris, France. Abstract MOPEB0339. **2.** AIDSinfo. https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/23/women-with-hiv. Accessed January 28, 2020.

Presenting author: Nneka Nwokolo; nneka.x.nwokolo@viivhealthcare.com