Abstract Number 141 - (Oral)

VAGINAL CONTRACEPTIVE HORMONE EXPOSURE PROFOUNDLY ALTERED BY EFV- AND ATV/R-BASED ART

Clinical: (F) Clinical Pharmacology

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Background: Contraceptive hormones delivered by a vaginal ring result in stable systemic hormone exposure over 21 days of use, with concentrations that are lower than those observed with oral or injectable contraceptives. Drug-drug interactions (DDI) exist between oral hormonal contraceptives and some antiretroviral therapy (ART), but the impact of ART on hormone exposure when released from a vaginal ring is not known. We hypothesized that efavirenz (EFV)-based ART and atazanavir/ritonavir (ATV/r)-based ART would alter plasma concentrations of vaginally administered etonogestrel/ethinyl estradiol (ENG/EE).
Methods: A5316 was an international, multicenter, longitudinal, parallel group, pharmacokinetic (PK) evaluation of HIV-positive women ≥ 16 years old. A vaginal ring releasing ENG/EE 120/15 mcg/day was inserted at entry in three groups of participants: (1) not yet receiving ART (control group; n=25); (2) ART containing EFV 600mg daily (EFV group; n=25); (3) ART containing ATV/r 300/100mg daily (ATV/r group; n=24). Participants returned on days 7, 14, and 21 for single measurements of ENG and EE PK, assessed by a validated LC/MS/MS method. Plasma hormone PK exposure was compared between each ART group and the control group at each visit by geometric mean ratio (GMR) with 90% CI, and by Wilcoxon-rank sum at the primary endpoint (day 21). Demographics are summarized as mean (standard deviation) or frequency (%).
Results: Overall, 74 evaluable women were 35 (7.6) years of age, 72.5 (24.2) kg, 37 (50%) Black, and 26 (35%) Hispanic. ENG and EE PK results are described and compared between groups in the Table. Compared to the control group, participants in the EFV group had 76-79% lower ENG and 53-57% lower EE over 21 days (all $p<0.001$). In contrast, participants in the ATV/r group had 71-79% higher ENG (all $p<0.001$), yet 29-35% lower EE ($p=0.066$, 0.032 and 0.004 for days 7, 14 and 21, respectively) over 21 days compared to the control group.
Conclusion: Both EFV- and ATV/r-based ART altered systemic hormone exposure delivered via a vaginal ring; these changes were similar or greater to prior DDI studies with oral hormonal contraceptives. Women on EFV- or ATV/r-based ART should consider an alternative contraception method or barrier contraception in addition to the vaginal ring until the clinical relevance of these PK changes is better understood. These data highlight the importance of evaluating DDIs between ART and non-oral hormone contraceptive methods during novel drug product development.