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Pharmacogenetic interactions between antiretroviral drugs and vaginally-administered hormonal contraceptives

David W. Haas,
Vanderbilt University School of Medicine, Nashville, TN; Meharry Medical College, Nashville, TN, USA

Yoninah S. Cramer, MS,
Harvard TH Chan School of Public Health, Boston MA, USA; Frontier Science Foundation, Brookline, MA, USA

Catherine Godfrey, MD,
Division of AIDS, National Institutions of Allergy and Infectious Disease, National Institutes of Health, Bethesda, MD, USA

Susan L. Rosenkranz, PhD,
Harvard TH Chan School of Public Health, Boston MA, USA; Frontier Science Foundation, Brookline, MA, USA

Francesca Aweeka, PharmD,
Department of Clinical Pharmacy, School of Pharmacy, University of California San Francisco, San Francisco, CA, USA

Baiba Berzins, MPH,
Division of Infectious Diseases, Northwestern University, Chicago, IL, USA

Robert Coombs, MD,
Departments of Medicine and Laboratory Medicine, University of Washington, Seattle, WA, USA

Kristine Coughlin, BA,
Frontier Science & Technology Research Foundation, Inc, Amherst, NY, USA

Laura E. Moran, MPH,
Social & Scientific Systems, Silver Spring, MD, USA

David Gingrich, BS,
Department of Clinical Pharmacy, School of Pharmacy, University of California San Francisco, San Francisco, CA, USA

Corresponding Author: David W. Haas, M.D. Professor of Medicine, Pharmacology, Pathology, Microbiology & Immunology, Vanderbilt Health - One Hundred Oaks, 719 Thompson Lane, Ste. 47183, Nashville, TN 37204, Phone: 1-615-936-8594, Fax: 1-615-936-2644, david.haas@vumc.org.

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Carmen D. Zorrilla,
University of Puerto Rico School of Medicine, San Juan, Puerto Rico

Paxton Baker,
Vanderbilt University Medical Center, Nashville, TN, USA

Susan E. Cohn, MD,
Division of Infectious Diseases, Northwestern University, Chicago, IL, USA

Kimberly K. Scarsi, PharmD,
Department of Pharmacy Practice and Science, College of Pharmacy; University of Nebraska Medical Center, Omaha, NE, USA

AIDS Clinical Trials Group A5316 Study Team

Abstract

Objective: In AIDS Clinical Trials Group study A5316, efavirenz significantly lowered plasma concentrations of etonogestrel and ethinyl estradiol, given as a vaginal ring, while atazanavir/ritonavir increased etonogestrel and lowered ethinyl estradiol concentrations. We characterized the pharmacogenetics of these interactions.

Methods: In A5316, women with HIV enrolled into control (no antiretrovirals), efavirenz (600 mg daily with nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs)), and atazanavir/ritonavir (300/100mg daily with NRTIs) groups. On day 0, a vaginal ring was inserted, releasing etonogestrel/ethinyl estradiol 120/15 mcg/day. Intensive plasma sampling for antiretrovirals was obtained on days 0 and 21, and single samples for etonogestrel and ethinyl estradiol were obtained on days 7, 14 and 21. Seventeen genetic polymorphisms were analyzed.

Results: The 72 participants in this analysis included 25, 24 and 23 in the control, efavirenz and atazanavir/ritonavir group, respectively. At day 21 in the efavirenz group, *CYP2B6* genotype was associated with increased plasma efavirenz exposure ($p=3.2\times10^{-3}$), decreased plasma concentrations of etonogestrel ($p=1.7\times10^{-3}$), and decreased ethinyl estradiol ($p=6.7\times10^{-4}$). Compared to controls, efavirenz reduced median etonogestrel concentrations by at least 93% in *CYP2B6* slow metabolizers versus ~75% in normal and intermediate metabolizers. Efavirenz reduced median ethinyl estradiol concentrations by 75% in *CYP2B6* slow metabolizers versus ~41% in normal and intermediate metabolizers. No other polymorphisms were significantly associated with hormone or antiretroviral pharmacokinetics.

Conclusions: *CYP2B6* slow metabolizer genotype worsens the pharmacokinetic interaction of efavirenz with hormonal contraceptives administered by vaginal ring. Efavirenz dose reduction in *CYP2B6* slow metabolizers may reduce, but will likely not eliminate, this interaction.

Introduction

It is important that women of reproductive potential who are living with HIV be provided with effective contraceptive options. Unfortunately, drug-drug interactions between some antiretroviral therapies (ART) and hormonal contraceptives hinder available options for effective family planning. Efavirenz-containing ART significantly lowers plasma exposure to progestin contraceptives given orally or via subdermal implant, [1–5] which may reduce

hormonal contraception effectiveness.[6] HIV protease inhibitors that are combined with ritonavir increase progestin exposure, but may decrease estrogen exposure.[7, 8] These drug-induced changes in plasma hormone exposure are likely due to antiretroviral effects on hormone metabolism by cytochrome P450 (CYP) 3A4, the isoenzyme believed to mediate progestin metabolism, and multiple CYP and glucuronidation pathways associated with estrogen metabolism.[8] In addition, some studies have identified somewhat lower antiretroviral exposure when combined with hormonal contraceptives,[7, 8] possibly due to progestin and estrogen influences on drug metabolizing enzymes.[9, 10]

Vaginal rings are currently available for hormone replacement therapy and for contraception, and in development as vehicles to simultaneously deliver antiretrovirals for HIV prevention and progestins for contraception. Progestins delivered by combined hormonal contraceptive vaginal rings reach systemic concentrations sufficient to prevent ovulation, similar to oral progestins. Protocol A5316 of the AIDS Clinical Trials Group (ACTG) characterized effects of efavirenz- and atazanavir/ritonavir (atazanavir/r)-containing ART on plasma pharmacokinetics (PK) of etonogestrel and ethinyl estradiol administered by vaginal ring over 21 days.[11] On Day 21, concomitant efavirenz was associated with 79% lower etonogestrel and 59% lower ethinyl estradiol concentrations compared to the control group not on ART, while concomitant atazanavir/r was associated with 71% higher etonogestrel and 38% lower ethinyl estradiol concentrations. There were no statistically significant changes in plasma efavirenz or atazanavir exposure.

There is extensive literature regarding the pharmacogenetics of efavirenz [12]. Frequent *CYP2B6* polymorphisms predict increased plasma efavirenz exposure, including *CYP2B6* 516G→T (rs3745274) [13–17], 983T→C (rs28399499) [17–20], and 15582C→T (rs4803419) [17]. A *CYP2A6* polymorphism, −48T→G (rs28399433), may also affect efavirenz pharmacokinetics [21–24] when present with *CYP2B6* slow metabolizer genotypes [21, 24]. These polymorphisms explain approximately 10-fold greater plasma efavirenz exposure in slow versus normal metabolizers [17]. *CYP2B6* slow metabolizer genotypes (i.e., two copies of decreased-function or no-function alleles) are present in approximately 30% of Asians, 25% of Africans, and 5% of Europeans.

The present study characterized the impact of known functional pharmacogenetic variants on drug-drug interactions between ART and plasma hormone exposure among A5316 participants.

Methods

Protocol A5316 (NCT01903031) was a multisite, international, non-randomized, open-label, three-group parallel PK study among women living with HIV. Primary results are described elsewhere [11]. All study procedures followed the Declaration of Helsinki and were approved by ethics boards at each participating clinical site. Eligible participants were at least 16 years of age, were of reproductive potential, were willing to use a second, non-hormonal form of contraception during the study period, and agreed to avoid concurrent hormonal therapies or interacting medications.

Participants enrolled between December 2014 and September 2016, and were assigned to one of three study groups based on ART use at screening. The control group comprised women who had not yet begun ART with CD4+ T-cell counts of at least 350 cells/mm^3. The efavirenz group comprised women receiving efavirenz 600 mg daily plus at least two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), and the atazanavir/ritonavir (atazanavir/r) group comprised women receiving atazanavir/r 300mg/100mg daily, tenofovir 300mg daily, plus at least one additional NRTI. Women on ART were required to be on stable ART for at least 30 days and have screening plasma HIV-1 RNA ≤400 copies/mL. For all participants, a vaginal ring releasing etonogestrel/ethinyl estradiol 120/15 μg/day was inserted on day 0. Prior to placement of the vaginal ring on day 0, participants in the ART groups underwent intensive 8-hour PK sampling to analyze efavirenz, atazanavir and ritonavir. With an observed ART dose, plasma for antiretroviral assays were collected pre-dose and 1, 3, 4, 5, and 8 hours post-dose. Participants returned on days 7, 14 and 21 for single plasma samples for hormone PK (etonogestrel and ethinyl estradiol). On day 21, 8-hour ART PK sampling was repeated before removing the vaginal ring. Adherence to ART and the vaginal ring were evaluated by self-report.[25] The 8-hour PK sampling was rescheduled if any of the prior three ART doses were missed, or if the vaginal ring was outside of the body during a specified time leading up to the PK sampling. This time (12 hours) was based on the known PK of the hormones, time to appropriate concentrations, and half-life. Hormone and antiretroviral concentrations were analyzed by LC-MS/MS. All PK assays were validated in accordance with guidance from the Food and Drug Administration. [26] Efavirenz, atazanavir, and ritonavir PK parameters were estimated using Phoenix WinNonLin® version 7.0 (Certara USA, Inc., Princeton, NJ). AUC was calculated using non-compartmental methods over the 8-hour intensive PK sampling ($AUC_{0–8h}$). Resultant PK parameters were $\log_{10}$ transformed to approximate normality.

Characterization of Genetic Polymorphisms

We genotyped polymorphisms that are known to predict plasma efavirenz PK (11–15). For efavirenz, *CYP2B6* 983T→C and 15582C→T, and *CYP2A6* rs28399433 were assayed using MassARRAY® iPLEX Gold (Sequenom Inc., San Diego, California, USA), while *CYP2B6* 516G→T was genotyped by Taqman. The *CYP3A5*3* variant 6986A→G (rs776746) (22) was genotyped by MassARRAY® iPLEX Gold. For atazanavir, *UGT1A1* rs887829 which is associated with bilirubin levels was genotyped [27]. No SNPs are known to be associated with atazanavir/r PK [27]. For etonogestrel and ethinyl estradiol SNPs were genotyped that have been genome-wide associated with estradiol phenotypes, including rs1864729 [28] , rs2414095, rs2445762 [29], rs117585797 [30], rs727428 [31]. For *CYP3A4* we genotyped rs17277546 [32], rs34670419 [30], rs62471956 [33], rs34670419 [30], and *CYP3A4* SNPs associated with changes in *in vivo* activity, rs28371759, rs35599367 [34]. For *CYP3A5* we genotyped rs4646450 [35] and rs776746 [34]. For *CYP1A1* we genotyped rs2470893 [36], rs2472297 [37], rs2470893 [38], which have been associated with various traits in genome-wide association studies. For *CYP1A2* we genotyped SNPs associated with altered *in vivo* activity, including rs2069514, rs762551, rs56276455, rs72547516, rs28399424, and rs56107638 [34].

Human DNA was extracted from whole blood. Genotyping was done in the Vanderbilt DNA Resources Core using MassARRAY® iPLEX Gold (Agena Bioscience™, California, USA) and Taqman (ThermoFisher Scientific, Massachusetts, USA). Final Sequenom assay design is available upon request. Laboratory personnel with no knowledge of clinical data performed genotyping. Ample duplicate and blank assays were included to assure validity, and all samples were assayed in duplicate. Genotyping efficiency was 100% for all SNPs. Of 27 SNPs assayed, we excluded 10 with minor allele frequencies less than 5%, leaving 17 for association analyses.

Statistical analysis

The population for analysis of antiretroviral exposure comprised participants for whom intensive ARV sampling was conducted on both days 0 and 21, and who had genetic data available. Genetic associations were assessed using linear regression models. Statistical analyses for associations between PK parameters and composite *CYP2B6* genotype levels were performed with STATA version 15.1 (StataCorp, College Station, Texas, USA). Composite *CYP2B6* genotype that predicts 12 levels of progressively higher plasma efavirenz exposure was defined based on combinations of four SNPs as follows: normal metabolizer genotype (1: 15582CC-516GG-983TT or 2: 15582CT-516GG-983TT); intermediate metabolizer genotype (3: 15582TT-516GG-983TT; 4: 15582CC-516GT-983TT; 5: 15582CC-516GG-983CT; 6: 15582CT-516GT-983TT; or 7: 15582CT-516GG-983CT); and slow metabolizer genotype (8: 15582CC-516TT-983TT; 9: 15582CC-516GT-983CT; or 10: 15582CC-516GG-983CC) [17]. With slow metabolizer genotypes, two additional composite genotypes were defined by the presence of a *CYP2A6* SNP as follows: 11: −48GT; and 12: −48GG. Statistical analyses for associations with SNPs were performed with PLINK version 1.07 [39]. For composite *CYP2B6* genotype associations in the efavirenz group we did not correct for multiple comparisons because the primary analysis focused on this genotype and etonogestrel and ethinyl estradiol concentrations in the efavirenz group. this was the primary focus of analyses. For other SNPs we corrected for 17 comparisons, giving a significance cut-off of P = 0.0029. For *CYP2B6*, directionality of β coefficients considers *CYP2B6* normal metabolizer genotype as the reference (i.e., a positive β indicates that *CYP2B6* slow metabolizer genotype is associated with a greater PK parameter value). Two-sided tests were used for all analyses. All SNPs were in Hardy-Weinberg equilibrium after correcting for multiple comparisons. Only one SNP, *CYP2B6* rs3745274, deviated nominally from Hardy-Weinberg equilibrium (p = 0.041).

Results

Study participants

The total group for analysis comprised 72 participants with both PK and genotype data, and included 25 in the control group, 24 in the efavirenz group, and 23 in the atazanavir/r group. Participants enrolled at ACTG sites in Asia, South America, Sub-Saharan Africa, and the United States. In the total group, median age was 34 years, 35 (49%) self-identified as Black, 26 (36%) reported Hispanic ethnicity, and median baseline weight was 67.5 kg. Characteristic of participants by study group are provided in Table 1. Black participants were overrepresented in the efavirenz group, Asian/Pacific Islander participants

overrepresented in the atazanavir/r group, and *CYP2B6* slow metabolizer genotypes underrepresented in the atazanavir/r group. Frequencies of non-*CYP2B6* SNPs by study group are available in Supplemental Online Material.

CYP2B6/CYP2A6 associations with plasma efavirenz PK parameters

As expected, among the 24 efavirenz group participants, *CYP2B6* slow metabolizer genotypes were associated with higher plasma efavirenz $\log_{10}$ $AUC_{0–8h}$, $\log_{10}$ C_{max} and $\log_{10}$ C_{min} values at days 0 and 21. For example, for *CYP2B6* genotype (stratified into 3 levels) and $\log_{10}$ plasma efavirenz $AUC_{0–8h}$ at day 0: β coefficient 0.27, $P = 4.5 \times 10^{-5}$. Relationships between *CYP2B6/CYP2A6* genotype, stratified into 3 genotype levels, and $\log_{10}$ plasma efavirenz $AUC_{0–8h}$ values at days 0 and 21, are presented in Figure 1. These relationships stratified into 12 *CYP2B6/CYP2A6* genotype levels are presented in Supplemental On-line Material. Relationships between *CYP2B6* genotype and each efavirenz PK parameter are presented in Table 2. These genetic associations persisted after adjusting for weight and/or age (data not shown).

CYP2B6/CYP2A6 and etonogestrel and ethinyl estradiol concentrations

Relationships between *CYP2B6/CYP2A6* genotype, stratified into 3 genotype levels, and $\log_{10}$ ethinyl estradiol and $\log_{10}$ ethinyl estradiol at day 21 are presented in Figure 2. These relationships stratified into 12 *CYP2B6/CYP2A6* genotype levels are presented in Supplemental On-line Material. Detailed information regarding *CYP2B6* genotype, stratified into 3 genotype levels, $\log_{10}$ ethinyl estradiol and $\log_{10}$ ethinyl estradiol are presented in Table 2. Among the 24 efavirenz group participants, *CYP2B6* slow metabolizer genotypes were associated with significantly lower plasma concentrations of both etonogestrel and ethinyl estradiol at day 21. For example, considering *CYP2B6* genotype (stratified into 3 levels) and $\log_{10}$ plasma etonogestrel concentrations, the β coefficient was −0.21, $P = 1.7 \times 10^{-3}$, and considering $\log_{10}$ plasma ethinyl estradiol concentrations, the β coefficient was −0.19, $P = 6.7 \times 10^{-4}$. These genetic associations persisted after adjusting for weight and/or age (data not shown). Plasma hormone concentrations below limits of quantification on day 21 occurred only among participants with *CYP2B6* slow metabolizer genotypes, including 3 participants with plasma ethinyl estradiol concentrations below 5 pg/mL, and 5 participants with plasma etonogestrel concentrations below 25 pg/mL (Figure 2).

On Day 21, the median $\log_{10}$ etonogestrel concentration was 3.27 pg/mL in the non-ART control group, but was 2.70 pg/mL, 2.64 pg/mL, and at most 2.10 pg/mL in *CYP2B6* normal, intermediate, and slow metabolizers, respectively, which represent 73%, 77% and at least 93% reductions in median absolute etonogestrel concentrations.

On Day 21, the median $\log_{10}$ ethinyl estradiol concentration was 1.33 pg/mL in the non-ART control group, but was 1.10 pg/mL, 1.10 pg/mL, and 0.72 pg/mL in *CYP2B6* normal, intermediate, and slow metabolizers, respectively, which represent 41%, 41%, and at least 75% reductions in median absolute ethinyl estradiol concentrations.

Within the control group and atazanavir/r group, each group analyzed separately, there were no associations between *CYP2B6/CYP2A6* slow metabolizer genotypes and plasma concentrations of either etonogestrel or ethinyl estradiol at day 21 ($P > 0.05$ for each model).

Plasma efavirenz PK, etonogestrel and ethinyl estradiol concentrations

To assess whether the association of *CYP2B6/CYP2A6* with etonogestrel and ethinyl estradiol concentrations was mediated by plasma efavirenz exposure, we characterized such relationships (Table 3 and Figure 3). Among the 24 efavirenz group participants, increased plasma efavirenz exposure was significantly associated with decreased plasma concentrations of both etonogestrel and ethinyl estradiol at day 21. Day 21 efavirenz $AUC_{0–8h}$ were significantly associated with day 21 $\log_{10}$ plasma etonogestrel concentrations (β coefficient −0.80, $P = 6.2 \times 10^{-8}$) and day 21 $\log_{10}$ plasma ethinyl estradiol concentrations (β coefficient −0.57, $P = 5.2 \times 10^{-5}$). Participants with plasma etonogestrel and ethinyl estradiol concentration below limits of quantification on day 21 tended to have the highest plasma efavirenz $AUC_{0–8h}$ values (Figure 3). Considering each efavirenz PK parameter, plasma etonogestrel and plasma ethinyl estradiol concentration at day 21 were significantly associated with efavirenz $AUC_{0–8h}$, C_{min} and C_{max} at day 0 and/or day 21. For all parameters, P-values for association were lower for day 0 efavirenz PK parameters than for day 21 efavirenz PK parameters. The lowest P-values for association for both etonogestrel and ethinyl estradiol were with efavirenz $AUC_{0–8h}$ at day 0. Relationships between each efavirenz PK parameter, etonogestrel and ethinyl estradiol concentrations are presented in Table 3.

In A5316, geometric mean efavirenz C_{min} concentrations were 36% lower on day 21 (with hormones) than on day 0 (without hormones). In the present analysis, the proportion change in median $\log_{10}$ efavirenz C_{min} was similar regardless of *CYP2B6* genotype level, and was −0.24 $\log_{10}$ (42.5% reduction), −0.2 $\log_{10}$ (36.9% reduction), and −0.15 $\log_{10}$ (29.9% reduction) with *CYP2B6* normal, intermediate, and slow metabolizer genotypes, respectively.

Other polymorphisms, etonogestrel and ethinyl estradiol concentrations

Among the 24 efavirenz group participants, and after adjusting for *CYP2B6/CYP2A6* composite genotype, and correcting for multiple comparisons, there were no statistically significant associations between any of the 17 SNPs and concentrations of either etonogestrel or ethinyl estradiol at day 21. For $\log_{10}$ etonogestrel, the lowest P-values was for rs727428 which is intronic between *SHBG* and *ATP1B2* (P =0.16), and for $\log_{10}$ ethinyl estradiol was for *UGT1A1* rs887829 (P = 0.011).

Among the 25 control group participants, without adjusting for *CYP2B6/CYP2A6* composite genotype but correcting for multiple comparisons, there were no statistically significant associations between any of the 17 SNPs and concentrations of either etonogestrel or ethinyl estradiol at day 21. For $\log_{10}$ etonogestrel the lowest P-values was for *CYP3A5* rs776746 (P = 0.078), and for $\log_{10}$ ethinyl estradiol was also *CYP3A5* rs776746 (P = 0.026).

Among the 23 atazanavir/r group participants, without adjusting for *CYP2B6/CYP2A6* composite genotype but correcting for multiple comparisons, there were no statistically significant associations between any of the 17 SNPs and concentrations of either etonogestrel or ethinyl estradiol at day 21. For etonogestrel the lowest P-values was for

CYP19A1 rs2445762 (P = 0.018), and for ethinyl estradiol was rs2472297 which is intronic between *CYP1A1* and *CYP1A2* (P = 0.16).

Discussion

Primary analyses from study A5316 showed that, compared to women with HIV but not yet receiving ART, efavirenz-based ART was associated with significantly reduced plasma exposure of both etonogestrel and ethinyl estradiol released from a vaginal ring. [11] The present study extended that observation by showing that, in the efavirenz arm, plasma etonogestrel and ethinyl estradiol concentrations were reduced to a significantly greater extent among *CYP2B6* slow metabolizers than among *CYP2B6* intermediate and normal metabolizers. Efavirenz is known to induce hepatic CYP3A4 and other CYP isoforms. We hypothesize that higher plasma efavirenz concentrations, which result from reduced CYP2B6 activity, cause greater induction of CYP3A4 and therefore more rapid plasma clearance of both etonogestrel and ethinyl estradiol. This mechanism is supported by the highly significant inverse correlation between day 21 plasma efavirenz exposure and plasma concentrations of both etonogestrel and ethinyl estradiol. These findings support another pharmacogenetic evaluation of a similar progestin, levonorgestrel, which shares the same metabolic pathway as etonogestrel. When efavirenz-based ART was combined with a levonorgestrel-releasing contraceptive implant, *CYP2B6* 516G→T was associated with lower levonorgestrel C_{max} and AUC. [40]

The present study suggests that the detrimental interaction between efavirenz and both etonogestrel and ethinyl estradiol administered by vaginal ring could be reduced by individualizing efavirenz dosing based on *CYP2B6* genotype. However, even with *CYP2B6* normal metabolizer genotypes the magnitude of effect is substantial (73% lower etonogestrel and 41% lower ethinyl estradiol concentrations), suggesting that individualizing efavirenz dosing based on *CYP2B6* genotype would not be sufficient to mitigate this effect. We suspect that drug-drug interactions between efavirenz and other concomitant medications could be similarly reduced by individualizing efavirenz dosing based on *CYP2B6* genotype. Physiologically-based pharmacokinetic modeling of levonorgestrel, a progestin with a similar metabolism pathway as etonogestrel, predicted that dose reduction of efavirenz to 400 mg daily would not significantly influence the clinical significance of the drug-drug interaction between efavirenz and the progestin (53% lower levonorgestrel with efavirenz 600 mg versus 45% lower levonorgestrel with efavirenz 400 mg).[41] However, the present study suggests that influence of efavirenz dose reduction on the extent of the drug-interaction may vary depending on *CYP2B6* genotype.

The effect of efavirenz-based ART on vaginally administered ethinyl estradiol in A5316 was greater (59% lower exposure) than previously described between efavirenz and oral ethinyl estradiol, which only observed a 10% lower exposure of oral ethinyl estradiol. [4] The former study was an HIV-negative, healthy volunteer, cross-over, PK intraindividual comparison of ethinyl estradiol from a combined oral contraceptive pill administered with or without efavirenz. That trial was entirely enrolled in the United States, 68% of participants were White and 21% were Black, and pharmacogenetics were not analyzed. In A5316, all participants were living with HIV, the efavirenz group was receiving fully suppressive ART,

and enrolled from diverse international clinical trials sites, reflected in a high proportion of Black participants in both the control and ART groups (44% and 64%, respectively). The potential mechanism for differences is the extent of the drug-drug interaction between efavirenz and ethinyl estradiol given orally or via a vaginal ring is unclear, but it is possible that more patients with *CYP2B6* slow metabolizer genotypes were included in A5316. Results of the present study are consistent with a recent report describing the pharmacogenetic interaction between efavirenz and etonogestrel delivered by subdermal implant. In that study, among 19 women receiving efavirenz-based antiretroviral therapy, *CYP2B6* 516G→T was associated with 43% lower etonogestrel C_{min} and 34% lower $AUC_{0–24weeks}$.[42]

Study A5316 previously showed that, compared to women with HIV but not yet receiving ART, atazanavir/r was associated with 71% higher plasma etonogestrel concentrations and 38% lower ethinyl estradiol concentrations. The present study showed that, in the atazanavir/r arm, there were no significant associations between 17 candidate SNPs and concentrations of either etonogestrel or ethinyl estradiol at day 21 after controlling for multiple comparisons. Similarly, in the control groups there were no significant associations between 17 candidate SNPs and concentrations of either etonogestrel or ethinyl estradiol at day 21 after controlling for multiple comparisons.

Efavirenz 600 mg daily is being phased out in many low- and middle-income settings in favor of efavirenz 400mg daily.[43] This dose reduction is reported to be associated with approximately 25% lower efavirenz exposure across *CYP2B6* normal-, intermediate- and slow-metabolizer genotype groups.[44] Study A5316 observed modestly lower efavirenz exposure during vaginal ring use. The efavirenz minimum concentration was 36% lower during hormone use, but remained above the concentration proposed to be associated with efavirenz effectiveness.[45] In the present study, none of the genotypes studied were associated with the magnitude of effect of vaginal ring use on plasma efavirenz exposure. Therefore, the risk of drug-drug interaction between vaginal ring hormones and ART will not be mitigated by genotype, and patients in the normal metabolizer genotypes will remain at greatest risk of sub-therapeutic concentrations, particularly in the context of suboptimal adherence.

This study had several limitations. Given the small sample size we could only evaluate relatively frequent genetic polymorphisms. With relatively few individuals representing any given genotype, this study should be considered exploratory. Hormone and ART adherence was assessed by self-report and not by direct measures of adherence. In addition, the study was not designed to evaluate the pharmacodynamic relationship between hormone concentrations and ovulation suppression or other measures of contraceptive effectiveness.

In summary, *CYP2B6* slow metabolizer genotype worsens the detrimental drug-drug interaction between hormones administered by vaginal ring (93% versus 73% lower etonogestrel concentrations, and 75% versus 41% lower ethinyl estradiol with *CYP2B6* slow versus normal metabolizer genotypes, respectively). These findings suggest that this detrimental interaction could be reduced, but not eliminated, by individualizing the efavirenz dose based on *CYP2B6* genotype. It is likely that drug-drug interactions between efavirenz

and other concomitant medications may be similarly reduced by individualized efavirenz dosing based on *CYP2B6* genotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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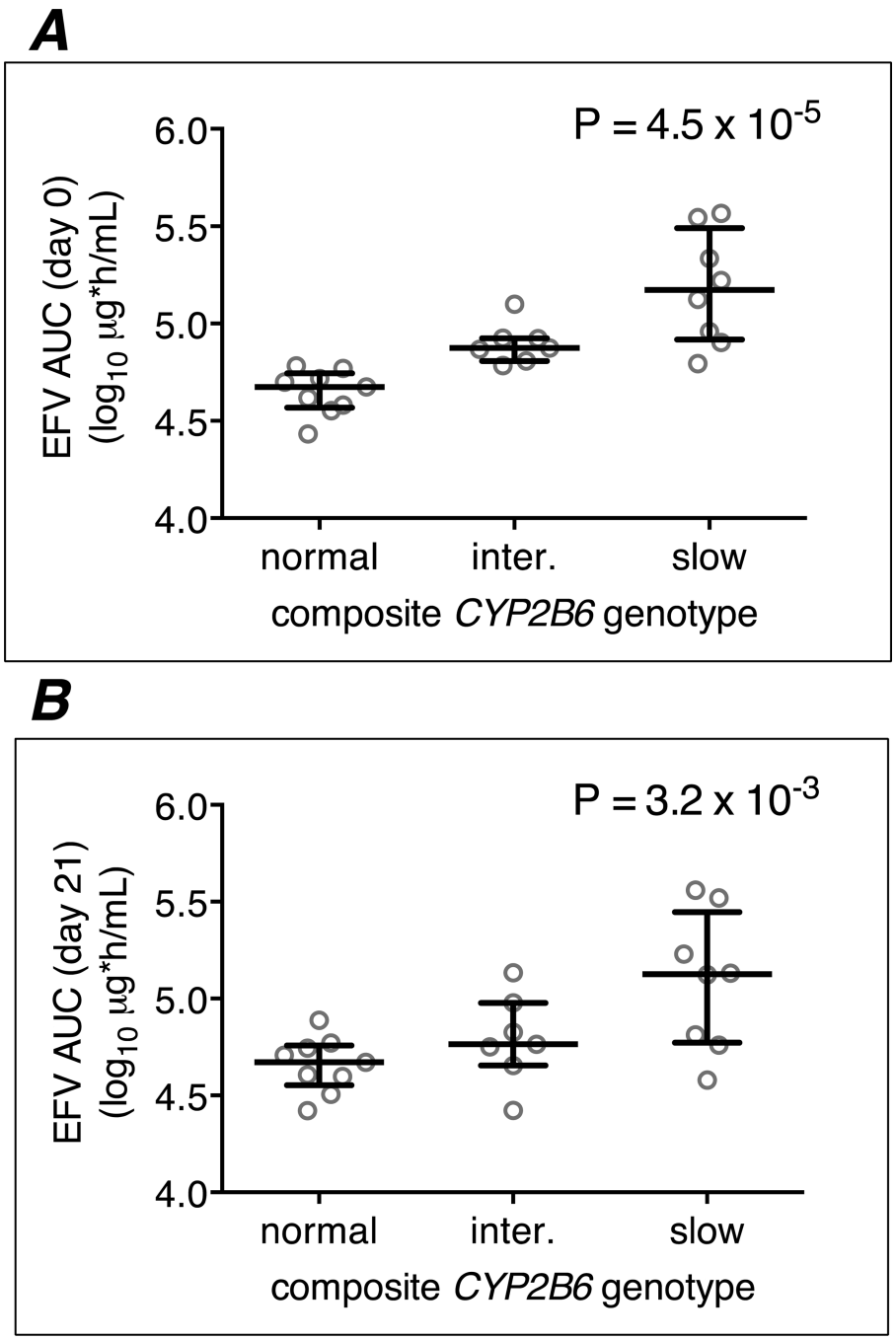

Figure 1. Relationships between *CYP2B6/CYP2A6* genotype levels and plasma efavirenz $\log_{10}$ $AUC_{0–8h}$ values among 24 efavirenz group participants.

Panel A: associations at day 0 with *CYP2B6/CYP2A6* genotype stratified into 3 levels; *Panel B:* associations at day 21 with *CYP2B6/CYP2A6* genotype stratified into 3 levels. Error bars indicate median and interquartile range. Linear regression model P-values are shown. EFV = efavirenz; AUC = area under the concentration-time curve.

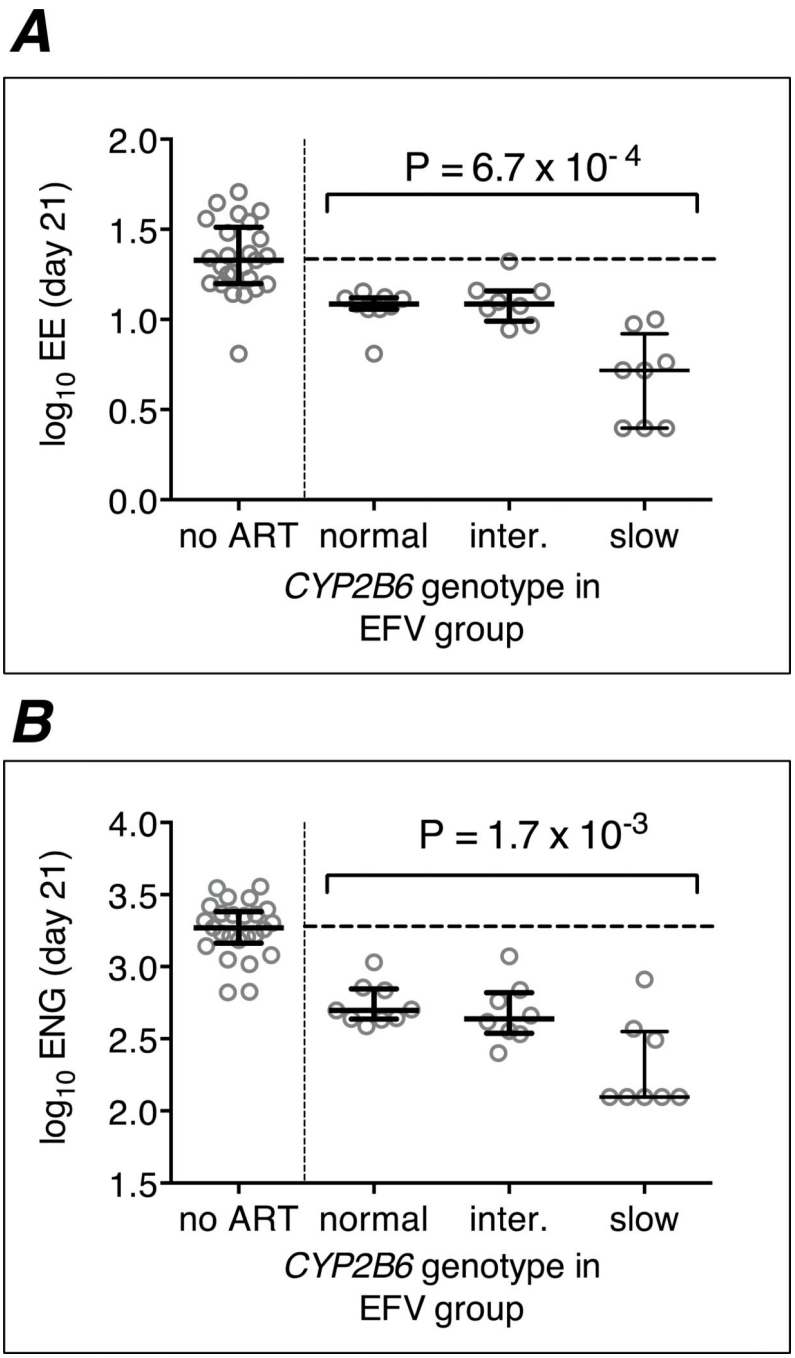

Figure 2. Relationships between *CYP2B6/CYP2A6* genotype levels and day 21 $\log_{10}$ etonogestrel and ethinyl estradiol concentrations among the 24 efavirenz group participants.

Panel A: associations of *CYP2B6/CYP2A6* genotype stratified into 3 levels and $\log_{10}$ ethinyl estradiol concentrations at day 21; *Panel B:* associations of *CYP2B6/CYP2A6* genotype stratified into 3 levels and $\log_{10}$ etonogestrel concentrations at day 21. Error bars indicate median and interquartile range. Linear regression model P-values are shown. ENG = etonogestrel; EE = ethinyl estradiol; EFV = efavirenz. Data from 25 individuals not receiving antiretroviral therapy (ART) are included to the left.

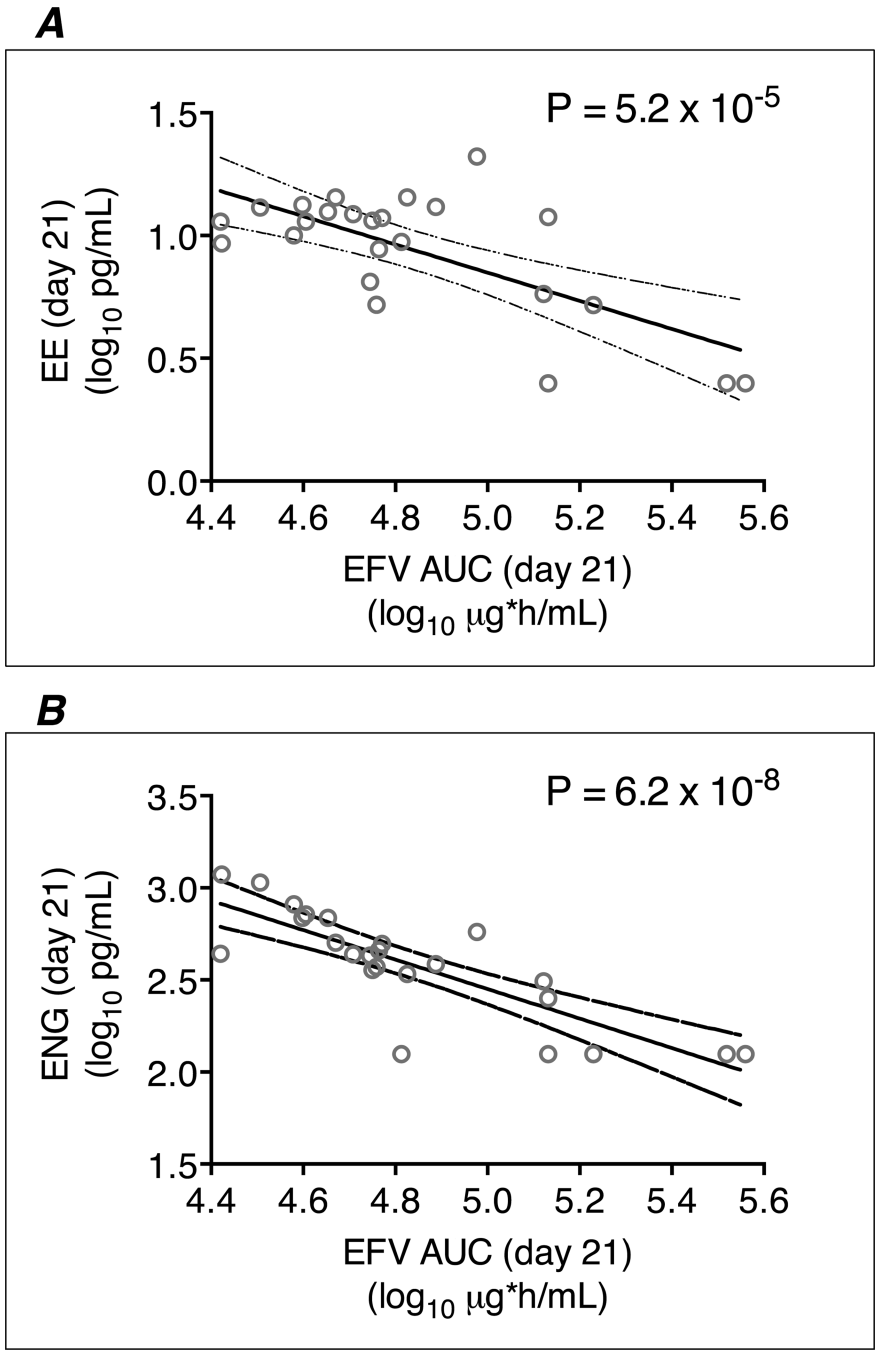

Figure 3. Relationships between day 21 plasma efavirenz $\log_{10}$ $AUC_{0–8h}$ values and day 21 $\log_{10}$ etonogestrel and ethinyl estradiol concentrations among the 24 efavirenz group participants.

Panel A: associations of plasma efavirenz $\log_{10}$ $AUC_{0–8h}$ values on day 21 and $\log_{10}$ ethinyl estradiol concentrations on day 21; *Panel B:* associations of plasma efavirenz $\log_{10}$ $AUC_{0–8h}$ values on day 21 and $\log_{10}$ etonogestrel concentrations on day 21; Line of regression and 95% confidence intervals are shown. EFV = efavirenz; AUC = area under the concentration-time curve; ENG = etonogestrel; EE = ethinyl estradiol.

Table 1.

Baseline characteristics of participants included in genetic association analyses

	Total (n=72)	Control Group (n=25)	Efavirenz Group (n=24)	Atazanavir/r Group (n=23)
Age in years, median (range)	34.0 (22 – 55)	31 (22 – 48)	36 (24 – 55)	37 (24 – 48)
Sex (female); n (%)	72 (100)	25 (100)	24 (100)	23 (100)
Race/Ethnicity; n (%)				
White	3 (4)	1 (4)	1 (4)	1 (4)
Black	35 (49)	11 (44)	16 (64)	9 (39)
Asian/ Pacific Islander[a]	8 (11)	3 (12)	0 (0)	5 (22)
Hispanic	26 (36)	10 (40)	8 (32)	8 (35)
Weight in kg, median (range)	67.5 (36.9 – 170.6)	66.8 (36.9 – 112.9)	68.9 (46.5 – 170.6)	64 (47.3 – 152.4)
***CYP2B6* metabolizer genotype; n (%)**				
normal	22 (31)	5 (20)	9 (38)	8 (35)
intermediate	32 (44)	12 (48)	7 (29)	13 (57)
slow	18 (25)	8 (32)	8 (33)	2 (9)

[a] defined based on NIH policy on reporting race and ethnicity data.

Table 2.

Relationships between *CYP2B6* genotype levels, plasma efavirenz pharmacokinetic parameters, and hormone concentrations among the 24 efavirenz group participants.

Pharmacokinetic parameter	day	*CYP2B6* Normal median (IQR)	*CYP2B6* Intermediate median (IQR)	*CYP2B6* Slow median (IQR)	β coefficient, P-value[a]
efavirenz					
AUC_{0-8h} (log_{10} ng*h/mL)	0	4.67 (4.57 – 4.74)	4.87 (4.81 – 4.92)	5.17 (4.92 – 5.49)	0.27, 4.5×10^{-5}
	21	4.67 (4.55 – 4.76)	4.76 (4.65 – 4.98)	5.13 (4.77 – 5.45)	0.21, 3.2×10^{-3}
C_{min} (log_{10} ng/mL)	0	3.12 (3.00 – 3.22)	3.39 (3.33 – 3.42)	3.59 (3.33 – 4.07)	0.27, 4.3×10^{-4}
	21	3.09 (2.93 – 3.16)	3.30 (3.09 – 3.37)	3.42 (3.29 – 3.91)	0.32, 3.0×10^{-2}
C_{max} (log_{10} ng/mL)	0	3.49 (3.40 – 3.61)	3.68 (3.60 – 3.75)	3.91 (3.71 – 4.19)	0.21, 7.0×10^{-4}
	21	3.51 (3.41 – 3.67)	3.60 (3.54 – 3.78)	3.89 (3.53 – 4.17)	0.16, 1.3×10^{-2}
etonogestrel					
concentration (log_{10} pg/mL)	21	2.70 (2.64 – 2.85)	2.64 (2.54 – 2.82)	2.10 (2.10 – 2.55)	−0.21, 1.7×10^{-3}
ethinyl estradiol					
concentration (log_{10} pg/mL)	21	1.09 (1.06 – 1.12)	1.09 (0.99 – 1.16)	0.72 (0.40 – 0.92)	−0.19, 6.7×10^{-4}

Abbreviations: AUC, area under the concentration time curve; C_{max}, maximum concentration; C_{min}, minimum concentration.

[a]P-values and beta coefficients were generated with linear regression models.

Table 3.

Relationships between efavirenz pharmacokinetic parameters and day 21 etonogestrel and ethinyl estradiol concentrations among the 24 efavirenz group participants.

Efavirenz pharmacokinetic parameter	day[a]	log_{10} etonogestrel β coefficient, P-value[a]	log_{10} ethinyl estradiol β coefficient, P-value[b]
AUC_{0-8h} (log_{10} ng*h/mL)	0	−0.80, 1.0×10^{-9}	−0.68, 5.9×10^{-7}
	21	−0.80, 6.2×10^{-8}	−0.57, 5.2×10^{-5}
C_{min} (log_{10} ng/mL)	0	−0.63, 3.4×10^{-7}	−0.58, 4.0×10^{-6}
	21	−0.27, 1.1×10^{-1}	−0.20, 1.0×10^{-1}
C_{max} (log_{10} ng/mL)	0	−0.88, 5.4×10^{-9}	−.075, 1.2×10^{-5}
	21	−0.86, 4.7×10^{-7}	−0.67, 1.4×10^{-4}

Abbreviations: AUC, area under the concentration time curve; C_{max}, maximum concentration; C_{min}, minimum concentration.

[a]Day 0 or 21 refers to the day on which efavirenz pharmacokinetic parameters were determined.

[b]P-values and beta coefficients were generated with linear regression models.