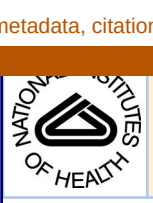

Published in final edited form as:

J Acquir Immune Defic Syndr. 2010 December ; 55(4): 473–482. doi:10.1097/QAI.0b013e3181eb5ff5.

Contraceptive Efficacy of Oral and Transdermal Hormones When Co-Administered With Protease Inhibitors in HIV-1–Infected Women: Pharmacokinetic Results of ACTG Trial A5188

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Abstract

Background—Pharmacokinetic (PK) interactions between lopinavir/ritonavir (LPV/r) and transdermally delivered ethinyl estradiol (EE) and norelgestromin (NGMN) are unknown.

Methods—Using a standard noncompartmental PK analysis, we compared EE area under the time–concentration curve (AUC) and NGMN AUC during transdermal contraceptive patch administration in HIV-1–infected women on stable LPV/r to a control group of women not on highly active antiretroviral therapy (HAART). In addition, EE AUC after a single dose of a combination oral contraceptive pill including EE and norethindrone was measured before patch placement and was compared with patch EE AUC in both groups. Contraceptive effects on LPV/r PKs were estimated by measuring LPV/r AUC at baseline and during week 3 of patch administration.

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Results—Eight women on LPV/r, and 24 women in the control group were enrolled. Patch EE median $AUC_{0–168\ h}$ was 45% lower at 6010.36 pg·h·mL^{-1} in those on LPV/r versus 10911.42 pg·h·mL^{-1} in those on no HAART ($P = 0.064$). Pill EE median $AUC_{0–48}$ hours was similarly 55% lower at 344.67 pg·h·mL^{-1} in those on LPV/r versus 765.38 pg·h·mL^{-1} in those on no HAART ($P = 0.003$). Patch NGMN $AUC_{0–168\ h}$ however, was 138.39 ng·h·mL^{-1}, 83% higher in the LPV/r group compared with the control AUC of 75.63 ng·h·mL^{-1} ($P = 0.036$). After 3 weeks on the patch, $LPVAUC_{0–8\ h}$ decreased by 19%, ($P = 0.156$).

Conclusions—Although PKs of contraceptive EE and NGMN are significantly altered with LPV/r, the contraceptive efficacy of the patch is likely to be maintained. Larger studies are indicated to fully assess contraceptive efficacy versus risks of the transdermal contraceptive patch when co-administered with protease inhibitors.

Keywords

HIV; hormonal contraceptive; lopinavir/ritonavir; pharmacokinetics

Introduction

HIV-infected women represent half of HIV-infected persons globally, and the majority are of child-bearing potential.[1] Effective contraception is critical to rational family, and life-planning access to effective family planning is an essential component of prevention of maternal to child transmission of HIV infection and prevention of pediatric HIV infection.[2] Highly active antiretroviral therapy (HAART) has restored to HIV-infected women the potential to live a full life, including safer childbearing. Post-HAARTera data suggest that HIV-infected women have a similar rate of childbearing to those who are HIV uninfected.[3,4] For HIV-infected women, contraception can delay childbearing until viral replication can be controlled, thus reducing the risk of mother to child transmission of HIV. Condoms, although effective for the prevention of sexually transmitted infections, are less effective as contraception, with about a 15% pregnancy rate in the first year of use, much higher than that of hormonal contraception.[5] A more recent study in African HIV-infected women using condoms alone showed no reduction in the incidence of pregnancy.[6] Concomitantly, a recent study in a longitudinal cohort of American women showed hormonal contraception was used less often in those who were HIV infected than in HIV-uninfected women.[7]

For a large part of the world, in both developed and less developed regions, ritonavir (RTV)-boosted protease inhibitors (PIs) are an essential part of an effective HAART regimen for women of child-bearing potential who also require effective contraception. In currently published guidelines from the US Department of Health and Human Services, the use of fixed-dose combination of lopinavir/ritonavir (Kaletra, LPV/r)-based antiretroviral (ARV) therapies are now listed as “alternative” rather than as previously listed “preferred” regimens for virologic control, except in pregnant women, in whom twice-daily LPV/r + zidovudine/lamivudine remains a “preferred” regimen.[8,9] Preconception care guidelines published by Department of Health and Human Services also instruct that women of child-bearing potential be prescribed a regimen effective in preventing mother to child transmission of HIV,[8] in which LPV/r may then be considered “Preferred” However, clinicians may be cautious in recommending hormonal contraception due to the perceived excess risk of

metabolic complications and pharmacological interactions when RTV-boosted PI ARV agents are co-administered with hormonal contraceptives.

Hormonal contraceptive choices have expanded and include new delivery systems. One of these methods is the transdermal contraceptive patch (OrthoEvra, hereafter "patch"), approved by the Food and Drug Administration in November 2001. Studies of the patch have found contraceptive efficacy in terms of ovarian suppression and cycle control comparable to oral contraceptives, but with higher rates of compliance.[10,11] After a single application of ORTHO EVRA, both ethinyl estradiol (EE) and norelgestromin (NGMN) reach a plateau by approximately 48 hours and steady state is reached within 2 weeks of application. The mean steady state C_{ss} concentrations ranged from 0.305 to 1.53 ng/mL for NGMN and from 11.2 to 137 pg/mL for EE in 3 pooled studies.[12] The patch is applied once a week for 3 weeks, then removed for 1 week of a 4-week cycle.

This report describes the results of AIDS Clinical Trials Group study 5188, a phase II, nonrandomized, multicenter trial examining the pharmacokinetic (PK) interaction between the PI, LPV/r, and the transdermal contraceptive patch and single-dose oral contraceptive hormone PKs.

Methods

Study Population

Subjects were nonpregnant, premenopausal HIV-1–infected women ≥13 years old who were either on stable LPV/r (400 mg/100 mg twice a day) in combination with dual nucleoside therapy (NRTIs) for at least 14 days before study entry (LPV/r arm) or were not receiving ARV therapy or receiving NRTIs only (control arm). When the tablet formulation of LPV/r became available during the course of the study, some subjects switched from the gelcaps to the current tablet formulation while on study. Since LPV/r was not a study provided drug, subjects were switched by their provider or pharmacy according to availability of the tablets in their area. Subjects who switched formulations before study entry were required to be on the tablet formulation for at least 7 days before study entry. Subjects had not used any additional PIs or nonnucleoside reverse transcriptase inhibitors within 30 days before entry. Furthermore, subjects had not received depomedroxyprogesterone (DMPA) within 180 days, injectable combination hormones (eg, Lunelle) within 90 days, or oral hormonal contraceptives within 60 days of study entry. Subjects may have received the patch (OrthoEvra, "patch") before entry. Subjects were required to have a $CD4^+$ cell count ≥200 cells per cubic millimeter and HIV-1 RNA <55,000 copies per milliliter within 45 days before study entry.

Subjects could not have initiated, stopped, or changed doses of medications that are substrates for cytochrome p450 3A4 within 30 days before study entry. Smokers ≥35 years old were excluded, whereas subjects <35 years old who intended to maintain stable smoking habits throughout the study were eligible. Subjects refrained from alcohol consumption within 48 hours of intensive PK sampling. Subjects weighing >198 pounds were excluded.

Study Design

This study was an open-label, 4-week, nonrandomized, steady-state study that examined the interaction between LPV/r and the patch in HIV-1–infected women. To compare the effect of treatment with LPV/r on orally administered EE versus controls, at 5–7 days after the start of the first menses after study entry both the LPV/r arm subjects and the control arm subjects received a single-dose oral contraceptive pill (Ortho Novum 1/35, “pill”) containing 35 mcg of EE and 1 mg of norethindrone, a second-generation progestin. The single oral dose component serves as a control in that PK changes seen with oral administration may be attributed to the effect of LPV/r on first pass metabolism occurring in the gastrointestinal tract; an effect likely absent when EE is administered via the patch.

Intensive EE PK was performed after pill administration at 0 (predose), 1, 2, 4, 6, 8, 12, 24, 34, and 48 hours postdose. Subjects received the single oral dose pill on day 1 and were started the patch on day 3 (48 hours later). Subjects received the patch for 3 weeks and replaced the patch each week. During the week-3 patch cycle, blood samples for EE and NGMN PK were obtained immediately after the patch was placed (baseline), then again at 12–48 hours, at 48–72 hours, and at 7 days after patch placement.

LPV/r study arm subjects underwent intensive blood sampling for LPV and RTV PK parameters at study entry just before the pill administration, and 2 weeks after the patch was started (at steady state hormone levels). LPV and RTV PK samples were drawn at 0 (predose of LPV), 1, 2, 3, 4, 6, and 8 hours postdosing of LPV/r.

Subjects completed a self-report questionnaire at baseline about potential factors affecting adherence, including drug and alcohol use. Adherence to ARV medication was assessed over the prior 4 days at each study visit using a self-report questionnaire developed by the AIDS Clinical Trials Group.[13]

The study was projected to enroll 27 evaluable subjects in both the LPV/r-based arm and the control arm for a total of 54 evaluable subjects, to provide at least 80% power to detect a 40% mean difference in the patch EE area under the time–concentration curve (AUC) between the 2 study arms at a significance level of 0.05.

This protocol was approved by the Biomedical Institutional Review Boards at each of the participating AIDS Clinical Trials Group sites. Each patient provided written informed consent. The study was performed at 9 adult and pediatric AIDS Clinical Trials Group sites between May 2005 and November 2006.

Hormonal Assays

Plasma concentrations of EE and NGMN were analyzed by high-performance liquid chromatography as follows: A 500-μL sample aliquot was fortified with 25 μL of internal standard working solution. Analytes were isolated by extracting with 10:90 ethyl acetate/hexane. The solvent was evaporated and the remaining residue was derivatized with dansyl chloride. The derivatized analytes were extracted into hexane, the hexane was evaporated and the remaining residue was reconstituted with 100 μL of acetonitrile and 200 μL of water. The final extract was analyzed via high-performance liquid chromatography with tandem

mass spectrometry detection. Assays were performed at Pharmaceutical Product Development (PPD), Inc. Bioanalytical Laboratory in Richmond, VA. The lower and upper limits of quantification (LLQ and ULQ) for EE concentrations were 2 pg/mL and 500 pg/mL, respectively, and the LLQ and ULQ for NGMN concentrations were 0.02 ng/mL and 5 ng/mL, respectively. Samples had been collected and allowed to clot for 30 minutes, then centrifuged at 1100g for 20 minutes and frozen at −20 to −70°C until shipped to PPD Laboratory and kept frozen at −20° C before analysis.

Serum concentrations of progesterone were analyzed using a direct chemiluminescent immunoassay (ADVIA Centaur) at Quest Diagnostics Laboratory in Nichols, CA. The validated analytical range of the assay was 0.15–60 ng/mL for progesterone. Serum samples had been allowed to clot for 30 minutes, then centrifuged at 1100–1300g for 10 to 15 minutes and frozen at −20 to −70°C until shipped to Quest Diagnostics Laboratory.

Lopinavir and RTV Assays

Plasma concentrations of LPV and RTV were determined by liquid chromatography/tandem mass spectrometry using validated methods approved by the DAIDS-funded Pharmacology Quality Assurance Program. Assays were carried out within the University of California-San Francisco's AIDS Clinical Trials Group Pharmacology Support Laboratory. For LPV, the method has a LLQ of 50 ng/mL and interassay and intra-assay coefficient of variations ranging from 6.0% to 9.9% and 3.3% to 6.4%, respectively. For RTV the method has a LLQ of 25 ng/mL, interassay and intra-assay coefficient of variations ranging from 4.2% to 10.6% and 1.1% to 9.1%, respectively.

Virologic and Immunologic Markers

Blood plasma HIV-1 RNA and $CD4^+$ cell counts were evaluated at screening (within 45 days before entry), pre-entry (within 30 days before entry), entry, and at study week 4 (3 weeks after the patch started). HIV-1 RNA copies were determined from blood plasma using Roche Ultra-Sensitive assay with LLQ of 50 copies per milliliter or Roche reverse transcriptase—polymerase chain reaction (Amplicor) HIV-1 Monitor assay with LLQ of 400 copies per milliliter in a Division of AIDS-approved laboratory. $CD4^+$ cell counts were performed at local Clinical Laboratory Improvement Amendments (CLIA)-approved immunology laboratories.

PK Analyses

PK parameters for EE, NGMN, lopinavir, and RTV were determined using standard noncompartmental methods and defined as follows. The AUC was determined for patch EE and NGMN from 0 to 168 hours (7 days) after placement of the patch. Pill EE AUC was determined from 0 to 48 hours after administration of the pill. Based on sampling from 0 to 8 hours the LPV and RTV AUC was calculated from 0 to 12 hours postdose based on the assumption that the 12-hour concentration is the same as the 0-hour concentration for bid dosing. All AUC estimates were calculated using the linear trapezoidal rule. Concentrations below the lower limit of quantification (below the lower limit if quantification [BLQ]) were assigned a value of 0.5 BLQ. The minimum concentration (C_{min}) for LPV, RTV, patch EE, and NGMN was calculated as the minimum concentration observed during the sampling/

dosing period, and the maximum concentration (C_{max}) was calculated as the maximum concentration observed over 0–168 hours for EE (patch) and NGMN (patch) or over 0–12 hours of sampling for EE (pill) and for LPV and RTV. C_{min} values were determined using a value of half the LLQ for concentration levels below the LLQ. For pill C_{min}, *C*48 h was used since only a single dose was administered. *C*48 h was defined as the concentration observed at the scheduled sample time of 48 hours. Missing samples at scheduled 48 hours time points were treated as missing and not included in PK analysis.

Statistical Data Analyses

PK parameter estimations and statistical analyses were performed with the Statistical Analysis Systems, version 9.1 software package (SAS Institute, Cary, NC). The effects of LPV/r on PKs of patch EE and NGMN were evaluated by comparing EE and NGMN PK parameters observed from women on LPV/r with those observed from women not on LPV/r during the third week of the patch cycle, using the nonparameteric Wilcoxon rank-sum test. The effect of LPV/r on PKs of pill EE was evaluated by comparing pill EE PK parameters observed from women on LPV/r with those observed from women not on LPV/r after taking a single dose of the pill, using the nonparameteric Wilcoxon rank-sum test. The effects of the patch on PKs of LPV and RTV were evaluated by comparing LPV and RTV PK parameters from the same women before first patch placement and after third patch placement, using the nonparameteric sign-rank test. The role of first-pass metabolism in EE disposition was evaluated by comparing the change (ratio) of EE AUCs between pill and patch in women on LPV/r with that in women not on LPV/r, using the nonparametric Wilcoxon rank-sum test. Linear regression analyses were performed to evaluate effects of subject's body weight and body mass index (BMI) on patch and pill EE and NGMN PK AUC. All the statistical conclusions were based on 2-sided tests with a significance level of 0.05.

Results

Demographic Characteristics

Thirty-two women were enrolled in A5188: 8 in the LPV/r arm and 24 in the no ART or NRTI only (control) arm. Although the accrual target was 27 evaluable subjects in each arm, the study was closed prematurely due to slow accrual (LPV/r, 30% accrual and control arm, 89% accrual). The LPV/r arm included background NRTI use as follows: combined zidovudine/lamivudine (4 subjects), stavudine + lamivudine (1 subject), stavudine and emtricitabine (1 subject), and combined zidovudine/lamivudine/abacavir (2 subjects). The control arm included 21 subjects not taking ART, and 3 subjects on combined zidovudine/lamivudine/abacavir. All subjects receiving LPV/r had HIV RNA level <400 copies per milliliter at baseline. Median $CD4^+$ cell counts at baseline were 550 and 440 in the LPV/r and control arm, respectively.

Table 1 summarizes the demographics of all 32 subjects at baseline. The median age at study entry (30 years) and median weight (72 kg) were similar between arms. Of the 32 total women, 66% were Hispanic, 25% were black and 6% were white. The majority (94%) had never used injection drugs and none were currently using them. Three women were current

smokers (1 in LPV/r arm and 2 in the control arm). Of the 32 subjects, 25 (78%) women had full or partially evaluable data (7 in the LPV/r arm and 18 in the control arm). Seven subjects (22%) went off study and/or treatment prematurely (1 in the LPV/r arm and 6 in the control arm). Three subjects were noncompliant, 2 women did not receive study drugs, 1 subject discontinued prematurely due to a confounding medical condition, and 1 subject in the control arm withdrew consent after reports of increased risk of deep venous thrombosis with the use of the patch were published. There were no significant differences in baseline characteristics between women who completed the study, and the 32 total women enrolled in the study.

Adherence

Adherence data were collected for 4 days before LPV/r sampling as described above for 8 subjects in the LPV/r arm, although 2 of these did not have LPV/r sampling completed. Of those who did have LPV/r sampling completed, 3 patients missed 1 or 2 doses of LPV/r in 4 days before sampling. No subjects missed any dose of LPV/r within 1 day before PK sampling. All missed doses occurred in the patch administration phase.

Contraceptive Patch PKs

The median trajectory plots of patch EE and NGMN concentrations over time are presented in Figure 1. Four subjects in the LPV/r and 15 subjects in the control arm were available to determine patch EE PK parameters, which are summarized in Table 2. Three subjects were receiving gel cap formulation of LPV/r and, therefore, did not contribute to the EE analysis because of the concern for potentially different formulation effect with gel caps versus tablets. The intention was that these subjects would be replaced so EE levels were not performed on the samples from the gel cap–treated subjects, although NGMN levels were performed. The median patch EE concentrations were lower at all sample times in the LPV/r arm compared with the control arm. Median EE $AUC_{0–168\ h}$ was 45% lower ($P = 0.064$) and C_{min} 28% lower in the LPV/r arm ($P = 0.395$). Seven subjects in the LPV/r arm (3 on the gelcap formulation) and 17 subjects in the control arm were available for NGMN PK analysis. Median patch NGMN concentrations were higher at all sample times in subjects on LPV/r. The $AUC_{0–168\ h}$ of NGMN was 83% higher ($P = 0.036$), and C_{min} was 134% higher in the LPV/r treated subjects ($P = 0.036$). Body weight and BMI did not have an effect on EE or NGMN $AUC_{0–168\ h}$.

Contraceptive Pill PKs

The median trajectory plots of pill EE concentrations over time are also shown in Figure 1. Pill EE concentrations were lower at all sample times, except for predose, in the subjects on LPV/r compared with the control arm. Five subjects in the LPV/r arm and 16 subjects in the control arm were available to determine pill EE PK parameters, which are summarized in Table 2. Median EE $AUC_{0–48\ h}$ and $C_{48\ h}$ were significantly lower: 55% ($P = 0.003$) and 76% ($P = 0.023$), respectively, in the LPV/r arm when compared with controls. Body weight and BMI had no effect on the $AUC_{0–48\ h}$ of EE after a single dose of contraceptive pill.

Progesterone

Median progesterone concentrations dropped substantially from baseline in all study subjects as expected with effective contraception. LPV/r did not affect progesterone concentrations. Median progesterone concentrations (ng/mL) at baseline and week 4 were 2.82 (n = 6) and 0.39 (n = 8), respectively, in the LPV/r arm and 1.39 (n = 19) and 0.47 (n = 20) in the control arm. The median progesterone changes were not significantly different between the 2 arms.

Lopinavir/Ritonavir PKs

The median trajectory plots of LPV and RTV concentrations over 8 hours are presented in Figure 2. Six subjects were available to determine LPV and RTV PK parameters, which are summarized in Table 3. Two of these women were on the gelcap LPV/r formulation and reported 100% adherence within 3 days before sampling. Median LPV and RTV concentrations were lower at all sample times when the patch was used compared with when the same subjects were not using the patch. When the patch was being used, median LPV $AUC_{0–12\ h}$, C_{min} and C_{max} were decreased by 19% ($P = 0.156$), 27% ($P = 0.219$), and 22% ($P = 0.313$), respectively. Similarly, median RTV concentrations were lower at all time points (Fig. 2); however IQRs overlapped in the presence and absence of the patch. The median RTV $AUC_{0–12\ h}$, C_{min}, and C_{max} were decreased by 24% ($P = 0.031$), 14% ($P = 0.438$), and 8% ($P = 0.031$), respectively (Table 3).

Virologic and Immunologic Response

HIV-1 RNA levels for all subjects in the LPV/r arm (n = 7) were <400 copies per milliliter at baseline and week 4. In the control arm, 26% (6 of 23) and 30% (6 of 20) subjects had baseline and week 4 HIV-1 RNA levels <400 copies per milliliter, respectively. Only 3 of the control subjects were on combination ART.

In the LPV/r arm, the median $CD4^+$ cell count at week 4 increased by 15%, (baseline CD4+ cell count: 590 cells/mm^3, week 4: 680 cells/mm^3). However, in the control arm, the median $CD4^+$ cell count at week 4 declined by 10% (baseline $CD4^+$ cell count: 540, week 4: 487 cells/mm^3). The change from baseline to week 4 were significantly different between the 2 study arms ($P = 0.034$).

Adverse Events

Over the 4-week course of the study, a single grade-3 symptom (generalized aches and pains) possibly related to treatment was reported in the LPV/r arm. Three subjects in the LPV/r arm reported seven symptoms of grades 1 or 2, which were dizziness/lightheadedness, headache, nausea, and fatigue. Fourteen subjects in the control arm reported grade 1 or 2 symptoms, which were generalized aches, fatigue, increased bleeding, dizziness/lightheadedness, increased cramping, headache, and nausea with and without vomiting. There were no significant changes from baseline to week 4 in hematological or chemical laboratory abnormalities in either arm or between arms. There was no significant change in body weight over the course of the study.

Discussion

We found significant differences in contraceptive patch EE concentrations (45% lower) and NGMN concentrations (83% higher) in subjects taking LPV/r compared with those not on PI therapy. Several RTV-boosted PIs have been shown to decrease oral contraceptive estradiol levels with decreases in EE AUC of 37%–50%,[8] similar to the changes in EE seen here. Steroidogenic enzymes produce and metabolize estrogens and progestins. These enzymes, located in the liver and the gut are members of the cytochrome P450 (CYP450) oxidases and metabolize many other substances. Any substrate metabolized by the CYP450 system can affect steroid hormone synthesis and metabolism. Conversely, steroid hormones may affect other substances through this same mechanism.[14] PIs are substrates of the CYP450 system and as such have potential to interact with contraceptive hormones through inhibition or induction of the cytochrome system or through effects on glucuronidation. In previous studies, RTV has been associated with a 41% decrease in oral contraceptive EE AUC.[15] LPV/r, when given with continuous oral contraceptives, decreases EE concentrations by 42%, presumably due to overall enzyme induction although the mechanism of the interaction has not been confirmed.[16] There have been no previous studies on the interaction between ARVs and transdermal contraceptives.

Transdermal delivery systems were designed to minimize the first pass effect associated with metabolism of drug by gut cytochrome enzymes. The changes in EE overall PK exposure in this study were similar whether administered orally or transdermally suggesting first pass metabolism is of limited importance in driving the magnitude of the overall drug–drug interaction. Previous PK studies have shown that the serum EE and NGMN concentrations remain steady over 7 days of patch use with mean steady state C_{ss} concentrations ranging from 0.305 to 1.53 ng/mL for NGMN and from 11.2 to 137 pg/mL for EE.[11] At steady-state dosing, serum concentrations of EE and NGMN remain stable with no significant accumulation of hormone.[12] In the current study, the lack of difference in change in EE levels with LPV/r with the 2 different routes of administration suggest that changes associated with PI therapy were related to changes in metabolism in the liver rather than by enzymes in the gut.

In the absence of other drugs, the patch EE PK profile differs from that of oral contraceptives in that it is characterized by higher overall exposure but lower peak concentrations. Total exposure is approximately 60% higher and peak concentrations approximately 25% lower in women using the patch compared with women on an oral contraceptive containing EE 35 μg.[12] In general, increased estrogen exposure may increase the risk of adverse events such as venous thromboembolic disease (VTE), gall bladder disease, and nausea, but it is unclear whether EE-associated serious adverse events are increased in women using the patch compared with women using oral contraceptives. VTE is a known risk of all combined hormonal contraceptives. One published study showed no difference in risk for VTE between the patch and a 35-μg EE pill, Ortho Cyclen.[17] However, data from another study suggests that women who use the patch have a 2-fold increased risk of VTE compared with women who using a 35 μg EE oral contraceptive.[18] The decreased EE concentrations seen with co-administration of LPV/r suggest that estrogen-mediated side

effects such as headache and nausea could be decreased, but the effect on the risk of VTE is more complex and may involve the progestin component of hormonal contraceptives.

The increased NGMN concentrations observed in the presence of the patch could lead to increased rates of progestin side effects. The third-generation progestins, including NGMN, are designed to have no androgenic effects, so side effects such as acne, weight gain, and lipid abnormalities, seen with earlier contraceptive progestins, should not be seen. However, the observed association of an increased risk of VTE seen with third-generation progestins is of concern. A meta-analysis comparing the risk of venous thrombosis among users of oral contraceptives with the second-generation progestin levonorgestrel to users of oral contraceptives with third-generation progestins, primarily desogestrel or gestodene, found an adjusted odds ratio of 1.7 [95% confidence interval (CI): 1.4 to 2.0] for third versus second generation oral contraceptives (19). A more recent case–control study found the risk of VTE increased by an adjusted odds ratio of 3.6 (95% CI: 2.9 to 4.6) for users of oral contraceptives with levonorgestrel compared with nonusers and by an adjusted odds ratio of 5.6–7.3 for users of oral contraceptives with third-generation progestins compared with nonusers,[20] though norgestimate and its derivative NGMN were not included in this study. Jick et al[21] compared users of levonorgestrel-containing oral contraceptives with users of the patch and found no difference in risk for idiopathic VTE among women 39 or younger. In a population-based study including over 10.4 million women-years of observation, the risk of VTE was not increased among users of oral contraceptives including norgestimate, the precursor of NGMN (rate ratio 1.19, 95% CI: 0.96 to 1.47) compared with users of levonorgestrel-containing oral contraceptives with the same estrogen dose, but the risk was increased with all other third-generation progestins, with rate ratios of 1.64–1.88.[22] Decreased estrogen dose and longer duration of use were associated with decreased risk. Thus NGMN use may not be associated with the same risk of venous thrombosis as other third-generation progestins, and the risk may be reduced by the decreased estrogen concentrations seen with concomitant LPV/r use.

Risks associated with the use of hormonal contraception however need to be assessed in the context of risks associated with no contraception. Risks for major morbidity and mortality associated with pregnancy generally outweigh the risks of hormonal contraception by a factor of approximately 20:1 for nonsmoking women younger than 40 and smokers less than 35 years.[23] More recent data suggest oral contraceptive use over 378,000 person-years of observation may provide a net benefit over nonusers[24] and discouraging recent statistics in maternal mortality[25] suggest the risks of pregnancy continue to substantially outweigh the risks associated with hormonal contraception. Another recent review suggested that because older women with more prior pregnancies face even higher risk of pregnancy associated deaths, effective contraception has an even greater benefit in this population.[26]

The implications regarding contraceptive efficacy of EE and NGMN in the LPV/r-treated women are of prime interest to clinicians and women. No evidence of ovulation was seen during patch use in this study according to the progesterone levels observed, and although progesterone levels can vary with luteal phase, the substantial decrease in progesterone levels observed is inconsistent with ovulation. Given the increase in NGMN levels, contraceptive efficacy would be expected to be maintained with patch use despite the lower

EE levels observed. Progestins alone can be used for contraception. Studies have shown that the contraceptive mechanisms of progestin-only contraceptives include suppression of ovulation, suppression of progesterone production by the corpus luteum, changes in the endometrium rendering it less hospitable to implantation, and cervical mucus changes inhibiting sperm transport.[27,28] Injectable progestins (eg, DMPA, Depo-provera) are one of the more frequently used contraceptive methods globally, and have recently been studied in HIV-infected women. Cohn et al[29] found no significant changes in medroxyprogesterone acetate levels among 54 HIV-infected women using ARV regimens that included nevirapine, efavirenz, or the PI nelfinavir compared with those in 16 controls using other ARV regimens or on no ARVs. DMPA was well tolerated, no women had evidence of ovulation during the 12-week study, and minor adverse effects observed were similar to those seen in HIV-uninfected women,[30] Although this study demonstrated the safety and efficacy of a PI-based regimen (eg, nelfinavir) with injectable progestins, it did not evaluate ARV regimens that included RTV.

The addition of estrogen compounds, usually EE, to contraceptive preparations increases the rate of ovulatory suppression and reduces the rate of breakthrough bleeding compared with progestin only preparations. EE alone at 50 μg/day does not consistently inhibit ovulation but the combination of EE at doses of 20–40 μg/day and low doses of progestins does inhibit ovulation.[31] Given that doses of EE of 20 μg/day combined with progestins inhibit ovulation and are contraceptive, the levels of EE seen in this study using patch delivered 20 μg/day EE with LPV/r were adequate to inhibit ovulation. The substantial decrease in progesterone levels observed in all the subjects studied indicates suppression of ovulation occurred in all patients including the one patient who complained of breakthrough bleeding. Whether the lower EE levels seen with LPV/r use will be associated with more breakthrough bleeding could not be assessed in this small study. Breakthrough bleeding can result in contraceptive failure if women discontinue use of the contraceptive due to concerns that the bleeding itself is a sign of contraceptive failure or other serious side effect.

The decreases seen in the PK parameters of LPV/r in the presence of the patch are statistically significant for the RTV AUC and C_{max} despite the small sample numbers, but the IQR overlap in patch and nonpatch RTV levels make these data difficult to interpret. Previous data[32] suggests that the LPV C_{min} observed in the study is generally above a target therapeutic trough of 1000 ng/mL, and RTV levels are quite low: 5%–6% of target trough concentrations for full dose therapy as expected given the lower doses of RTV used in pharmacologic boosting. One previous study of RTV PKs at 100 mg twice daily reported a median C_{min} of 230 ng/mL.[33] Clearly the RTV median C_{min} in the presence of the patch observed in our study is substantially below that. Overall, the trend observed in this study with overall decreased LPV exposure, and the low RTV trough observed raises concerns about early treatment failure and acquisition of resistance. Decreased RTV exposure could lead to ineffective RTV boosting activity leading to similar concerns about early failure and acquisition of resistance, especially in the setting of pre-existing partial resistance that often occurs in salvage situations. Although the changes in C_{min} for RTV associated with patch use were not statistically significant, the clinical significance of such low levels, particularly regarding risk of resistance merits further evaluation.

This study was closed prematurely due to slow recruitment into the LPV/r arm. Concurrent with the opening of this study, many women who had been previously stable on LPV/r-based regimens were switched to a once-daily PI regimen, and many women of childbearing potential requiring treatment for HIV were started preferentially on once-daily regimens, limiting the available population. Simultaneously, news reports raising concerns about a possible increased risk of VTE in patch users limited both subject and clinician interest in the study, although as outlined above, published results were contradictory. Although target enrollment was not reached, the data obtained are sufficient to indicate a PK interaction between LPV/r and the patch. Although EE levels were decreased significantly in the presence of the patch, the corresponding increase in NGMN levels and the progesterone levels observed suggest that contraceptive efficacy of the patch in women treated with LPV/r is likely to be maintained, but larger studies are needed to fully assess risks versus contraceptive efficacy. At this time, however, based on the results of this trial, we have no data to justify withholding hormonal contraception based on a woman's HIV infection or treatment status.

This study describes some of the PK interactions between EE and progestins in women on potent ARV therapy and confirms significant PK interactions between a newer contraceptive delivery device and a PI-containing ART regimen. An ongoing effort to investigate potential interactions between the next generations of contraceptive agents and both the current and next generations of ART is crucial to preserve the overall health of HIV-infected women, prevent pregnancy and inadvertent maternal to child transmission of HIV, and to allow family-planning when women's health has been optimized in the presence of HIV.

Acknowledgments

The authors gratefully acknowledge the patients and the Adult AIDS Clinical Trials Group and Pediatric AIDS Clinical Trials Group sites that participated in this study, especially given the complex, month-long PK studies which often required weekend and holiday time as follows: LaShonda Spencer, MD; Alice Stek, MD-Los Angeles County Medical/University of Southern California (Site 5048) NICHD #NO1-HD-3-3345; NICHD #NO1-HD-8-0001; Lorraine Sanchez-Keeland, PA-C & Connie A. Funk, RN, MPH-University of Southern California (Site 1201) CTU Grant # AI069428 GCRC Grant # MOIRR00043; Elvia Pérez-Hernández, BS, MEd, MA, MPH and Rodrigo Diaz-Velazco, MD, City Hospital at San Juan (Site 5031) CTU Grant # AI69415; Kenneth Fife, MD and Janet Hernandez, RN, Indiana University (Site 2601) CTU Grant# AI025859; Deborah McMahon, MD, and Carol Oriss, BSN RN, University of Pittsburgh (Site 1001) CTU Grant #1 U01 AI 069494-01; Manuel Revuelta, MD, and Donna Mildvan, MD, Beth Israel Medical Center (Site 2851) CTU Grant #AI46370; Monica Carten, MD, and M. Graham Ray, RN, MSN, University of Colorado Health Sciences Center, Denver (Site 6101) CTU Grant #AI054907 and RR025780; Valery Hughes, FNP, and Christina Megill, RPA-C-Weill Med College of Cornell University, The Cornell CTU (Site 7803) CTU Grant # AI-69419 and RR024996. The authors gratefully acknowledge Katherine D. LaGuardia, MD, of Ortho-McNeill-Janssen for her advocacy on behalf of contraceptive research in HIV infected women. The team would also like to thank Apsara Nair, MS, who served as data manager and Song Yu, PhD, who helped with data analyses.

This research was supported in part by the Adult AIDS Clinical Trials Group funded by the National Institute of Allergy and Infectious Diseases, the Perinatal/Pediatric Clinical Trials network (N01HD33345) funded by the National Institute of Child Health and Human Development, and by Ortho-McNeill-Janssen Pharmaceuticals, Inc. who kindly provided the transdermal patches and the birth control pills (eg, Ortho-Novum 1/35 pills) and funding for hormonal assays.

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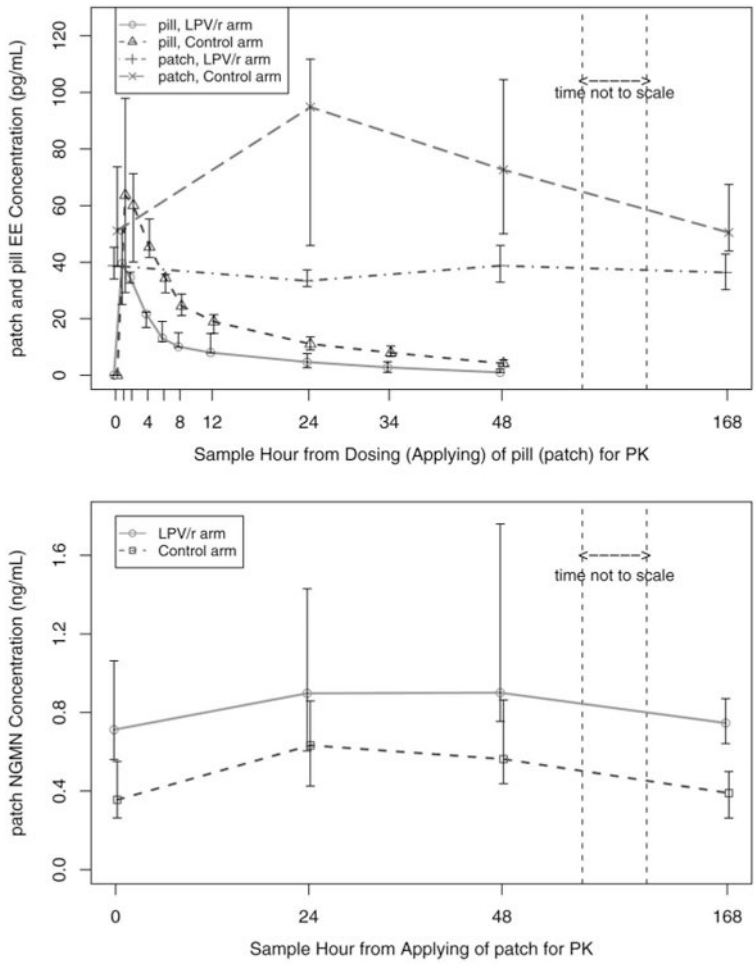

Figure 1.
Median Plot with quartiles, EE and NGMN concentrations.

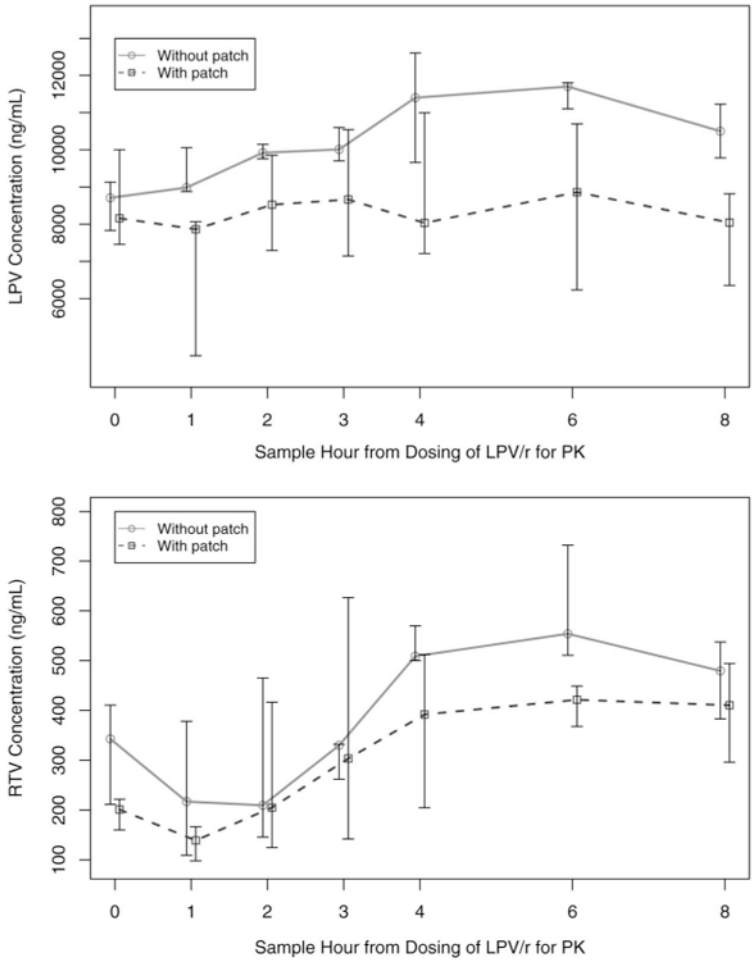

Figure 2.
Median plot with quartiles, LPV and RTV concentrations.

Table 1
Baseline Characteristics for All Subjects Enrolled

		Study Arm	
	Total, n = 32	**LPV/r, n = 8**	**Control, n = 24**
Age in yrs			
Median	30	28	31
18–29	16 (50%)	5 (63%)	11 (46%)
30–39	13 (41%)	2 (25%)	11 (46%)
40–49	3 (9%)	1 (13%)	2 (8%)
Weight (kg)			
Median (IQR)	72 (61.2, 79.3)	72 (59.5, 83.4)	71 (61.2, 78.6)
Race/ethnicity			
White non-Hispanic	2 (6%)	1 (13%)	1 (4%)
Black non-Hispanic	8 (25%)	1 (13%)	7 (29%)
Hispanic	21 (66%)	6 (75%)	15 (63%)
Other	1 (3%)	0 (0%)	1 (4%)
Background ARV regimen		4 ZDV/3TC	3 ABC/ZDV/3TC
		1 d4T/3TC	
		1 d4T/FTC	
		2 ABC/ZDV/3TC	
CD4 cells (cells/mm^3), median (IQR)		n = 8, 550 (384–691)	n = 23, 440 (346–634)
No. subjects w/RNA copies ≤400		n = 8, 8 (100%)	n = 23, 6 (26%)

LPV, lopinavir; ZDV, zidovudine; 3TC, lamivudine; ABC, abacavir; FTC, emtricitabine; d4T, stavudine; IQR, interquartile range.

Table 2

Oral Contraceptive Pill (OrthoNovum 1/35, Pill) EE and Transdermal Contraceptive Patch (OrthoEvra, Patch) EE and NGMN PK Parameters by Study Arm

			Control Arm		LPV/r Arm			
			n	Median (IQR)	n	Median (IQR)	Change (%)*	*P*†
EE	Patch	$AUC_{0-168\ h}$ (pg·h·mL^{-1})	15	10911.42 (7548.36–15667.44)	4	6010.36 (5140.83–7388.01)	−45	0.064
		C_{min} (pg/mL)	15	44.40 (4.59–67.60)	4	32.10 (28.60–39.15)	−28	0.395
	Pill	$AUC_{0-48\ h}$ (pg·h·mL^{-1})	16	765.38 (680.48–890.69)	5	344.67 (310.43–476.52)	−55	0.003
		C_{48} (pg/mL)	16	4.15 (3.11–5.81)	5	1.00 (1.00–2.13)	−76	0.023
NGMN	Patch	$AUC_{0-168\ h}$ (ng·h·mL^{-1})	17	75.63 (59.20–121.13)	7	138.39 (106.44–234.75)	83	0.036
		C_{min} (ng/mL)	17	0.27 (0.22–0.43)	7	0.63 (0.51–0.89)	134	0.036

*Median comparison of LPV/r arm over control arm. The minus sign "–" represents decrease.

†Wilcoxon rank-sum test of comparing PK parameters between LPV/r arm and control arm.

Table 3

Median (IQR) PK Parameters of LPV and RTV

	LPV 400 mg (n = 6)				RTV 100 mg (n = 6)			
PK Parameter	**Without Patch**	**With Patch**	**Change* (%)**	***P*†**	**Without Patch**	**With Patch**	**Change* (%)**	***P*†**
$AUC_{0\text{-}12h}$ (ng·h·mL^{-1})	120,193 (115180–123,105)	98,250 (58200–122,080)	−19 (−45 to −13)	0.156	4801 (3957–7564)	3301 (3225–4141)	−24 (−36 to −18)	0.031
C_{min} (ng/mL)	8590 (7620–9190)	7520 (3200–8080)	−27 (−64 to 19)	0.219	209 (87–395)	120 (83–173)	−14 (−33 to 7)	0.438
C_{max} (ng/mL)	12,000 (104,00–12,700)	9300 (7560–11,900)	−22 (−23 to −15)	0.313	562 (509–780)	537 (450–714)	−8 (−223 to −27)	0.031

*Median (IQR) change from baseline (without patch) to steady state (with patch).

†Wilcoxon sign-rank test between LPV/r without patch and LPV/r with patch.

IQR, interquartile range.