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Steady-state pharmacokinetics of rilpivirine under different meal conditions in HIV-1-infected Ugandan adults

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Objectives: To investigate the effect of food on the steady-state pharmacokinetics of rilpivirine when administered as a fixed-dose combination tablet containing tenofovir disoproxil fumarate, emtricitabine plus rilpivirine (TDF/FTC/RPV) in HIV-1-infected Ugandan patients.

Methods: This was an open-label, three-period, longitudinal pharmacokinetic study with patients serving as their own controls. Fifteen consenting and virologically suppressed HIV-1-infected adults were switched from an efavirenz-based regimen to TDF/FTC/RPV for 56 days. Enrolled patients underwent 24 h blood sampling with TDF/FTC/RPV dosing in the fasted state (day 42), with a low-fat meal (11 g of fat/353 kcal, day 49) and with a moderate-fat meal (19 g of fat/589 kcal, day 56; reference). A viral load assessment was performed on day 56.

Results: Rilpivirine AUC_{0-24} was significantly decreased by 16% (geometric mean ratio, 90% CI: 0.84, 0.73–0.96) during administration in the fasted state when compared with AUC_{0-24} during administration with a moderate-fat meal. Similarly, rilpivirine C_{24} was significantly decreased by 21% (0.79, 0.65–0.97) in the fasted state compared with a moderate-fat meal. Pharmacokinetic parameters were unchanged during administration with a low-fat meal, except for C_{24}, which was significantly increased by 15% (1.15, 1.01–1.31) when compared with the moderate-fat meal. Rilpivirine C_{max} was similar under the three meal conditions. Virological suppression was unchanged at the end of the study.

Conclusions: A food effect was observed for steady-state pharmacokinetic parameters of rilpivirine (AUC_{0-24} and C_{24}) when TDF/FTC/RPV was administered in the fasted state compared with the moderate-fat meal. The TDF/FTC/RPV formulation can be administered with either a low-fat or moderate-fat meal.

Keywords: Complera, food–drug interactions, sub-Saharan Africa

Introduction

Over 24 million people are living with HIV in sub-Saharan Africa,[1] the region that also experiences the highest prevalence of food insecurity.[2] ART is the cornerstone for management of HIV, but few treatment options are available in African countries. The WHO recommends that first-line antiretroviral regimens should include one of two NNRTIs, either efavirenz or nevirapine.[3] Although these drugs are efficacious, some patients may experience treatment-limiting toxicities, drug resistance or drug interactions with these agents; hence the need for more treatment options.

During periods of food insufficiency, patients may experience difficulties coping with recommendations to administer drugs with food. Also, patients may miss meals if they have illnesses that reduce their food intake or they may intentionally miss meals to observe religious or cultural rites. For these categories of patients, antiretroviral drugs that can be administered without regard to meals are preferred.

Rilpivirine is an NNRTI that is indicated, in combination with other agents, for the management of HIV-1 infection in adults.[4] After oral dosing, the maximal concentration (C_{max}) is achieved between 4 and 5 h. Rilpivirine undergoes metabolism via the cytochrome P450 (CYP) 3A pathway and the terminal elimination half-life is 50 h, making it suitable for once-daily dosing.[5] In two healthy volunteer studies conducted using single supratherapeutic doses of rilpivirine (100 and 75 mg), the $AUC_{0-\infty}$ was 33%–43% lower in the fasted state compared with exposures when

rilpivirine was administered with food.[6,7] Similarly, C_{max} was 41%–46% lower in the fasted state compared with rilpivirine administration with food.[6,7] In 2011, a fixed-dose combination single-tablet regimen (Complera®; Gilead Sciences, Foster City, CA, USA) was released containing 200 mg of emtricitabine, 25 mg of rilpivirine and 300 mg of tenofovir disoproxil fumarate, to be taken once daily with a meal.[8] In a single-dose, food-effect study with this formulation, the rilpivirine $AUC_{0-\infty}$ was increased by 9% with a light meal and increased by 16% with a standard meal.[9]

In clinical practice, the influence of meal conditions on rilpivirine pharmacokinetics (PK) will typically occur at steady-state. Furthermore, it is important to evaluate the food effects of approved drugs in the target patient population in the local setting where diet and meals often differ from the standardized Western meals used in drug development studies.

This study aimed to investigate the steady-state PK of rilpivirine in HIV-1-infected Ugandan patients during administration of tenofovir disoproxil fumarate/emtricitabine/rilpivirine (TDF/FTC/RPV) under three different meal conditions and to assess the short-term safety and tolerability of this formulation.

Methods

Study design

This was an open-label, three-period, longitudinal PK study with patients serving as their own controls. The Joint Clinical Research Centre Institutional Review Board Uganda approved the study and the trial protocol was registered at www.PACTR.org (PACTR201301000480567).

Eligibility criteria

HIV-1-infected patients were recruited from the Infectious Diseases Institute clinic, Makerere University College of Health Sciences, Kampala. All patients provided written informed consent before undergoing any study procedures. Study patients were aged between 18 and 65 years (inclusive) and receiving tenofovir disoproxil fumarate, efavirenz plus either emtricitabine or lamivudine for ≥6 months. Patients were excluded if they had persistent diarrhoea, anaemia (serum haemoglobin <8 g/dL) or plasma HIV-1 RNA >400 copies/mL. Patients were also excluded if serum creatinine or liver transaminases were above three times the upper limits of normal, or if they had a history of cardiac disease or QT intervals exceeding 450 ms (men) or 470 ms (women) on screening electrocardiogram, or if they were taking CYP3A4 inhibitors or inducers, antacids, gastric acid suppressive agents or herbal medications, or if they were consuming grapefruit juice. The study excluded pregnant or breastfeeding women.

Study procedures

Enrolled subjects stopped all antiretroviral drugs in their prior antiretroviral regimen on day 0. From day 1 to day 56, patients received TDF/FTC/RPV (Complera®; Lot code: HBKP) as one tablet administered once daily. The study allowed 6 weeks of therapy on study drug (days 1–41) prior to PK evaluations in order to allow for elimination of efavirenz and minimize the risk of a residual induction effect on CYP3A4 by efavirenz.[10,11]

Subjects self-administered study drug with their usual diet between days 1 and 41 and were admitted for observed dosing and 24 h intensive PK sampling on days 42, 49 and 56. On day 42, study drug administration was performed after an overnight fast. On day 49, dosing was performed with a standardized low-fat breakfast (353 kcal); on day 56, dosing was performed after a moderate-fat breakfast (589 kcal). Standardized meals consisted of a local Ugandan banana staple (*matooke*), tomatoes and onions with different quantities of fat (low-fat meal, 11 g of fat; and moderate-fat meal, 19 g of fat). At each PK sampling visit, serial blood specimens were obtained from each patient pre-dose (C_0) and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 h post-dosing. Prior to discharge on days 43 and 50 (after completing 24 h PK visits), patients administered study drug in hospital following a standardized low-fat meal and moderate-fat meal, respectively. On days 43 and 50, food baskets were given to patients containing the respective items for preparing five study meals at home over the ensuing 5 days (days 44–48 and 51–55). The patients were taught to prepare the study meals and reminded to self-administer study drug with food while at home.

Adherence

Medication adherence was assessed by pill counts and patient self-report. Adequacy of food supply was assessed by examining food baskets during four home visits conducted between days 44 and 55 (inclusive). Patients were switched back to their original antiretroviral regimen on day 57 and discharged from study after a follow-up visit on day 70.

Safety assessments

The severity of clinical and laboratory adverse experiences was reported using the US NIH Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.[12] On day 42, blood samples were obtained for laboratory investigations (complete blood count, serum transaminases and serum creatinine). A viral load assessment was performed on day 56.

PK assessments

Blood samples were processed at the Makerere University–Johns Hopkins University laboratory within 1 h of collection of each sample. Plasma obtained by centrifugation was stored at −80°C. For quantification of rilpivirine, samples were shipped in a single batch to the Department of Molecular and Clinical Pharmacology, University of Liverpool. Rilpivirine and the internal standard (^{13}C-d4-rilpivirine) were isolated from plasma using protein precipitation. Quantification was performed using a Thermo Scientific Quantum Ultra triple quadrupole LC-MS/MS system. A Fortis C18 reverse-phase LC fused-core column was used and chromatograms were analysed using Thermo Scientific LC Quan software. The lower limit of quantification was 0.5 ng/mL and the upper limit of quantification was 400 ng/mL. At all quality control levels, inter- and intra-assay coefficients of variation (CV) were <7%. The assay was validated prior to the analysis of clinical samples and in accordance with FDA guidelines.[13]

Data analysis

Demographic characteristics of study patients at screening were summarized (medians, IQR). Plots of plasma concentration versus time curves were produced for rilpivirine. Rilpivirine concentrations were summarized [*n*, geometric mean (GM) and its associated CV and CI]. The rilpivirine PK parameters C_{max}, concentrations at 0 h (C_0) and 24 h (C_{24}) and time to maximal concentration (T_{max}) were derived directly from the data, while AUC_{0-24} values were calculated by non-compartmental methods (WinNonlin®; Pharsight, Mountain View, CA, USA) using nominal sampling times. The CIs were determined using logarithms of the individual GM values; the calculated values were subsequently expressed as linear values. Day 56 (moderate fat) data were used as the reference and comparisons were presented as GM ratios (GMRs). A food effect was assumed if the 90% CI for GMRs of rilpivirine PK parameters between moderate-fat and either fasted or low-fat meal treatments was not contained within the equivalence limits of 80%–125%.

Table 1. Demographic parameters of study patients at screening ($n=15$)

	Median (IQR)
Age (years)	40.8 (36.4–44.3)
Weight (kg)	58.5 (51–67)
BMI (kg/m^2)	22.0 (19.6–24.8)
Haemoglobin (g/dL)	13.2 (11.9–14.1)
ALT (IU/L)	21 (17–34)
AST (IU/L)	26 (19–33)
Glucose (mg/dL)	88 (83–97)
Urea (mg/dL)	9 (7–10)
Creatinine (mg/dL)	0.74 (0.67–0.82)
ECG corrected QT interval (ms)	430 (398–449)

Initial studies using rilpivirine as a single agent showed a more marked food effect than subsequent studies of rilpivirine coformulated with tenofovir disoproxil fumarate plus emtricitabine.[7,9] In both studies, the effect on C_{max} was greater than AUC. Assuming a C_{max} food effect as previously reported[9] and a CV of 41%,[9] a sample size of 15 would yield 80% power to detect a 33% change in AUC or C_{max} between fasted and fed states ($\alpha=0.05$).

Results

The characteristics of the enrolled patients are shown in Table 1. All 15 enrolled subjects were receiving efavirenz (600 mg once daily) and lamivudine (300 mg once daily) plus tenofovir disoproxil fumarate (300 mg once daily) prior to enrolment and median (IQR) duration on regimen was 2.15 (1.0–5.1) years. All subjects had HIV-1 RNA <400 copies/mL at enrolment and median (IQR) CD4 count was 493 (334–657) cells/mm^3. Twelve patients took co-trimoxazole (960 mg once daily) for opportunistic infection prophylaxis while 3 patients were on dapsone (100 mg once daily). No subject reported missed doses of study drug in the 3 days prior to the PK sampling visits and no disallowed study drugs were reported during the study. Figure 1 illustrates plasma concentration–time profiles of rilpivirine under the three meal conditions.

Using the dosing with the moderate-fat meal as reference, the rilpivirine AUC_{0-24} was significantly decreased by 16% (GMR, 90% CI: 0.84, 0.73–0.96) during administration in the fasted state. Similarly, rilpivirine C_{24} was significantly decreased by 21% (0.79, 0.65–0.97) in the fasted state compared with a moderate-fat meal. For AUC_{0-24} and C_{24}, a food effect was observed as the lower bound of the 90% CI was outside the 80%–125% equivalence limits. During administration with a low-fat meal, PK parameters were unchanged, except for C_{24}, which was significantly increased by 15% (1.15, 1.01–1.31) when compared with C_{24} during administration with a moderate-fat meal (Table 2).

The median rilpivirine T_{max} was 4 h in the fasted state and with a moderate-fat meal and 3 h with a low-fat meal.

Safety

All adverse events reported during the study were of grade 1 severity. Adverse events considered at least possibly related to rilpivirine are shown in Table S1 (available as Supplementary data at *JAC* Online). All patients had HIV-1 RNA <400 copies/mL at the end of rilpivirine dosing. No serious adverse events or deaths were reported.

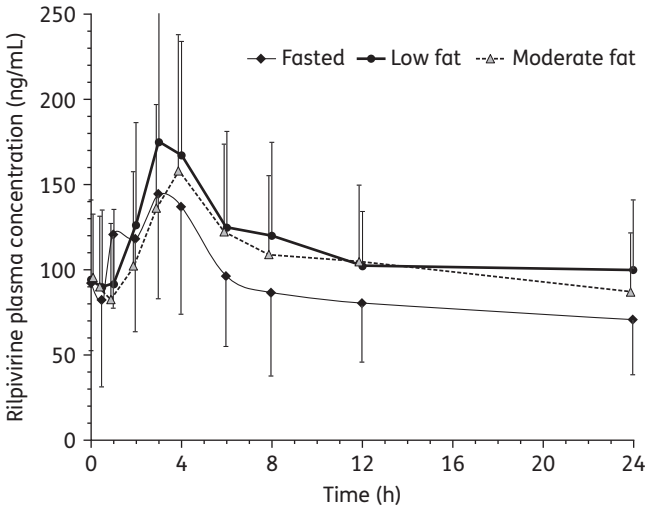

Figure 1. Mean (SD) plasma concentration–time profiles of rilpivirine during administration in the fasted state (day 42), with a low-fat meal (day 49) and with a moderate-fat meal (day 56). Number of study patients=15.

Discussion

In the fasted state, rilpivirine PK parameters (C_{24} and AUC_{0-24}) were significantly lower compared with the same parameters observed during dosing with a moderate-fat meal. However, the magnitude of difference suggests a mild food effect for these parameters and, notably, peak concentrations were not affected by food. In contrast, PK parameters were similar (except for C_{24}) when dosing with a low-fat meal when compared with the moderate-fat meal. Our findings are in agreement with Custodio *et al.*,[9] who report only marginal differences in single-dose PK parameters using study meals with similar quantities of fat to the present study. Taken together, these findings point towards a reduced impact of fat composition on rilpivirine absorption with the new single-tablet regimen formulation.

As a precaution, the study was designed to simulate a single missed meal on day 42 while the two fed states were maintained during the 6 days prior to the respective PK sampling visits. Assuming a carryover effect from the day prior to PK sampling when rilpivirine was administered with food, the magnitude of reductions in the fasted state could be underestimated. Consequently, the study supports the current recommendation to administer rilpivirine with food.

Efficacy thresholds for rilpivirine PK parameters have not been defined among patients. Population PK estimates for rilpivirine obtained from pooled data ($n=679$) report mean ± SD AUC_{0-24} of 2235 ± 851 ng·h/mL and C_0 was 79 ± 35 ng/mL.[8] Key PK parameters obtained in the present study (AUC_{0-24} and C_0/C_{24}) appear similar to these target values during dosing with either a low-fat or moderate-fat meal. Although AUC_{0-24} and C_{24} appeared lower than the target values during dosing in the fasted state, no study patient experienced virological failure during the study. In the current study, a single missed meal at the time of dosing led to a 16%

Table 2. PK parameters for rilpivirine during administration in the fasted state, with a low-fat meal and with a moderate-fat meal

	GM (90% CI)			GMR (90% CI)	
PK parameter	fasted	low fat	moderate fat*	fasted/moderate fat	low fat/moderate fat
C_0 (ng/mL) CV	85 (75–109) 43%	87 (74–114) 50%	89 (80–111) 39%	0.94 (0.76–1.16)	0.97 (0.80–1.18)
C_{24} (ng/mL) CV	63 (57–85) 46%	92 (82–117) 41%	80 (72–102) 40%	**0.79 (0.65–0.97)**	**1.15 (1.01–1.31)**
C_{max} (ng/mL) CV	157 (143–195) 36%	175 (156–217) 38%	159 (141–204) 43%	0.99 (0.88–1.12)	1.10 (0.98–1.24)
AUC_{0-24} (ng·h/mL) CV	2007 (1819–2499) 37%	2582 (2336–3108) 33%	2392 (2157–2918) 35%	**0.84 (0.73–0.96)**	1.08 (0.97–1.20)

Bold type indicates significant change in PK parameters compared with reference (*).

reduction in rilpivirine AUC. This is unlikely to be clinically significant, assuming patients adhere to rilpivirine and take subsequent doses with food. Notably, other drugs in the regimen (tenofovir disoproxil fumarate and emtricitabine) contribute to antiretroviral efficacy and food has a relatively benign impact on these drugs.[14] In a healthy volunteer study, tenofovir $AUC_{0-\infty}$ was increased by 28%–38% with food, a change that is not considered clinically relevant, while emtricitabine concentrations were not affected by food.[9]

In contrast to rilpivirine C_{24}, rilpivirine pre-dose concentrations (C_0) were unchanged during the study. Pre-dose concentrations approximated rilpivirine concentrations at the end of the prior dosing interval and, in all cases, rilpivirine was to be administered with food. On day 42, the pre-dose concentrations represented rilpivirine concentrations ~24 h after dosing at home with a non-standardized meal. Similarly, on days 49 and 56, the pre-dose concentrations represented dosing 24 h after rilpivirine dosing while at home with a low-fat meal and moderate-fat meal, respectively. Importantly, unchanged pre-dose concentrations would suggest that steady-state had been achieved for rilpivirine and that the lower rilpivirine C_{24} observed on day 42 was not influenced by persisting CYP3A induction after discontinuing efavirenz.

We studied an HIV-infected population because rilpivirine concentrations are reported to be generally lower in HIV-infected patients compared with healthy volunteers[8] and actual patient data are critical to understand the impact of the food dosing on rilpivirine PK in clinical practice. Other strengths of the study include the use of local African meals as in previous work[15,16] and virological monitoring during the study.

Nevertheless, our study had several limitations. The study provided food baskets for patients, trained patients on the preparation of low-fat and moderate-fat meals and conducted home visits to ensure food supplies were adequate. Despite these efforts, the study could not verify the actual composition of meals consumed at home as drug dosing with food was not directly observed while patients were at home. Even though patients were instructed to consume all the study meals prepared at home, it is possible that meals or food supplies could have been shared with others. Furthermore, the study does not address the issue of dosing in the fasted state on consecutive days. This scenario could occur during periods of food scarcity and it is possible that rilpivirine trough concentrations could decrease below the levels reported in this study. Lack of food is associated with non-adherence to ART,[17–21] potentially compounding missed meals with intermittent dosing, but the interplay between food availability, drug dosing with food and adherence to ART was beyond the scope of this study. With studies conducted in patients, a disease effect (e.g. from HIV or opportunistic infections) could impact PK parameters differently during the study periods. However, it is unlikely that this occurred in this study as patients had relatively high CD4 counts at enrolment and no opportunistic infections occurred during the study.

In conclusion, a food effect was observed for steady-state PK parameters of rilpivirine (AUC_{0-24} and C_{24}) when the TDF/FTC/RPV single-tablet regimen was administered in the fasted state compared with a moderate-fat meal. In contrast, PK parameters were similar (except for C_{24}) with a low-fat or moderate-fat meal. Consistent with the current labelling information, the TDF/FTC/RPV tablet can be administered with a low-fat or moderate-fat meal. In the Ugandan setting, when prescribing rilpivirine, clinicians should consider whether patients have access to daily meals and educate patients on the importance of taking rilpivirine along with a low-fat or moderate-fat meal.

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Author contributions

S. H. K., D. J. B., C. M. and M. L. contributed to the design of the study. M. L., L. M., M. K. and S. W. participated in recruitment of patients and data collection. L. E. performed the bioanalytical assays. M. L., J. B. S. and L. E. analysed the data. M. L., C. M., D. J. B., S. H. K. and P. B.-K. interpreted the data. M. L. drafted the first version and all authors reviewed the manuscript and approved the final version of the manuscript.

Supplementary data

Table S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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