Rilpivirine is a nonnucleoside reverse transcriptase inhibitor approved for treatment of HIV-1 infection in antiretroviral-naive adult patients. Potential interactions with drug transporters have not been fully investigated. Transport by and inhibition of drug transporters by rilpivirine were analyzed to further understand the mechanisms governing rilpivirine exposure and determine the potential for transporter-mediated drug-drug interactions. The ability of rilpivirine to inhibit or be transported by ABCB1 was determined using ABCB1-overexpressing CEMvBL100 cells and Caco-2 cell monolayers. The Xenopus laevis oocyte heterologous protein expression system was used to clarify if rilpivirine was either transported by or inhibited the function of influx transporters SLC01A2, SLC01B1, SLC01B3, SLC22A2, SLC22A6, and SLC22A8. The ability of rilpivirine to inhibit or be transported by SLC22A1 was determined using SLC22A1-expressing KCL22 cells. Rilpivirine showed higher accumulation in SLC22A1-overexpressing KCL22 cells than control cells (27% increase, \( P = 0.03 \)) and inhibited the functionality of SLC22A1 and SLC22A2 transport with 50% inhibitory concentrations (IC\(_{50}\)) of 28.5 \( \mu M \) and 5.13 \( \mu M \), respectively. Inhibition of ABCB1-mediated digoxin transport was determined for rilpivirine, which inhibited digoxin transport in the B-to-A direction with an IC\(_{50}\) of 4.48 \( \mu M \). The maximum rilpivirine concentration in plasma in patients following a standard 25-mg dosing regimen is around 0.43 \( \mu M \), lower than that necessary to substantially inhibit ABCB1, SLC22A1, or SLC22A2 in vitro. However, these data indicate that SLC22A1 may contribute to variability in rilpivirine exposure and that interactions of rilpivirine with substrates of SLC22A1, SLC22A2, or ABCB1 may be possible.

The absorption of rilpivirine is affected by gastric pH. Omeprazole and famotidine reduced the rilpivirine maximum concentration (\( C_{\text{max}} \)) by 40% and 85%, respectively, although intake of famotidine 12 h prior to rilpivirine did not affect rilpivirine absorption (3). Food also influences rilpivirine absorption, with an \( \sim 40\% \) increase in drug exposure seen when rilpivirine is taken with a normal or high-calorie meal compared with that seen under fasted conditions. Rilpivirine is metabolized primarily by cytochrome P450 3A (CYP3A), and drugs which inhibit or induce CYP3A may alter rilpivirine exposure in patients (4). Rilpivirine inhibits CYP3A4, CYP2B6, and CYP2C19 in vitro, although the ability of the drug to inhibit these enzymes in vivo is not fully known (5).

A recent phase III, randomized trial in treatment-naive HIV-1-infected adults (ECHO) demonstrated that rilpivirine was non-inferior (efficacy) to efavirenz and had an improved safety profile (1, 2). However, rilpivirine did show a higher virological failure rate than efavirenz (13% versus 6%), which was also observed in a parallel phase III trial (THRIVE) (6). The causes of this higher incidence of the virological failure rate are not fully understood, although the possibility of inadequate penetration of drug into tissues or infected cells may be a factor. Drug transporter proteins are involved in the movement of many drugs between blood and tissues and may be a factor in the disposition of several antiretrovirals (7), and an increased understanding of the role of transporters in rilpivirine disposition may help explain the observed virological failure.
were selected using FDA and International Transporter Consortium guidelines (10, 11).

MATERIALS AND METHODS

Materials. CEM and CEMVBL100 cells were donated by Ross Davey, Bill Walsh Cancer Research Laboratories (St. Leonards, Australia). Caco-2 cells were purchased from the European Collection of Cell Cultures (Salisbury, United Kingdom). SLC22A1-overexpressing KCL22 cells and mock-transfected KCL22 cells were donated by Athina Giannoudis, Department of Hematology, Royal Liverpool University Hospital (Liverpool, United Kingdom). [3H]rilpivirine (specific activity = 20.00 mCi/mmol) and nonradiolabeled rilpivirine were gifts from Tibotec (Mechelen, Belgium). [3H]estrone-3-sulfate (specific activity = 50 Ci/mmol), [3H]tetrathyl ammonium (specific activity = 55 Ci/mmol), [3H]aminohippuric acid (specific activity = 5 Ci/mmol), and [14C]mannitol (specific activity = 55 Ci/mmol) were purchased from American Radiolabeled Chemicals (MO). [3H]digoxin (specific activity = 50 Ci/mmol) and [3H]metformin (specific activity = 0.1 Ci/mmol) were purchased from PerkinElmer (Boston, MA). [3H]laminopropionate (specific activity = 5 Ci/mmol) was purchased from Moravek Biochemicals (CA). Lopinavir was a gift from Abbott (IL). Tariquidar (XR9576) was purchased from Xenova (Sloane, United Kingdom). cDNA clones were purchased from Source BioScience United Kingdom (Nottingham, United Kingdom). mRNA transfection kits were purchased from Ambion Ltd. (Huntingdon, United Kingdom). 

Accumulation experiments using CEM and CEMVBL100 cells. CEM and CEMVBL100 cells were maintained in cell culture medium (RPMI, 10% [vol/vol] fetal calf serum [FCS]) prior to the experiment (37°C, 5% CO2). CEM cells are a wild-type T-lymphoblastoid cell line. CEMVBL100 cells are CEM cells which have greatly increased ABCB1 expression (selected using vinblastine up to a concentration of 100 ng/ml). On the day of the experiment, CEM and CEMVBL100 cells of a constant cell density (1 ml, 5 × 10^6 cells/ml) were incubated (37°C, 5% CO2) for 30 min in cell culture medium (RPMI, 10% [vol/vol] FCS) containing either radiolabeled rilpivirine (20 μM) or a control ABCB1 substrate, lopinavir (1 μM). A separate incubation was undertaken where CEMVBL100 cells were preincubated prior to the substrate addition in cell culture medium containing the potent non-competitive ABCB1 inhibitor tariquidar (RPMI, 10% [vol/vol] FCS, 300 nM tariquidar, 30 min). Tariquidar was also included during the 30-min transport buffer contained tariquidar (300 nM). The transport buffer in the apical (for transport in the A-to-B direction) and basolateral (for transport in the B-to-A direction) chambers was replaced with transport buffer containing rilpivirine (20 μM) with or without 300 nM tariquidar. Samples (50 μl) were taken from the receiver compartment at 0, 30, and 60 min and replaced with an equal volume of transport buffer. Samples were analyzed using a liquid scintillation counter (Beckman Tri-Carb). 

Drug accumulation in transporter RNA-injected oocytes. Oocytes were harvested from sacrificed adult female Xenopus laevis frogs and treated with modified Barth’s solution not containing calcium (88 mM NaCl, 1 mM KCl, 15 mM HEPES, 100 U penicillin, 100 μg streptomycin, pH 7.4) but containing collagenase (1 mg/ml, 22°C, 60 rpm, 1 h). Cells were transferred to Barth’s solution containing calcium (88 mM NaCl, 1 mM KCl, 15 mM HEPES, 100 U penicillin, 100 μg streptomycin, pH 7.4) and stored in a cold room at 8°C. Healthy cells were selected and injected with transporter cRNA (50 ng per oocyte, 1 ng/nl) or sterile water (50 nl) and maintained in Barth’s solution containing calcium to allow transporter expression (5 days for SLC01B3-injected oocytes, 3 days for all other conditions, 18°C). Barths’ solution was replaced daily, and damaged oocytes were removed.

Drug accumulation in transporter RNA-injected Xenopus laevis oocytes. Drug accumulation studies using X. laevis oocytes were performed as described previously with slight modifications (15). For experiments determining rilpivirine transport, radiolabeled rilpivirine was incubated in Hanks balanced salt solution (pH 7.4) with at least 6 oocytes per condition in a 48-well Nunc flat-bottom plate (500 μl, 20 μM, room temperature, shaking at 60 rpm, 1 h). Radiolabeled positive-control drugs were tested alongside rilpivirine to confirm successful transporter expression. The positive-control drugs used were estrone-3-sulfate (1 μM) for SLC01A2, SLC01B1, and SLC01B3; aminohippuric acid (1 μM) for SLC22A6, and metformin (2 μM) for SLC22A2. Inhibition of drug trans-
porters by rilpivirine was initially assessed by co-incubating positive-control substrates with 10 µM rilpivirine. SLC22A2-mediated metformin transport was reduced in the presence of rilpivirine; therefore, a 50% inhibitory concentration (IC50) curve was determined using 1, 2.5, 5, 10, 25, 50, and 100 µM rilpivirine. All incubations were terminated by transferring oocytes to cell strainers and washing in ice-cold HBSS to remove extracellular drug. Each oocyte was placed in a separate scintillation vial, followed by addition of 100 µl 10% SDS. After disintegration of the oocytes by the SDS, 4 ml scintillation fluid was added to all vials, which were then loaded into a liquid scintillation analyzer (Beckman Tri-Carb). Results are expressed as the concentration (µM) of drug in oocytes ± standard deviation (SD), assuming that each oocyte had a volume of 1 µl (15).

Creation and culture of mock-transfected and SLC22A1-expressing KCL22 cells. KCL22 cells were maintained in cell culture medium (RPMI, 10% [vol/vol] FCS, 100 U/ml penicillin, 100 µg/ml streptomycin, 10 mM HEPES, 100 µM nonylphenol, and 30 µM amiloride). All experiments were performed using SLC22A1-expressing KCL22 cells and mock-transfected KCL22 cells. KCL22 cells were created previously by Athina Giannoudis at the Department of Hematology, Royal Liverpool University Hospital, Liverpool, United Kingdom (16). In the previous work, SLC22A1-overexpressing KCL22 cells were created by transfecting plasmid pcDNA3-hSLC22A1 into cells by nucleofection. Similarly, mock-transfected KCL22 cells were created by transfecting the empty vector pcDNA3.1 into cells by nucleofection. Transfected cells were selected using neomycin, and stable cell lines were established. KCL22 cells were used for human SLC22A1 transfection because it expresses a small basal amount of SLC22A1 in comparison to other chronic myelogenous leukemia cell lines (17).

Rilpivirine accumulation and inhibitory potential in SLC22A1-overexpressing KCL22 cells. On the day of the experiment, the mock-transfected KCL22 cells and SLC22A1-expressing KCL22 cells of a constant cell density (1 ml, 2.5 × 10^6 cells/ml) were incubated (37°C, 5% CO2) for 30 min in cell culture medium (RPMI, 10% [vol/vol] FCS) containing either rilpivirine (20 µM) or the control SLC22A1 substrate tetrathyl ammonium (1 µM). A separate incubation was undertaken, where SLC22A1-expressing KCL22 cells were preincubated prior to the substrate addition into cell culture medium containing the potent SLC22A1 inhibitor prazosin (RPMI, 10% [vol/vol] FCS, 100 µM prazosin, 30 min). Prazosin was also included during the 30-min substrate incubation. Following incubation, cells were centrifuged (800 g, 1°C, 1 min) and processed for analysis as described for CEM cells. Using intracellular radioactivity readings, cellular drug concentrations (µM) ± SD were determined in each cell line, assuming a 1-pl volume per cell.

The inhibitory potential of rilpivirine for SLC22A1 transport was assessed. Accumulation of tetrathyl ammonium (5.5 µM) was determined when cells were coincubated with a log range of rilpivirine concentrations (0, 1, 2.5, 5, 10, 25, 50, 100 µM). A parallel experiment was performed using prazosin as a positive-control SLC22A1 inhibitor. Data were plotted using Prism (version 5) software, and slopes were used to calculate the relative IC50 (the amount of drug needed to achieve 50% SLC22A1 inhibition, as determined from the maximum and minimum extremes of the nonlinear regression plot).

Statistical analysis. Data were analyzed using SPSS (version 19) for Windows. IC50 curves were generated using Prism (version 5) for Windows. All data were tested for normality using the Shapiro–Wilk test. An independent t test was used to determine the significance of normally distributed data, and the Mann-Whitney U test was used for all other data. A two-tailed P value of <0.05 was accepted as being statistically significant.

RESULTS

Rilpivirine accumulation in wild-type and ABCB1-overexpressing CEM cells. Cellular accumulation of rilpivirine was determined in CEM and ABCB1-overexpressing CEMvB100 cells, and the effect of the ABCB1 inhibitor tariquidar on this accumulation was investigated (Fig. 1A). Rilpivirine accumulation in CEMvB100 cells (54.1 ± 1.6 µM) was not significantly different from that in CEM cells (48.7 ± 1.9 µM, P = 0.11). Tariquidar treatment did not alter rilpivirine accumulation in CEMvB100 cells (P = 0.23). The control ABCB1 substrate lopinavir had lower accumulation in CEMvB100 cells (10.3 ± 0.9 µM) than in CEM cells (17.9 ± 1.5 µM, P < 0.01) (Fig. 1B). This difference in lopinavir accumulation between CEM and CEMvB100 cells was lost when CEMvB100 cells were treated with tariquidar (19.8 ± 0.7 µM, P = 0.10).

Impact of tariquidar on rilpivirine Caco-2 cell monolayer permeation. The P_app values obtained for rilpivirine with and without tariquidar are given in Fig. 1C. All P_app values and efflux ratio calculations were made using the samples taken after 60 min of incubation as sink conditions were maintained. Rilpivirine showed significantly higher transport in the B-to-A direction (P_app = 6.6 × 10^-6 ± 0.6 × 10^-6 cm s^-1) than in the A-to-B direction (P_app = 4.0 × 10^-6 ± 0.7 × 10^-6 cm s^-1, P < 0.01). The efflux ratio (P_app in the B-to-A direction/P_app in the A-to-B direction) of rilpivirine at 60 min was 1.65. When incubations were repeated in the presence of the ABCB1 inhibitor tariquidar, no significant alteration in rilpivirine permeation was determined in either the A-to-B direction (P_app = 3.9 × 10^-6 ± 0.7 × 10^-6 cm s^-1, P = 0.88) or the B-to-A direction (P_app = 6.6 × 10^-6 ± 0.9 × 10^-6 cm s^-1, P = 0.93).

Impact of rilpivirine on digoxin Caco-2 cell monolayer permeation. The ability of rilpivirine to inhibit ABCB1-mediated transport of digoxin was assessed using Caco-2 cell monolayers (Fig. 1D). Permeation of 1 µM digoxin in the A-to-B direction was significantly increased when it was coincubated with rilpivirine at 1 µM (P_app = 2.1 × 10^-6 ± 0.3 × 10^-6 cm s^-1, P = 0.01), 3 µM (P_app = 4.2 × 10^-6 ± 1.6 × 10^-6 cm s^-1, P = 0.04), 10 µM (P_app = 10.9 × 10^-6 ± 2.5 × 10^-6 cm s^-1, P < 0.01), and 30 µM (P_app = 12.1 × 10^-6 ± 0.2 × 10^-6 cm s^-1, P < 0.01) compared with that for the rilpivirine-free controls (P_app = 1.3 × 10^-6 ± 0.1 × 10^-6 cm s^-1). Permeation of 1 µM digoxin in the B-to-A direction was significantly decreased when it was coincubated with 10 µM rilpivirine [P_app = (22.2 ± 6.0) × 10^-6 cm s^-1, P = 0.02] and 30 µM rilpivirine [P_app = (18.2 ± 2.7) × 10^-6 cm s^-1, P = 0.01], compared with rilpivirine-free control incubations [P_app = (64.2 ± 8.6) × 10^-6 cm s^-1]. Rilpivirine reduced permeation in the A-to-B direction, permeation in the B-to-A direction, and the efflux ratio of digoxin with IC50 of 4.24 µM (95% confidence interval [CI], 2.94 to 6.10 µM), 4.48 µM (95% CI, 2.52 to 7.96 µM), and 1.08 µM (95% CI, 0.67 to 1.73 µM), respectively. The control ABCB1 inhibitor tariquidar increased the permeation of digoxin in the A-to-B direction (P_app = 16.6 × 10^-6 ± 3.4 × 10^-6 cm s^-1, P = 0.02) and decreased the permeation of digoxin in the B-to-A direction (P_app = 14.7 × 10^-6 ± 3.6 × 10^-6 cm s^-1, P < 0.01), resulting in a digoxin efflux ratio of 0.9 (Fig. 1D).

Rilpivirine accumulation and inhibitory potential in transporter cRNA-injected Xenopus laevis oocytes. The accumulation of rilpivirine was determined in SLCO1A2, SLCO1B1, SLCO1B3, SLC22A2, SLC22A6, and SLC22A8 cRNA-injected X. laevis oocytes. Water-injected oocytes were also included in accumulation experiments to determine passive diffusion of the drug into oocytes, and control substrates were used to validate functional transporter expression. The control substrates used were estrone-3-sulfate (SLC22A8, SLCO1A2, SLCO1B1, SLCO1B3), aminohippuric acid (SLC22A6), and metformin (SLC22A2). The ability of rilpivirine to inhibit accumulation of control substrates was also assessed. The amount of drug accumulation in transporter cRNA-injected oocytes compared to that in water-injected control oocytes was determined and is given in Fig. 2.
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Rilpivirine accumulation was not altered in oocytes expressing SLC22A2 (68.55 ± 12.22 μM, P = 0.14), SLC22A6 (54.80 ± 5.44 μM, P = 0.09), SLC22A8 (62.67 ± 5.91 μM, P = 0.72), SLCO1A2 (66.50 ± 6.93 μM, P = 0.65), SLCO1B1 (67.72 ± 15.16 μM, P = 0.38), or SLCO1B3 (73.27 ± 10.03 μM, P = 0.41) in comparison to that in water-injected control oocytes (60.31 ± 2.81 μM) (Fig. 2A). Estriol-3-sulfate accumulation was higher in oocytes expressing SLC22A2 (0.62 ± 0.10 μM, P = 0.002), SLCO1A2 (3.63 ± 0.52 μM, P < 0.001), SLCO1B1 (5.95 ± 0.62 μM, P < 0.001), and SLCO1B3 (0.45 ± 0.04 μM, P = 0.009) than in water-injected control oocytes (0.24 ± 0.05 μM). Aminohippuric acid accumulation was higher in oocytes expressing SLC22A6 (6.07 ± 0.54 μM, P = 0.002) than in water-injected control oocytes (0.22 ± 0.01 μM). Metforin accumulation was higher in oocytes expressing SLC22A2 (1.36 ± 0.16 μM, P < 0.001) than in water-injected control oocytes (0.23 ± 0.06 μM). Rilpivirine at 10 μM did not alter the accumulation of estrone-3-sulfate in oocytes expressing SLC22A2 (P = 0.92), SLCO1A2 (P = 0.83), SLCO1B1 (P = 0.38), or SLCO1B3 (P = 0.53) (Fig. 2B) and also did not alter the accumulation of aminohippuric acid in oocytes expressing SLC22A6 (P = 0.64) (Fig. 2C). Accumulation of metforin in oocytes expressing SLC22A2 was reduced in the presence of rilpivirine; therefore, the IC500 determined for rilpivirine and the control SLC22A2 inhibitor quinidine were 5.13 μM and 40.45 μM, respectively (Fig. 2D).

Rilpivirine accumulation and inhibitory potential in SLC22A1-expressing KCL22 cells. The accumulation of rilpivirine in transfected SLC22A1-expressing KCL22 cells and mock-transfected KCL22 cells was determined and compared to the rilpivirine accumulation in cells coincubated with the SLC22A1 inhibitor prazosin. Accumulation of the control SLC22A1 substrate tetraethyl ammonium was also determined.

Rilpivirine showed a small but statistically significantly higher accumulation in SLC22A1-expressing KCL22 cells (88.8 ± 5.9 μM, P = 0.031) than in mock-transfected cells (70.0 ± 8.0 μM) (Fig. 3B). The control inhibitor prazosin caused a small but significant decrease in rilpivirine cellular accumulation in SLC22A1-expressing cells (14% reduction, P = 0.04). Tetraethyl ammonium showed higher accumulation in SLC22A1-expressing KCL22 cells (1.6 ± 0.02 μM, P < 0.01) than in mock-transfected cells (0.12 ± 0.01 μM) (Fig. 3A). Prazosin decreased tetraethyl ammonium cellular accumulation in SLC22A1-expressing cells (77% reduction, P < 0.01). The inhibition of SLC22A1 was determined using a concentration range of rilpivirine and prazosin and used to calculate IC500 (Fig. 3C). Rilpivirine inhibited tetraethyl ammonium accumulation in SLC22A1-overexpressing cells with a relative IC500 of 28.5 μM. Prazosin (100 μM) achieved an 84% reduction in cellular tetraethyl ammonium accumulation and a relative IC500 of 2.3 μM, which are similar to data in the literature (18).

DISCUSSION

Drug interactions involving antiretroviral drugs can potentially lead to therapy failure and/or exacerbate adverse drug reactions. In this study, we have investigated the interactions of rilpivirine...
with a selection of key drug transporters to improve our understanding of the factors involved in rilpivirine pharmacokinetics. The results from accumulation and bidirectional monolayer permeation experiments confirm that rilpivirine is not transported by ABCB1. The extent of rilpivirine transport by ABCB1 was not significant compared to the transport of the positive controls lopinavir and the cardiac glycoside digoxin. Indeed, the FDA guidelines recommend that a drug should achieve an efflux ratio of at least 2 in Caco-2 cell monolayers and show a greater than 50% reduction in efflux ratio when an ABCB1 inhibitor is used, in order for ABCB1 transport to be considered relevant in vivo (19).

In our Caco-2 cell experiment, rilpivirine achieved an efflux ratio of only 1.65, with no alteration observed when tariquidar was used to inhibit ABCB1. The small efflux ratio obtained for rilpivirine suggests that active efflux in the gut is unlikely to be important in vivo. Therefore, no other intestinal efflux transporters were assessed in this study.

Rilpivirine inhibited ABCB1-mediated transport of digoxin through Caco-2 cell monolayers. This suggests that rilpivirine may influence the movement of ABCB1 substrates across cell membrane barriers which are high in ABCB1 expression, such as the mucosal surface epithelial cells in the intestine, the biliary canalicular surface of hepatocytes in the liver, the brush border membrane of renal proximal tubular cells in the kidney, and the blood-brain barrier (8, 20–22). However, rilpivirine did not alter the exposure of the ABCB1 substrate digoxin in healthy volunteers, which suggests that the observed in vitro inhibition of ABCB1 by rilpivirine is not clinically relevant (4).

In oocyte accumulation studies, rilpivirine was not a substrate of any transporter tested but did inhibit SLC22A2-mediated transport of the antidiabetic drug metformin with an IC50 of 5.13 μM. Therefore, there is the potential for an interaction between rilpivirine and other SLC22A2 substrates, although this will depend on the concentration of inhibitor [I] and the IC50 (i.e., [I]/IC50). Given that the rilpivirine concentration (Cmax = 0.43 μM) (3) is less than the IC50, it seems unlikely that this will be a mechanism of clinically relevant interactions or would fully explain the small increase in creatinine levels in patients taking rilpivirine (8). This is in contrast to the findings for dolutegravir, as the drug causes notable inhibition of SLC22A2 in vitro (IC50 = 1.9 μM) at a concentration which is about 4-fold lower than the Cmax ([I]/IC50 = 4.2) (23). This inhibition is consistent with the 10 to 14% increase in serum creatinine observed in patients taking dolutegravir (24). A recent publication by Weiss et al. used transfected HEK293 cells to show that rilpivirine was a weak inhibitor of SLCO1B1 and SLCO1B3 only at superphysiological concentrations (5). Furthermore, there have been no clinical interactions reported which would suggest that rilpivirine can alter the disposition of SLCO substrates; therefore, the potential for SLCO-mediated interactions is unlikely.

SLC22A1 is predominantly expressed in the liver and acts to remove substrates from the blood and into hepatic cells. The nu-
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To be competitive, the IC50 may be different for other drug substrates. Transporters also exhibit affinities for transporters and since this interaction is likely to differ between rilpivirine and other SLC22A1 substrates. However, it should be noted that passive diffusion of rilpivirine predominated in KCL22 cells and the level of transport by SLC22A1 was low in comparison.

In summary, rilpivirine shows inhibition of ABCB1, SLC22A1, and several protease inhibitors inhibit SLC22A1-mediated transport of these transporters in vitro (25, 26). In the accumulation studies using transfected KCL22 cells, rilpivirine inhibited SLC22A1-mediated transport of tetrathyrid ammonium, which suggests the potential for an interaction between rilpivirine and other SLC22A1 substrates. However, it is not possible to rule out the possibility of the involvement of these transporters in rilpivirine-mediated drug-drug interactions because of the differences in extrapalating from in vitro data to in vivo phenotypes. Since different substrates have different affinities for transporters and since this interaction is likely to be competitive, the IC50 may be different for other drug substrates. Also, rilpivirine may concentrate in specific tissues, raising the concentrations available for transporter inhibition.

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