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Clinical Perspective on Drug-Drug Interactions with the Non-nucleoside Reverse Transcriptase Inhibitor Rilpivirine

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Abstract

Rilpivirine (TMC278) is a non-nucleoside reverse transcriptase inhibitor approved in combination with other antiretrovirals for the treatment of HIV-1 infection in treatment-naive adults (Edurant® 25 mg once daily; Complera® [USA]/Eviplera® [EU] once daily single-tablet regimen). Rilpivirine should be administered with a meal to optimize bioavailability. Its solubility is pH dependent. Rilpivirine is primarily excreted via the feces with negligible renal elimination. Rilpivirine is predominantly metabolized by cytochrome P450 3A4. There is no clinically relevant effect of age, gender, bodyweight, race, estimated glomerular filtration rate, or hepatitis B/C coinfection status on rilpivirine pharmacokinetics in adults. Drug-drug interactions were investigated with cytochrome P450 3A substrates, inducers and inhibitors, drugs altering intragastric pH, antiretrovirals, and other often coadministered drugs. Rilpivirine 25 mg once daily does not have a clinically relevant effect on exposure of coadministered drugs. Coadministration with cytochrome P450 3A inhibitors (ketoconazole, ritonavir-boosted protease inhibitors, telaprevir) results in increased rilpivirine plasma concentrations, but these are not considered clinically relevant; no dose adjustments are required. Coadministration of rilpivirine with cytochrome P450 3A inducers (e.g. rifampin, rifabutin) or compounds increasing gastric pH (e.g. omeprazole, famotidine) results in decreased rilpivirine plasma concentrations, which may increase the risk of virologic failure and resistance development. Therefore, strong cytochrome P450 3A inducers and proton-pump inhibitors are contraindicated. Histamine-2 receptor antagonists and antacids can be coadministered with rilpivirine, provided doses are temporally separated. No dose adjustments are required when rilpivirine is coadministered with: acetaminophen, phosphodiesterase type 5 inhibitors (sildenafil, etc.), atorvastatin (and other statins), oral contraceptives (ethinyl estradiol, norethindrone), chlorzoxazone (cytochrome P450 2E1 substrate), methadone, digoxin, tenofovir disoproxil fumarate, didanosine and other nuceos(t)ide reverse transcriptase inhibitors, and HIV integrase inhibitors (raltegravir, dolutegravir, GSK1265744).

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Key words

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Introduction

Rilpivirine (RPV, TMC278) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) approved for use in combination with other antiretroviral (ARV) agents for the treatment of HIV-1 infection in treatment-naive adults[1,2]. In the USA, Europe and several countries worldwide RPV combined with other ARVs is approved for the treatment of treatment-naive adults with a viral load ≤ 100,000 copies/ml[1,2]. These approvals were based on the 48-week primary results of two global phase III trials demonstrating the sustained efficacy of RPV 25 mg and non-inferiority to efavirenz, both with a background regimen of two nucleos(t)ide reverse transcriptase inhibitors (N[t]RTI)[3,4]. Rilpivirine showed better tolerability than efavirenz, with lower incidences of grade 2-4 adverse

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events possibly related to treatment, lipid abnormalities, rash, dizziness, and abnormal dreams/nightmares[3,4]. Furthermore, the results of these trials after 96 weeks of treatment were consistent with the findings of the week 48 primary analysis[5]. Rilpivirine is also available in a single tablet ARV regimen with tenofovir disoproxil fumarate/emtricitabine (Complera® [USA], Eviplera® [EU]).

The pharmacokinetics of RPV have been assessed in all phase I, II, and III trials conducted to date, to specifically characterize the pharmacokinetics of RPV in healthy volunteers and HIV-1-infected patients, and to evaluate the impact of demographic factors and the effects of coadministration with other drugs. No relationship between exposure to RPV and adverse events or clinically relevant changes in laboratory parameters in HIV-infected patients has been identified in either the phase II or the phase III trials[3,4,6]. There was a dose- and exposure-related prolongation of QT interval for supratherapeutic doses of RPV (3- or 6-times the approved dose) in HIV-1-infected patients[6]. However, RPV at the approved 25 mg once-daily dose did not prolong QT interval in healthy volunteers[7]. In both of these trials, the comparator efavirenz at its therapeutic dose of 600 mg once daily also prolonged the QT interval[6,7].

An analysis of the potential covariates affecting virologic outcome at week 48 with RPV in phase III trials indicated that treatment adherence was most important, followed by RPV exposure, and baseline viral load[8]. Circumstances in which ARV plasma concentrations could be substantially reduced (e.g. certain drug-drug interactions) are important to take into account as they may pose an increased risk of virologic failure and possible development of viral resistance. Moreover, situations, such as drug-drug interactions, leading to increased ARV plasma concentrations are also important for consideration as they may result in an increased risk of adverse events.

The aim of this review is to provide a detailed overview of the pharmacokinetics and drug-drug interaction data accumulated to date for RPV. This includes drugs frequently used by HIV-1-infected patients, as well as those with a potential for interaction with RPV due to their metabolic pathway. The clinical relevance of each interaction will be described.

Clinical pharmacokinetics of rilpivirine

Rilpivirine is a diarylpyrimidine derivative that is orally bioavailable, with maximum plasma concentrations attained approximately 4-5 hours after administration[9,10]. It has a long terminal elimination half-life of approximately 45-50 hours that facilitates once-daily dosing[9-11].

The oral bioavailability of RPV is maximized after intake under fed conditions, with exposure 40% lower upon fasted intake[12]. Therefore, RPV should always be administered with a meal to optimize its bioavailability. It was shown that the exposure to RPV was similar when administered with a regular or a high-fat breakfast[12]. However, compared with a regular breakfast, exposure to RPV was approximately 50% lower when administered with only a protein-rich nutritional drink, which is, therefore, not recommended. Potential factors that could have contributed to this result include the liquid nature and/or the specific content of the nutritional drink. The solubility of RPV decreases with increasing pH, so drugs that increase gastric pH may reduce its oral bioavailability and specific precautions are warranted[1,2].

Rilpivirine exposure increased dose-proportionally over the dose range of 25-150 mg once daily in healthy volunteers[11], although in HIV-1-infected patients, a less than dose-proportional increase has been observed[13]. Exposure to RPV is generally lower in HIV-1-infected patients compared with healthy volunteers[11,13,14].

Rilpivirine is 99.7% bound to plasma proteins, mostly to albumin[1]; this protein binding is concentration-independent. The distribution of RPV into compartments other than plasma, such as cerebrospinal fluid or genital tract secretions, is the subject of ongoing research. Rilpivirine 25 mg once daily achieves plasma concentrations well in excess of the 50% effective concentration (EC_{50}) for wild-type and NNRTI-resistant viruses[13].

The cytochrome P450 (CYP) enzyme CYP3A4 has a predominant role in the metabolism of RPV[15], but CYP2C19 and to a lesser extent CYP2C8/9/10 may also be involved. Mild induction of CYP3A4 by RPV has been observed, but only at supratherapeutic doses of RPV, and this is not of clinical importance with RPV 25 mg once daily[16].

Excretion of RPV occurs primarily via the feces (85.1%), with limited renal elimination (< 1% unchanged compound)[17].

Factors influencing the pharmacokinetics of rilpivirine

The interindividual variability of the RPV pharmacokinetic parameters is generally low-to-moderate, with a coefficient of variation of about 25-45% for all parameters, and not dose-dependent.

The potential impact of different intrinsic factors on RPV pharmacokinetics was explored with covariate

modeling (pooled data from phase III trials)[14]. There was no effect of age, bodyweight, estimated glomerular filtration rate, or hepatitis B and/or C coinfection status. Although a slightly higher mean exposure to RPV was observed in Asian and female patients, which was partly explained by differences in bodyweight, the ranges of exposures in these two subgroups were largely similar to the overall population. Thus, this finding was not considered clinically relevant.

In a specific phase I study, the overall impact of mild-to-moderate hepatic impairment on RPV pharmacokinetics was found to be limited and not considered clinically relevant. No dose adjustment of RPV is necessary in patients with mild-to-moderate hepatic impairment[18]. The impact of severe hepatic impairment has not been assessed.

Drug-drug interactions with rilpivirine

As RPV is metabolized predominantly by CYP3A4, the potential for interactions with coadministered drugs that either induce or inhibit this metabolic pathway is of particular interest. A range of drug-drug interaction studies have been conducted to evaluate the effects of coadministration of other CYP3A substrates, inducers and inhibitors, a CYP2E1 substrate, drugs that alter intragastric pH, and drugs that are likely to be coadministered, including other ARVs. An overview of these data is provided below, along with current recommendations for clinical practice[1,2].

In order to control as many factors as possible, drug-drug interaction studies are typically carried out in healthy volunteers. A major drawback of conducting interaction studies in HIV-infected individuals is the need for combination ARV therapy, with the assessment of an interaction between two drugs often being confounded by effects of other drugs in the regimen. Also, subtherapeutic exposure to ARVs in the HIV-infected population should be avoided to decrease the risk of resistance development. Therefore, all interaction studies described here for RPV have been performed in healthy volunteers. It is anticipated that the type and magnitude of interaction will be generally comparable in HIV-infected patients, and dosing recommendations presented here apply for the HIV-infected population.

Most of the drug-drug interaction studies were performed using RPV 150 mg once daily (six times higher than the approved RPV dose), to assess the maximal potential impact of RPV on the pharmacokinetics of coadministered drugs. Any interaction occurring with the therapeutic dose of RPV (25 mg once daily) would be expected to be either similar to, or more likely lower than, that observed at 150 mg. Based on the dose-proportional pharmacokinetics of RPV in healthy volunteers, there is no indication of saturation of RPV metabolism up to 150 mg as this would lead to a more than a dose-proportional increase in RPV exposure. Therefore, any dosing implications based on the results of the drug-drug interaction trials with RPV at a dose of 150 mg can be extrapolated to a dose of 25 mg. Coadministration of RPV with drugs that induce CYP3A could decrease RPV plasma concentrations, which could potentially reduce the therapeutic effect of RPV and therefore, these should not be used.

Although RPV plasma concentrations obtained with supratherapeutic RPV doses (three or 12 times the therapeutic dose) have been associated with changes in the QT interval corrected by Fridericia's formula (QTcF)[7], it is anticipated that in practice, any increased RPV plasma concentrations that occur with coadministration of drugs that inhibit CYP3A would have no clinical effect on QTcF. The 25 mg therapeutic dose was not associated with QTcF prolongation in a specifically designed thorough QT trial[7]. Using modeling and simulation based on the pharmacokinetic and electrocardiogram data from all thorough QT trials across a wide range of RPV plasma concentrations, it was established that there would be no clinically relevant effect or safety concern for mean increases in maximum concentration (C_{max}) of RPV of up to 85% (1.85-fold). Several drug-drug interaction trials have been performed with RPV and strong inhibitors of CYP3A, all of which showed mean increases in RPV C_{max} below 85% (1.85-fold).

The drug-drug interaction data are summarized in four tables. Table 1 summarizes the effect of HIV ARV agents on the pharmacokinetics of RPV, and table 2 summarizes the effect of RPV on the pharmacokinetics of HIV ARV agents. Similarly for non-ARV medication (including non-HIV ARVs), table 3 summarizes the effect of coadministered drugs on the pharmacokinetics of RPV and table 4 summarizes the effect of RPV on the pharmacokinetics of other drugs.

Cytochrome P450 3A metabolic interactions

Cytochrome P450 3A inhibitors

Lopinavir/ritonavir

The combination of lopinavir and ritonavir inhibits CYP3A4 and induces CYP2C9 and CYP2C19[37]. In a randomized, open-label, two-period crossover trial with

Table 1. Summary of the effect of HIV antiretroviral agents on the pharmacokinetics of rilpivirine

Coadministered drug	Dose schedule: Coadministered drug	Dose schedule: RPV	(n)	Pharmacokinetic effect	Mean ratio (90% CI) of RPV pharmacokinetic parameters with/without coadministered drug (No effect = 1): C_{max}	AUC	C_{min}
Protease inhibitors							
Lopinavir/ ritonavir[19]	400/100 mg bid 20 days	150 mg qd 10 days	15	↑	1.29 (1.18, 1.40)	1.52 (1.36, 1.70)	1.74 (1.46, 2.08)
Darunavir/ ritonavir[20]	800/100 mg qd 22 days	150 mg qd 11 days	14	↑	1.79 (1.56, 2.06)	2.30 (1.98, 2.67)	2.78 (2.39, 3.24)
Nucleos(t)ide reverse transcriptase inhibitors							
Tenofovir disoproxil fumarate[21]	300 mg qd 16 days	150 mg qd 8 days	16	↔	0.96 (0.81, 1.13)	1.01 (0.87, 1.18)	0.99 (0.83, 1.16)
Didanosine (Janssen, data on file)	400 mg qd 14 days	150 mg qd 7 days	21	↔	1.00 (0.90, 1.10)	1.00 (0.95, 1.06)	1.00 (0.92, 1.09)
Integrase inhibitors							
Raltegravir[22]	400 mg bid 11 days	25 mg qd 11 days	23	↔	1.12 (1.04, 1.20)	1.12 (1.05, 1.19)	1.03 (0.96, 1.12)
Dolutegravir[23]	50 mg qd 5 days	25 mg qd 11 days	16	↔	1.10 (0.99, 1.22)	1.06 (0.98, 1.16)	1.21 (1.07, 1.38)
S/GSK1265744[23]	30 mg qd 12 days	25 mg qd 12 days	11	↔	0.96 (0.85, 1.09)	0.99 (0.89, 1.09)	0.92 (0.79, 1.07)

All drug-drug interaction trials have been performed in non-HIV infected volunteers. RPV: rilpivirine; (n): maximum number of volunteers with data; CI: confidence interval; C_{max}: maximum plasma concentration; AUC: area under the concentration time curve; C_{min}: minimum plasma concentration; bid: twice daily; qd: once daily.

14-day washout, 16 healthy volunteers in the fed state received RPV alone (150 mg once daily for 10 days) or RPV (150 mg once daily from day 11 to 20) plus lopinavir/ritonavir (400/100 mg twice daily for 20 days)[19]. There were no clinically relevant pharmacokinetic changes for any of the drugs. The exposure to RPV was increased (1.52-fold increase in AUC_{24h} and 1.29-fold increase in C_{max}) by coadministration with lopinavir/ritonavir (Table 1). As the mean increase in C_{max} was less than 1.85-fold, this is not expected to be of clinical relevance or cause safety concerns. Rilpivirine did not affect the pharmacokinetics of lopinavir or ritonavir (Table 2). Rilpivirine can therefore be coadministered with lopinavir/ritonavir without dose adjustments.

Darunavir/ritonavir

Darunavir and ritonavir are both substrates of CYP3A4 and the combination inhibits CYP3A4- and CYP2D6-mediated metabolism. In a randomized, open-label, two-period crossover trial with 14-day washout, 16 healthy volunteers in the fed state received RPV alone (150 mg once daily for 11 days) or RPV (150 mg once daily from day 12 to 22) plus darunavir/ritonavir (800/100 mg once daily for 22 days)[20]. There were no clinically relevant pharmacokinetic changes for any of the drugs. The exposure to RPV was increased (2.30-fold increase in AUC_{24h} and 1.79-fold increase in C_{max}) when coadministered with darunavir/ritonavir (Table 1). As the mean increase in C_{max} was less than 1.85-fold, this is not expected to be clinically relevant or cause safety concerns. Exposure to darunavir was not affected by RPV coadministration; ritonavir exposure was decreased by only 15% (AUC_{24h}) compared to administration of darunavir/ritonavir alone (Table 2). Therefore, RPV and darunavir/ritonavir can be coadministered without dose adjustments.

Table 2. Summary of the effect of rilpivirine on the pharmacokinetics of HIV antiretroviral agents

Coadministered drug	Dose schedule: Coadministered drug	Dose schedule: RPV	(n)	Pharmacokinetic effect	Mean ratio (90% CI) of coadministered drug pharmacokinetic parameters with/without RPV (No effect = 1): C_{max}	AUC	C_{min}
Protease inhibitors							
Lopinavir	400 mg bid 20 days	150 mg qd 10 days	15	↔	0.96 (0.88, 1.05)	0.99 (0.89, 1.10)	0.89 (0.73, 1.08)
Ritonavir[19]	100 mg bid 20 days	150 mg qd 10 days	15	↔	0.89 (0.73, 1.08)	0.96 (0.84, 1.11)	1.07 (0.89, 1.28)
Darunavir	800 mg qd 22 days	150 mg qd 11 days	15	↔	0.90 (0.81, 1.00)	0.89 (0.81, 0.99)	0.89 (0.68, 1.16)
Ritonavir[20]	100 mg qd 22 days	150 mg qd 11 days	15	↓	0.83 (0.72, 0.95)	0.85 (0.78, 0.91)	0.78 (0.68, 0.90)
Nucleos(t)ide reverse transcriptase inhibitors							
Tenofovir disoproxil fumarate[21]	300 mg qd 16 days	150 mg qd 8 days	16	↑	1.19 (1.06, 1.34)	1.23 (1.16, 1.31)	1.24 (1.10, 1.38)
Didanosine (Janssen, data on file)	400 mg qd 14 days	150 mg qd 7 days	13	↔	0.96 (0.80, 1.14)	1.12 (0.99, 1.27)	NA
Integrase inhibitors							
Raltegravir[22]	400 mg bid 11 days	25 mg qd 11 days	23	↔	1.10 (0.77, 1.58)	1.09 (0.81, 1.47)	1.27 (1.01, 1.60)
Dolutegravir[23]	50 mg qd 5 days	25 mg qd 11 days	16	↔	1.13 (1.06, 1.21)	1.12 (1.05, 1.19)	1.22 (1.15, 1.30)
S/GSK1265744[23]	30 mg qd 12 days	25 mg qd 12 days	11	↔	1.05 (0.96, 1.15)	1.12 (1.05, 1.19)	1.14 (1.04, 1.24)

All drug-drug interaction trials have been performed in non-HIV infected volunteers. RPV: rilpivirine; (n): maximum number of volunteers with data; CI: confidence interval; C_{max}: maximum plasma concentration; AUC: area under the concentration time curve; C_{min}: minimum plasma concentration; bid: twice daily; qd: once daily; NA: no information available.

Ketoconazole

The broad-spectrum antifungal ketoconazole is mainly metabolized through CYP3A4 and is a strong inhibitor of this enzyme[38-40]. In a randomized, open-label, two-period crossover trial with 14-day washout, 16 healthy volunteers in the fed state received RPV alone (150 mg once daily for 11 days) or RPV (150 mg once daily from day 12 to 22) plus ketoconazole (400 mg once daily for 22 days)[15,24]. There were no clinically relevant pharmacokinetic changes for either drug. The exposure to RPV increased (1.49-fold increase in AUC_{24h} and 1.30-fold increase in C_{max}) when coadministered with ketoconazole (Table 3). As the mean increase in C_{max} was less than 1.85-fold, it is not expected to be clinically relevant and does not cause safety concerns. Exposure to ketoconazole was decreased by 24% (AUC_{24h}) by coadministration of RPV at this high 150 mg dose (Table 4), which may be explained by modest induction of CYP3A by RPV at higher doses. However, RPV 25 mg once daily has no relevant effect on CYP3A activity *in vivo*[16], and hence this effect is likely not relevant at the approved RPV dose. These data show that RPV 25 mg once daily and ketoconazole can be coadministered without dose adjustments. Since ketoconazole is a more potent inhibitor of CYP3A4 than other azole antifungal agents such as fluconazole, voriconazole, itraconazole and posaconazole[41,42], the effect of other azole antifungals on RPV pharmacokinetics is not expected to exceed that of

ketoconazole. Therefore, these can also be coadministered without dose adjustments.

Anti-hepatitis C virus drugs

Patients with HIV-1 infection are frequently coinfected with hepatitis C virus (HCV) since these viruses share transmission routes. As such, patients coinfected with HIV-1 and HCV may need combined treatment with ARV and anti-HCV drugs. Coadministration of telaprevir and RPV increases the RPV AUC_{24h} and C_{max} by 1.78- and 1.49-fold, respectively (Table 3), likely due to CYP3A inhibition by telaprevir[35], which is not considered clinically relevant as the mean increase in C_{max} was less than 1.85-fold. There was a slight decrease in telaprevir AUC_{8h} (8%), which is not considered clinically relevant (Table 4). Dose adjustment is not necessary when coadministering RPV and telaprevir, nor when RPV is coadministered with the investigational oral, once-daily HCV NS3/4A protease inhibitor simeprevir[36] (Tables 3 and 4).

Cytochrome P450 3A inducers

Efavirenz and nevirapine

Both efavirenz and nevirapine are approved NNRTIs for the treatment of HIV-1 infection. Highly active antiretroviral therapy (HAART) using two NNRTIs in combination is not recommended in any regimen[43,44]. Therefore, it is not recommended to coadminister RPV with another NNRTI. However, ARVs are sometimes switched during treatment due to toxicity or tolerability issues, or for simplification of an ARV regimen. Therefore, it is also important to consider drug-drug interactions when switching ARV regimens. Efavirenz and, to a lesser extent, nevirapine both result in CYP3A4 and CYP2B6 induction[45,46], an effect that may persist for days or weeks after their cessation due to their relatively long elimination half-lives and the turnover of the CYP enzymes. Therefore, there is the potential that plasma concentrations of any agent administered subsequently are still affected by a switch in NNRTI treatment.

A study to evaluate the pharmacokinetics of RPV 25 mg once daily over 28 days after a switch from efavirenz 600 mg once daily has been carried out in healthy volunteers[47]. After the efavirenz intake ceased and participants were switched to RPV, the RPV pharmacokinetics were initially lower (AUC_{24h} 46% lower on day 1, 18% on day 14, and 16% on day 21), but by day 28 they had returned to levels comparable to those when RPV was administered without prior efavirenz treatment. These data supported further clinical evaluation of a switch from efavirenz to RPV in HIV-1-infected, suppressed patients. The results of such a study indicate that inductive effects of efavirenz on RPV metabolism after a switch may indeed not be clinically relevant when efavirenz is replaced by RPV in previously suppressed patients. A phase IIb, open-label multicenter pilot study evaluated switching because of side effects from the efavirenz/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen to the RPV/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen in 50 virologically suppressed patients[48,49]. All 49 patients who were dosed completed the study through 24 weeks and remained virologically suppressed over this time period.

Rifampin and rifabutin

Rifampin and rifabutin are used in the treatment of mycobacterial infections. Both drugs are substrates and inducers of CYP enzymes, including CYP3A4[50,51]. The interaction between RPV and rifampin was investigated in a randomized, three-period, open-label crossover trial with 14-day washouts, in 16 healthy volunteers in the fed state who received RPV alone (150 mg once daily for seven days), rifampin alone (600 mg once daily for seven days), or RPV (150 mg once daily for seven days) plus rifampin (600 mg once daily for seven days)[15]. Exposure to RPV was decreased (80% decrease in AUC_{24h} and 69% decrease in C_{max}) when coadministered with rifampin (Table 3). Coadministration of RPV did not affect the pharmacokinetics of rifampin or its (active) metabolite 25-desacetyl rifampin (Table 4). In a similar trial with rifabutin[25], exposure to RPV was decreased (46% decrease in AUC_{24h} and 35% decrease in C_{max}) when coadministered with rifabutin (Table 3). Coadministration of RPV did not affect the pharmacokinetics of rifabutin or its (active) metabolite, 25-*O*-desacetyl rifabutin (Table 4).

Due to the clinically relevant effect of both rifampin and rifabutin on RPV pharmacokinetics, RPV should not be coadministered with rifampin, rifabutin, or the closely-related rifapentine.

Also, other strong inducers of CYP3A should not be coadministered with RPV. These include carbamazepine, oxcarbazepine, phenobarbital, phenytoin, systemic dexamethasone (more than single dose), and products containing St John's wort (*Hypericum perforatum*).

Table 3. Summary of the effect of other drugs including non-HIV-antiretrovirals on the pharmacokinetics of rilpivirine

	Dose schedule				Mean ratio (90% CI) of RPV pharmacokinetic parameters with/without coadministered drug (No effect = 1)		
Coadministered drug	**Coadministered drug**	**RPV**	**(n)**	**Pharmacokinetic effect**	**C_{max}**	**AUC**	**C_{min}**
Ketoconazole[15,24]	400 mg qd 22 days	150 mg qd 11 days	15	↑	1.30 (1.13, 1.48)	1.49 (1.31, 1.70)	1.76 (1.57, 1.97)
Rifampin[15]	*600 mg qd 7 days*	*150 mg qd 7 days*	16	↓	*0.31 (0.27, 0.36)*	*0.20 (0.18, 0.23)*	*0.11 (0.10, 0.13)*
Rifabutin[25]	*300 mg qd 11 days*	*150 mg qd 11 days*	16	↓	*0.65 (0.58, 0.74)*	*0.54 (0.50, 0.58)*	*0.51 (0.48, 0.54)*
Sildenafil[26]	50 mg single dose	75 mg qd 12 days	16	↔	0.92 (0.85, 0.99)	0.98 (0.92, 1.05)	1.04 (0.98, 1.09)
Atorvastatin[27]	40 mg qd 4 days	150 mg qd 15 days	16	↔	0.91 (0.79, 1.06)	0.90 (0.81, 0.99)	0.90 (0.84, 0.96)
Ethinylestradiol/ Norethindrone[28]	35 µg/1 mg qd 21 days	25 mg qd 15 days	15	↔	↔*	↔*	↔*
Methadone[29,30]	60 to 100 mg qd individualized dose	25 mg qd 11 days	12	↔	↔*	↔*	↔*
Omeprazole[31]	*20 mg qd 12 days*	*150 mg single dose*	16	↓	*0.42 (0.32, 0.54)*	*0.44 (0.35, 0.55)*	*NA*
		150 mg qd 11 days	16	↓	*0.60 (0.48, 0.73)*	*0.60 (0.51, 0.71)*	*0.67 (0.58, 0.78)*
Famotidine[32]	*40 mg single dose 2 hours before RPV*	*150 mg single dose*	*23*	↓	*0.15 (0.12, 0.19)*	*0.24 (0.20, 0.28)*	*NA*
	40 mg single dose 4 hours after RPV	150 mg single dose	24	↔	1.21 (1.06, 1.39)	1.13 (1.01, 1.27)	NA
	40 mg single dose 12 hours before RPV	150 mg single dose	24	↔	0.99 (0.84, 1.16)	0.91 (0.78, 1.07)	NA
Acetaminophen[33]	500 mg single dose	150 mg qd 11 days	16	↔	1.09 (1.01, 1.18)	1.16 (1.10, 1.22)	1.26 (1.16, 1.38)
Chlorzoxazone[33]	500 mg single dose	150 mg qd 16 days	16	↑	1.17 (1.08, 1.27)	1.25 (1.16, 1.35)	1.18 (1.09, 1.28)
Digoxin[34]	0.5 mg single dose	25 mg qd 16 days	22	↔	↔*	↔*	↔*
Telaprevir[35]	750 mg Q8H 18 days	25 mg qd 11 days	16	↑	1.47 (1.19, 1.80)	1.79 (1.45, 2.20)	1.89 (1.51, 2.35)
Simeprevir[36] (Janssen, data on file)	150 mg qd 11 days	25 mg qd 11 days	24	↔	1.04 (0.95, 1.13)	1.12 (1.05, 1.19)	1.25 (1.16, 1.35)

All drug-drug interaction trials have been performed in non-HIV infected volunteers; *Italic font represents clinically relevant interactions: coadministration of these drugs with rilpivirine (RPV) is contraindicated or specific dosing requirements apply (i.e. separated intake for famotidine)*; *Comparison based on historic controls. (n): maximum number of volunteers with data; CI: confidence interval; C_{max}: maximum plasma concentration; AUC: area under the concentration time curve; C_{min}: minimum plasma concentration; qd: once daily; NA: no information available; Q8H: every eight hours.

Table 4. Summary of the effect of rilpivirine on the pharmacokinetics of other drugs including non-HIV-antiretrovirals

Coadministered drug	Dose schedule: Coadministered drug	Dose schedule: RPV	(n)	Pharmacokinetic effect	Mean ratio (90% CI) of coadministered drug pharmacokinetic parameters with/without RPV (No effect = 1): C_{max}	AUC	C_{min}
Ketoconazole[15,24]	400 mg qd 22 days	150 mg qd 11 days	14	↓	0.85 (0.80, 0.90)	0.76 (0.70, 0.82)	0.34 (0.25, 0.46)
Rifampin[15]	*600 mg qd 7 days*	*150 mg qd 7 days*	*16*	↔	*1.02 (0.93, 1.12)*	*0.99 (0.92, 1.07)*	*NA*
25-desacetyl rifampin[15]			*16*	↔	*1.00 (0.87, 1.15)*	*0.91 (0.77, 1.07)*	*NA*
Rifabutin[25]	*300 mg qd 11 days*	*150 mg qd 11 days*	*17*	↔	*1.03 (0.93, 1.14)*	*1.03 (0.97, 1.09)*	*1.01 (0.94, 1.09)*
25-O-desacetyl rifabutin[25]			*17*	↔	*1.07 (0.98, 1.17)*	*1.07 (1.02, 1.11)*	*1.12 (1.03, 1.22)*
Sildenafil[26]	50 mg single dose	75 mg qd 12 days	16	↔	0.93 (0.80, 1.08)	0.97 (0.87, 1.08)	NA
N-desmethyl sildenafil[26]			16	↔	0.90 (0.80, 1.02)	0.92 (0.85, 0.99)	NA
Atorvastatin[27]	40 mg qd 4 days	150 mg qd 15 days	16	↔	1.35 (1.08, 1.68)	1.04 (0.97, 1.12)	0.85 (0.69, 1.03)
Atorvastatin lactone[27]			16	↓	0.93 (0.84, 1.03)	0.82 (0.77, 0.88)	0.74 (0.63, 0.86)
2-hydroxy-atorvastatin[27]			16	↑	1.58 (1.33, 1.87)	1.39 (1.29, 1.50)	1.32 (1.10, 1.58)
4-hydroxy-atorvastatin[27]			16	↑	1.28 (1.15, 1.43)	1.23 (1.13, 1.33)	NA
Total HMG-CoA reductase activity[27]			16	↑	1.39 (1.14, 1.70)	1.21 (1.12, 1.30)	1.13 (0.92, 1.39)
Ethinylestradiol[28]	35 µg qd 21 days	25 mg qd 15 days	17	↔	1.17 (1.06, 1.30)	1.14 (1.10, 1.19)	1.09 (1.03, 1.16)
Norethindrone[28]	1 mg qd 21 days		17	↔	0.94 (0.83, 1.06)	0.89 (0.84, 0.94)	0.99 (0.90, 1.08)
R (–) Methadone[29,30]	60 to 100 mg qd individualized dose	25 mg qd 11 days	13	↓	0.86 (0.78, 0.95)	0.84 (0.74, 0.95)	0.78 (0.67, 0.91)
S(+) Methadone[29,30]				↓	0.87 (0.78, 0.97)	0.84 (0.74, 0.96)	0.79 (0.67, 0.92)
Omeprazole[31]	*20 mg qd 11 days*	*150 mg single dose*	*15*	↔	*0.94 (0.75, 1.18)*	*0.99 (0.89, 1.11)*	*NA*
5-hydroxy omeprazole[31]			*15*	↔	*1.03 (0.87, 1.22)*	*1.06 (0.99, 1.12)*	*NA*
Omeprazole sulfone[31]			*15*	↔	*0.90 (0.75, 1.07)*	*0.94 (0.83, 1.06)*	*0.94 (0.78, 1.13)*
Omeprazole[31]	*20 mg qd 22 days*	*150 mg qd 11 days*	*15*	↓	*0.86 (0.68, 1.09)*	*0.86 (0.76, 0.97)*	*NA*

(Continue)

Table 4. Summary of the effect of rilpivirine on the pharmacokinetics of other drugs including non-HIV-antiretrovirals *(continued)*

Coadministered drug	Dose schedule: Coadministered drug	Dose schedule: RPV	(n)	Pharmacokinetic effect	Mean ratio (90% CI) of coadministered drug pharmacokinetic parameters with/without RPV (No effect = 1): C_{max}	AUC	C_{min}
5-hydroxy omeprazole[31]			*15*	↔	*1.07 (0.91, 1.25)*	*1.09 (1.02, 1.16)*	*NA*
Omeprazole sulfone[31]			*15*	↓	*0.85 (0.69, 1.03)*	*0.76 (0.65, 0.88)*	*NA*
Acetaminophen[33]	500 mg single dose	150 mg qd 11 days	16	↔	0.97 (0.86, 1.10)	0.92 (0.85, 0.99)	NA
Acetaminophen glucuronide[33]			16	↔	0.96 (0.90, 1.03)	1.01 (0.95, 1.07)	NA
Acetaminophen sulfate[33]			16	↔	1.00 (0.94, 1.07)	0.95 (0.88, 1.02)	NA
Chlorzoxazone[33]	500 mg single dose	150 mg single dose	16	↔	0.96 (0.82, 1.12)	0.97 (0.87, 1.07)	NA
6-hydroxy chlorzoxazone[33]			16	↔	0.99 (0.94, 1.04)	0.94 (0.89, 0.98)	NA
Chlorzoxazone[33]		150 mg qd 16 days	16	↔	0.98 (0.85, 1.13)	1.03 (0.95, 1.13)	NA
6-hydroxy chlorzoxazone[33]			16	↔	0.97 (0.90, 1.05)	0.97 (0.87, 1.07)	NA
Digoxin[34]	0.5 mg single dose	25 mg qd 16 days	22	↔	1.06 (0.97, 1.17)	0.98 (0.93, 1.04)	NA
Telaprevir[35]	750 mg Q8H 18 days	25 mg qd 11 days	16	↓	0.95 (0.78, 1.17)	0.92 (0.75, 1.13)	0.87 (0.67, 1.12)
Simeprevir[36] (Janssen, data on file)	150 mg qd 11 days	25 mg qd 11 days	24	↔	1.12 (0.99, 1.27)	1.06 (0.94, 1.19)	0.96 (0.83, 1.11)

All drug-drug interaction trials have been performed in non-HIV infected volunteers*; Drugs in italic are contraindicated with rilpivirine (RPV) because of their clinically relevant effect on RPV exposure (see Table 3).* (n): maximum number of volunteers with data; CI: confidence interval; C_{max}: maximum plasma concentration; AUC: area under the concentration time curve; C_{min}: minimum plasma concentration; qd: once daily; NA: no information available; Q8H: every eight hours.

Potential drug interactions involving other drugs metabolized by cytochrome P450 3A

Sildenafil

Sildenafil is a phosphodiesterase type-5 inhibitor used for treatment of erectile dysfunction and pulmonary arterial hypertension. It undergoes predominantly hepatic metabolism (mainly CYP3A4) and is converted to an active metabolite, *N*-desmethyl sildenafil, with properties similar to the parent drug. In a randomized, open-label, two-period crossover trial with 14-day washout, 16 healthy volunteers in the fed state received either sildenafil alone (50 mg single dose) or RPV (75 mg once daily for 12 days) plus sildenafil (50 mg single dose on day 12). There were no clinically relevant pharmacokinetic changes for either drug[26]. The steady state pharmacokinetics of RPV were not affected by the single dose of sildenafil (Table 3), and the exposure to sildenafil and its active metabolite were unaffected when steady state RPV was coadministered (Table 4). These data also suggest there is no effect of RPV 75 mg once daily on CYP3A4 enzyme activity. Consequently, it was concluded that

RPV 25 mg once daily and sildenafil (or other phosphodiesterase-5 inhibitors) can be coadministered without dose adjustments.

Statins

Atorvastatin is often used in HIV-infected patients to treat hypercholesterolemia, hypertriglyceridemia, and dyslipidemia[52]. Atorvastatin is a competitive inhibitor of hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase and is primarily metabolized by CYP3A4 to the active metabolites 2-hydroxy and 4-hydroxy atorvastatin, and the inactive atorvastatin lactone. Atorvastatin is also a known substrate of organic anion-transporting polypeptides (OATP)[53]. In a randomized, open-label, two-period crossover trial with 14-day washout, 16 healthy volunteers in the fed state received atorvastatin alone (40 mg once daily for four days) or RPV (150 mg once daily for 15 days) plus atorvastatin (40 mg once daily on days 12-15)[27]. There were no clinically relevant pharmacokinetic changes in either drug. Exposure to RPV was not affected by coadministration with atorvastatin (Table 3). The AUC_{24h} of atorvastatin was not affected by RPV coadministration, although C_{max} increased 1.35-fold and C_{min} decreased 15% (Table 4). The pharmacokinetic parameters of 2-hydroxy and 4-hydroxy atorvastatin were increased by 23-58%. These small observed changes in the pharmacokinetics of atorvastatin, its metabolites, and the total HMG-CoA reductase activity (sum of atorvastatin and the two active metabolites) are not considered to be clinically relevant. The ratio of 2-hydroxy atorvastatin to atorvastatin AUC_{24h} increased 1.34-fold when atorvastatin was coadministered with RPV, compared with administration of atorvastatin alone. This may be due to some induction of CYP3A4-mediated metabolism by RPV at the 150 mg dose, which is not of clinical importance with RPV 25 mg once daily. These data also indicate that no major interaction of RPV is mediated via the OATP1BA transporter, even at this high RPV dose. Rilpivirine 25 mg once daily and atorvastatin can be coadministered without dose adjustments[27].

In addition, no clinically relevant changes in the RPV pharmacokinetics are anticipated when coadministered with any of the other statins. Though a number of the statins are inhibitors of CYP3A (pravastatin and pitavastatin excluded), this effect on CYP3A enzyme activity is only limited and, therefore, not expected to result in any safety concerns. Clinically relevant interactions with the different statins are mostly mediated either via CYP enzymes or via inhibition of OATP, neither of which is affected to a clinically relevant extent by RPV 25 mg once daily, as described above. Therefore, based on the available data for RPV and the known *in vivo* mechanisms of interactions for different statins, no dose adjustments are needed when RPV is coadministered with fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin.

Ethinyl estradiol and norethindrone

Ethinyl estradiol (17α-ethinyl estradiol, an estrogen) and norethindrone (a progestin) are commonly used in oral contraceptive formulations, alone or in combination. The metabolism of 17α-ethinyl estradiol is predominantly mediated by CYP3A4[54] and CYP2C9 (and to a lesser extent CYP2C8, CYP2C19, and CYP3A5), whilst norethindrone is metabolized by CYP3A[55]. Also, 17α-ethinyl estradiol is an inhibitor of CYP2C19, CYP3A4, and CYP2B6[54]. In an open-label trial, during two successive oral contraceptive cycles, 18 healthy women received ethinyl estradiol/norethindrone 35 µg/1 mg once daily for 21 days, with a seven-day pill-free period: in treatment A this was administered alone, while in treatment B it was administered in combination with RPV 25 mg once daily[28]. There were no clinically relevant pharmacokinetic changes in any of the drugs. Based on historical controls, exposure to RPV was not significantly affected by coadministration with ethinyl estradiol and norethindrone (Table 3), and the pharmacokinetics of both ethinyl estradiol and norethindrone were unaffected by coadministration with RPV 25 mg (Table 4). The C_{max} of ethinyl estradiol was increased 1.17-fold when coadministered with RPV 25 mg, but this is not considered to be clinically relevant[28]. Furthermore, no clinically relevant changes in concentrations of luteinizing hormone, follicle-stimulating hormone, or progesterone were observed when RPV 25 mg was coadministered with ethinyl estradiol and norethindrone. The approved dose of RPV 25 mg can be coadministered with estrogen and/or progestogen-based contraceptives without any dose adjustments.

Methadone

Methadone is a synthetic narcotic analgesic for the treatment of opiate dependence[56]. Intravenous drug use is one of the main modes of HIV transmission. As such, some HIV-infected individuals may also receive methadone therapy. Methadone is administered as a racemic mixture; a combination of *R*(–) and *S*(+) isomers,

with the *R*– isomer mostly responsible for its therapeutic effects[57]. Methadone is primarily metabolized to an inactive metabolite by *N*-demethylation, but its metabolism is variable between subjects. CYP3A4, and to a lesser extent CYP2D6, are considered predominant in the metabolism of methadone[57,58], but its metabolism is not fully understood.

In an open-label, single-sequence trial, 13 HIV-negative volunteers on prior individualized stable methadone maintenance therapy (the range of doses was 60-100 mg once daily) received RPV 25 mg once daily for 11 days in the fed state in combination with methadone[29,30]. Exposure to RPV was within the range observed in other trials with healthy volunteers (Table 3). Exposure to methadone was somewhat reduced by coadministration of RPV (Table 4); the magnitude of the effect was very similar for both *R*(–) and *S*(+) isomers (16% reduction in AUC_{24h}), suggesting the effect is not specific to a particular isomer. None of the participants experienced methadone withdrawal symptoms during coadministration of RPV, and the effect of RPV was not considered clinically relevant. These data show that RPV 25 mg once daily and methadone can be coadministered without *a priori* dose adjustments. Clinical monitoring for methadone withdrawal symptoms is recommended, and methadone maintenance therapy may need to be adjusted for some patients[29,30].

Modifications of gastric pH

The solubility of RPV is pH-dependent. Therefore, there is a potential for interactions to occur with drugs that have an effect on gastric pH, such as proton-pump inhibitors, histamine-2 (H_2) receptor antagonists, and antacids[59].

Proton-pump inhibitors

Omeprazole is a proton-pump inhibitor which inhibits gastric acid secretion and increases gastric pH[60] from a class of drugs widely used for treatment of gastric ulcers and reflux. The metabolism of omeprazole is mostly mediated via CYP2C19, which is responsible for the formation of 5-hydroxy omeprazole, while formation of the sulfone metabolite is dependent on CYP3A4[61].

In an open-label, randomized, two-period crossover trial with 14-day washout, 16 healthy volunteers in the fed state received RPV alone (150 mg once daily for 11 days) or RPV (150 mg once daily on days 12-22) plus omeprazole (20 mg once daily for 22 days)[31]. All treatments were taken under fed conditions within 10 minutes after breakfast.

Exposure to RPV was reduced by coadministration of omeprazole (40% reduction in AUC_{24h} and C_{max} after multiple doses of RPV at steady state, Table 3). Exposure to omeprazole was decreased by multiple doses of RPV, with the AUC_{24h} of omeprazole reduced by 14% (Table 4). The AUC_{24h} ratio of 5-hydroxy omeprazole to omeprazole increased 1.27-fold after coadministration of multiple doses of RPV, suggesting a modest induction of CYP2C19-mediated metabolism at this supratherapeutic dose (six times) of RPV. Based on the observed reduction in RPV exposure, proton-pump inhibitors should not be coadministered with RPV.

Histamine-2 receptor antagonists

Famotidine is an H_2 receptor antagonist that inhibits gastric acid production[62]. With H_2 receptor antagonists, the effect on gastric pH is shorter in duration than with proton-pump inhibitors[63], so there is the potential to use temporal dosing separation to avoid an interaction. In a randomized, open-label, four-period crossover trial with 14-day washout, 24 healthy volunteers received either RPV alone (150 mg single dose, fed state) or RPV (150 mg single dose, fed state) plus famotidine (40 mg single dose, administered 12 hours before RPV, two hours before RPV, or four hours after RPV)[32]. The pharmacokinetics of RPV were unaffected by famotidine administered 12 hours previously or four hours after the RPV dose (Table 3). Most of the gastric absorption of RPV occurs during the first four hours after intake. However, exposure to RPV was decreased (85% decrease in C_{max} and 76% decrease in AUC_{∞}) by coadministration of famotidine two hours before the RPV dose (Table 3), as the effect of famotidine on gastric pH would have been maximal during the absorption phase of RPV. Rilpivirine and famotidine (or another H_2 receptor antagonist) can be coadministered if the doses are temporally separated: H_2 receptor antagonists should be given at least 12 hours before or at least four hours after RPV.

Antacids

Rilpivirine dosing requires a time separation of doses from antacids, as is also the case for other ARVs such as ritonavir-boosted atazanavir. Due to the short-lived effect of antacids on gastric pH relative to H_2 receptor antagonists[64], antacids can be administered at least two hours before or at least four hours after RPV.

Other interaction studies with HIV antiretroviral drugs

Nucleos(t)ide reverse transcriptase inhibitors

Tenofovir disoproxil fumarate

Tenofovir, an N(t)RTI that is administered as the prodrug tenofovir disoproxil fumarate as part of HAART, is primarily excreted by the kidney and is not a substrate for CYP enzymes[65]. In a randomized, two-period, open-label trial with 14-day washout, 16 healthy volunteers in the fed state received RPV alone (RPV 150 mg once daily for eight days) or RPV (150 mg once daily: either on days 1-8 or on days 9-16) plus tenofovir disoproxil fumarate (300 mg once daily for 16 days)[21]. There were no clinically relevant pharmacokinetic changes in either drug. Rilpivirine pharmacokinetics were not affected by tenofovir disoproxil fumarate coadministration (Table 1). Exposure to tenofovir was increased (1.23-fold for AUC_{24h} and 1.19-fold for C_{max}) by RPV coadministration (Table 2), but these were only limited changes that are not considered clinically relevant[21]. There was no effect of RPV on the urinary excretion of tenofovir.

The intestinal absorption of tenofovir disoproxil fumarate involves P-glycoprotein-mediated efflux of tenofovir disoproxil, and inhibition of intestinal P-glycoprotein has been shown to result in increased exposure to tenofovir when coadministered with other ARVs[66,67]. *In vitro* studies indicated that there is a potential for RPV to inhibit transepithelial permeation of P-glycoprotein substrates, with an apparent 50% inhibitory concentration (IC_{50}) value of 9.2 µM (3.4 µg/ml), potentially explaining the mechanism for the observed interaction with tenofovir at this high dose of RPV. Any effect with the RPV 25 mg dose is anticipated not to exceed that observed with RPV 150 mg, and is not expected to result in clinically relevant changes in tenofovir pharmacokinetics.

In addition, RPV has been coadministered with tenofovir disoproxil fumarate as a background N(t)RTI agent in a large number of HIV-1-infected patients in the phase III studies[3,4] and the phase IIb study[6]. Patients were instructed to take their N(t)RTI background medication at the same time as RPV, with a meal. In all three studies, RPV was well tolerated regardless of the background N(t)RTI regimen, and in the phase III studies, only one patient in the RPV group, versus two in the control (efavirenz) group, switched the tenofovir disoproxil fumarate/emtricitabine background regimen for tolerability reasons (renal impairment) during the first 48 weeks[3,4].

Any potential effect of RPV 25 mg on tenofovir exposure is thus considered to be of no clinical relevance. The long-term clinical data indicate that RPV and tenofovir disoproxil fumarate can be coadministered without dose adjustments[3,4,6]. The once-daily single-tablet regimen of RPV 25 mg with emtricitabine/tenofovir disoproxil fumarate has been shown to be bioequivalent to the individual pharmaceutical formulations of these drugs given in combination[68].

Didanosine

Didanosine, an N(t)RTI used as part of HAART, is primarily excreted by the kidney[69]. In contrast to RPV, enteric-coated didanosine is recommended to be taken on an empty stomach because food decreases its exposure[70]. In a randomized, two-period, open-label trial with 14-day washout, 16 healthy volunteers received RPV alone (150 mg once daily for seven days, fed state) or RPV (150 mg once daily, in the fed state: either on days 1-7 or on days 8-14, and taken two hours after didanosine) plus didanosine (400 mg once daily for 14 days, fasted). There were no clinically relevant changes in RPV pharmacokinetics upon coadministration of didanosine (Table 1), and little difference in the pharmacokinetics of didanosine (Table 2) (Janssen, data on file). No dose adjustments are required when coadministered; however, the timing of the intake of didanosine should be separated from RPV (at least two hours before or at least four hours after RPV) due to the differences in the requirements for concurrent food intake, and due to the presence of antacids in some didanosine formulations.

Other nucleos(t)ide reverse transcriptase inhibitors

No interactions are expected between RPV and drugs that are primarily renally eliminated and this includes most of the N(t)RTIs. Specifically, no interactions are expected between RPV and abacavir, emtricitabine, lamivudine, or zidovudine. *In vivo* findings suggest that RPV and N(t)RTIs can be coadministered without dose adjustments[1,2]. These N(t)RTIs have all been coadministered with RPV in many patients as the various background regimens of the phase III trials without any apparent clinically relevant pharmacokinetic interaction[3,4]. *In vitro* data show no effect of RPV on alcohol

dehydrogenase, through which abacavir is primarily metabolized, which further suggests that an interaction of RPV with abacavir is unlikely. Also, in the phase IIb dose-finding trial[6] there was no effect of the different RPV doses on the pharmacokinetics of zidovudine.

Other HIV antiretroviral agents

Integrase inhibitors

The metabolism of the integrase strand transfer inhibitor raltegravir is mediated by UDP-glucuronosyltransferase (UGT), primarily UGT1A1[71]. In a phase I, open-label, randomized crossover trial in HIV-negative volunteers, participants received in one session RPV 25 mg once daily alone for 11 days, and in another session raltegravir 400 mg twice daily for four days immediately followed by coadministration of RPV 25 mg once daily and raltegravir 400 mg twice daily for 11 days[22]. The RPV pharmacokinetics were unaffected by coadministration of raltegravir (Table 1). Also, RPV did not affect the pharmacokinetics of raltegravir (Table 2) and raltegravir-glucuronide (its main metabolite) to a clinically relevant extent. The results of this study showed that RPV 25 mg once daily and raltegravir 400 mg twice daily can be coadministered without dose modifications.

A trial to evaluate the pharmacokinetic interaction between RPV 25 mg once daily and the investigational agents dolutegravir 50 mg once daily or GSK1265744 30 mg once daily, also showed that RPV 25 mg once daily can be coadministered with these integrase inhibitors without dose modifications[23] (Tables 1 and 2).

Other interaction studies with non-antiretroviral drugs

Acetaminophen (paracetamol)

Acetaminophen, a widely used painkiller, undergoes hepatic metabolism via glucuronidation, sulfation, and conjugation of intermediate metabolites with glutathione[72]. The latter can be compromised by glutathione depletion, possibly leading to accumulation of a minor but toxic intermediate, N-acetyl-p-benzoquinoneimine[73]. In a randomized, open-label, two-period crossover trial with 14-day washout, 16 healthy volunteers in the fed state received either a single dose of acetaminophen (500 mg) or RPV (150 mg once daily for 11 days) plus acetaminophen (500 mg single dose on day 11)[33]. This study showed that there were no clinically relevant pharmacokinetic changes for either drug. Exposure to RPV was not affected by coadministration of acetaminophen (Table 3). Furthermore, no relevant changes were seen in the pharmacokinetics of acetaminophen or its glucuronide or sulfate conjugates after coadministration with RPV (Table 4)[33]. In addition, this study indicated that RPV does not have an effect on uridine diphosphate glucuronosyltransferase *in vivo* (the main metabolic pathway for acetaminophen)[33]. This confirms that RPV and acetaminophen can be coadministered without dose adjustments.

Chlorzoxazone

Chlorzoxazone is a muscle relaxant used as a selective probe to assess CYP2E1 activity since CYP2E1 is the major enzyme involved in the 6-hydroxylation of chlorzoxazone into its major metabolite, 6-hydroxy-chlorzoxazone[74]. In an open-label trial, healthy volunteers received RPV (150 mg once daily on days 4-15 in the fed state) plus chlorzoxazone (500 mg single doses on days 1, 4, and 15, taken two hours postprandial)[33]. A total of 19 volunteers completed the trial and 16 were included in the analysis. Exposure to RPV increased (1.25-fold increase in AUC_{24h}) after a single dose of chlorzoxazone, which is not considered clinically relevant (Table 3). Exposure to chlorzoxazone and its metabolite, as well as the ratio of 6-hydroxy-chlorzoxazone to chlorzoxazone AUC_{last} values, were unaffected by coadministration with RPV (Table 4). These data indicate that RPV does not inhibit or induce CYP2E1 activity *in vivo* and clinically relevant interactions are not anticipated between RPV and drugs that are primarily metabolized by CYP2E1, such as anesthetics (e.g. halothane).

Digoxin

As mentioned above, RPV has been shown to inhibit P-glycoprotein *in vitro*. A phase I, open-label, randomized crossover trial in 22 HIV-negative volunteers investigated the effect of steady state RPV 25 mg once daily on the single-dose pharmacokinetics of the probe P-glycoprotein substrate digoxin[34]. Rilpivirine 25 mg once daily did not affect the pharmacokinetics of digoxin (Table 4). The pharmacokinetic parameters of RPV were comparable to those seen previously in healthy volunteers. These data indicate that RPV at the recommended dose does not have an effect on P-glycoprotein activity *in vivo*.

Conclusions

Rilpivirine has a long elimination half-life that facilitates once-daily dosing, with maximum plasma concentrations around four to five hours after dosing, and oral bioavailability maximized under fed conditions. Drug-drug interaction studies have shown that RPV can be coadministered with a wide variety of ARV agents as well as other medications. Most drug-drug interactions are not expected to be of clinical relevance or cause safety concerns, and do not result in the need for dose adjustment. Some drugs shown to cause significant decreases in RPV exposure are contraindicated for coadministration with RPV as this may be associated with an increased risk of virologic failure and possible development of viral resistance, i.e. strong CYP3A inducers (such as rifampin, rifabutin) and proton-pump inhibitors (such as omeprazole). However, other agents that have an effect on gastric pH can be coadministered with RPV provided there is temporal separation of the intakes (H_2 antagonists and antacids). Further drug-drug interaction studies are underway. For up-to-date specific information, the appropriate prescribing information should always be consulted.

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