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Drug Interactions with New and Investigational Antiretrovirals

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Abstract

More than 20 individual and fixed-dose combinations of antiretrovirals are approved for the treatment of human immunodeficiency virus (HIV) infection. However, owing to the ongoing limitations of drug resistance and adverse effects, new treatment options are still required. A number of promising new agents in existing or new drug classes are in development or have recently been approved by the US FDA. Since these agents will be used in combination with other new and existing antiretrovirals, understanding the potential for drug interactions between these compounds is critical to their appropriate use. This article summarizes the drug interaction potential of new and investigational protease inhibitors (darunavir), non-nucleoside reverse transcriptase inhibitors (etravirine and rilpivirine), chemokine receptor antagonists (maraviroc, vicriviroc and INCB 9471), integrase inhibitors (raltegravir and elvitegravir) and maturation inhibitors (bevirimat).

Advances in the treatment of human immunodeficiency virus (HIV) infection include the discovery of new antiretroviral agents and an improved understanding of the optimal combination of these agents for therapeutic benefit. Currently, the most potent antiretroviral regimens are those that include a combination of medications targeting different stages of the HIV life cycle. In 2007, two new classes of antiretrovirals were approved by the US FDA, and a number of other novel antiretrovirals in new classes and existing classes are being developed. All of these drugs are promising options for treatment-experienced patients. However, each class has a unique drug-interaction profile, making the optimal combination of these drugs challenging. Encouragingly, some of these new agents are not substrates of either cytochrome P450 (CYP) enzymes or drug transport proteins. This increases their potential to be used in combination with currently available antiretroviral agents without concern for subtherapeutic or supratherapeutic exposures. This article reviews the drug-drug interaction data, as well as drug-drug interaction potential, for antiretrovirals that have recently become available or are currently undergoing later phase clinical study. New protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs) are featured, as are new agents in the chemokine receptor antagonist class, the integrase inhibitor class, and the maturation inhibitor class. A summary of interactions between antiretrovirals can be found in tables I-III, and a summary of interactions between these new antiretrovirals and concomitant medications is presented in table IV.

1. Protease Inhibitors

1.1 Darunavir

Darunavir is a new protease inhibitor recently approved for the treatment of HIV-1-infected patients. In the US, the approved dose of darunavir is 600 mg, administered in conjunction with 100 mg of ritonavir, every 12 hours with food. Darunavir is recommended for use in treatment-experienced (multiple protease inhibitor-resistant) adult patients (figure 1a).

1.1.1 Pharmacology—The molecular weight of darunavir is 593.73 g/mol.[1] Darunavir maintains activity against multidrug-resistant strains of HIV-1. This may be due, in part, to darunavir's higher binding affinity to the HIV protease enzyme. The derived binding affinity constant of darunavir is >0.0045 nmol/L, which is approximately 1000-fold greater than those of indinavir, nelfinavir and saquinavir.[2] Darunavir maintains a binding affinity that is more than 100-fold higher than those of amprenavir, atazanavir, lopinavir and tipranavir in the presence of wild-type protease. Darunavir's dissociative half-life from the protease enzyme is also much higher (>240 hours) than those of other protease inhibitors, suggesting that darunavir remains bound and active *in vivo* throughout the plasma elimination process.[3]

The median concentration at which 50% of the maximum darunavir drug effect is achieved (EC_{50}) ranges from 1 to 8.5 nmol/L.[1] The 90% effective concentration ranges from 2.7 to 13 nmol/L.[2] Darunavir is approximately 95% bound to plasma α_1 -acid glycoprotein.[1] *In vitro* observations of clinically relevant darunavir plasma concentrations at 4.7 to 52 base-equivalent ng/mL found that the mean plasma protein binding of darunavir ranges from 92% to 94%.[4] As expected, when darunavir concentrations increase within this *in vitro* system, the fraction of unbound darunavir increases. A study of 118 HIV-positive, treatment-experienced individuals calculated a median inhibitory quotient (IQ) of 36.3 (range 0.5–1150), assuming 95% protein binding in the calculation of free drug concentration.[5]

In vitro, the major mechanism of darunavir absorption is through passive transcellular diffusion. However, darunavir is both a substrate and an inhibitor of the enzyme P-glycoprotein (with an apparent 50% inhibitory concentration [IC_{50}] of 32.9 μ mol/L, or 19 μ g/mL). Since darunavir is coadministered with ritonavir (also a P-glycoprotein inhibitor), it is possible that this combination could affect the intestinal absorption of other compounds that are also substrates of P-glycoprotein.[6] However, no full-intensive pharmacokinetic studies investigating any clinically relevant drug-drug interactions between darunavir/ritonavir and other P-glycoprotein substrates have been conducted. Evaluation of the function of the efflux transporter multidrug resistance protein (MRP) 1 in a group of seven healthy volunteers who took 900 mg of darunavir and 100 mg of ritonavir once daily for 10 days resulted in decreased MRP1 expression without decreased messenger RNA expression or efflux function *in vivo*. Compared with baseline, the geometric mean ratio (GMR) for MRP1 expression declined by 0.58 (95% CI 0.51, 0.65; $p < 0.001$). The expression of MRP1 was 41% higher (GMR 1.41) in CD4 cells than in all peripheral blood mononuclear cells (PBMCs).[7]

Darunavir is metabolized almost exclusively by the hepatic CYP3A4 enzyme.[8] Three major metabolites of darunavir have been identified, all of which demonstrate at least 90% less activity against wild-type HIV strains in comparison with darunavir. The darunavir metabolite M19 forms by carbamate hydrolysis, metabolite M23 forms through aliphatic hydroxylation, and metabolite M29 forms through aromatic hydroxylation. Three minor darunavir metabolites have also been identified: M27 and M28 both form by alicyclic hydroxylation and metabolite M6 forms through an unspecified pathway.[9]

In human liver microsomes, darunavir inhibits the activity of CYP1A2, CYP2C9, CYP2C19 and CYP2D6.[10] In human hepatocytes, and in human subjects, darunavir induces CYP3A4 activity. As a CYP3A4 substrate, darunavir also demonstrates competitive inhibition of CYP3A4, yielding an inhibitory constant (K_i) value of 0.40 $\mu\text{mol/L}$ (0.22 $\mu\text{g/mL}$), which is within the range of clinical relevance. When darunavir is administered with other CYP3A4 inhibitors (such as ritonavir), the net result is inhibition of CYP3A4 activity. [10] Since darunavir's K_i values for CYP2B6, CYP2C9, CYP2C19 and CYP2D6 are at least 60-fold higher than for CYP3A4, there is less potential for clinically relevant drug-drug interactions through these enzymes.[9]

1.1.2 Pharmacokinetics—The absolute bioavailability of a 600 mg dose of darunavir is 37%. The addition of 100 mg of ritonavir increases the bioavailability to 82%. Owing to an overall net inhibition of CYP3A4 and P-glycoprotein activity, coadministration of ritonavir with darunavir results in a 14-fold increase in the darunavir area under the plasma concentration-time curve (AUC) compared with administration of darunavir alone.[11]

In healthy volunteers, the median terminal elimination half-life is 15 (range 12.7–16.4) hours.[4] In a study of a single 150 mg intravenous dose administered after 2 days of oral ritonavir given 100 mg twice daily, the mean volume of distribution was 131 L.[2] Pharmacokinetic parameters for darunavir obtained from 119 HIV-positive participants included a median steady-state AUC over a 12-hour dosing interval (AUC_{12}) of 61 668 (range 33 857–106 490) $\text{ng} \cdot \text{h/mL}$ and a median trough plasma concentration (C_{trough}) of 3539 (range 1255–7368) ng/mL . [1]

Food increases the bioavailability of darunavir when coadministered with ritonavir by approximately 30%, regardless of the composition of the meal.[12] Most of darunavir (81.7%) is eliminated through faeces and 12.2% is eliminated through urine. The proportion of unchanged darunavir eliminated in the faeces is 6.8% when administered alone and 41.2% when administered with ritonavir.[11]

1.1.3 Drug-Drug Interactions—Significant drug-drug interactions occur between darunavir/ritonavir and certain other antiretrovirals and anti-infectives, HMG Co-A reductase inhibitors, phosphodiesterase inhibitors, oral contraceptives and selective serotonin reuptake inhibitors (SSRIs). Many of these interactions predictably occurred through inhibition or induction of CYP3A4,[13] although some were unexpected.

Darunavir/Ritonavir and Protease Inhibitors: A 14-day evaluation in healthy subjects coadministered darunavir/ritonavir 400 mg/100 mg with saquinavir 1000 mg in hard-gel capsule formulation observed a reduction in darunavir exposure. The darunavir AUC_{12} , peak plasma concentration (C_{max}) and minimum plasma concentration (C_{min}) decreased by a mean of 26%, 17% and 42%, respectively. Saquinavir exposure also slightly decreased: the AUC_{12} and C_{max} by 6% and the C_{min} by 18%. Additionally, the combined administration of darunavir, ritonavir and saquinavir was associated with an increased incidence of adverse events and trial discontinuations.[14] Because of these observations, it is recommended that saquinavir and darunavir not be administered together.

Two studies in healthy subjects investigated dosing strategies to overcome a decline in darunavir exposure when combined with lopinavir/ritonavir. In one study, darunavir/ritonavir was administered at 1200 mg/100 mg twice daily in combination with standard lopinavir/ritonavir 400 mg/100 mg twice daily. In the second study, darunavir/ritonavir was administered at 1200 mg/100 mg twice daily in combination with increased lopinavir/ritonavir 533 mg/133 mg twice daily. Both strategies failed to prevent a decrease in darunavir exposure. When the darunavir dose was doubled, the AUC_{12} , C_{max} and C_{min}

decreased by 38%, 21% and 51%, respectively. When the darunavir dose was doubled and the lopinavir/ritonavir dose was increased, the darunavir AUC_{12} , C_{max} and C_{min} decreased by 41%, 21% and 55%, respectively. Lopinavir exposure was minimally influenced in both trials (~9% increase in the AUC_{12}). In contrast to the saquinavir investigations, no increases in adverse events were reported with this combination of protease inhibitors. However, based on the pharmacokinetic interaction, coadministration of darunavir/ritonavir with lopinavir is not recommended.[15]

The interaction between indinavir and darunavir/ritonavir was studied using a dose of darunavir that is lower than the currently licensed dose. Twice-daily administration of indinavir 800 mg with darunavir/ritonavir 400 mg/100 mg increased both indinavir and darunavir concentrations. The AUC and C_{min} of indinavir increased by 23% and 125%, respectively, while the AUC and C_{min} of darunavir increased by 24% and 44%, respectively. Although the appropriate dose of indinavir given in combination with darunavir/ritonavir has not yet been established, in cases of intolerance to this combination, it is suggested that the indinavir dose be reduced from 800 mg to 600 mg twice daily.[16]

The interaction between atazanavir and darunavir/ritonavir was also studied using a lower than currently licensed dose of darunavir. Coadministration of atazanavir 300 mg once daily with darunavir/ritonavir 400 mg/100 mg twice daily had no significant effect upon the AUC and C_{min} of either atazanavir or darunavir in a study of 13 healthy subjects. The C_{max} , AUC and C_{min} of darunavir increased by only 2%, 3% and 1%, respectively. Compared with atazanavir exposure when atazanavir/ritonavir was given alone, the C_{max} decreased by a mean of 11%, the AUC increased by 8% and the C_{min} increased by 52%. Based on these results, no adjustment in dose is considered necessary when atazanavir is administered with darunavir/ritonavir.[16]

Darunavir/Ritonavir and Entry Inhibitors: Since maraviroc is a CYP3A4 substrate (see section 3.1 for more details), concomitant administration with darunavir/ritonavir was predicted to increase maraviroc exposure. Therefore, in a 10-day, two-way crossover drug interaction study in healthy subjects, a 50% lower dose than the standard recommended dose of maraviroc was used. When administered at 150 mg twice daily in combination with darunavir/ritonavir or placebo, the AUC_{12} and C_{max} of maraviroc were 2.3- to 4-fold higher with darunavir/ritonavir than with placebo. Darunavir/ritonavir exposures were not significantly altered. These results are consistent with findings from other studies[17,18] administering maraviroc with ritonavir-boosted protease inhibitors.[19] Thus, when coadministered with darunavir/ritonavir, the maraviroc dosage should be reduced by 50% to 150 mg twice daily.

A combination of twice-daily therapy with 90 mg of the fusion inhibitor enfuvirtide and standard darunavir/ritonavir dosage has been studied in HIV-infected patients. No difference was observed between the pharmacokinetic parameters of darunavir in the presence of enfuvirtide and the pharmacokinetic parameters of darunavir administered alone. The effects of darunavir/ritonavir on enfuvirtide have not been investigated.[20,21]

Darunavir/Ritonavir and Reverse Transcriptase Inhibitors: No dose adjustment is warranted when darunavir is coadministered with nevirapine, tenofovir and efavirenz. The combination of darunavir with efavirenz should be used with caution.[8]

Nevirapine is a substrate and inducer of CYP3A4 enzyme activity. When darunavir/ritonavir 400 mg/100 mg was added to a stable antiretroviral regimen that contained nevirapine 200 mg twice daily, in a study of HIV-positive individuals, the combination resulted in a 24% increase in the mean AUC_{12} of darunavir, a 40% increase in the mean C_{max} and no influence

on the C_{min} . This combination resulted in increases in the nevirapine AUC_{12} and C_{min} (by 27% and 47%, respectively), while no significant effect on the C_{max} was observed. Based on these results, no dose adjustment is necessary in the coadministration of darunavir/ritonavir with nevirapine.[22]

A modest interaction has been observed with the coadministration of darunavir/ritonavir 300 mg/100 mg and tenofovir 300 mg. The pharmacokinetic parameters of this combination were evaluated in a randomized, crossover study in 12 healthy subjects. When administered with darunavir/ritonavir, the tenofovir AUC from 0 to 24 hours (AUC_{24}), C_{max} and C_{min} increased by a mean of 22%, 24% and 37%, respectively. When administered with tenofovir, the darunavir AUC_{12} , C_{max} and C_{min} were increased by a mean of 21%, 16% and 24%, respectively. Since these are only modest increases with no observed increase in adverse events, no dose adjustment is necessary with this combination.[23]

Etravirine is a new NNRTI recently approved by the FDA. The pharmacokinetic interaction between etravirine (100 or 200 mg twice daily, phase III formulation) and darunavir/ritonavir (600 mg/100 mg twice daily) has been investigated in 23 healthy subjects. Coadministration of etravirine 100 mg with darunavir/ritonavir decreased the etravirine AUC_{12} , C_{max} and C_{min} by a mean of 37%, 32% and 49%, respectively. Increasing the dose of etravirine to 200 mg (the dose approved by the FDA) resulted in increases in the etravirine AUC_{12} , C_{max} and C_{min} by a mean of 80%, 81% and 67%, respectively, compared with etravirine 100 mg given alone.

Compared with the observed exposure of darunavir administered alone, no significant change in darunavir exposure occurred when darunavir was given with etravirine in studies of HIV-infected patients.[24] Phase III trials of etravirine indicate that safe and effective etravirine exposures are achieved when etravirine is administered in combination with darunavir and ritonavir.[25] Thus, etravirine can be given in combination with darunavir/ritonavir at the approved dose of 200 mg twice daily without any dose adjustments.[26]

Since darunavir/ritonavir inhibits CYP3A4 and efavirenz induces CYP3A4, a decrease in darunavir exposure and an increase in efavirenz exposure would be predicted for these drugs when administered concomitantly. This was confirmed in a study in healthy subjects with the combination of darunavir/ritonavir 300 mg/100 mg given twice daily and efavirenz 600 mg given once daily. With this combination, the C_{min} and C_{max} of efavirenz increased by a mean of 15% to 17%, respectively, while the AUC_{24} increased by 21%. Darunavir exposure decreased with this combination: the C_{min} by 31%, the C_{max} by 15% and the AUC_{12} by 13%.[27] The combination of darunavir with efavirenz should be used with caution. No dose adjustment is recommended for this combination, but clinical monitoring for toxicity associated with increased exposure to efavirenz should be considered.

Darunavir/Ritonavir and HMG-CoA Reductase Inhibitors: Atorvastatin is an HMG-CoA reductase inhibitor commonly used by HIV-infected patients for the management of hyperlipidaemia. Atorvastatin is >98% bound to plasma proteins and is extensively metabolized by CYP3A4 to active metabolites, which accounts for ~70% of HMG-CoA reductase inhibitory activity.[28] In a pharmacokinetic study that expected an inhibitory effect of darunavir/ritonavir on the metabolism of atorvastatin, darunavir/ritonavir 300 mg/100 mg given twice daily was combined with atorvastatin 10 mg given daily to ten healthy subjects. The pharmacokinetics of 40 mg of atorvastatin administered alone were compared with the pharmacokinetics of 10 mg of atorvastatin administered daily and coadministered with darunavir/ritonavir 300 mg/100 mg twice daily ($n = 15$ healthy subjects). The 10 mg dose of atorvastatin administered with darunavir/ritonavir had an AUC_{24} that was only 15% lower than that of the standard 40 mg dose of atorvastatin administered alone. Atorvastatin

did not significantly affect the pharmacokinetics of darunavir/ritonavir. Therefore, it is recommended that atorvastatin 10 mg once daily be utilized by patients receiving darunavir/ritonavir to provide atorvastatin exposures similar to 40 mg when given alone.[29]

A study of 14 healthy subjects given pravastatin 40 mg with or without darunavir/ritonavir found a significant increase in pravastatin exposures. Darunavir/ritonavir increased the $C_{\max}$ of pravastatin by an average of 63% (from a mean $\pm$ SD of 50.9 ± 67.6 to 86.9 ± 88.4 ng/mL), the AUC_{24} by 81% (from 92.0 ± 86.4 to 175 ± 159 ng $\cdot$ h/mL) and the time to reach the maximum concentration ($t_{\max}$) by 50% (from 1.0 to 1.5 hours). Therefore, it is recommended that pravastatin be initiated at the lowest possible dose in patients receiving darunavir/ritonavir, and then increased gradually with careful monitoring.[30]

Darunavir/Ritonavir and Oral Contraceptives: When administered concurrently with darunavir/ritonavir, hormonal contraceptive concentrations decline significantly. When darunavir/ritonavir 600 mg/100 mg twice daily was administered in combination with daily ethinylestradiol 0.035 mg and norethisterone (norethindrone) 1.0 mg (Ortho-Novum® 1/35) in 19 HIV-infected women, the mean ethinylestradiol AUC_{24} , $C_{\max}$ and $C_{\min}$ declined 44%, 32% and 62%, respectively. The mean AUC_{24} , $C_{\max}$ and $C_{\min}$ of norethisterone declined 14%, 10% and 30%, respectively. Darunavir/ritonavir concentrations were not significantly altered. Pharmacodynamic analyses of the serum concentrations of progesterone, luteinizing hormone and follicle-stimulating hormone showed a lesser suppression of hormone concentrations when darunavir/ritonavir was administered in conjunction with Ortho-Novum® 1/35 than with administration of Ortho-Novum® 1/35 alone. These results suggest that oral contraceptives may have reduced efficacy when administered with darunavir/ritonavir.[31]

Darunavir/Ritonavir and Phosphodiesterase 5 Inhibitors: Sildenafil, vardenafil and tadalafil are approved for the treatment of erectile dysfunction. These compounds are predominantly metabolized by CYP3A4 and have strong recommendations for dose reduction when given concurrently with other protease inhibitors.[32] The effects of darunavir/ritonavir 400 mg/100 mg administered twice daily to steady state on the pharmacokinetics of a single 25 mg dose of sildenafil were examined in 16 healthy male subjects. The sildenafil $C_{\max}$ decreased by 38% when sildenafil 25mg was coadministered with darunavir/ritonavir, compared with when sildenafil 100mg was administered alone. Darunavir plasma concentrations were not affected by this single dose. Therefore, a dose-reduction recommendation for coadministration of phosphodiesterase 5 inhibitors with darunavir/ritonavir is as follows: a single dose of sildenafil not exceeding 25mg within a 48-hour time period, a single dose of vardenafil not exceeding 2.5mg within a 72-hour time period and a single dose of tadalafil not exceeding 10mg within a 72-hour time period.[1]

Darunavir/Ritonavir and Selective Serotonin Reuptake Inhibitors: SSRIs are commonly used in HIV-infected patients. Sertraline is primarily metabolized by CYP3A4 and paroxetine is metabolized by CYP2D6. Drug-drug interactions between darunavir/ritonavir, paroxetine and sertraline were investigated in a randomized, multiple-dose, crossover study in 36 healthy subjects. Combined administration of darunavir/ritonavir 400 mg/100 mg twice daily with either paroxetine 20 mg once daily or sertraline 50 mg once daily were compared with the administration of these drugs alone. The paroxetine AUC_{12} , $C_{\max}$ and $C_{\min}$ decreased by a mean of 39%, 36% and 37%, respectively, while the fraction of unbound (free) paroxetine increased by 25–35%. The sertraline AUC_{12} , $C_{\max}$ and $C_{\min}$ decreased by a mean of 49%, 44% and 49%, respectively, while the fraction of unbound sertraline was not altered. Darunavir/ritonavir exposure was not significantly altered, and the drug combinations were well tolerated.[33] Since the exact correlation between the SSRI concentration and clinical response has not been defined, the clinical significance of the

reduction in exposure is unknown. No empirical dose adjustment for paroxetine or sertraline is currently recommended, although closely monitored dose titration may be warranted.

Darunavir/Ritonavir and Anti-Infectives: Rifabutin is both an inducer and a substrate of CYP3A enzymes. Although no data are available for this interaction, coadministration of darunavir/ritonavir is expected to increase rifabutin concentrations and decrease darunavir concentrations, similarly to other ritonavir-boosted protease inhibitors. If coadministration is necessary, it is suggested that rifabutin be administered 150 mg every other day or three times weekly.[1]

Rifampicin (rifampin) is a potent inducer of CYP3A4 enzyme activity. Coadministration of rifampicin with most protease inhibitors significantly decreases their plasma concentrations. Thus, it is anticipated that coadministration of darunavir with rifampicin will cause a significant decrease in darunavir plasma concentrations. No data are currently available on the pharmacokinetics of darunavir in the presence of rifampicin, but coadministration of these two agents is not recommended.[1]

Clarithromycin is a macrolide antibacterial agent indicated for prophylaxis and treatment of *Mycobacterium avium* complex. Clarithromycin is also commonly used to treat pharyngitis, tonsillitis and upper respiratory infections such as *Chlamydia pneumoniae* and *Streptococcus pneumoniae*. [34] The primary and active metabolite of clarithromycin, 14-hydroxy-clarithromycin, is produced through CYP3A-mediated oxidation, *N*-demethylation, and hydroxylation.[35] Clarithromycin inhibits CYP3A enzyme activity and thus has the potential for significant interaction with protease inhibitors. Although no significant interaction has been observed between clarithromycin and the overall exposure of ritonavir in plasma, ritonavir increases the exposure of clarithromycin by 77% and extensively inhibits the formation of 14-hydroxy-clarithromycin.[36] The pharmacokinetics of the coadministration of darunavir/ritonavir 400 mg/100 mg twice daily and clarithromycin 500 mg twice daily were examined in a three-way crossover study in 18 healthy subjects. Pharmacokinetic assessments were performed after 7 days. The AUC₁₂ and C_{max} of darunavir decreased by 17% and 13%, respectively. The least square mean AUC ratio of darunavir administered alone compared with coadministration with clarithromycin was 0.87 (90% CI 0.75, 1.01). The least square mean ratio for the C_{max} of darunavir administered alone compared with coadministration with clarithromycin was 0.83 (90% CI 0.72, 0.96). The AUC₁₂ and C_{max} of clarithromycin increased by 57% and 26%, respectively. The least square mean AUC ratio of clarithromycin administered alone compared with coadministration with darunavir was 1.57 (90% CI 1.35, 1.84). The least square mean ratio for the C_{max} of clarithromycin administered alone compared with coadministration with darunavir was 1.26 (90% CI 1.03, 1.54). All concentrations of 14-hydroxy-clarithromycin were below the lower limit of quantification (50 ng/mL).[17] Similar variations in the pharmacokinetics of clarithromycin have been reported when clarithromycin was administered in conjunction with other protease inhibitors, and these variations have had little effect upon clinical outcome.[36-38] Since it is unlikely that the observed changes in exposure will have clinical significance, no dose adjustment is required for darunavir or clarithromycin in patients with normal renal function. A 50% dose reduction is recommended for clarithromycin when coadministered with darunavir for individuals with creatinine clearance of 30–60 mL/min. A 75% clarithromycin dose reduction is recommended for individuals with creatinine clearance of <30 mL/min.[1]

Ketoconazole is both a substrate and an inhibitor of CYP3A4. A study in 15 healthy subjects demonstrated that the combination of twice-daily darunavir/ritonavir 400 mg/100 mg and ketoconazole 200 mg increased the darunavir AUC₁₂ by 42%, the C_{max} by 21% and the C_{min} by 73%. The mean AUC₁₂, C_{max} and C_{min} of ketoconazole increased by 212%, 111%

and 868%, respectively. Based on these data, it is recommended that ketoconazole should not be given at doses greater than 200 mg once daily when combined with darunavir/ritonavir. Although there are no data, the effects on itraconazole are expected to be similar, and thus a maximum daily dose of 200 mg is also recommended.[39] No data currently exist for the interaction between fluconazole and darunavir/ritonavir, although a clinical trial to investigate these effects is currently under way. Given that fluconazole is a moderate inhibitor of CYP3A4 enzyme activity, it is anticipated that plasma concentrations of darunavir will increase, and a dose adjustment may be warranted.

Darunavir/Ritonavir and Acid-Reducing Agents: Gastrointestinal issues are common among patients with HIV infection, and symptoms are often treated with acid-reducing agents such as histamine H₂-receptor antagonists (e.g. ranitidine) or proton pump inhibitors (e.g. omeprazole). A multiple-dose study conducted in 16 healthy subjects compared the pharmacokinetics of darunavir/ritonavir 400 mg/100 mg administered twice daily alone with those in combination with ranitidine 150 mg twice daily or omeprazole 20 mg once daily. Both ranitidine and omeprazole combinations were well tolerated and had no significant effect on the pharmacokinetics of darunavir/ritonavir.[18]

2. Non-Nucleoside Reverse Transcriptase Inhibitors

Two new NNRTIs, one recently approved and the other in phase III clinical development, have the potential for drug-drug interactions.

2.1 Etravirine

Etravirine (TMC125) is a second-generation NNRTI, which was recently approved by the FDA for treatment-experienced patients with resistance to an NNRTI and other antiretroviral agents (figure 1b). Etravirine, administered with or without a protease inhibitor or enfuvirtide, is the first NNRTI to show clinical efficacy after 24 weeks in patients who have demonstrated failure to respond to treatment with both a protease inhibitor and either nevirapine or efavirenz.[40]

2.1.1 Pharmacology—The molecular weight of etravirine is 435.277 g/mol.[41] Etravirine is a highly flexible, diaryl pyrimidine (DAPY) compound. Its structural flexibility facilitates multiple binding complexes with both wild-type and mutant HIV strains, and thus it has a high genetic barrier to the development of resistance.[42] Etravirine is highly bound to human plasma proteins (>99%).[43] It is predominantly metabolized by CYP3A4, CYP2C9 and CYP2C19, with minor glucuronidation.[44] Etravirine is a moderate inducer of CYP3A4 and acyl glucuronides and a moderate inhibitor of CYP2C9 and CYP2C19.[45] *In vitro*, etravirine metabolism is reduced by CYP3A4 inhibitors (i.e. indinavir) and is increased by CYP3A4 inducers (i.e. nevirapine).[46] Renal elimination of etravirine is minimal (<1.2%).[47]

Four formulations of etravirine have been investigated in pharmaceutical clinical trials: TF002, TF034, TF035 and F060. Formulation TF035 was administered in most phase I and phase II trials. Formulation F060, with enhanced bioavailability, was introduced in phase I–IV clinical trials and is now commercially available.[45]

2.1.2 Pharmacokinetics—Etravirine has a 30- to 40-hour systemic half-life and a distribution half-life of 3.9–5.4 hours.[47] The pharmacokinetic activity of etravirine (TF035) was evaluated in two phase I, 7-day randomized, crossover studies in healthy subjects. In the first study, 24 subjects (23 male, 1 female) were given etravirine 100 mg twice daily, followed by etravirine 200 mg once daily. The least square mean ratios comparing the pharmacokinetic parameters of once-daily and twice-daily administration

were as follows: $C_{\min}$ 0.74 (90% CI 0.69, 0.80), $C_{\max}$ 1.42 (90% CI 1.34, 1.51) and AUC_{24} 1.05 (90% CI 0.96, 1.14). In the second study, 41 subjects (22 male, 19 female) were given etravirine 200 mg twice daily followed by etravirine 400 mg once daily. The least square mean ratios comparing the pharmacokinetic parameters of once-daily and twice-daily administration were as follows: $C_{\min}$ 0.75 (90% CI 0.72, 0.79), $C_{\max}$ 1.44 (90% CI 1.37, 1.50) and AUC_{24} 1.03 (90% CI 1.00, 1.07). These results indicate that the $C_{\min}$ of etravirine is 25–26% lower with a once-daily dosage regimen than with a twice-daily regimen, although equal daily administration results in similar overall daily systemic exposures.[48]

Etravirine exposure is reduced by 50% when administered in a fasted state.[47] The effect of food and the type of meal on etravirine pharmacokinetics was investigated in a randomized, open-label, three-way, crossover trial in two groups of 12 healthy subjects. A 100 mg dose of etravirine (F060) was administered under the following five conditions: fasting, a standardized low-fat breakfast, a snack, a high-fat meal and a high-fibre meal. Etravirine pharmacokinetics were evaluated over 96 hours. When administered with a standardized meal, the mean etravirine AUC_{12} values in the two groups were 1417 ± 1140 ng • h/mL and 1191 ± 700 ng • h/mL. The mean $C_{\max}$ values in the two groups were 129 ± 64 ng/mL and 138 ± 61 ng/mL. Under fasting conditions, the $C_{\max}$ and AUC_{12} of etravirine decreased by 44% and 51%, respectively. With a high-fibre meal, the etravirine $C_{\max}$ and AUC_{12} decreased by 25%. Pharmacokinetic parameters were similar between the conditions in which subjects were provided with breakfast and either a high-fat meal or a snack. Therefore, it is recommended that etravirine should be administered with food.[49]

Finally, etravirine may be administered in patients with mild or moderate hepatic impairment without dose adjustment. In a study comparing the exposures of 200 mg of etravirine administered twice daily in HIV-negative volunteers with mild (Child-Pugh Class A, $n = 8$) or moderate (Child-Pugh Class B, $n = 8$) hepatic impairment with healthy matched controls ($n = 16$), etravirine exposures were comparable. After 8 days, the mean etravirine AUC_{12} value among volunteers with mild hepatic impairment was 9546 ± 2630 ng • h/mL, while the mean etravirine AUC_{12} value among matched healthy controls was 10650 ± 1688 ng • h/mL. After 8 days, the mean etravirine AUC_{12} value among volunteers with moderate hepatic impairment was 7665 ± 4122 ng • h/mL, while the mean etravirine AUC_{12} value among matched healthy controls was 8584 ± 1560 ng • h/mL.[50]

2.1.3 Drug-Drug Interactions—Drug-drug interaction data for etravirine are available for selected nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, protease inhibitors and gastric acid-reducing agents. Sildenafil may require dose adjustment when administered in conjunction with etravirine. Efavirenz, nevirapine, tipranavir/ritonavir, fosamprenavir/ritonavir, atazanavir/ritonavir, unboosted protease inhibitors and clarithromycin should not be coadministered.[25,46]

Etravirine and Protease Inhibitors: Etravirine decreases saquinavir exposure probably through induction of CYP3A4 enzyme activity. A single dose of saquinavir 1200mg given to 12 healthy subjects after 14 days of etravirine (TF035) 900 mg twice daily resulted in the saquinavir AUC and $C_{\max}$ being decreased by a mean of 52% (90% CI 20, 71) and 46% (90% CI 14, 55), respectively.[51]

Full-dose ritonavir is known to both inhibit and induce CYP3A4 activity and to induce glucuronidation.[52] In a study of 11 healthy subjects, a single dose of etravirine (TF035) 400 mg was administered after ritonavir 600 mg twice daily for 7 days. Ritonavir significantly decreased the etravirine AUC_{12} by 46% (range 27–59%) and the $C_{\max}$ by 32% (range 15–45%).[53] The observed decrease in etravirine exposure when administered with

full-dose ritonavir provides evidence for glucuronidation as a second metabolic pathway for etravirine.[53] Full-dose ritonavir and etravirine should not be coadministered.[25]

When indinavir and etravirine are coadministered, indinavir concentrations decrease and etravirine concentrations increase. Ten healthy subjects were given indinavir 800 mg three times daily with etravirine (TF035) 1600 mg twice daily for 14 days. The GMRs for the etravirine AUC_{12} , C_{max} and C_{min} comparing etravirine administered with indinavir and etravirine alone were 1.51 (90% CI 1.20, 1.90), 1.51 (90% CI 1.16, 1.97) and 1.52 (90% CI 1.20, 1.91), respectively. The GMRs for the indinavir AUC_8 , C_{max} and C_{min} comparing etravirine administered with indinavir and indinavir alone were 0.54 (90% CI 0.46, 0.62), 0.72 (90% CI 0.58, 0.89) and 0.24 (90% CI 0.18, 0.34), respectively.[53] Based on these data, indinavir and etravirine should not be combined.

Unexpected drug interactions can occur with ritonavir-boosted protease inhibitors. Fosamprenavir alone has been shown to induce CYP3A4 enzyme activity, while low-dose ritonavir is a potent CYP3A4 inhibitor.[54] In a two-way, open-label, pharmacokinetic drug interaction study with eight HIV-infected patients, coadministration of etravirine, fosamprenavir and ritonavir was investigated. All patients were taking a stable regimen of fosamprenavir/ritonavir 700 mg/100 mg twice daily. Etravirine (TF035) 800 mg twice daily was added to the regimen for 14 days. With this combination, the AUC_{12} , C_{max} and C_{min} of amprenavir increased by 69%, 62% and 77%, respectively. The pharmacokinetic parameters of etravirine were similar to those observed in historical controls.[55] Coadministration of etravirine and fosamprenavir/ritonavir should be avoided. If concomitant use is required, patients should be monitored carefully for adverse events associated with increased amprenavir exposure, including nausea, vomiting, paraesthesias, elevated liver enzymes and neuropathy.[25]

Tipranavir administered without ritonavir induces CYP3A4 enzyme activity.[56] Tipranavir/ritonavir has been found to potently inhibit hepatic and intestinal CYP3A4/5 enzyme activity after a single dose and to moderately induce hepatic and intestinal CYP3A4/5 enzyme activity over time. However, the net effect is CYP3A4/5 inhibition once steady-state conditions are achieved.[57] In a study of 24 healthy subjects, tipranavir/ritonavir 500 mg/200 mg twice daily decreased the exposure of etravirine (TF035) 800 mg twice daily by 76%. The etravirine AUC_{12} , C_{max} and C_{min} , administered with tipranavir/ritonavir, declined by a mean of 76% (90% CI 67, 82), 71% (90% CI 60, 78) and 82% (90% CI 75, 87), respectively. Etravirine slightly increased tipranavir exposure, with the AUC_{12} , C_{max} and C_{min} increasing by a mean of 18% (90% CI 3, 36), 14% (90% CI 2, 27) and 24% (90% CI -4, 59). Ritonavir exposures were similarly increased. Owing to the clinically significant decrease in etravirine exposure when administered with tipranavir/ritonavir, these two drugs should not be used in combination.[58]

Dual-boosted protease inhibitor therapy, once a management strategy of interest, has now fallen out of favour because of the complex drug interactions and lack of documented benefit compared with single-boosted protease inhibitor therapy. The pharmacokinetic influence of etravirine (TF035) 800 mg twice daily was evaluated in 15 HIV-infected patients on a stable regimen of twice-daily lopinavir/ritonavir/saquinavir at varying dosages: 400 mg/100 mg/1000 mg (n = 6), 400 mg/100 mg/800 mg (n = 5), 400 mg/200 mg/800 mg (n = 1) and 533 mg/133 mg/800 mg (n = 3). Pharmacokinetic treatment ratios comparing drug concentrations on etravirine with those off etravirine were computed in a combined analysis of subject data (n = 11) from all dosage conditions. When combined with etravirine, the lopinavir AUC_{12} , C_{max} and C_{min} were 82%, 84% and 76%, respectively, of those without etravirine; the saquinavir AUC_{12} , C_{max} and C_{min} were 87%, 85% and 87%, respectively, of those without etravirine, and the ritonavir AUC_{12} , C_{max} and C_{min} were 88%,

89% and 87%, respectively, of those without etravirine. Statistically significant decreases were noted only for the lopinavir $C_{\max}$ ($p = 0.03$) and AUC_{12} ($p = 0.04$). However, with these observed changes being relatively small (11–24%), clinical significance is unlikely. No clinically significant changes were observed in the pharmacokinetic parameters of saquinavir and ritonavir ($p > 0.3$).[59]

Etravirine and Reverse Transcriptase Inhibitors: Only the NRTI didanosine has been evaluated in an interaction study with etravirine, with no clinically significant changes in the pharmacokinetics of either drug. Fourteen healthy subjects were given etravirine (TF035) 800 mg twice daily with didanosine 400 mg once daily.[60] For etravirine, the GMRs for the AUC_{12} , $C_{\max}$ and $C_{\min}$ were 1.11 (90% CI 0.98, 1.24), 1.16 (90% CI 1.02, 1.32) and 1.04 (90% CI 0.93, 1.17), respectively. For didanosine, the GMRs for the AUC_{24} and $C_{\max}$ were 0.99 (90% CI 0.79, 1.25) and 0.91 (90% CI 0.58, 1.42), respectively. These findings were confirmed in a study evaluating staggered administration of etravirine and didanosine.[61] Based on these data, no dose adjustments are recommended for this combination.

When administered with nevirapine or efavirenz, etravirine exposure significantly decreases. In a 14-day study of five healthy subjects, nevirapine 200 mg twice daily reduced the AUC_{12} and $C_{\max}$ of a single dose of etravirine (TF035) 900 mg by 55% and 36%, respectively.[51] In a larger study of 12 healthy subjects given efavirenz 600 mg once daily for 14 days, etravirine exposure (the $C_{\max}$ and AUC_{12}) decreased by 18% and 40%, respectively: the GMRs for the $C_{\max}$ and AUC_{12} for a single dose of etravirine 900 mg were 0.83 (90% CI 0.73, 0.93) and 0.59 (90% CI 0.52, 0.68), respectively.[53] Since nevirapine and efavirenz are both substrates and inducers of CYP3A4/5 enzyme activity, it is anticipated that coadministration of these drugs with etravirine will result in either unchanged or reduced nevirapine and efavirenz exposures. Therefore, it is recommended that these drugs not be given in combination.[25]

A study evaluating the pharmacokinetics and safety of etravirine administered once or twice daily after multiple doses of efavirenz found that efavirenz-dependent CYP3A induction persists for at least 14 days after efavirenz is stopped. Healthy volunteers ($n = 24$, 10 females) received etravirine 400 mg once daily or etravirine 200 mg twice daily for 14 days, followed by 14 days of efavirenz 600 mg once daily. After this time, each subject received their initial etravirine regimen for another 14 days. Full pharmacokinetic assessments before and after the 14-day administration of efavirenz indicated that etravirine exposure decreased in both treatment groups. The etravirine $C_{\max}$ and AUC_{24} decreased by 22% and 32%, respectively, in those receiving etravirine 400 mg once daily. For those who took etravirine 200 mg twice daily, the etravirine $C_{\max}$ and AUC_{24} decreased by 19% and 26%, respectively. Efavirenz concentrations were detectable in all subjects 7 days after the drug was stopped. The decrease in etravirine exposure was not considered clinically significant, and therefore no dosage adjustment is necessary when switching from efavirenz to etravirine.[62]

Etravirine and Integrase Inhibitors: Elvitegravir and raltegravir are members of the newest class of antiretroviral agents (see section 4), and they are metabolized by CYP3A4 (elvitegravir) and glucuronidase enzymes (elvitegravir and raltegravir). Elvitegravir is currently administered with ritonavir. An investigation into the pharmacokinetic interaction between elvitegravir/ritonavir 150 mg/100 mg once daily and etravirine (F060) 200 mg twice daily was conducted in a study of 34 healthy subjects (17 male, 17 female). No clinically relevant drug interactions were found between elvitegravir/ritonavir and etravirine.[43]

Similarly, there is no interaction between etravirine and raltegravir, as determined in a crossover study of 19 healthy subjects. All subjects received raltegravir 400 mg and etravirine (F060) 200 mg twice daily. Raltegravir minimally increased the AUC_{12} , C_{max} and C_{min} of etravirine by 10%, 4% and 17%, respectively. Etravirine decreased the AUC_{12} , C_{max} and C_{min} of raltegravir by 10%, 11% and 34%, respectively. The observed small decreases in the pharmacokinetic parameters of raltegravir may stem from the induction of glucuronidation by etravirine.[63]

Etravirine and Phosphodiesterase 5 Inhibitors: Fifteen healthy subjects were given a single dose of sildenafil 50 mg after 13 days of etravirine (TF035) 800 mg twice daily.[44] The mean decline in the sildenafil AUC_{12} was 57% (range 49–64%), suggesting that etravirine induction of CYP3A4 reduced these concentrations. Therefore, it is advised that the dose of sildenafil be increased and titrated according to the clinical effect when coadministered with etravirine.

Etravirine and Selective Serotonin Reuptake Inhibitors: No dose adjustment is required when etravirine and paroxetine are administered together. This interaction was studied in 16 healthy subjects given etravirine (TF035) 125 mg twice daily and paroxetine 20 mg once daily. Minimal changes were observed in the pharmacokinetic parameters of both drugs. Etravirine increased the AUC_{12} and C_{max} of paroxetine by 3% and 6%, respectively. Paroxetine increased the AUC_{12} , C_{max} and C_{min} of etravirine by 1%, 5% and 7%, respectively.[64]

Etravirine and Acid-Reducing Agents: Acid-reducing agents do not affect the pharmacokinetics of etravirine to a clinically significant extent. In a study of 19 healthy subjects (12 male, 7 female) given ranitidine 150 mg twice daily and a single dose of etravirine (F060) 100 mg, no change was noted in the AUC_{12} (GMR 0.86; 90% CI 0.76, 0.97) or C_{max} (GMR 0.94; 90% CI 0.75, 1.17) of etravirine. In a study of 19 healthy subjects given omeprazole 40 mg once daily and a single dose of etravirine 100 mg, the AUC_{12} and C_{max} of etravirine increased by a mean of 41% (range 22–62%) and 17% (range 0–43%), respectively.[65] This interaction is likely to be due to competitive inhibition of CYP2C19. However, no dosage adjustment is required to accommodate this interaction.

Etravirine and Methadone: Methadone is a racemic mixture of two enantiomers, *R*-methadone and *S*-methadone. *S*-methadone is pharmacologically inactive and is more protein bound than *R*-methadone. *R*-methadone is pharmacologically active and displays a greater mean plasma clearance, volume of distribution and mean elimination half-life than *S*-methadone.[66] Methadone undergoes stereoselective hepatic metabolism primarily by CYP2B6 and is also metabolized to a much lesser extent by CYP3A4.[67] In an open-label study of 16 healthy male subjects on stable therapy with methadone, etravirine (F060) 100 mg was administered twice daily for 14 days. No clinically significant changes in methadone exposure were observed. For *R*-methadone administered alone, the (mean $\pm$ SD) C_{max} was 222 ± 74 ng/mL and the AUC_{24} was 3807 ± 1301 ng $\cdot$ h/mL. After 14 days of coadministration with 100 mg of etravirine twice daily, the C_{max} of *R*-methadone was 228 ± 75 ng/mL and the AUC_{24} was 4038 ± 1309 ng $\cdot$ h/mL. For *S*-methadone administered alone, the C_{max} was 285 ± 103 ng/mL and the AUC_{24} was 4378 ± 1809 ng $\cdot$ h/mL. After 14 days of the coadministration with 100 mg of etravirine twice daily, the C_{max} of *S*-methadone was 264 ± 107 ng/mL and the AUC_{24} was 4029 ± 1834 ng $\cdot$ h/mL.[68]

No methadone withdrawal symptoms were observed. However, owing to the long elimination half-life of methadone (7–59 hours), 14 days of therapy may not be of sufficient duration to see an effect. Given these results, methadone dose adjustment is not necessary

when coadministered with etravirine.[69] However, patients should be monitored for withdrawal symptoms, and some patients may require a dose adjustment for methadone.[25]

Etravirine and Anti-Infectives: Clarithromycin inhibits CYP3A4 and is also converted by CYP3A4 to its active metabolite, 14-hydroxy-clarithromycin. Etravirine is a substrate and inducer of CYP3A4. Sixteen healthy male subjects participated in a randomized, open-label, two-period, crossover trial in which the pharmacokinetics of etravirine 200 mg twice daily were investigated alone and in combination with clarithromycin 500 mg twice daily. The overall exposure of clarithromycin decreased in the presence of etravirine, while concentrations of its metabolite, 14-hydroxy-clarithromycin, increased. Etravirine exposure increased as well. The least square mean ratios for the pharmacokinetic parameters of etravirine administered in combination with clarithromycin compared with etravirine alone were AUC₁₂ 142% (90% CI 134, 150), C_{max} 146% (90% CI 138, 156) and C_{min} 146% (90% CI 136, 158). The least square mean ratios for the pharmacokinetic parameters of 14-hydroxy-clarithromycin when clarithromycin was administered in combination with etravirine compared with etravirine alone were 121% (90% CI 105, 139) for the AUC₁₂, 133% (90% CI 113, 156) for the C_{max} and 105% (90% CI 90, 122) for the C_{min}. Since 14-hydroxy-clarithromycin has reduced activity against *Mycobacterium avium* complex, overall activity against these organisms may be affected, and it is recommended that an alternative agent, such as azithromycin, be considered.[70]

Etravirine and Antimycobacterials: Rifampicin, a potent inducer of CYP enzymes, is not recommended for use with etravirine. Although no study has been conducted to specifically investigate this interaction, it is likely that rifampicin will cause a significant decrease in etravirine exposure.[25]

Both etravirine and rifabutin are substrates and inducers of CYP3A4 enzyme activity. Rifabutin is commonly used as prophylaxis against *Mycobacterium avium* complex disease in patients with advanced HIV disease. The 24-hour pharmacokinetic profiles of rifabutin and its active metabolite, 25-*O*-desacetyl rifabutin, were examined in the presence of etravirine. In this open-label, randomized, two-period, crossover trial, 16 healthy HIV-negative subjects took rifabutin 300 mg once daily for 14 days followed by a 14-day washout period. Following the washout period, each subject took etravirine (TF035) 800 mg twice daily for 7 days followed by the combination of etravirine (TF035) 800 mg twice daily and rifabutin 300 mg once daily for 14 days. In the 11 subjects included in the final analysis, steady-state exposures of the etravirine concentration at 12 hours (C₁₂) decreased by approximately 37%. These effects are comparable to the decrease in etravirine when coadministered with protease inhibitors. Steady-state exposures of rifabutin and 25-*O*-desacetyl rifabutin at 24 hours postdose declined by approximately 17% when coadministered with etravirine. Since these effects are not considered to be clinically relevant, rifabutin may be administered in conjunction with etravirine without dose adjustment.[71]

Etravirine and Azole Antifungals: Formal studies have not been conducted to elucidate the effects of etravirine coadministration. Based upon known pharmacological properties of etravirine and fluconazole, coadministration of these two agents is not expected to significantly affect the exposure of either drug. Based upon the known properties of ketoconazole and itraconazole, it is anticipated that if either agent is coadministered with etravirine, the plasma concentrations of etravirine will decrease and the concentration of either ketoconazole or itraconazole will decrease. These azole antifungals should be used with caution in a patient who is taking etravirine and may require a dose adjustment, depending on other drugs in the patient's medication regimen.[25]

Etravirine and HMG-CoA Reductase Inhibitors: Atorvastatin is primarily metabolized by CYP3A4. Sixteen healthy subjects participated in a randomized, open-label, two-period, crossover trial aimed at characterizing the pharmacokinetic parameters of etravirine (TF035) 800 mg twice daily in conjunction with atorvastatin 40 mg once daily. Etravirine exposure was not affected by the presence of atorvastatin. The overall exposure of atorvastatin was decreased by 37% in the presence of etravirine and a 27% increase in the exposure of atorvastatin's active metabolite, 2-hydroxy-atorvastatin, was observed. The least square mean ratios for the pharmacokinetic parameters of atorvastatin administered in combination with etravirine compared with atorvastatin alone were 63% (90% CI 58, 68) for the AUC₂₄ and 104% (90% CI 84, 130) for the C_{max}. The least square mean ratios for the pharmacokinetic parameters of 2-hydroxy-atorvastatin when atorvastatin was administered in combination with etravirine compared with atorvastatin alone were 127% (90% CI 119, 136) for the AUC₂₄ and 175% (90% CI 160, 194) for the C_{max}. [72]

2.2 Rilpivirine

Rilpivirine (TMC278) is a diarylpyrimidine compound with a higher genetic barrier to resistance compared with currently approved NNRTIs. This high genetic barrier may be due in part to its internal flexibility, enabling it to adjust its configuration in HIV-1 reverse transcriptase in the presence of mutations (figure 1c).

2.2.1 Pharmacology—The molecular weight of rilpivirine is 366.4 g/mol.[73] The EC₅₀ of rilpivirine against wild-type HIV-1 strains is 0.5 nmol/L (0.19 ng/mL). Rilpivirine is a substrate of CYP3A4 enzyme activity and is slowly metabolized in human hepatocytes through glutathione-dependent conjugative metabolism. Rilpivirine is over 99% bound to human plasma proteins in a concentration-dependent manner.[74]

2.2.2 Pharmacokinetics—Pharmacokinetic parameters of rilpivirine were examined in a randomized, double-blind, placebo-controlled, dose-ranging study in antiretroviral-naïve, HIV-infected, men. Forty-seven patients received rilpivirine 25 to 150 mg as monotherapy for 7 days. Full pharmacokinetic profiles completed on days 1 and 7 indicated that rilpivirine was rapidly and well absorbed. The C_{max} was attained by 3–4 hours, and the terminal elimination half-life was estimated at 48 hours. After 7 days of a 50 mg dose, the mean ± SD C_{max} was 366 ± 125 ng/mL and the AUC₂₄ was 4904 ± 1677 ng • h/mL. With a 100 mg dose, the mean ± SD C_{max} was 712 ± 351 ng/mL and the AUC₂₄ was 9517 ± 4397 ng • h/mL. Plasma concentrations increased with increasing doses of rilpivirine but were not dose proportional. The 75 mg dose of rilpivirine was selected for development and is being evaluated in phase III clinical trials. The plasma concentrations obtained with this dose are above the target concentration of 13.5 ng/mL, the EC₅₀ for wild-type virus adjusted for protein binding.[75]

Rilpivirine should be administered with food. A study of rilpivirine 100 mg in 12 healthy Caucasian men found that under fed conditions, the C_{max} of rilpivirine is approximately 71% higher and the AUC from 0 to 48 hours (AUC₄₈) is approximately 45% higher compared with concentrations observed in a fasted state.[76]

2.2.3 Drug-Drug Interactions

Rilpivirine and Protease Inhibitors: Rilpivirine 150 mg once daily and darunavir/ritonavir 800 mg/100 mg once daily were coadministered in 16 healthy subjects. Darunavir/ritonavir increased the AUC₂₄, C_{max} and C_{min} of rilpivirine by 230%, 79% and 278%, respectively. Rilpivirine had no clinically relevant effect on darunavir/ritonavir exposure. It is likely that the increase in rilpivirine exposure is a result of CYP3A4 inhibition.[77] Specific dose

recommendations for coadministration of rilpivirine and darunavir have yet to be determined. No data combining rilpivirine with other protease inhibitors are available.

Rilpivirine and Reverse Transcriptase Inhibitors: Fifteen healthy subjects participated in a study evaluating the steady-state interaction between once-daily administration of rilpivirine 150 mg and tenofovir 300 mg. Tenofovir had no effect on the pharmacokinetics of rilpivirine (a mean 2% increase in the AUC_{24} , a 3% decrease in the C_{max} and no change in the C_{min}). However, tenofovir exposure was increased in the presence of rilpivirine, with a mean 24% increase in the AUC_{24} , a 21% increase in the C_{max} and a 21% increase in the C_{min} . [78] Although the effect of rilpivirine on tenofovir exposure is statistically significant, it is not considered clinically relevant, and no dose modifications are recommended.

Rilpivirine and HMG-CoA Reductase Inhibitors: Atorvastatin 40 mg once daily had no significant effect on the pharmacokinetics of rilpivirine (150 mg once daily) in a study of 16 healthy subjects. However, rilpivirine increased the C_{max} of atorvastatin by 35%, but did not change the AUC_{24} or C_{min} . The AUC_{24} of the 2-hydroxy and 4-hydroxy metabolites of atorvastatin also increased by 39% and 23%, respectively. Overall, the AUC of total HMG-CoA reductase activity (calculated by the AUC sum of atorvastatin with the two metabolites) increased by 20%. [79] Therefore, no dose reduction in atorvastatin is necessary with concomitant rilpivirine therapy.

Rilpivirine and Anti-Infectives: The pharmacological effect of administration of rilpivirine and anti-infectives has yet to be determined in clinical studies.

Rilpivirine and Azole Antifungals: The pharmacokinetic interaction between rilpivirine 150 mg once daily and ketoconazole 400 mg once daily was examined in a study of 16 healthy subjects. In the presence of ketoconazole, the AUC_{24} , C_{max} and C_{min} of rilpivirine increased by a mean of 49%, 30% and 76%, respectively. In the presence of rilpivirine, the AUC_{24} , C_{max} and C_{min} of ketoconazole decreased by a mean of 24%, 15% and 66%. Specific dosage recommendations for coadministration of these medications have yet to be formulated, but it is clear that this should be diligently monitored. [80]

Rilpivirine and Antimycobacterials: Rifampicin, a potent inducer of CYP3A4, is not recommended for use with rilpivirine. A study of the coadministration of rilpivirine and rifampicin in 16 healthy, HIV-negative subjects found that the AUC and C_{min} of rilpivirine were reduced by 80% and 89%, respectively, over a 24-hour period in the presence of rifampicin. Rifampicin exposure was not changed. [81]

Rilpivirine and Acid-Reducing Agents: Since the solubility of rilpivirine decreases in solutions with increasing pH, coadministration of drugs that increase gastric pH may influence its absorption. A randomized, single-dose, four-way, crossover trial was conducted to examine the pharmacokinetic effect of coadministration of rilpivirine and famotidine, a commonly used H_2 -receptor antagonist. Twenty-four healthy male subjects completed four treatment conditions, each separated by a 14-day washout period. Rilpivirine 150 mg was administered alone and with famotidine 40 mg given 2 hours before, 12 hours before or 4 hours after a single dose of rilpivirine 150 mg with food. Intra-gastric pH was measured for 24 hours, and the pharmacokinetics of famotidine and rilpivirine were assessed up to 24 and 168 hours after the dose, respectively. When famotidine was given 2 hours beforehand, the rilpivirine C_{max} and the AUC from time zero to infinity (AUC_{∞}) were reduced by 85% and 76%, respectively, in comparison with when rilpivirine was administered alone. This interaction is suspected to result from the reduced solubility of rilpivirine with increased gastric pH levels. When famotidine was given 12 hours beforehand, or 4 hours afterwards, rilpivirine pharmacokinetics were not significantly affected. Famotidine pharmacokinetics

were not affected by rilpivirine with any dosing strategy. Based on these findings, famotidine can be combined with rilpivirine, provided it is given 12 hours before or 4 hours after the rilpivirine dose.[82]

3. Chemokine Receptor Antagonists

3.1 Maraviroc

Maraviroc is a first-in-class CCR5-receptor antagonist approved by the FDA in August 2007 for use in treatment-experienced patients with drug resistance to multiple antiretrovirals. Maraviroc prevents HIV-1 entry by blocking coreceptor binding via reversible non-competitive inhibition and preventing further fusion to host CD4+ cell membranes (figure 1d).

3.1.1 Pharmacology—The molecular weight of maraviroc is 513.67 g/mol.[83] The geometric mean IC_{90} for wild-type HIV-1 is 2.0 nmol/L. This IC_{90} was determined in PBMC replication assays using viral clades A, B, C, D, E, F, G, J and O, with geometric means of the IC_{90} values ranging from 0.51 to 4.4 nmol/L. Maraviroc is approximately 75% bound to albumin and α_1 -acid glycoprotein.[84]

Maraviroc is primarily metabolized by CYP3A4 and its metabolism is inhibited by approximately 70% *in vitro* when combined with potent CYP3A4 inhibitors such as ketoconazole. Metabolism of maraviroc is not altered in the presence of CYP2C9 (sulphaphenazole) or CYP2D6 (quinidine) inhibitors.[85] As the IC_{50} of maraviroc is greater than 30 μ mol/L, it has limited inhibitory potential for the following enzymes: CYP3A4, CYP2B6, CYP2D6, CYP2C8, CYP2C9, CYP2C19 and CYP1A2.[85] In healthy subjects, maraviroc does not affect the pharmacokinetics of cortisol or midazolam, two CYP3A4 substrates. A dose-ranging study of maraviroc (25 mg twice daily to 600 mg once daily) demonstrated no change in 6 β -hydroxycortisol/cortisol urinary ratios in 51 healthy subjects.[86] Maraviroc 300 mg twice daily for 7 days increased the AUC and C_{max} of oral midazolam by <20%, suggesting no clinically relevant interaction.[86,87]

Maraviroc also has high affinity for the efflux transporter P-glycoprotein (Michaelis-Menten constant [K_m] = 37 μ mol/L). Caco-2 permeability studies demonstrated polarized transport of maraviroc with an efflux ratio (basolateral $\rightarrow$ apical/apical $\rightarrow$ basolateral) of >10. This high efflux ratio suggests that an inhibitor of efflux could significantly enhance the absorption of maraviroc. For example, digoxin has also been reported to have an efflux ratio of 10, and this ratio is reduced in the presence of known P-glycoprotein inhibitors such as verapamil (50%) and CP-100356 (75%). P-glycoprotein inhibitors, therefore, would have the potential to increase the absorption of maraviroc.[88]

3.1.2 Pharmacokinetics—Largely owing to enterocyte metabolism by CYP3A4 and efflux by P-glycoprotein, the dose-dependent bioavailability of maraviroc is 23–33%. [89-91] In healthy subjects, the volume of distribution of maraviroc is 2.8 L/kg, and apparent oral clearance is 10.5 mL/min/kg. The t_{max} ranges from 0.5 to 4 hours and the terminal elimination half-life from 14 to 18 hours. The pharmacokinetic parameters in HIV-infected patients are similar to those in healthy subjects. In addition to hepatic metabolism, renal clearance accounts for approximately 20–25% of the elimination of maraviroc. [89,90,92,93]

No sex or ethnicity (Caucasian vs Asian males) differences have been found in the pharmacokinetics of maraviroc.[90,94] In patients with mild and moderate liver impairment (Child-Pugh class A and B, respectively), the single-dose maraviroc AUC increased by 25% and 46%, and the C_{max} was increased by 11% and 32%, respectively. However, it is unlikely

that these changes will warrant an adjustment in dosage.[95] Caution is advised for using maraviroc in mild or moderate liver impairment. Pharmacokinetic evaluations have not yet been conducted in patients with severe hepatic impairment or renal impairment, or in pregnant, elderly or paediatric populations.[90]

Compared with the fasted state, high-fat meals reduce maraviroc exposure by 33%, and low-fat meals reduce maraviroc exposure by 20%. However, this does not appear to significantly affect antiviral activity, as no diet restrictions were made in phase III trials demonstrating safety and efficacy.[89,90]

3.1.3 Drug-Drug Interactions—As maraviroc is metabolized by CYP3A4 and transported by P-glycoprotein, dosage adjustment is required when CYP3A4 and/or P-glycoprotein inhibitors or inducers are administered concomitantly. The maraviroc dose should be reduced when combined with lopinavir, saquinavir, atazanavir and ritonavir-boosted elvitegravir, and increased when combined with efavirenz and etravirine. The investigators for the following drug interaction studies did not report the effect of maraviroc on the concomitant regimen unless indicated otherwise.

Maraviroc and Protease Inhibitors: In an investigation of maraviroc pharmacokinetics in five HIV-infected subjects taking lopinavir/ritonavir 400 mg/100 mg twice daily, stavudine 40 mg twice daily, and lamivudine 150 mg twice daily, a single dose of maraviroc 300 mg was administered. Comparing the pharmacokinetic data with the day 1 data from a historic control of HIV-infected subjects, the maraviroc GMRs for the AUC_{12} and C_{max} were 2.65 (90% CI 1.61, 4.35) and 1.80 (90% CI 1.03, 3.14). Therefore, a dose reduction strategy of maraviroc to 150 mg twice daily is necessary when administered with lopinavir/ritonavir. [96,97]

In 12 healthy male subjects, maraviroc 100 mg given twice daily combined with saquinavir 1200 mg three times daily yielded maraviroc GMRs for the AUC_{12} and C_{max} of 4.25 (90% CI 3.47, 5.19) and 3.32 (90% CI 2.45, 4.49), respectively.[98,99] Therefore, maraviroc dosing should be reduced from 300 mg twice daily to 150 mg twice daily in combination with unboosted saquinavir.

Healthy subjects were recruited to study the combined effects of CYP3A4 inhibitors and inducers on the pharmacokinetics of maraviroc. The combination of maraviroc 300 mg twice daily with lopinavir/ritonavir 400 mg/100 mg twice daily increased maraviroc exposure in 11 subjects: the GMRs for the maraviroc AUC_{12} and C_{max} were 3.95 (90% CI 3.43, 4.56) and 1.97 (90% CI 1.66, 2.34), respectively. When efavirenz 600 mg once daily was added to this regimen, the GMRs for the maraviroc AUC_{12} and C_{max} were 2.53 (90% CI 2.24, 2.87) and 1.25 (90% CI 1.01, 1.55), respectively. The combination of maraviroc 100 mg twice daily with saquinavir/ritonavir 1000 mg/100 mg twice daily increased maraviroc exposure in healthy subjects: the maraviroc GMRs for the AUC_{12} and C_{max} were 9.77 (90% CI 7.87, 12.14) and 4.78 (90% CI 3.41, 6.71), respectively. When efavirenz 600 mg was added to this regimen, the maraviroc GMRs for the AUC_{12} and C_{max} were 5.00 (90% CI 4.26, 5.87) and 2.26 (90% CI 1.64, 3.11), respectively.[90,100,101] Therefore, the maraviroc dose should be reduced when combined with lopinavir/ritonavir or saquinavir/ritonavir, including regimens that contain efavirenz.

A dose-adjustment trial demonstrated that a 75% reduction (from 100 mg to 25 mg) in the maraviroc dose with saquinavir/ritonavir still resulted in a 40% increase in the AUC compared with maraviroc 100 mg twice daily alone. However, reducing the dose of maraviroc to 25 mg resulted in a 40% reduction in the C_{max} compared with maraviroc 100 mg alone. Since the smallest dosage size for maraviroc is 150 mg as an unscored, film-

coated tablet (with no recommendations for splitting or crushing), and the dose-limiting toxicities for maraviroc appear to be related to the C_{max} rather than the AUC, reducing the dose of maraviroc to 150 mg twice daily is reasonable. When combining maraviroc with saquinavir/ritonavir, close monitoring of the adverse effects and toxicity of maraviroc is advised.[99]

In a two-way crossover study with tipranavir/ritonavir 500 mg/200 mg twice daily, maraviroc 150 mg twice daily resulted in GMRs for the AUC_{12} and C_{max} of 1.02 (90% CI 0.85, 1.23) and 0.86 (90% CI 0.61, 1.21), respectively, suggesting no significant interaction. [99,102] Thus, a standard dosage of maraviroc (300 mg twice daily) should be used when coadministered with tipranavir/ritonavir.

The interaction between maraviroc and atazanavir with or without ritonavir was studied in 12 healthy subjects. Maraviroc 300 mg twice daily was given with either atazanavir 400 mg once daily or atazanavir/ritonavir 300 mg/100 mg once daily. When combined with atazanavir alone, the GMRs for the AUC_{12} and C_{max} of maraviroc were 3.57 (90% CI 3.30, 3.87) and 2.09 (90% CI 1.72, 2.55), respectively, and with atazanavir/ritonavir they were 4.88 (90% CI 4.40, 5.41) and 2.67 (90% CI 2.32, 3.08), respectively.[90,99,103] Therefore, the maraviroc dose should be reduced to 150 mg twice daily when combined with any atazanavir therapy.

Maraviroc and Reverse Transcriptase Inhibitors: The effect of maraviroc 300 mg on lamivudine (150 mg twice daily) or zidovudine (300 mg twice daily) was evaluated in 11 healthy subjects. The GMRs for the lamivudine AUC_{12} and C_{max} were 1.14 (90% CI 0.984, 1.323) and 1.16 (90% CI 0.875, 1.542), respectively. The GMRs for the zidovudine AUC_{12} and C_{max} were 0.98 (90% CI 0.79, 1.22) and 0.92 (90% CI 0.68, 1.24), respectively, for zidovudine. Therefore, no dosage adjustment is required when maraviroc is combined with zidovudine and lamivudine.[87,104]

To investigate the effects of efavirenz on maraviroc pharmacokinetics, 12 healthy subjects were given maraviroc 100 mg twice daily with efavirenz 600 mg once daily. The AUC_{12} and C_{max} GMRs for maraviroc during efavirenz therapy were 0.487 (90% CI 0.414, 0.573) and 0.436 (90% CI 0.304, 0.624), respectively. When the dose of maraviroc was increased to 200 mg twice daily, the GMRs for the AUC_{12} and C_{max} were 1.09 (90% CI 0.868, 1.37) and 1.16 (90% CI 0.774, 1.75), respectively. This study demonstrated that the effects of enzyme induction on maraviroc pharmacokinetics can be overcome by doubling the dose. [101,105]

In HIV-infected subjects, the GMRs for the maraviroc AUC_{12} and C_{max} were 0.469 (90% CI 0.303, 0.724) and 0.665 (90% CI 0.408, 1.09), respectively, for those taking efavirenz with lamivudine/zidovudine (n = 8) and 0.483 (90% CI 0.313, 0.746) and 0.764 (90% CI 0.468, 1.25), respectively, for those taking efavirenz with didanosine/tenofovir (n = 8). The maraviroc GMRs of the AUC_{12} and C_{max} for those taking nevirapine (with lamivudine and tenofovir) were 1.01 (90% CI 0.651, 1.55) and 1.54 (90% CI 0.943, 2.51), respectively. These data confirm the interaction seen in healthy subjects, and the maraviroc dosage should be increased to 600 mg twice daily when combined with efavirenz, but a standard dosage can be used when combined with nevirapine.[96,97]

In a two-period crossover study of the effects of etravirine with or without darunavir/ritonavir on the pharmacokinetics of maraviroc, healthy subjects were enrolled. Etravirine was administered 200 mg twice daily, maraviroc 150 mg twice daily and darunavir/ritonavir 600 mg/100 mg twice daily. Etravirine alone decreased the maraviroc AUC_{12} and C_{max} by 53% and 60%, respectively, while the combination of etravirine and darunavir/ritonavir

increased the maraviroc AUC_{12} and C_{max} by 210% and 77%, respectively.[106] Therefore, an increase in the maraviroc dose is required when combined with etravirine alone, but it may not be necessary if there are other components of the medication regimen that inhibit maraviroc metabolism.

Maraviroc and Integrase Inhibitors: In a study of 36 healthy subjects, the combination of elvitegravir/ritonavir 150 mg/100 mg with maraviroc 150 mg did not affect concentrations of elvitegravir (the GMRs for the AUC_{12} and C_{max} were 1.1 and 0.99, respectively) or ritonavir (the GMRs for the AUC_{12} and C_{max} were 0.98 and 0.92, respectively). However, maraviroc concentrations increased: the GMRs for the AUC_{12} and C_{max} were 2.86 (90% CI 2.33, 3.51) and 2.15 (90% CI 1.71, 2.69), respectively.[107] The combination of ritonavir-boosted elvitegravir will require a 50% dose reduction in maraviroc, which is similar to other ritonavir-containing regimens.

A phase IV trial in 18 healthy subjects (16 males and 2 females, aged 18–55 years) investigated the interaction between raltegravir and maraviroc. The following dosing sequence was administered: raltegravir 400 mg twice daily was given for 3 days, followed by a 2-day washout period, followed by maraviroc 300 mg twice daily given for 6 days, followed by 3 days of maraviroc combined with raltegravir in the doses listed above. When combined, the exposures of both drugs decreased. The maraviroc AUC_{12} , C_{max} and C_{min} GMRs were 0.86 (90% CI 0.80, 0.92), 0.79 (90% CI 0.67, 0.94) and 0.90 (90% CI 0.85, 0.96), respectively. The raltegravir AUC_{12} , C_{max} and C_{min} GMRs were 0.63 (90% CI 0.44, 0.90), 0.67 (90% CI 0.41, 1.08) and 0.72 (90% CI 0.58, 0.91), respectively. Since the reduction in maraviroc exposure was not considered to be clinically significant, no dosage adjustment was recommended. The marked reduction in raltegravir exposure may be a cause for concern, but no recommendations have yet been made in the US Department of Health and Human Services (DHHS) treatment guidelines or the raltegravir prescribing information. Given the large inter- and intrasubject variability in the pharmacokinetics of raltegravir (three of the subjects had increased, rather than decreased, raltegravir exposure) more studies are needed to understand this interaction.[101,108]

Maraviroc and Anti-Infectives: In 12 healthy male subjects, ketoconazole 400 mg once daily in combination with maraviroc 100 mg twice daily produced a significant increase in the maraviroc AUC_{12} and C_{max} GMRs: 5.01 (90% CI 3.98, 6.29) and 3.38 (90% CI 2.38, 4.78), respectively. Because of the profound drug-drug interactions, these two compounds should not be used together.[99]

The potent CYP3A enzyme-inducing capacity of rifampicin produces profound declines in maraviroc exposure. In 12 healthy subjects given the combination of rifampicin 600 mg once daily and maraviroc 100 mg twice daily, the maraviroc AUC_{12} and C_{max} declined by 67% and 70%, respectively. Doubling the maraviroc dose to 200 mg twice daily overcame the reduction in the AUC_{12} and C_{max} seen with maraviroc 100 mg plus rifampicin 600 mg once daily (the GMRs for the AUC_{12} and C_{max} increased to 0.99 and 0.97, respectively). [105] The combination of maraviroc, rifampicin and protease inhibitors was not studied. However, it is recommended that this combination use the unadjusted dose of maraviroc. [90,101]

No data have been generated for the combination of maraviroc and rifabutin. The induction potential of rifabutin may decrease maraviroc exposures; however, rifabutin is considered not to have a clinically significant effect on the pharmacokinetics of CYP substrates. The DHHS treatment guidelines (November 2008) state that dosage adjustment is not warranted in concomitant administration of maraviroc and rifabutin, but close monitoring of viral response may be needed.[109]

The effect of maraviroc on the pharmacokinetics of midazolam was studied in 12 healthy subjects using a double-blind, placebo-controlled, crossover study design. Maraviroc was administered at 300 mg twice daily for 7 days and midazolam was given as a single dose of 7.5 mg on day 7. The GMRs for the midazolam AUC₁₂ and C_{max} (maraviroc vs placebo) were 1.18 (90% CI 1.04, 1.34) and 1.21 (90% CI 0.92, 1.60), respectively, showing that maraviroc has a minor effect on midazolam pharmacokinetics, which is likely to be the case for other substrates of CYP3A4. No dosage adjustment is required for concomitant administration of maraviroc and midazolam.[87]

In 14 healthy female subjects, the effect of maraviroc on the pharmacokinetics of ethinylestradiol and levonorgestrel was studied in a double-blind, placebo-controlled, crossover study. Maraviroc was administered at 300 mg twice daily for 10 days with a single dose on day 11, and ethinylestradiol 30 µg and levonorgestrel 150 µg were given once daily on days 2–8. Comparing maraviroc plus ethinylestradiol/levonorgestrel with placebo plus ethinylestradiol/levonorgestrel, the AUC₂₄ and C_{max} GMRs for ethinylestradiol were 0.996 (90% CI 0.945, 1.06) and 0.984 (90% CI 0.913, 1.06), respectively, and the AUC₂₄ and C_{max} GMRs for levonorgestrel were 0.977 (90% CI 0.92, 1.04) and 1.00 (90% CI 0.93, 1.08), respectively. No dosage adjustment is necessary when combining maraviroc with these oral contraceptives.[87]

3.2 Vicriviroc

Vicriviroc is a reversible noncompetitive CCR5 chemokine receptor inhibitor that is currently in phase III studies (figure 1e).

3.2.1 Pharmacology—The molecular weight of vicriviroc is 533.63 g/mol. In human plasma, approximately 84% is bound to proteins.[110] The *in vitro* binding affinity (K_i) of vicriviroc for CCR5 receptors is 0.8 nmol/L. The geometric mean EC₅₀ values for various HIV-1 CCR5-tropic isolates range from 0.04 to 2.3 nmol/L, and EC₉₀ values range from 0.45 to 18 nmol/L. Zidovudine, lamivudine, efavirenz, indinavir and enfuvirtide are reported to have synergistic effects on HIV-1 replication with vicriviroc using a CCR5-tropic clinical isolate *in vitro*. [110]

Using recombinant CYP enzymes, vicriviroc metabolites are formed by CYP3A4, CYP3A5 and CYP2C9. CYP3A4 is a major contributor to metabolite formation, and CYP3A5 and CYP2C9 are minor contributors. This is confirmed by human liver microsomal incubations. When combined with the potent CYP3A4 inhibitor ketoconazole, vicriviroc metabolism is 90% inhibited. Furthermore, incubation with an anti-CYP3A4/5 specific antibody inhibits >80% of vicriviroc metabolism.[111]

Vicriviroc is not a significant substrate of P-glycoprotein. The efflux ratio obtained from Caco-2 permeability studies is approximately 0.6, meaning that more vicriviroc is absorbed than effluxed from the enterocyte.[112]

3.2.2 Pharmacokinetics—In HIV-infected individuals, the pharmacokinetic profile of vicriviroc has been studied at doses of 10, 25 and 50 mg twice daily. Steady-state conditions are reached in approximately 12 days, with a linear dose-pharmacokinetic relationship. The reported median steady-state pharmacokinetic parameters using 50 mg twice daily include an AUC₁₂ of 2290 ng • h/mL, C_{max} of 342 ng/mL, C_{min} of 117 ng/mL, t_{max} of 1.5 hours, elimination half-life of 28 hours, apparent oral clearance of 21 L/h and volume of distribution of 778 L.[113]

A slight food effect is evident with vicriviroc absorption. A comparison of a high-fat meal and fasting conditions in 20 healthy subjects given a single dose of vicriviroc 50 mg found a

$C_{\max}$ decrease of 58% (range 52–65%), although the relative oral bioavailability was 107% (range 101–113%). Because exposure is minimally affected, as shown by the relative oral bioavailability, vicriviroc can be administered without regard to food.[114]

3.2.3 Drug-Drug Interactions—Vicriviroc interactions have been evaluated with selected NRTIs, efavirenz and multiple protease inhibitors. For the following drug interactions, no data have been reported on the effect of vicriviroc on the concomitant regimen.

Vicriviroc and Protease Inhibitors: In a study of 46 healthy subjects, the pharmacokinetic profile of vicriviroc 10 mg given twice daily was evaluated in combination with ritonavir 100 mg once daily, 100 mg twice daily, 200 mg twice daily or 400 mg twice daily. Ritonavir increased the vicriviroc AUC_{12} and $C_{\max}$ by 469–585% and 301–395%, respectively.[115] This demonstrated that regardless of the ritonavir dose, vicriviroc exposure was increased to a similar extent. Dosage adjustment will not be necessary, because vicriviroc will require boosting by ritonavir (30 mg/100 mg once daily).

The pharmacokinetics of vicriviroc 15 mg once daily in combination with ritonavir 100 mg once or twice daily in 40 healthy subjects were compared with those of vicriviroc combined with the following ritonavir-enhanced regimens: atazanavir/ritonavir 300 mg/100 mg once daily (n = 8), indinavir/ritonavir 800 mg/100 mg twice daily (n = 8), fosamprenavir/ritonavir 700 mg/100 mg twice daily (n = 8), nelfinavir/ritonavir 1250 mg/100 mg twice daily (n = 8; 3 dropped out) and saquinavir/ritonavir 1000 mg/100 mg twice daily (n = 8). No clinically significant changes were noted in vicriviroc exposure with any of the protease inhibitor combinations. The GMRs for the AUC_{12} and $C_{\max}$ of vicriviroc with atazanavir were 1.11 (90% CI 1.08, 1.15) and 1.1 (90% CI 1.0, 1.21), respectively; with indinavir were 1.03 (90% CI 0.89, 1.19) and 0.93 (90% CI 0.82, 1.05), respectively; with fosamprenavir were 0.98 (90% CI 0.81, 1.18) and 1.0 (90% CI 0.81, 1.24), respectively; with nelfinavir were 0.96 (90% CI 0.86, 1.08) and 0.88 (90% CI 0.76, 1.03), respectively; and with saquinavir were 1.11 (90% CI 0.99, 1.24) and 1.18 (90% CI 1.08, 1.29), respectively.[116] Therefore, no dosage adjustment is needed when vicriviroc is combined with these boosted protease inhibitor regimens. Similarly, a study in 24 healthy subjects found the exposure of vicriviroc combined with ritonavir to be similar to that of vicriviroc combined with lopinavir/ritonavir, suggesting no vicriviroc dosage adjustment will be needed should these drugs be combined during therapy.[117]

A study of the interaction between vicriviroc 15 mg and tipranavir/ritonavir 500 mg/200 mg twice daily was evaluated in eight healthy subjects, and vicriviroc exposures were compared with a dosage regimen of vicriviroc/ritonavir 15 mg/100 mg twice daily. No difference in vicriviroc exposure was found.[118]

Vicriviroc and Reverse Transcriptase Inhibitors: No significant interactions occur between vicriviroc (50 mg twice daily) and lamivudine (150 mg twice daily) or zidovudine (300 mg twice daily). In 36 healthy subjects, the GMRs for the AUC_{12} and $C_{\max}$ of vicriviroc in combination with zidovudine/lamivudine compared with vicriviroc alone were 0.91 (90% 0.77, 1.09) and 0.92 (90% 0.77, 1.10), respectively. Similarly, the AUC_{12} and $C_{\max}$ GMRs for zidovudine were 0.93 (90% 0.76, 1.14) and 0.92 (90% 0.68, 1.25), respectively, and the AUC_{12} and $C_{\max}$ GMRs for lamivudine were 0.96 (90% 0.81, 1.13) and 0.85 (90% 0.69, 1.05), respectively.[119] Additionally, no significant interaction was seen in 24 healthy subjects when vicriviroc 10 mg twice daily was combined with tenofovir 300 mg once daily.[120]

Efavirenz significantly induces the metabolism of vicriviroc. In 36 healthy subjects, efavirenz 600 mg once daily for 14 days decreased the AUC_{24} and C_{max} of vicriviroc 10 mg once daily by a mean of 81% (90% CI 74, 86) and 67% (90% CI 56, 75), respectively. When ritonavir 100 mg was added to the vicriviroc regimen once daily, the inductive effects were attenuated. The vicriviroc AUC_{24} and C_{max} increased by 384% (90% CI 279, 529) and 196% (90% CI 147, 261), respectively. Therefore, vicriviroc and efavirenz may be administered together, provided that ritonavir is also utilized in the regimen.[121]

3.3 INCB 9471

INCB 9471 is a reversible noncompetitive CCR5 antagonist which has recently completed phase IIa studies. This compound binds to CCR5 receptors slightly differently from other CCR5 receptor antagonists, and its favourable pharmacokinetic profile allows once-daily administration and no requirement for boosting (figure 1f).[122]

3.3.1 Pharmacology—The molecular weight of INCB 9471 is 559.67 g/mol. *In vitro*, the mean IC_{90} of INCB 9471 for preventing infection of PBMCs was 9.3 nmol/L. In assays using the native ligand for chemokine receptors, INCB 9471 was shown to have high receptor selectivity for CCR5, with an IC_{50} of 7.1 nmol/L. INCB 9471 is 84% bound to plasma proteins.[123] The protein-binding corrected IC_{90} is 50–60 nmol/L.[124]

INCB 9471 is a weak inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 activity (IC_{50} values all $>25 \mu\text{mol/L}$). It was also reported that based on reporter gene assay results, the drug is unlikely to induce CYP3A4.[124]

3.3.2 Pharmacokinetics—In a single dose-ranging study in 12 healthy subjects receiving INCB 9471 2.5 mg to 300 mg, the C_{max} ranged from 8.9 to 1300 nmol/L, the t_{max} from 1.9 to 1.4 hours, the elimination half-life from 3.4 to 48.0 hours and the AUC_{∞} from 59 to 21 163 nmol • h/L.[124] In a repeat-dose study in 12 healthy subjects, the pharmacokinetics of INCB 9471 50 mg twice daily, 100 mg twice daily, 150 mg once daily and 200 mg once daily were assessed and exhibited a dose-linear relationship. The C_{max} ranged from 437 to 1363 nmol/L, the t_{max} from 2.1 to 2.7 hours, the C_{min} from 231 to 416 nmol/L and the AUC during the dosage interval (AUC_T) from 3843 to 16 802 nmol • h/L. The elimination half-life was approximately 42 to 56 hours. The C_{min} for the 200 mg dose (416 nmol/L) was 8-fold higher than the protein binding-adjusted IC_{90} in PBMCs.[124] Therefore, the 200 mg once-daily dose is being studied in phase IIb investigations.

3.3.3 Drug-Drug Interactions—Minimal information is available on the pharmacokinetic drug-drug interaction potential of INCB 9471. In one study in 12 healthy subjects, INCB 9471 25 mg twice daily was combined with ritonavir 100 mg twice daily. Compared with INCB 9471 alone, ritonavir increased the AUC_{12} and C_{max} by 1300% and 55%, respectively.[125] Therefore, INCB 9471 will most likely require dose adjustment when combined with boosted protease inhibitor regimens.

4. Integrase Inhibitors

4.1 Raltegravir

Raltegravir, also known as MK 0518, is an integrase strand transfer inhibitor from the hydroxypyrimidine carboxamide class.[126] It is active against multidrug-resistant CCR5-tropic and CXCR4-tropic HIV-1, and the drug has activity against HIV-2.[127] Raltegravir blocks the ability of integrase to catalyse the stepwise process by which HIV-1 DNA is inserted into host cell DNA (figure 1g).

4.1.1 Pharmacology—The molecular weight of raltegravir is 482.507 g/mol. In 50% human serum, the raltegravir IC₉₅ (mean ± SD) is 31 ± 20 nmol/L. Raltegravir is approximately 83% bound to human plasma proteins.[126]

Raltegravir is primarily metabolized in the liver through uridine diphosphate glucuronosyltransferase (UGT) 1A1-mediated glucuronidation. A study investigating the excretion of a 200 mg dose of raltegravir in eight healthy subjects estimated the fraction of raltegravir metabolized by UGT1A1 to be 0.7.[128] Raltegravir is neither a potent inhibitor nor an inducer of CYP enzymes or drug transporters and thus has reduced potential for antiretroviral drug interactions. Based on these properties, raltegravir is not expected to alter the pharmacokinetics of drugs that are substrates of CYP3A4, UGT1A1, UGT2B7 or P-glycoprotein. Since raltegravir is not metabolized by CYP3A or transported by P-glycoprotein, pharmacokinetic enhancement with low-dose ritonavir is not required to achieve therapeutic concentrations.[126]

4.1.2 Pharmacokinetics—In a study of 24 healthy male subjects, raltegravir was rapidly absorbed ($t_{\max}$ ~3 hours). The volume of distribution of raltegravir is approximately 6–7 L/kg, the apparent oral clearance is 0.5 L/h/kg and the terminal elimination half-life is ~9 hours.[129] Bioavailability is estimated at 30%. A dose-ranging study in 35 antiretroviral-naïve HIV-1-infected subjects given doses of raltegravir 100, 200, 400 and 600 mg twice daily demonstrated that the geometric mean C₁₂ in each dosage group exceeded the estimated IC₉₅ of 33 nmol/L.[130] A high-fat meal slows the rate of raltegravir absorption, increasing the C₁₂ by 750%, the AUC₁₂ by 19% and the $t_{\max}$ by 7.3 hours and decreasing the C_{max} by 34%.[131]

Raltegravir is generally well tolerated in patients with moderate hepatic impairment or severe renal insufficiency. These conditions have no clinically important effects upon the pharmacokinetics of raltegravir, and no dose adjustment is required.[132]

4.1.3 Drug-Drug Interactions—Pharmacokinetic drug-drug interaction studies have demonstrated clinically insignificant changes in raltegravir exposure when coadministered with efavirenz, ritonavir, tenofovir[126] and tipranavir.[133]

Raltegravir and Protease Inhibitors: No adjustment in the dosage of raltegravir is required for coadministration with ritonavir, atazanavir or tipranavir. In the presence of ritonavir, the GMRs for the raltegravir AUC₁₂, C_{max} and C₁₂ are 0.84, 0.99 and 0.76, respectively. These results are not considered clinically significant.[134]

A study of the effects of atazanavir on the pharmacokinetics of raltegravir was conducted in 12 healthy subjects; the C₁₂ values of raltegravir increased by 95% in the presence of atazanavir compared with raltegravir administered alone.[131] Despite this pharmacological change, the combination of atazanavir and raltegravir was not associated with any adverse events, and no dose adjustment appears necessary.[126] In a study of 15 healthy subjects, the combination of tipranavir and ritonavir decreased the C₁₂ values of raltegravir by 55%.[135] However, the C₁₂ values were shown to span a 5-log range in the phase III BENCHMRK studies.[136] As a result, the decrease associated with tipranavir/ritonavir coadministration is not considered to be of clinical concern. Moreover, approximately 100 subjects received raltegravir in combination with tipranavir/ritonavir in the BENCHMRK studies. Comparable efficacy was observed in this subgroup relative to those not receiving tipranavir/ritonavir.[137] Taken together, these data indicate that tipranavir/ritonavir may be coadministered with raltegravir without dose adjustment of raltegravir. Since raltegravir concentrations may be decreased when administered in conjunction with tipranavir/ritonavir, the therapeutic efficacy of raltegravir should be monitored closely.

Raltegravir and Reverse Transcriptase Inhibitors: Since raltegravir is primarily metabolized by glucuronidation and displays no inductive or inhibitory action on CYP enzymes *in vitro*, raltegravir is not expected to affect the pharmacokinetic activity of NNRTIs.

The interactions between raltegravir 400 mg twice daily and tenofovir 300 mg once daily were examined in a three-period, open-label study in ten healthy subjects. When coadministered with tenofovir, the GMRs for the AUC_{12} , C_{max} and C_{12} of raltegravir were 1.49 (90% CI 1.15, 1.94), 1.64 (90% CI 1.16, 2.32) and 1.03 (90% CI 0.73, 1.45), respectively. For tenofovir, the GMRs for the AUC_{24} , C_{max} and C_{24} were 0.90 (90% CI 0.82, 0.99), 0.77 (90% CI 0.69, 0.85) and 0.87 (90% CI 0.74, 1.02), respectively. Since tenofovir is primarily eliminated through both glomerular filtration and active tubular secretion, these results indicate an expected lack of interaction between tenofovir and raltegravir.[138]

The interaction between raltegravir/ritonavir and efavirenz was examined in 12 healthy subjects. Coadministration of efavirenz 600 mg once daily with single doses of raltegravir 400 mg decreased the AUC and C_{max} of raltegravir by 36% and the C_{min} by 21%. The observed reduction in raltegravir pharmacokinetics was not considered clinically meaningful. Ritonavir dosing has marginal effects on raltegravir pharmacokinetics, as determined by the C_{12} , $AUC_{1\infty}$ and C_{max} GMRs of 0.99 (90% CI 0.70, 1.40), 0.84 (90% CI 0.70, 1.01) and 0.76 (90% CI 0.55, 1.04), respectively.[134,139] A summary of the interactions between raltegravir and etravirine is provided in section 2.1.3.

Raltegravir and Sedatives: The interaction between a single, 2.0 mg dose of midazolam hydrochloride syrup (2 mg/mL) and raltegravir 400 mg twice daily was evaluated in ten healthy subjects (7 male, 3 female) who participated in a two-period, open-label, fixed-sequence dosing study. The GMRs comparing the pharmacokinetic parameters of midazolam/raltegravir and midazolam alone were 0.92 (90% CI 0.82, 1.03) for the AUC_{∞} and 1.03 (90% CI 0.87, 1.22) for the C_{max} . This result provides additional evidence to indicate that raltegravir is neither an inducer nor an inhibitor of CYP enzyme activity.[140]

Raltegravir and Antibacterials: The pharmacokinetic interaction between rifampicin 600 mg daily and a single 400 mg dose of raltegravir was evaluated in a two-period, open-label, fixed-sequence dosing study of ten healthy subjects (7 male, 3 female). Raltegravir exposure was decreased by 40% when combined with rifampicin, and caution should be used when these drugs are combined.[141]

Raltegravir and Oral Contraceptives: Combining raltegravir 400 mg twice daily with an oral contraceptive containing ethinylestradiol and norgestimate does not alter the overall exposure to the oral contraceptive.[142]

4.2 Elvitegravir

Elvitegravir is currently in phase III clinical trials (figure 1h).

4.2.1 Pharmacology—The molecular weight of elvitegravir is 447.884 g/mol.[143] Elvitegravir demonstrates potent, selective inhibition of viral DNA integration into host chromosomal DNA at an adjusted IC_{50} of 16 nmol/L.[144] Elvitegravir is primarily metabolized by CYP3A. It undergoes secondary metabolic processing by glucuronidation through UGT1A1 and UGT1A3. The metabolic activity of UGT1A1 produces the metabolite M1, while that of UGT1A3 produces the metabolite M4. Both metabolites are less potent than the parent drug. M1 is 5- to 18-fold less potent and M4 is 10- to 38-fold less

potent in antiviral activity assays, and both metabolites are not present in plasma in substantial concentrations. Thus, M1 and M4 do not appear to contribute to the antiviral activity of elvitegravir.[144]

4.2.2 Pharmacokinetics—Pharmacokinetic data generated in studies with both treatment-naïve and treatment-experienced populations demonstrated an approximate 20-fold enhancement in elvitegravir exposure when administered in combination with low-dose ritonavir. HIV-infected patients taking 800 mg once daily exhibited a mean (CV) AUC₂₄ of 5510 ng • h/mL (54%), C_{max} of 940 ng/mL (54%), C_{min} of 13.6 (69%) and elimination half-life of 3.8 hours at steady state. Pharmacokinetic parameters in HIV-infected patients given elvitegravir 50 mg once daily combined with ritonavir 100 mg included an AUC₂₄ of 8840 ng • h/mL (26%), C_{max} of 745 ng/mL (20%), C_{min} of 135 ng/mL (37%) and mean elimination half-life of 8.6 hours.[145] Ritonavir-boosted dosing conditions serve to enhance the oral bioavailability of elvitegravir while reducing its systemic clearance, resulting in overall net inhibition of elvitegravir metabolism.

A study in 32 Japanese healthy male subjects determined that the absorption of elvitegravir is approximately 3-fold higher in the presence of food. Based on this finding, it is recommended that elvitegravir be taken with food.[146]

4.2.3 Drug-Drug Interactions—Drug-drug interaction studies evaluating the pharmacokinetics of NRTIs and NNRTIs have been completed. These studies demonstrated that elvitegravir/ritonavir can be coadministered with zidovudine, didanosine, stavudine, abacavir and tipranavir without the need for dose adjustment. Coadministration of elvitegravir/ritonavir with NNRTIs also does not result in drug-drug interactions. No additional drug interaction information for elvitegravir is available at this time.

Elvitegravir and Protease Inhibitors: In a study in healthy subjects, coadministration of elvitegravir with tipranavir/ritonavir was not found to produce any significant change in the steady-state pharmacokinetics of either drug. Subjects in this crossover study received one of the following for 14 days: elvitegravir/ritonavir 200 mg/100 mg once daily, tipranavir/ritonavir 500 mg/200 mg twice daily or elvitegravir 200 mg once daily plus tipranavir/ritonavir 500 mg/200 mg twice daily. The percent GMRs for the AUC_τ, C_{max} and C_{trough} during the dosage interval (C_τ) of elvitegravir administered with tipranavir/ritonavir compared with elvitegravir/ritonavir alone were 92.4 (90% CI 78.7, 108), 106 (90% CI 89.4, 126) and 90.4 (90% CI 69.8, 117), respectively. The GMRs for the AUC_τ, C_{max} and C_τ of tipranavir/ritonavir administered with elvitegravir compared with tipranavir/ritonavir alone were 88.9 (90% CI 80.0, 98.8), 91.6 (90% CI 83.8, 100) and 88.9 (90% CI 77.4, 102), respectively. No dose adjustment is necessary when coadministering elvitegravir and tipranavir/ritonavir.[147]

Similarly, a study in 20 healthy subjects showed no significant interaction between elvitegravir and darunavir/ritonavir. Participants received either elvitegravir/ritonavir 125 mg/100 mg once daily, darunavir/ritonavir 600 mg/100 mg twice daily or elvitegravir 125 mg once daily plus darunavir/ritonavir 600 mg/100 mg twice daily. The GMRs for the AUC_τ, C_{max} and C_τ of elvitegravir administered with darunavir/ritonavir compared with elvitegravir/ritonavir alone were 111 (90% CI 99.1, 122), 113 (90% CI 103, 124) and 118 (90% CI 106, 131), respectively. The GMRs for the AUC_τ, C_{max} and C_τ of darunavir/ritonavir administered with elvitegravir compared with darunavir/ritonavir alone were 88.7 (90% CI 82.3, 95.6), 89.4 (90% CI 85.0, 94.1) and 82.8 (90% CI 73.7, 92.9), respectively. No dose adjustment is necessary when coadministering elvitegravir and darunavir/ritonavir. [147,148]

Elvitegravir and Reverse Transcriptase Inhibitors: A study of 31 healthy subjects found that the mean exposures of a single tablet of didanosine 400 mg were approximately 15% lower upon coadministration with elvitegravir/ritonavir 200 mg/100 mg. The GMRs for the didanosine $C_{\max}$ and AUC administered with elvitegravir/ritonavir compared with didanosine administered alone were 0.84 (90% CI 0.67, 1.05) and 0.86 (90% CI 0.75, 0.99), respectively.[144] Similar results were seen with stavudine 40 mg. The GMRs for the stavudine $C_{\max}$ and AUC when coadministered with elvitegravir/ritonavir were 0.99 (90% CI 0.93, 1.06) and 1.07 (90% CI 1.05, 1.08), respectively.[144]

Abacavir undergoes partial hepatic biotransformation via glucuronyltransferase.[149] Since elvitegravir undergoes secondary metabolism by glucuronyltransferase, the interaction between elvitegravir/ritonavir 200 mg/100 mg and abacavir was examined in 26 healthy subjects. All subjects received a single 600 mg dose of abacavir on treatment day 1, elvitegravir/ritonavir 200 mg/100 mg once daily on treatment days 5–14, and elvitegravir/ritonavir 200 mg/100 mg plus abacavir 600 mg on treatment day 15. Abacavir pharmacokinetics were not affected when combined with elvitegravir. The GMRs for the abacavir $C_{\max}$ and AUC when administered with elvitegravir/ritonavir were 0.88 (90% CI 0.82, 0.94) and 0.84 (90% CI 0.81, 0.86), respectively.[144] Coadministration with abacavir had no significant impact on the pharmacokinetic parameters of elvitegravir.

Zidovudine undergoes partial hepatic biotransformation via glucuronyltransferase.[150] The pharmacokinetic interaction between elvitegravir/ritonavir and zidovudine and its glucuronide was studied in 28 healthy subjects. Elvitegravir/ritonavir was administered at 200 mg/100 mg once daily and zidovudine at 300 mg twice daily. Pharmacokinetic parameters were observed with a two-way crossover study design for up to 27 days. Upon coadministration with elvitegravir/ritonavir, the pharmacokinetic parameters of elvitegravir, zidovudine and the glucuronide of zidovudine were not altered. The GMRs for the zidovudine $C_{\max}$ and AUC were 0.88 (90% CI 0.77, 1.01) and 0.86 (90% CI 0.80, 0.93), respectively, and the GMRs for the zidovudine glucuronide $C_{\max}$ and AUC were 1.11 (90% CI 1.01, 1.21) and 1.05 (90% CI 1.01, 1.08), respectively.[144]

Coadministration of elvitegravir/ritonavir with the fixed-dose combination formula of emtricitabine/tenofovir disoproxil fumarate did not yield any clinically significant drug-drug interactions between all compounds in 26 healthy subjects.[151]

An evaluation of the pharmacokinetic interaction between elvitegravir/ritonavir and lamivudine has not been completed; however, given the lack of a pharmacokinetic interaction with coadministration of elvitegravir/ritonavir and emtricitabine, a pharmacokinetic interaction with coadministration of elvitegravir/ritonavir and lamivudine is unlikely.[151]

No clinically relevant drug-drug interactions between elvitegravir/ritonavir and etravirine (TMC125) have been found. The results of a study of 34 healthy subjects (17 male, 17 female) demonstrated that coadministration of elvitegravir/ritonavir 150 mg/100 mg once daily and etravirine (F060) 200 mg twice daily is well tolerated and that no dose adjustment is required for coadministration of these two drugs. The GMRs for the $C_{\max}$, AUC₂₄ and C₂₄ of elvitegravir (with ritonavir) administered with etravirine compared with elvitegravir administered alone with ritonavir were 1.07 (90% CI 1.01, 1.13), 1.06 (90% CI 1.0, 1.13) and 1.06 (90% CI 0.97, 1.16), respectively.[44] The GMRs for etravirine alone were not reported.

Elvitegravir and Chemokine Receptor Antagonists: A study of the pharmacokinetic interaction between elvitegravir/ritonavir 150 mg/100 mg twice daily and maraviroc 150 mg

twice daily in 36 healthy subjects demonstrated no effects on elvitegravir exposure, but maraviroc exposure increased by 115% (C_{max}) and 186% (AUC_{12}). This increased exposure is within the range of increases observed when maraviroc is administered in combination with other CYP3A4 inhibitors. Since elvitegravir is metabolized by CYP3A4 and maraviroc is a CYP3A4 substrate, a reduced dose of maraviroc (150 mg) should be administered when combined with elvitegravir/ritonavir.[107]

Elvitegravir and Acid-Reducing Agents: The pharmacokinetics of elvitegravir/ritonavir 50 mg/100 mg alone or coadministered with an antacid or omeprazole 40 mg were evaluated in a study of 12 seronegative subjects. Coadministration with the antacid or omeprazole occurred either simultaneously with elvitegravir/ritonavir or 2 or 4 hours apart from elvitegravir/ritonavir administration. Coadministration of elvitegravir/ritonavir with the antacid decreased the C_{max} , AUC and C_{min} of elvitegravir by 47%, 45% and 41%, respectively. A 2-hour dose separation between the two drugs decreased elvitegravir exposure by 10–20%, and a 4-hour dose separation resulted in a < 5% decrease in comparison with elvitegravir alone. Coadministration of elvitegravir and omeprazole did not affect the exposures of either drug. Therefore, elvitegravir/ritonavir may be coadministered with omeprazole but should be separated from an antacid by at least 2 hours.[152]

5. Maturation Inhibitors

5.1 Bevirimat (PA 457)

Bevirimat (PA 457) is the first compound in the novel class of antiretrovirals called maturation inhibitors, and it is currently in phase II development (figure 1i). Bevirimat inhibits HIV-1 gag processing, which blocks conversion of p25 to p24, a viral core protein. This results in defective viral core condensation and noninfectious viral particles. In essence, this compound is a protease inhibitor, but rather than directly inhibiting the enzyme, bevirimat attaches to the cleavage site of gag between the capsid protein and SP1. The capsid protein is a building block for a structure that surrounds and protects the viral RNA, which is required for maturation into an infectious virion, and SP1 is a transcriptional factor that HIV uses to activate proviral DNA transcription. Since this cleavage site is highly conserved, this mechanism may be favourable with respect to the development of resistance. [153] The IC_{50} for wild-type HIV-1 is approximately 10 nmol/L (5.8 ng/mL).[153] The protein binding-adjusted IC_{90} is estimated to be 2.3 μ g/mL.[154]

5.1.1 Pharmacology—The molecular weight of bevirimat is 584.83 g/mol. The protein binding to human serum albumin is reported to be greater than 99.5%, with no significant binding to α_1 -acid glycoprotein (Martin DE, Panacos Pharmaceuticals Inc., personal communication).

Bevirimat is a substrate of UGTs. The primary pathway of biotransformation is glucuronidation by UGT1A3.[155] Bevirimat also exhibits weak to moderate inhibition of the UGTs 1A1, 1A3, 1A4, 1A8, 1A10 and 2B7.[155]

In studies using human liver microsomes, the IC_{50} values of bevirimat for CYP1A2, CYP2C19, CYP2D6 and CYP3A4 were >100 μ mol/L. The IC_{50} of CYP2C9 was 10 μ mol/L.[155] In a multiple-dose study in healthy subjects, the GMRs for urinary 6 β -hydroxycortisol/cortisol ratios (a crude measure of CYP3A induction) ranged from 1.02 (90% CI 0.528, 1.96) to 1.36 (90% CI 0.693, 2.67), suggesting no important inductive effects of bevirimat on CYP3A enzyme activity.[156] Bevirimat does not interact with P-glycoprotein.[157]

5.1.2 Pharmacokinetics—In a study in 24 healthy male subjects given single doses of bevirimat 25 to 250 mg, the $t_{\max}$ was achieved in approximately 2 hours, and the AUC_{∞} and $C_{\max}$ dose-exposure relationships were linear, ranging from approximately 170 to 2000 $\mu\text{g} \cdot \text{h/mL}$ and from 3 to 30 $\mu\text{g/mL}$, respectively.[154] In a multiple-dose study in 36 healthy subjects evaluating doses from 25 to 200 mg once daily, an accumulation in bevirimat exposure was seen between day 1 and day 10. The terminal elimination half-life for all doses ranged from 56 to 70 hours, and the steady-state oral clearance ranged from 173.9 to 185.2 mL/h.[156] Pharmacokinetic parameters were similar in a multiple-dose study in 32 HIV-infected patients: the mean (CV) elimination half-life was 62.7 hours (19%) and the mean oral clearance was 210 mL/h.[158] In phase II studies, doses up to 400 mg are being investigated.

5.1.3 Drug-Drug Interactions

Bevirimat and Protease Inhibitors: When coadministered with ritonavir, bevirimat exposure decreases. This is probably due to the UGT-inductive effects of ritonavir. Bevirimat 200 mg once daily was coadministered with ritonavir 100 or 200 mg twice daily. These combinations were well tolerated. The AUC_{24} and $C_{\max}$ of bevirimat decreased in a dose-dependent manner when combined with ritonavir. The GMRs for the AUC_{24} and $C_{\max}$ of bevirimat were 0.83 (90% CI 0.75, 0.92) and 0.96 (90% CI 0.87, 1.06), respectively, when combined with ritonavir 100 mg twice daily. When combined with ritonavir 200 mg twice daily, the GMRs for the AUC_{24} and $C_{\max}$ of bevirimat were 0.69 (90% CI 0.62, 0.77) and 0.83 (90% CI 0.75, 0.92), respectively. No notable changes were seen in ritonavir exposures.[159] The clinical significance of these changes in exposure are being further evaluated.

In a study of 48 healthy subjects, the combination of bevirimat and atazanavir was well tolerated, with no increase in bilirubin levels and no pharmacokinetic interactions being observed. Bevirimat 200 mg once daily was combined with atazanavir 400 mg once daily. Compared with the exposure of either drug alone, the GMRs for the AUC_{24} and $C_{\max}$ were 0.92 (90% CI 0.81, 1.09) and 0.96 (90% CI 0.85, 1.09), respectively, for bevirimat and 0.94 (90% CI 0.78, 1.13) and 0.94 (90% CI 0.82, 1.07), respectively, for atazanavir.[160] Therefore, no dose adjustment should be necessary when combining bevirimat and atazanavir.

6. Conclusions

Potent new antiretroviral drugs in existing and novel classes offer treatment-experienced HIV-infected patients the chance of durable, long-term suppression of HIV replication. However, the increase in antiretroviral drug options also increases the complexity of using novel combinations of these agents together. Most new agents have significant drug-drug interaction challenges, and the clinical significance of these interactions cannot always be determined in well controlled studies that take place in healthy subjects. A thorough knowledge of how these drugs are metabolized and eliminated from the body will assist in predicting and managing important and potentially detrimental drug-drug interactions.

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Fig. 1. Chemical structures of **(a)** darunavir, **(b)** etravirine, **(c)** rilpivirine, **(d)** maraviroc, **(e)** vicriviroc, **(f)** INCB 9471 **(g)** raltegravir, **(h)** elvitegravir and **(i)** bevirimat.

Table I

Interactions of new/investigational antiretrovirals (ARVs) with other ARVs: nucleoside reverse transcriptase inhibitors (NRTIs) and first-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) and dosage recommendations for the target drug

Drug class	Target drug	NRTI			First-generation NNRTI			
		ZDV	3TC	ddI	TDF	D4T	ABC	EFV
PI	Darunavir, RTV boosted				↔, no dose adjustment needed			↔, no dose adjustment needed
NNRTI	Etravirine			↑, no dose adjustment needed	↓, no dose adjustment needed			↓, do not coadminister
	Rilpivirine				↔, no dose adjustment needed			
CCR5 antagonists	Maraviroc	↔, no dose adjustment needed	↔, no dose adjustment needed		↔, no dose adjustment needed			↓, adjust dose
	Vicriviroc, RTV boosted	↔, no dose adjustment needed	↔, no dose adjustment needed		↔, no dose adjustment needed			↔, no dose adjustment needed
Integrase inhibitor	Raltegravir		No dose adjustment needed		↑, no dose adjustment needed			↓, no dose adjustment needed
	Elvitegravir, RTV boosted	↑, no dose adjustment needed		↓, no dose adjustment needed	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed	No dose adjustment needed

3TC = lamivudine; ABC = abacavir; D4T = stavudine; ddI = didanosine; EFV = efavirenz; NVP = nevirapine; PI = protease inhibitor; RTV = ritonavir; TDF = tenofovir; ZDV = zidovudine; ↑ indicates an increase in the concentration of the target drug; ↓ indicates a decrease in the concentration of the target drug; ↔ indicates no change in the concentration of the target drug.

Table II

Interactions of new/investigational antiretrovirals (ARVs) with other ARVs; protease inhibitors (PIs) and dosage recommendations for the target drug

Drug class	Target drug	PI									
		DRV	TPV	IDV	NFV	ATV	SQV	LPV	RTV	LPV	DRV
PI	Darunavir, RTV boosted			↔, no dose adjustment needed		↔, no dose adjustment needed	↓, do not coadminister	↓, do not coadminister			
NNRTI	Etravirine					↑, no dose adjustment needed ^a			↓, do not coadminister (RTV 600 mg)		
	Rilpivirine										↑, no dose adjustment needed
CCR5 antagonist	Maraviroc			↑, adjust dose	↑, adjust dose	↑, adjust dose	↑, adjust dose	↑, adjust dose	↑, adjust dose		↑, adjust dose
	Vicriviroc, RTV boosted			↔, no dose adjustment needed	↔, no dose adjustment needed	↔, no dose adjustment needed	↔, no dose adjustment needed	↔, no dose adjustment needed			↔, no dose adjustment needed
	INCB 9471								↑, dose adjustment likely		
Integrase inhibitor	Raltegravir					↑, no dose adjustment needed			↓, no dose adjustment needed		
	Elvitegravir, RTV boosted					↑, no dose adjustment needed					↑, no dose adjustment needed
Maturation inhibitor	Bevirimat					↔, no dose adjustment needed			↓, dose adjustment may be needed		

^aUnboosted ATV not recommended.

ATV = atazanavir; DRV = darunavir; IDV = idinavir; LPV = lopinavir; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; RTV = ritonavir; SQV = saquinavir; TPV = tipranavir; ↑ indicates an increase in the concentration of the target drug; ↓ indicates a decrease in the concentration of the target drug; ↔ indicates no change in the concentration of the target drug.

Table III

Interactions of new/investigational antiretrovirals (ARVs) with other ARVs: second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) and CCR5 antagonists

Drug class	Target drug	Second-generation NNRTI	CCR5 antagonist
		etravirine	maraviroc
PI	Darunavir, RTV boosted	↔, no dose adjustment needed	↔, no dose adjustment needed
NNRTI	Etravirine		↔, no dose adjustment needed
CCR5 antagonist	Maraviroc	↓, adjust dose	
Integrase inhibitor	Raltegravir	↓, no dose adjustment needed	
	Elvitegravir, RTV boosted	↔, no dose adjustment needed	↔, no dose adjustment needed

PI = protease inhibitor; **RTV** = ritonavir; ↑ indicates an increase in the concentration of the target drug; ↓ indicates a decrease in the concentration of the target drug; ↔ indicates no change in the concentration of the target drug.

Table IV

Interactions between new/investigational antiretrovirals (ARVs) and non-ARVs

ARV	HMG CoA reductase inhibitors	Oral contraceptives	PDE-5 inhibitors	Selective serotonin reuptake inhibitors	Anti-infectives	Acid-reducing agents	Sedatives and opioid analgesics
Darunavir	Increased atorvastatin exposure; adjust atorvastatin dose. Increased pravastatin exposure; adjust pravastatin dose	Decreased ethinylestradiol/norethisterone exposure; contraceptive may not be effective	Increased sildenafil, vardenafil and tadalafil exposures; reduce PDE-5 inhibitor dose	Decreased paroxetine and sertraline exposures; clinical significance unknown; close monitoring and titration recommended	Increased rifabutin exposure; adjust dose. Increased ketoconazole and itraconazole exposures; maximum daily dose of 200 mg for both ketoconazole and itraconazole	Ranitidine: no dose adjustment needed. Omeprazole: no dose adjustment needed	
Rilpivirine	Increased atorvastatin exposure; no dose adjustment needed				Decreased ketoconazole exposure; increased rilpivirine exposure; no specific dose adjustment recommendations available; monitor closely	Famotidine: decreased rilpivirine absorption; administer famotidine or other histamine H ₂ -receptor blocking acid reducer 12 h before or 4 h after rilpivirine	
Etravirine			Decreased sildenafil exposure; adjust sildenafil dose	Minimally increased paroxetine exposure; minimally increased etravirine exposure; no dose adjustment needed		Ranitidine: no dose adjustment needed. Omeprazole: minimally increased etravirine exposure; no dose adjustment needed	Methadone: no dose adjustment needed; monitor for methadone withdrawal
Maraviroc		Ethinylestradiol/levonorgestrel; no dose adjustment needed			Ketoconazole: increased maraviroc exposure; do not coadminister. Rifampicin (rifampin): decreased maraviroc exposure; adjust dose		Midazolam: no dose adjustment needed
Raltegravir		Ethinylestradiol/norgestimate; no dose adjustment needed			Rifampicin: decreased raltegravir exposure; use caution when coadministering		Midazolam: no dose adjustment needed
Elvitegravir						Antacid: decreased elvitegravir exposure; separate by at least 2 h. Omeprazole: no dose adjustment needed	

PDE = phosphodiesterase.