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Review

Pharmacokinetics and drug–drug interactions of antiretrovirals: An update

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ABSTRACT

Current antiretroviral treatment has allowed HIV infection to become a chronic manageable condition with many HIV patients living longer. However, available antiretrovirals are not without limitations, for example the development of resistance and adverse effects. Consequently, new drugs in existing and novel classes are urgently required to provide viable treatment options to patients with few remaining choices. Darunavir, etravirine, maraviroc and raltegravir have been recently approved for treatment-experienced patients and other agents such as rilpivirine, vicriviroc and elvitegravir are currently under phase III study. Clinical studies are necessary to optimise potential treatment combinations and to manage drug–drug interactions to help avoid toxicity or therapy failure. This review aims to summarise the pharmacokinetics and key drug–drug interaction studies for newly available antiretrovirals and those in development. Further information regarding drug–drug interactions of well established antiretrovirals and those recently approved are readily available online at sites such as http://www.hiv-druginteractions.org, http://www.clinicaloptions.com/hiv, http://hivinsite.ucsf.edu.

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1. Introduction

The advent of highly active antiretroviral therapy (HAART) targeting two distinct areas of the HIV lifecycle (reverse transcriptase and protease) has had a dramatic effect on the morbidity and mortality of HIV-infected individuals. However the global burden of HIV remains high with an estimated 33 million adults and children living with the disease at the end of 2007. Current treatment, when available, is not without limitations such as high pill burden, occurrence of adverse events and particularly development of resistance and cross-resistance between drug classes. The need for newer antiretrovirals in existing classes and development of therapies aimed at novel targets are paramount in order to provide broader treatment options to those with few choices remaining, as a result of multiple regimen failures or contraction of resistant virus.

Encouragingly, a number of agents have recently gained approval in existing and new drug classes whilst others are still at the developmental stage. Additions to established classes include the protease inhibitor darunavir and non-nucleoside reverse transcriptase inhibitors (NNRTI) etravirine and rilpivirine (formally TMC-278), although the latter is not yet licensed for clinical use. Maraviroc is the first antiretroviral approved to selectively target the CCR5 receptor and raltegravir is the first in the class of integrase inhibitors, providing two additional targets to combat the virus. Also of interest is the development of another integrase inhibitor (elvitegravir) and two new pharmacoenhancers, GS-9350 (Gilead Sciences, Inc.) and SPI-452 (Sequoia Pharmaceuticals, Inc.), which although in early stages of development are well tolerated and demonstrate potent inhibition of CYP3A metabolism without any antiviral activity (Gulnik et al., 2009; Mathias et al., 2009a).

Despite intensive research efforts a cure for HIV infection remains elusive. However as a result of improved antiretroviral treatment, the disease has become a chronic manageable illness in Western countries with infected patients generally living longer. Patients therefore not only require medications for HIV infection but also for related or unrelated co-morbidities, providing further challenges for healthcare providers and patients alike. Drug–drug interactions are common as a result of interacting metabolic pathways and it is of great importance that drug–drug interactions of newly available therapies are investigated to determine optimal treatment combinations and provide maximum therapeutic effect.

In basic terms, pharmacokinetics can be defined as 'what the body does to the drug', implying the absorption, distribution in tissues and cells, and elimination (or clearance) via hepatic and/or renal pathways. The concentrations of drug obtained over time can be related to the response or effect of the drug (pharmacodynamics) which can be beneficial (*i.e.* therapeutic) or potentially toxic (increased side-effects). Plasma concentrations can be used as a surrogate marker to link antiretroviral pharmacokinetics to antiviral response in the form of reduction in viral load, which has been demonstrated for protease inhibitors. However, with some antiretrovirals the relationship is not clear. For example, plasma pharmacokinetic parameters have yet to be definitively related to virological response for raltegravir, and CCR5-receptor occupancy demonstrates a better relationship with virological suppression than plasma concentrations for maraviroc (Jacqmin et al., 2008; Rosario et al., 2008). With newer antiretrovirals acting at novel target sites, the classical example of a plasma pharmacokinetic–pharmacodynamic relationship may not apply. Drug–drug interactions can clearly impact on the efficacy or toxicity of antiretrovirals and/or co-medications by altering drug concentrations either below a recommended threshold for therapeutic effect or above a cut-off for toxicity.

The present review will focus on the pharmacokinetics and known drug–drug interactions of newly available antiretrovirals. A number of agents currently under development will also be briefly discussed. Well established antiretrovirals have been extensively studied and reviewed elsewhere. Furthermore, information on drug–drug interactions of older antiretrovirals is summarised and readily accessible through online resources such as http://www.hiv-druginteractions.org, http://www.clinicaloptions.com/hiv, http://hivinsite.ucsf.edu.

2. Established drug classes

2.1. Protease inhibitors

It remains important to develop antiretrovirals in existing drug classes that are active against resistant viral strains in order to improve treatment options for failing patients or those naïve to treatment but harbouring virus resistant to recommended first-line therapy.

2.1.1. Darunavir

Darunavir is a peptidomimetic protease inhibitor with a high genetic barrier to resistance, active against wild-type HIV-1 and various protease inhibitor-resistant strains (De Meyer et al., 2005; Koh et al., 2003). It is structurally related to amprenavir; however it binds over 100 times more tightly to the HIV protease (King et al., 2004). Darunavir, boosted with ritonavir (600/100 mg twice daily with food) is approved for use in treatment-experienced patients with resistance to at least one protease inhibitor and has proven safety and efficacy as demonstrated in the POWER 1, 2 and 3 clinical trials (Clotet et al., 2007; Molina et al., 2007). Once daily dosing is recommended for treatment-naïve patients at a dose of 800/100 mg once daily with food (Janssen-Cilag Ltd., 2009b).

Overall, it appears that HIV-infected patients experience higher darunavir concentrations in comparison with healthy volunteers which can be potentially explained by higher concentrations of α-1-acid glycoprotein in patients (Janssen-Cilag Ltd., 2008). A relationship between darunavir area under the curve (AUC_{0-12}) and baseline α-1-acid glycoprotein was observed in an analysis of data from the TITAN study ($n = 285$) (Sekar et al., 2007c). Also a pop-

ulation pharmacokinetic model including HIV-infected patients and healthy individuals observed an inverse correlation between darunavir apparent oral clearance and α-1-acid glycoprotein concentrations (Vis et al., 2006). Darunavir in the presence of ritonavir (600/100 mg twice daily) is rapidly absorbed with peak concentrations reached 2.5–4 h post-dose (Janssen-Cilag Ltd., 2008) and absolute bioavailability being increased from 37% for darunavir alone (600 mg single dose) to 82% following administration with ritonavir (100 mg twice daily) (Sekar et al., 2006c). Darunavir is approximately 95% bound, primarily to α-1-acid glycoprotein in plasma (Sekar et al., 2006f). Following intravenous administration the mean volume of distribution was 88 L increasing to 131 L with ritonavir (100 mg twice daily) in healthy volunteers ($n = 8$) (Sekar et al., 2006c). In a dose ranging study (1200/100 mg once daily) a half-life of approximately 15 h was observed for darunavir (Sekar et al., 2006f) and a single intravenous dose (150 mg, 1 h infusion) in healthy volunteers determined total clearance values of approximately 33 L/h and 6 L/h in the absence and presence of ritonavir, respectively (Sekar et al., 2006c). Darunavir, like ritonavir, is a substrate and inhibitor of CYP3A4; a clinical study also observed induction of CYP2C9 and CYP2C19 and inhibition of CYP2D6, potentially attributable to ritonavir (Janssen-Cilag Ltd., 2008; Mamidi et al., 2005; Rittweger and Arasteh, 2007). Therefore there is vast potential for drug–drug interactions.

2.1.2. Darunavir drug–drug interactions

As darunavir and ritonavir are substrates and inhibitors of CYP3A4 a number of studies have been performed to determine potential drug–drug interactions between darunavir and medications that may be given in combination. The majority of studies have been carried out at lower darunavir doses than that approved for treatment but the outcomes should still apply to the recommended dose. Key drug–drug interactions where concentrations of darunavir or the co-medication were significantly altered (*i.e.* based on least squares mean ratios, 90% CI) and/or dose adjustments required are summarised (Table 1). Prezista® Summary of Product Characteristics/Prescribing Information or other electronic resources should be consulted for full drug–drug interaction information.

2.2. Non-nucleoside reverse transcriptase inhibitors (NNRTI)

Efavirenz and nevirapine form important components of first-line antiretroviral therapy due to factors such as potent activity, favourable dosing schedules and low pill burden. However sustainable use is limited by a low genetic barrier to resistance, with single mutations in the reverse transcriptase greatly reducing virus susceptibility to efavirenz and nevirapine. Compounds active against NNRTI-resistant virus would clearly provide opportunities to those failing therapy.

2.2.1. Etravirine

Over 10 years elapsed until successful development of the next generation NNRTI, etravirine. Etravirine is a diarylpyrimidine NNRTI with flexible binding to the reverse transcriptase in multiple conformations therefore allowing less susceptibility to drug-resistant mutations (Das et al., 2004). Etravirine is licensed for treatment of HIV patients resistant to current NNRTI and other antiretrovirals and has demonstrated 24-week safety and efficacy in the DUET-1 and 2 clinical studies in treatment-experienced patients (Lazzarin et al., 2007; Madruga et al., 2007); 48-week data are also available.

Etravirine is recommended at a dose of 200 mg twice daily to be taken with food (Janssen-Cilag Ltd., 2009a). Concentrations in HIV-infected individuals appear to be approximately 35–50% lower than those observed in healthy volunteers (Piscitelli et al., 2002a), the mechanism of which is unknown. Generally, differences in concentrations between HIV patients and healthy volunteers can be attributed to differential absorption due to differences in gut pH; however this has not been proven for etravirine. The absolute bioavailability of etravirine is not known as an intravenous formulation is unavailable; however absorption is increased by about 50% in the presence of food (Schöller-Gyüre et al., 2008a). Etravirine is highly bound to plasma proteins (~99.9%), primarily to albumin (99.6%) and α-1-acid glycoprotein (97.7–99.0%) *in vitro* (Andries et al., 2004; Janssen-Cilag Ltd., 2009a) and the terminal half-life ranges between 30 and 40 h (Piscitelli et al., 2002a). Following a population pharmacokinetic analysis of 575 patients included in the DUET studies apparent oral clearance and volume of the central compartment were estimated as 43.7 L/h and 422 L, respectively (Kakuda et al., 2008). Etravirine is metabolised by CYP3A4, CYP2C9 and CYP2C19 followed by glucuronidation, it is also a weak inducer of CYP34A and weak inhibitor of CYP2C9 and CYP2C19 (Janssen-Cilag Ltd., 2009a; Schiller and Youssef-Bessler, 2009), therefore management of drug–drug interactions is foreseeable with etravirine-containing therapy.

2.2.2. Etravirine drug–drug interactions

Known interactions which result in significant changes in pharmacokinetics or dose alterations of etravirine or co-medications are summarised (Table 2). For example, etravirine in combination with unboosted atazanavir is not recommended and dosage adjustment of fosamprenavir in the presence of etravirine may be necessary (Table 2). More complete drug–drug interaction information can be found in the Intelence® Summary of Product Characteristics or Prescribing information.

2.2.3. Rilpivirine

Rilpivirine (TMC278), like etravirine, is an NNRTI that has demonstrated activity against NNRTI-resistant viral strains due to the flexibility of interactions with the HIV reverse transcriptase. *In vitro*, little or no loss of activity has been reported against single NNRTI mutations, including the common K103N and activity is also retained against some double mutations completely resistant to other NNRTI (*e.g.* K103N + Y181C) (Goebel et al., 2006; Guillemont et al., 2005; Janssen et al., 2005). Currently rilpivirine is entering phase III clinical study and has shown promise as a once daily medication with good bioavailability, safety and tolerability. Preliminary efficacy data were initially established following two small phase IIa studies investigating TMC278 monotherapy *vs.* placebo (TMC278-C201 and TMC278-C202) (de Béthune et al., 2005; Goebel et al., 2006). Doses of 25, 75 and 150 mg once daily have been evaluated in comparison to efavirenz (600 mg once daily) plus Combivir® (lamivudine/zidovudine) or Truvada® (tenofovir/emtricitabine) and have demonstrated sustained efficacy at 48 weeks and continued to 96 weeks (TMC278-C204) in treatment-naïve patients (Molina et al., 2008; Pozniak et al., 2007; Santoscoy et al., 2008). The dose of 25 mg once daily has now been taken forward into phase III study. A mean terminal half-life between 34 and 55 h has been estimated and dose proportional pharmacokinetics in the range 25–150 mg once daily have been observed in healthy volunteers (de Béthune et al., 2005). Rilpivirine exposure is increased by 45% in the presence of food and should therefore be administered with a meal (Hoetelmans et al., 2005a). Rilpivirine is a substrate and inducer of CYP34A *in vitro* and like with other NNRTI drug–drug interactions are expected. However, based on *in vivo* data mild induction of CYP3A was reported at 300 mg once daily and a clinically relevant affect on CYP3A is not considered likely at chosen doses of 25 mg and 75 mg once daily (Crauwels et al., 2009b). Nanotechnology is currently being employed to evaluate the feasibility of a long acting formulation administered by intramuscular or subcutaneous injection. Single doses resulted in sustained rilpivirine concentrations for over 3 months in dogs and

Table 1
Key darunavir drug–drug interaction studies evaluating the effects on exposure summarised by means of least squares mean ratios and 90% confidence intervals (no change in exposure = LSM 1.00).

Co-medication	*N*	Dose		AUC_τ LSM (90% CI)		Recommendation	Reference
		DRV/RTV	Co-medication	DRV/RTV	Co-medication		
Lopinavir	14	1200/100 mg *bid*[a]	400/100 mg *bid*	0.62 (0.53–0.73)	1.09 (0.86–1.37)	Not recommended	Sekar et al. (2006e)
	15	1200 mg *bid*[a]	533/133 mg *bid*	0.59 (0.50–0.70)	1.09 (0.96–1.24)	Not recommended	Sekar et al. (2006e)
Saquinavir	14	400/100 mg *bid*	1000/100 mg *bid*	0.74 (0.63–0.86)	0.94 (0.76–1.17)	Not recommended	Sekar et al. (2007e)
Tenofovir	12	300/100 mg *bid*	300 mg *qd*	1.21 (0.95–1.54)	1.22 (1.10–1.35)	Consider monitoring renal function	Hoetelmans et al. (2007)
Efavirenz	12	300/100 mg *bid*	600 mg *qd*	0.87 (0.75–1.01)	1.21 (1.08–1.36)	Use with caution	Sekar et al. (2007d)
Etravirine	13	600/100 mg *bid*	100 mg *bid*	1.06 (1.00–1.13)	0.63 (0.54–0.73)	No dose adjustments necessary	Schöller-Gyüre et al. (2007b)
	10	600/100 mg *bid*	200 mg *bid*[b]	1.15 (1.05–1.26)	1.80 (1.56–2.08)	No dose adjustments necessary	Schöller-Gyüre et al. (2007b)
Nevirapine	8[c]	400/100 mg *bid*	200 mg *bid*	1.24 (0.97–1.57)	1.27 (1.12–1.44)	No dose adjustments necessary	Sekar et al. (2006d)
Atorvastatin	15	300/100 mg *bid*	40 mg *qd* alone 10 mg *qd* + DRV/RTV	No data	0.85 (0.76–0.97)	Titrate dose from 10 mg *qd* based on clinical response	Hoetelmans et al. (2004)
Pravastatin	14	600/100 mg *bid*	40 mg *qd*	No data	1.81 (1.23–2.66)	Titrate from lowest dose based on clinical response	Sekar et al. (2007b)
R-methadone	16	600/100 mg *bid*	60–200 mg *qd*	No data	0.84 (0.78–0.91)	No dose adjustment necessary	Sekar et al. (2006b)
Ethinyl estradiol	11	600/100 mg *bid*	0.035 mg (combined pill)	No data	0.56 (0.50–0.63)	Use alternative or additional contraception	Sekar et al. (2008c)
Norethindrone	11	600/100 mg *bid*	1 mg (combined pill)	No data	0.86 (0.75–0.98)	Use alternative or additional contraception	Sekar et al. (2008c)
Sildenafil	16	400/100 mg *bid*	100 mg *qd* 25 mg *qd* + DRV/RTV	No data	0.97 (0.86–1.09)	No more than 25 mg sildenafil over 48 h	Sekar et al. (2008a)
Paroxetine	16	400/100 mg *bid*	20 mg *qd*	1.02 (0.95–1.10)	0.61 (0.56–0.66)	Monitor paroxetine; titrate dose based on clinical response if necessary	Sekar et al. (2006a)
Sertraline	13	400/100 mg *bid*	50 mg *qd*	0.98 (0.84–1.14)	0.51 (0.46–0.58)	Monitor sertraline; titrate dose based on clinical response if necessary	Sekar et al. (2006a)
Clarithromycin	17	400/100 mg *bid*	500 mg *bid*	0.87 (0.75–1.01)	1.57 (1.35–1.84)	Caution is warranted, particularly in those with renal impairment. Consider dose reduction of 50% or 75% in patients with CrCL 30–60 and <30 ml/min, respectively.	Sekar et al. (2008d)
Ketoconazole	15	400/100 mg *bid*	200 mg *bid*	1.42 (1.23–1.65)	3.12 (2.65–368)	Maximum dose of 200 mg *qd* ketoconazole to be used	Sekar et al. (2008b)
Digoxin	14	600/100 mg *bid*	0.4 mg *qd*	No data	1.35 (1.00–1.82)	Start with lowest dose of digoxin; titrate and monitor digoxin concentrations	Sekar et al. (2007a)

AUC_τ: area under the concentration–time curve over the dosing interval; LSM: least squares mean; CI: confidence interval; *N*: number of participants; DRV: darunavir; RTV: ritonavir; *bid*: twice daily; *qd*: once daily; CrCL: creatinine clearance.

[a] Reference darunavir/ritonavir dose of 600/100 mg *bid*.

[b] Reference etravirine dose of 100 mg *bid*.

[c] HIV-infected patients.

Table 2
Key etravirine drug–drug interaction studies evaluating the effects on exposure summarised by means of least squares mean ratios and 90% confidence intervals (no change in exposure = LSM 1.00).

Co-medication	*N*	Dose		AUC_{τ}[a] LSM (90% CI)		Recommendation	Reference
		ETV	Co-medication	ETV	Co-medication		
Atazanavir	14	800 mg *bid*	400 mg *qd*	1.50 (1.41–1.59)	0.83 (0.63–1.09)	Not recommended unboosted	Schöller-Gyüre et al. (2006e)
Atazanavir	13	800 mg *bid*	300/100 mg *qd*	1.30 (1.18–1.44)	0.86 (0.79–0.93)	No dose adjustment necessary	Schöller-Gyüre et al. (2006e)
Darunavir	13	100 mg *bid*	600/100 mg *bid*	1.06 (1.00–1.13)	0.63 (0.54–0.73)	No dosage adjustment necessary	Schöller-Gyüre et al. (2007b)
	10	200 mg *bid*[b]	600/100 mg *bid*	1.15 (1.05–1.26)	1.80 (1.56–2.08)	No dosage adjustment necessary	Schöller-Gyüre et al. (2007b)
Fosamprenavir	8[c]	800 mg *bid*	700/100 mg *bid*	No data	1.69 (1.53–1.86)	Consider dose adjustment of fosamprenavir/ritonavir	Schöller-Gyüre et al. (2006d)
Lopinavir	13	1600 mg *bid*	400/100 mg *bid*	1.17 (0.96–1.43)	0.80 (0.49–1.07)	No dosage adjustment necessary	Piscitelli et al. (2002b)
Tipranavir	19	800 mg *bid*	500/200 mg *bid*	0.24 (0.18–0.33)	1.18 (1.03–1.36)	Not recommended	Schöller et al. (2006)
Efavirenz	12	900 mg single dose	600 mg *qd*	0.59 (0.52–0.68)	No data	Not recommended	Baede et al. (2002)
Nevirapine	5	900 mg single dose	200 mg *bid*	0.45[d]	No data	Not recommended	Baede et al. (2002)
Maraviroc	14	200 mg *bid*	300 mg *bid*	1.06 (0.99–1.14)	0.47 (0.38–0.58)	Recommended to increase maraviroc to 600 mg *bid*	Davis et al. (2007)
Raltegravir	19	200 mg *bid*	400 mg *bid*	1.10 (1.03–1.16)	0.90 (0.68–1.18)	No dosage adjustment necessary	Anderson et al. (2008)
Atorvastatin	16	800 mg *bid*	40 mg *qd*	1.10 (1.02–1.19)	0.63 (0.58–0.68)	Titrate atorvastatin dose based on clinical response	Schöller-Gyüre et al. (2007a)
R-Methadone	16	100 mg *bid*	60–130 mg *qd*	No data	1.06 (0.99–1.13)	No dosage adjustments necessary	Schöller-Gyüre et al. (2008c)
Ethinyl estradiol	16	200 mg *bid*	0.035 mg *qd* (combined pill)	No data	1.22 (1.13–1.31)	No dosage adjustment necessary	Schöller-Gyüre et al. (2006a)
Norethindrone	16	200 mg *bid*	1 mg *qd* (combined pill)	No data	0.95 (0.90–0.99)	No dosage adjustment necessary	Schöller-Gyüre et al. (2006a)
Sildenafil	14	800 mg *bid*	50 mg single dose	No data	0.43 (0.36–0.51)	Titrate sildenafil dose based on clinical response	Schöller-Gyüre et al. (2006b)
Clarithromycin	15	200 mg *bid*	500 mg *bid*	1.42 (1.34–1.50)	0.61 (0.53–0.69)	Consider alternatives to clarithromycin	Schöller-Gyüre et al. (2006c)
Ranitidine	16	100 mg *bid*	150 mg *bid*	0.86 (0.76–0.97)	No data	Not considered clinically relevant; no dosage adjustment necessary	Schöller-Gyüre et al. (2008b)
Omeprazole	17	100 mg *bid*	40 mg *qd*	1.41 (1.22–1.62)	No data	Not considered clinically relevant; no dosage adjustment necessary	Schöller-Gyüre et al. (2008b)
Rifabutin	12	800 mg *bid*	300 mg *qd*	0.63 (0.54–0.74)	0.83 (0.75–0.94)	Not considered clinically relevant; no dosage adjustment necessary	Schöller-Gyüre et al. (2006f)

AUC_{τ}: area under the concentration–time curve over the dosing interval; LSM: least squares mean; CI: confidence interval; *N*: number of participants; ETV: etravirine; *bid*: twice daily; *qd*: once daily.

[a] $AUC_{0-\infty}$ for single dose;

[b] Reference etravirine dose of 100 mg *bid*.

[c] HIV-infected patients.

[d] Calculation of CI not possible due to small sample size.

3 weeks in mice. Subcutaneous injection resulted in more stable plasma concentrations in dogs (5 mg/kg, 200 nm nanosuspensions) (Baert et al., 2009). A long acting preparation would be beneficial for ongoing HIV treatment or prophylaxis.

2.2.4. Rilpivirine drug–drug interactions

Few data are available regarding drug–drug interactions with rilpivirine due to its stage of development. However, rilpivirine (150 mg once daily) has been shown to decrease ketoconazole exposure (400 mg once daily) (van Heeswijk et al., 2006) and increase tenofovir exposure (300 mg once daily) (Hoetelmans et al., 2005b). Furthermore, ketoconazole increased rilpivirine pharmacokinetic parameters (AUC_{0-24}, C_{max}, C_{min} by 49%, 30%, 76%, respectively) (van Heeswijk et al., 2006) and tenofovir has been shown to have no effect on rilpivirine pharmacokinetics in healthy volunteers (Hoetelmans et al., 2005b). Recently, a study examined the potential interaction between rilpivirine (75 mg once daily) and sildenafil (50 mg single dose) in 16 healthy individuals and showed that neither drug had a significant affect on the other and could be co-administered without dose adjustment (Crauwels et al., 2009a). A study has recently been completed to investigate the potential interaction between rilpivirine and oral contraceptives and a study is currently ongoing assessing rilpivirine in combination with methadone (ClinicalTrials.gov, 2009a).

2.3. Nucleoside reverse transcriptase inhibitors (NRTI)

NRTI form the cornerstone of combination antiretroviral regimens. Like protease inhibitors and NNRTI, development of resistance and toxicities is problematic with compounds currently available in this class. Therefore, there is the need for new NRTI active against resistant viral strains with improved safety and tolerability.

2.3.1. Apricitabine

Apricitabine is a deoxycytidine analogue NRTI currently under clinical development with *in vitro* activity against NRTI resistant virus including the common M184V and thymidine analogue mutations (TAMs) (Cox and Southby, 2009). Promising efficacy and safety has been observed in both treatment-naïve and experienced patients in phase II study. A randomised placebo controlled study assessed apricitabine efficacy following 10 days of monotherapy (treatment-naïve patients) at doses of 200 mg, 400 mg, 600 mg, 800 mg twice daily and 800 mg and 1200 mg once daily. Plasma viral loads were significantly reduced at all doses compared to placebo after 7 days of therapy (primary end-point). There were no significant differences in efficacy between doses administered twice or once daily (Cahn et al., 2006). Short-term efficacy was studied over 21 days of a 48-week phase IIb study in treatment-experienced HIV patients failing therapy with M184V and other mutations. The study compared apricitabine 600 mg or 800 mg twice daily *vs.* lamivudine 150 mg twice daily in combination with background therapy that was not optimised until day 21. At day 21 both doses of apricitabine produced significant reductions in HIV RNA in comparison to lamivudine, with a similar safety profile (Cahn et al., 2007). Apricitabine pharmacokinetics are primarily linear in plasma at 400, 800 and 1600 mg (single dose) in healthy volunteers (Holdich et al., 2006). Absorption is rapid with maximum concentrations being reached 1.5–2 h post-dose with a plasma elimination half-life of about 3 h. Apricitabine can be administered without regard to food as plasma pharmacokinetics were similar under fasting conditions and following a high fat meal (Holdich and Sawyer, 2008). Apricitabine is excreted largely unchanged in urine and studies performed on isolated perfused rat kidney indicate that renal elimination is by glomerular filtration and active tubular secretion (Nakatani-Freshwater et al., 2006). Like other NRTI, apricitabine is a pro-drug and must be activated intracellularly. Apricitabine is phosphorylated by deoxycytidine kinase to the active triphosphate. Concentrations in peripheral blood mononuclear cell (PBMC) reach a maximum at approximately 3.5–4 h post-dose with an intracellular half-life between 6 and 7 h (Cahn et al., 2008; Holdich et al., 2007; Sawyer and Struthers-Semple, 2006). *In vitro* data show that apricitabine is not a substrate nor an inducer or inhibitor of any of the major cytochrome P450 enzymes (Sawyer and Cox, 2006). Furthermore no inhibition of glucuronidation has been observed and it is a weak inhibitor of p-glycoprotein (Cox and Southby, 2009). Clinically meaningful drug–drug interactions with other drugs that undergo hepatic metabolism are unlikely however there is potential for interactions between those that are renally eliminated or phosphorylated intracellularly by deoxycytidine kinase.

2.3.2. Apricitabine drug–drug interactions

Along with lamivudine and emtricitabine, apricitabine is a cytidine analogue and it is not recommended for the same type of nucleoside analogue to be combined. *In vitro*, apricitabine phosphorylation in PBMC was decreased in a concentration-dependent manner in the presence of lamivudine or emtricitabine; however apricitabine did not affect lamivudine or emtricitabine (Bethell et al., 2007). The interaction with lamivudine also reduced apricitabine activity against virus harbouring M184V (Bethell et al., 2007). In healthy volunteers, lamivudine in combination with apricitabine reduced apricitabine concentrations in PBMC by approximately 15% compared to apricitabine alone (Holdich et al., 2007). Co-administration of apricitabine (800 mg twice daily) with tipranavir/ritonavir (500/200 mg twice daily) resulted in an increase in apricitabine AUC and maximum concentration by approximately 40% and 25%, respectively in 18 healthy volunteers. The interaction is not thought to be clinically significant and no dosage adjustment necessary (Moore et al., 2007). The potential interaction between single (800 mg) and multiple dose (800 mg twice daily) apricitabine and trimethoprim-sulphamethoxazole (480 mg once daily) has also been investigated (Shiveley et al., 2008). Trimethoprim-sulphamethoxazole can be used as treatment and prophylaxis for *Pneumocystis carinii* pneumonia in HIV-infected patients. Apricitabine plasma $AUC_{0-\infty}$ and maximum concentrations were increased by 66% and 33%, respectively and steady-state AUC_{0-12} and maximum concentration by 57% and 22%, respectively in the presence of trimethoprim-sulphamethoxazole (Shiveley et al., 2008). However it is considered unlikely that the interaction is of clinical relevance. Similarly, lamivudine (deoxycytidine analogue) plasma concentrations have been shown to increase when in combination with trimethoprim-sulphamethoxazole due to competition for active tubular secretion (Moore et al., 1996).

3. Novel drug classes

3.1. CCR5-receptor antagonists

HIV utilises host chemokine receptors CCR5 and CXCR4 during entry into host cells (Allen et al., 2007; Lederman et al., 2006). HIV can be categorised according to the chemokine receptor it binds, for example virus that only binds CCR5 is termed the R5 strain. Likewise, X4 strains only bind CXCR4 and dual tropic R5/X4 strains can use both receptors (Berger et al., 1999; Briz et al., 2006). Chemokine receptors therefore provide a novel therapeutic target with blockage of the receptor preventing viral entry into host cells. August 2007 saw FDA approval of the first CCR5-receptor antagonist for treatment of HIV infection. Tropism testing is required prior to initiation of CCR5-receptor antagonists to ensure the patient is infected with susceptible virus, *i.e.* R5-tropic strain.

3.1.1. Maraviroc

Maraviroc is the first agent to be approved in the class of CCR5-receptor antagonists and is effective against CCR5-tropic virus. Maraviroc is reserved for highly treatment-experienced patients and has demonstrated lasting efficacy through to 96 weeks of treatment in a combined analysis of the MOTIVATE 1 and 2 clinical studies (Fatkenheuer et al., 2008; Gulick et al., 2008; Hardy et al., 2008).

Maraviroc is available to be taken with or without food and the recommended dose (150 mg, 300 mg, 600 mg twice daily) is dependent upon co-administered medications (Pfizer Limited, 2008). Maraviroc is rapidly absorbed with maximum concentrations being achieved between 0.5 and 4 h in healthy adults administered a single 300 mg dose (Abel et al., 2008e). Predicted absolute bioavailability at this dose is 33% (Abel et al., 2008d). Maraviroc is approximately 76% plasma protein bound with moderate affinity for both α-1-acid glycoprotein and albumin with a volume of distribution of 194 L (Abel et al., 2008d; Pfizer Limited, 2008; Walker et al., 2005). Following intravenous dosing (30 mg) total clearance and half-life were estimated as 44 L/h and 13 h, respectively (Abel et al., 2008d). Maraviroc is primarily and extensively metabolised by CYP3A4 without significant contribution from other enzymes (Hyland et al., 2008) and is a substrate for the efflux transporter p-glycoprotein which is thought to limit its absorption (Walker et al., 2005). There is no evidence to suggest that maraviroc modulates enzymes of the cytochrome P450 system at clinically relevant doses (Hyland et al., 2008).

3.1.2. Maraviroc drug–drug interactions

Although maraviroc is unlikely to affect the concentrations of other drugs, due to its route of metabolism, potentially drug interactions can occur and may warrant dosage adjustment of maraviroc (Abel et al., 2008a,c). Comprehensive clinical data are available evaluating maraviroc in combination with other antiretrovirals and commonly prescribed co-medications and along with incorporation of population modelling necessary dosage adjustments have been defined (Abel et al., 2009).

The general consensus is that maraviroc concentrations increase in the presence of protease inhibitors requiring dosage adjustment (Abel et al., 2008c). Formal interaction studies have been carried out in healthy adults following co-administration with atazanavir, saquinavir, ritonavir and boosted atazanavir, darunavir, fosamprenavir, lopinavir, saquinavir and tipranavir (Abel et al., 2008b,c; Luber et al., 2009). A dose of 150 mg twice daily is proposed in these circumstances, with the exception of tipranavir/ritonavir in which case 300 mg twice daily is required due to the lack of a clinically relevant interaction (Abel et al., 2008c). This is potentially a result of opposing effects of CYP3A4 inhibition and p-glycoprotein induction by tipranavir/ritonavir. Furthermore, no dose reduction is proposed in the presence of fosamprenavir/ritonavir (700/100 mg twice daily) due to decreased maraviroc but it is not yet known whether an increase in dose is necessary (Luber et al., 2009). In the presence of CYP3A inducers, such as efavirenz, maraviroc should be increased to 600 mg twice daily (Abel et al., 2008a), however when also in the presence of an inhibitor the net result is inhibition and dose reduction to 150 mg twice daily is recommended (Fig. 1) (Abel et al., 2008a). Celsentri® Summary of Product Characteristics and Selzentry® Prescribing Information should be consulted for full dosage adjustment summaries.

3.1.3. Vicriviroc

Vicriviroc (SCH-417690) is a small molecule CCR5 antagonist currently under evaluation in phase III clinical trials. *In vitro* activity has been demonstrated against a panel of genotypically diverse R5-tropic isolates. Furthermore, activity has been observed against strains with defined protease inhibitor, NNRTI and fusion inhibitor resistance patterns (Strizki et al., 2005). Vicriviroc has shown sustained efficacy out to 48 weeks in combination with optimised background therapy in treatment-experienced patients as part of randomised placebo controlled studies dosed at 10 and 15 mg once daily ($n = 118$) (Gulick et al., 2007) and at higher doses of 20/30 mg once daily ($n = 116$) (Zingman et al., 2008b). Based on efficacy and safety data 30 mg once daily was chosen for phase III studies (Zingman et al., 2008a). Following a phase II placebo controlled study in HIV patients ($n = 48$) receiving 14 days of vicriviroc monotherapy (10, 25, 100 mg twice daily) dose proportional pharmacokinetics were observed and the drug was rapidly absorbed and exhibits dose proportional pharmacokinetics and a half-life between 28 and 33 h, supportive of once daily dosing (Schurmann et al., 2007). Based on human liver microsome studies vicriviroc is primarily metabolised by CYP3A4 with potentially minor contributions from CYP3A5 and CYP2C9. No inhibition of CYP3A4, CYP2D6, CYP2C9, CYP2C19 and CYP1A2 was observed (Ghosal et al., 2007).

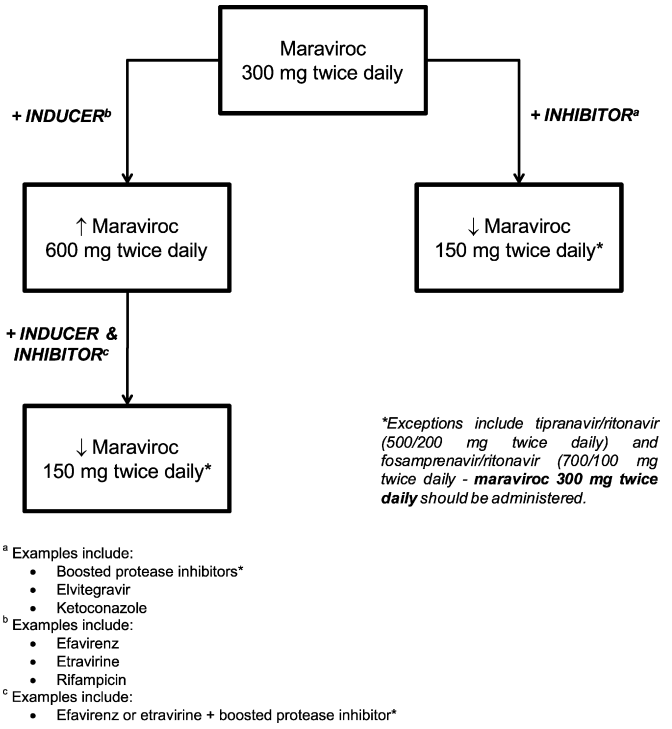

Fig. 1. Flow diagram outlining dosage adjustments of maraviroc when in combination with an enzyme inducer, inhibitor, or both (Celsentri® Summary of Product Characteristics and Selzentry® Prescribing Information should be consulted for full dosage adjustment information).

3.1.4. Vicriviroc drug–drug interactions

A handful of drug–drug interaction studies have been performed in healthy adults at doses other than 30 mg once daily that is now under phase III study. In general vicriviroc pharmacokinetic parameters increased in the presence of an inhibitor, namely ritonavir, and reduced following co-administration with the inducer efavirenz (Sansone et al., 2006b). However in the presence of both antiretrovirals the net result was inhibition of vicriviroc metabolism (Sansone et al., 2006b). Boosted protease inhibitors (with 100 mg ritonavir twice or once daily) atazanavir, fosamprenavir, saquinavir, indinavir, nelfinavir and tipranavir had no additional affects over that of ritonavir alone (Sansone-Parsons et al., 2007; Sansone et al., 2006a). Similar increases in vicriviroc (10 mg once daily) pharmacokinetic parameters were observed following co-administration with lopinavir/ritonavir (400/100 mg once daily) as that of ritonavir alone (100 mg once daily; Sansone

et al., 2005c). Vicriviroc has been shown to have no clinically significant effect on the concentrations of the oral contraceptive (ethinyl oestradiol 0.0035 mg + norethindrone 1 mg once daily) however when also combined with ritonavir, exposure of the oral contraceptive was reduced to a similar extent as that with ritonavir alone (Kasserra et al., 2008); other methods of contraception are recommended in this case. Nucleoside reverse transcriptase inhibitors that may be used in combination with vicriviroc have also been investigated. No significant effects have been observed with lamivudine/zidovudine (Combivir 150/300 mg + vicriviroc 50 mg twice daily) or tenofovir (300 mg once daily + vicriviroc 10 mg twice daily) (Sansone et al., 2005a,b).

3.2. Integrase inhibitors

Integration is part of the HIV lifecycle that consists of viral DNA being irreversibly inserted into the DNA of host cells and is catalysed by integrase. Integration occurs after reverse transcription takes place and is essential for viral replication to progress through to completion (Hazuda et al., 2009). Integrase is required for the three main events of integration (i) assembly with viral DNA, (ii) 3′ endonucleolytic processing and (iii) strand transfer, and it is the latter process that is the main focus of integrase inhibitors (Hazuda et al., 2009). Integrase inhibitors differ from other classes of antiretrovirals in that they only actively bind to the integrase enzyme when in complex with viral DNA (Hazuda et al., 2009). The FDA and EMEA granted approval of the first integrase inhibitor in 2007 and 2008, respectively.

3.2.1. Raltegravir

The Merck compound raltegravir (MK-0518) is the first integrase inhibitor to be approved for treatment of therapy-experienced patients resistant to existing antiretrovirals and inhibits strand transfer activity of HIV-1 integrase *in vitro*. An *in vitro* study has also demonstrated similar phenotypic susceptibility to HIV-2 clinical isolates obtained from integrase inhibitor-naïve patients potentially providing therapeutic options to HIV-2 infected individuals (Roquebert et al., 2008). Raltegravir has shown potent and durable viral suppression out to 48 weeks similar to that of efavirenz in a dose ranging study (100–600 mg twice daily) in treatment-naïve patients (Markowitz et al., 2007) and in treatment-experienced patients as part of a placebo controlled trial in combination with optimised background therapy (24-week data) (Grinsztejn et al., 2007).

Raltegravir is available as 400 mg film-coated tablets to be taken without regard to food; however food intake appears to increase pharmacokinetic variability in comparison to the fasted state (Merck Sharp & Dohme Limited, 2009). As part of single (10–1600 mg) and multiple dose (100–800 mg twice daily) placebo controlled studies in healthy volunteers raltegravir was rapidly absorbed and steady-state achieved within 2 days (Iwamoto et al., 2008d). Dose proportionality in trough concentrations (12 h post-dose) was observed between 100 and 800 mg but less so between 100 and 1600 mg (Iwamoto et al., 2008d). The absolute bioavailability of raltegravir has not yet been established. A moderate fat meal increased raltegravir pharmacokinetic parameters and a high fat meal increased AUC_{0-12} and maximum concentrations 2-fold and trough concentrations 4-fold compared to fasting. In contrast a low-fat meal decreased AUC_{0-12} and maximum concentrations by 46% and 52%, respectively compared to fasting state (Cocohoba and Dong, 2008; Merck Sharp & Dohme Limited, 2009). Raltegravir is approximately 83% bound to plasma proteins (Summa et al., 2008) with a terminal half-life of about 10–12 h, with a shorter alpha-phase of elimination (~1 h) accounting for the majority of the AUC (Iwamoto et al., 2008d). Following a study in healthy volunteers (200 mg single dose ^{14}C-raltegravir) the major route of metabolism was found to be glucuronidation via UDP-glucuronosyltransferase 1A1 (UGT1A1) to the raltegravir glucuronide; raltegravir was the main component found in the plasma (70% of the total radioactivity) (Kassahun et al., 2007). *In vitro* studies have suggested that raltegravir does not have any meaningful inhibitory effects on CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, 2B6 and does not induce CYP3A4 (Iwamoto et al., 2008a). *In vivo* data ($n = 10$) also confirmed that raltegravir does not inhibit or induce CYP3A4 on the basis that no changes in midazolam pharmacokinetic parameters were observed (Iwamoto et al., 2008a). Furthermore, raltegravir does not inhibit UGT1A1 and 2B7 enzymes or p-glycoprotein (Hazuda et al., 2009). Although it is unlikely that raltegravir will influence the pharmacokinetics of other therapeutics, drug–drug interactions are expected with co-medications that modulate UGT1A1-mediated metabolism of raltegravir.

3.2.2. Raltegravir drug–drug interactions

Formal drug–drug interaction studies have been conducted in healthy volunteers. Interactions with CYP3A4 substrates are not expected however interactions have been observed with atazanavir, omeprazole and rifampicin (Table 3). As no pharmacokinetic parameters have been associated with a threshold of raltegravir efficacy, the majority of interactions are thought not to be clinically relevant. It is advisable to also consult Insentress® Summary of Characteristics and Prescribing Information for drug–drug interaction summaries.

3.2.3. Elvitegravir

Elvitegravir (GS9137) is an integrase inhibitor that is currently under phase III development. It has demonstrated substantial short-term efficacy in a placebo controlled monotherapy study at various doses in treatment-naïve and experienced patients not currently receiving therapy (DeJesus et al., 2006). Furthermore, as part of a phase II dose ranging study elvitegravir/ritonavir (125/100 mg once daily) was statistically superior to comparator boosted protease inhibitors in treatment-experienced patients (Zolopa et al., 2007). *In vitro* a study has shown that elvitegravir has overlapping resistance profiles with that of raltegravir and other integrase inhibitors in development (Goethals et al., 2008), however another study demonstrated that, like raltegravir, elvitegravir may have some *in vitro* activity against HIV-2 clinical isolates (Roquebert et al., 2008). The major route of metabolism is CYP3A4/5 with UGT1A1/3 as a minor route and elvitegravir benefits from boosting with ritonavir allowing for once daily dosing (Ramanathan et al., 2007b). Following a single dose of boosted elvitegravir-^{14}C (50/100 mg) >90% of plasma radioactivity was elvitegravir (Ramanathan et al., 2007e). A recent study observed that the maximum inhibition of elvitegravir apparent oral clearance occurs with ritonavir doses between 50 and 100 mg (Mathias et al., 2009b). A dose of 150/100 mg once daily has been taken forward into further study.

3.2.4. Elvitegravir drug–drug interactions

Due to the route of metabolism, drug–drug interactions with elvitegravir are possible and a number of studies have been performed in healthy volunteers to assess potential combinations. No clinically relevant interactions were observed between elvitegravir and tipranavir, darunavir or fosamprenavir all boosted with ritonavir (Mathias et al., 2008; Ramanathan et al., 2007a). However co-administration of elvitegravir (200 mg once daily) with atazanavir/ritonavir (300/100 mg once daily) resulted in significant increases in elvitegravir AUC_{0-24}, C_{max} and C_{trough} by 100%, 85% and 188%, respectively, potentially mediated by UGT1A1/3 inhibition by atazanavir (Mathias et al., 2007a). Another study aimed to select an appropriate dose for the combination through simulation and bioequivalence testing and found that elvitegravir 85 mg once daily in combination with atazanavir/ritonavir provided

Table 3
Key raltegravir drug–drug interaction studies evaluating the effects on exposure summarised by means of least squares mean ratios and 90% confidence intervals (no change in exposure = LSM 1.00).

Co-medication	*N*	Dose		AUC_τ[a] LSM (90% CI)		Recommendation	Reference
		RGV	Co-medication	RGV	Co-medication		
Atazanavir	10	100 mg single dose	400 mg *qd*	1.72 (1.47–2.02)	No data	Further study warranted in patients; not thought to be clinically relevant, no dosage adjustment necessary	Iwamoto et al. (2008b)
Atazanavir	10	400 mg *bid*	300/100 mg *qd*	1.41 (1.12–1.78)	No data	Further study warranted in patients; not thought to be clinically relevant, no dosage adjustment necessary	Iwamoto et al. (2008b)
Lopinavir	12	400 mg *bid*	400/100 mg *bid*	↑ 1%	↔	No dosage adjustment necessary	Rhame et al. (2008)
Ritonavir	10	400 mg single dose	100 mg *bid*	0.84 (0.70–1.01)	No data	No dosage adjustment necessary	Iwamoto et al. (2008c)
Tipranavir	15	400 mg *bid*	500/200 mg *bid*	0.76 (0.49–1.19)	No data	No dosage adjustment necessary based on efficacy data	Hanley et al. (2009), Iwamoto et al. (2009), Wenning et al. (2009)
Efavirenz	9	400 mg single dose	600 mg *qd*	0.64 (0.52–0.80)	No data	Not considered clinically relevant; no dosage adjustment necessary	Iwamoto et al. (2008c)
Etravirine	19	400 mg *bid*	200 mg *bid*	0.90 (0.68–1.18)	1.10 (1.03–1.16)	No dosage adjustment necessary	Anderson et al. (2008)
Tenofovir	9	400 mg *bid*	300 mg *qd*	1.49 (1.15–1.94)	0.90 (0.82–0.99)	No dosage adjustment necessary	Wenning et al. (2008)
Tenofovir/lamivudine	6[b]	100 mg *bid*	300/300 mg *qd*	0.98 (0.57–1.67)	No data	No dosage adjustment necessary	Wenning et al. (2008)
	7[b]	200 mg *bid*	300/300 mg *qd*	1.58 (1.16–2.15)	No data	No dosage adjustment necessary	Wenning et al. (2008)
	6[b]	400 mg *bid*	300/300 mg *qd*	1.78 (0.86–3.66)	No data	No dosage adjustment necessary	Wenning et al. (2008)
	6[b]	600 mg *bid*	300/300 mg *qd*	1.42 (0.73–2.78)	No data	No dosage adjustment necessary	Wenning et al. (2008)
Ethinyl estradiol	19	400 mg *bid*	0.035 mg *qd* (combined pill)	No data	1.02 (0.93–1.04)	No dosage adjustment necessary	Anderson et al. (2007)
Norgestimate	19	400 mg *bid*	1 mg *qd* (combined pill)	No data	1.14 (1.08–1.21)	No dosage adjustment necessary	Anderson et al. (2007)
Omeprazole	10	400 mg single dose	20 mg *qd*	3.12 (2.13–4.56)	No data	Needs further characterisation in patients; no dosage adjustment necessary	Iwamoto et al. (2009)
Rifampicin	9	400 mg single dose	600 mg *qd*	0.60 (0.39–0.91)	No data	Efficacy data required; caution warranted in combination	Wenning et al. (2009)
	12	800 mg *bid*[c]	600 mg *qd*	1.27 (0.94–1.71)	No data	Efficacy data required; caution warranted in combination	Wenning et al. (2009)
Midazolam	10	400 mg *bid*	2 mg single dose	No data	0.92 (0.82–1.03)	No dosage adjustment necessary	Iwamoto et al. (2008a)

AUC_τ: area under the concentration–time curve over the dosing interval; LSM: least squares mean; CI: confidence interval; *N*: number of participants; RGV: raltegravir; *bid*: twice daily; *qd*: once daily; ↑: increase; ↔: no change.

[a] $AUC_{0-\infty}$ for single dose.

[b] HIV-infected patients.

[c] Reference raltegravir dose of 400 mg *bid*.

equivalent pharmacokinetic parameters to elvitegravir/ritonavir 150/100 mg once daily (Mathias et al., 2007a). A similar interaction was also observed between elvitegravir (125 mg once daily) and lopinavir/ritonavir (400/100 mg twice daily) with elvitegravir pharmacokinetic parameters increasing significantly (Mathias et al., 2007b). A dose adjustment from 150 mg to 85 mg has been suggested (Mathias et al., 2007b). The combination of elvitegravir/ritonavir (150/100 mg once daily) and etravirine (200 mg twice daily) resulted in small changes in pharmacokinetic parameters of each drug which were within the bounds defined by the study and were not clinically relevant ($n = 31$) (Ramanathan et al., 2008). No significant interactions were observed between zidovudine, zidovudine glucuronide, abacavir, stavudine (Ramanathan et al., 2007c), tenofovir or emtricitabine (Ramanathan et al., 2007b), however didanosine (400 mg single dose) C_{max} and AUC were 14% and 16% lower, respectively and outside the equivalence bounds for the study (Ramanathan et al., 2007c). Finally, a dose reduction in maraviroc is recommended if to be combined with elvitegravir/ritonavir based on data from 28 healthy volunteers in which maraviroc (150 mg twice daily) C_{max} and AUC_{0-12} were increased by 115% and 186%, respectively following co-administration with elvitegravir/ritonavir (150/100 mg once daily) (Ramanathan et al., 2007d).

3.3. Pharmacoenhancers

Two drug candidates for new pharmacoenhancers are currently under development. As some patients can be intolerant to ritonavir due to adverse events other boosters are urgently needed in order to allow protease inhibitor-based therapy. Both drugs are inhibitors of CYP3A but unlike ritonavir, lack antiviral activity. However, a new tablet formulation of Norvir® is currently under development which would not require refrigeration and potentially possessing similar benefits to Kaletra® tablets (improved bioavailability, lack of a food effect), therefore overcoming current limitations of the soft-gel formulation (Morris, 2009).

3.3.1. GS-9350

GS-9350 has been shown to be a potent mechanism-based inhibitor of CYP3A with potentially less metabolic side-effects than ritonavir. Boosting of midazolam by GS-9350 at doses of 50, 100 and 200 mg once daily were evaluated in healthy volunteers *vs.* ritonavir 100 mg ($n = 18$ per study arm) (Mathias et al., 2009a). GS-9350 exhibited non-linear pharmacokinetics and 100 mg and 200 mg inhibited midazolam clearance to a similar extent as that of ritonavir 100 mg. Overall the drug has been generally well tolerated and due to the formulation is suitable for co-formulation with other drugs (Mathias et al., 2009a). A phase II study is currently recruiting to assess the safety and efficacy of the QUAD tablet containing elvitegravir/emtricitabine/tenofovir/GS-9350 *vs.* Atripla® (efavirenz/emtricitabine/tenofovir) (ClinicalTrials.gov, 2009c) and a study is ongoing evaluating the safety and efficacy of atazanavir boosted with ritonavir *vs.* boosted with GS-9350 in treatment-naïve patients (ClinicalTrials.gov, 2009b).

3.3.2. SPI-452

The Sequoia compound SPI-452 has also demonstrated potent mechanism-based inhibition of CYP3A and is generally well tolerated at doses 25–200 mg. SPI-452 has been shown to substantially boost saquinavir concentrations (1000 mg) and increase darunavir and atazanavir trough concentrations (24 h concentration) approximately 29- and 13-fold, respectively (Gulnik et al., 2009).

3.3.3. Novel formulations and drug delivery systems

This topic is beyond the scope of this review to be discussed in any detail however it is of great interest for development of new agents and also improvement of current compounds. Novel formulations and drug delivery systems can help to overcome some of the limitations of current antiretroviral therapy, such as low bioavailability and severe side-effects and can also lead to reduced dosing frequency. Furthermore, sustained release formulations (*i.e.* once weekly or monthly dosing) would prove beneficial for pre/post exposure prophylaxis, prevention of mother to child transmission and maintenance therapy. Examples include nanosuspensions (described earlier for rilpivirine), bioadhesive drug delivery systems, ceramic implants and transdermal delivery, all of which have recently been reviewed in the context of HIV therapy by Ojewole et al. (2008).

4. Conclusion

The pharmacokinetics and key drug–drug interaction data for newly available antiretrovirals and those under development have been described and summarised. Understanding of antiretroviral pharmacology is important, particularly with emergence of novel drug classes, in order to determine optimal treatment strategies and to manage co-morbidities. Some of the newer antiretrovirals, *e.g.* maraviroc and raltegravir have little effect on co-medications, however interactions via undetermined mechanisms may be possible. Further clinical data evaluating pharmacoenhancers in development other than ritonavir are eagerly awaited, potentially widening treatment options to those intolerant of ritonavir.

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