Rilpivirine (RPV) is a second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI). It remains active against HIV strains harbouring mutations that affect first-generation agents. RPV is dosed once daily with food and has been coformulated into a single tablet containing tenofovir and emtricitabine. Two Phase III studies of treatment-naive patients found RPV and efavirenz to have similar safety and efficacy. However, suboptimal virological suppression with RPV occurred more commonly in patients with higher baseline viral loads (>100,000 copies/ml). The most common mutation that emerged during RPV therapy was E138K, which often occurred in combination with M184I. E138K is likely to cause cross-resistance to other NNRTIs thereby limiting the further utilization of this class.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have become important components of first-line treatment regimens for HIV-infected patients. First-generation agents, such as efavirenz (EFV) and nevirapine (NVP) are well tolerated and have demonstrated long-term efficacy and safety in several clinical trials. There are, however, limitations to EFV and NVP that include tolerability issues, a low genetic barrier to resistance and cross-resistance between agents. Additionally, resistance to these agents can be detected in up to 8% of patients at baseline, limiting their utilization in newly infected individuals [1].

The development of second-generation NNRTIs, including etravirine (ETR) and rilpivirine (RPV), has provided new options for patients that have either acquired or developed resistance to first-generation agents. RPV is the newest drug available in this class and has recently received European Commission and US Food and Drug Administration approved labelling for managing patients who are naive to antiretroviral therapy [2]. It is also under investigation for managing treatment-experienced patients and has recently been coformulated into one tablet with tenofovir and emtricitabine [3,4]. A long-acting injectable formulation is also under development [5]. This review serves to interpret the available clinical data and describe the role of RPV in the management of HIV-1 infection.

**Data sources**
A search of PubMed was conducted (January 2005 to April 2012) using the following key words: RPV and TMC278. Articles were evaluated for content and bibliographies were reviewed for additional information sources. A search for data available exclusively in abstracts from major infectious diseases and HIV conferences was also performed during the same time period with content evaluated for inclusion. Studies included in this review were in vitro investigations, Phase I, II and III clinical trials, retrospective analyses, and pharmacokinetic and pharmacodynamic evaluations.

**Pharmacology and mechanism of action**
HIV reverse transcriptase is one of three virally encoded enzymes (along with integrase and protease) essential for HIV replication. Following entry into CD4+T-lymphocytes, viral RNA is transcribed into DNA by the reverse transcriptase enzyme. NNRTIs inhibit this process by binding to an allosteric hydrophobic pocket resulting in a conformational change in the enzyme’s active site that prevents further viral RNA transcription.
RPV, like ETR, is a diarylpyrimidine NNRTI [2]. This structure is unique compared to first-generation agents, and allows for greater flexibility and conformational adaptation when binding to the reverse transcriptase enzyme [6]. It is this flexibility that is thought to afford second-generation agents their preserved activity and potency in the presence of resistance mutations that affect first-generation agents [7].

Pharmacokinetics

The pharmacokinetic profile of RPV has been assessed in both HIV-infected and non-infected individuals [8,9]. Three randomized double-blind placebo-controlled studies were conducted in a total of 90 healthy male volunteers and include the following: one trial with a multiple ascending dosing schedule (n=27, 25–150 mg once daily for 14 days) and two trials with single ascending dosing schedules (n=27, 12.5–50 mg and n=36, 50–300 mg) [8]. The results of these investigations demonstrated dose proportional pharmacokinetics and rapid absorption of RPV following single doses (median time to maximum concentration of 4 h in all groups). The half-life ranged from 34–55 h and was estimated to be approximately 38 h after 14 days of therapy, which is supportive of once-daily dosing. Overall, <0.03% of RPV was excreted unchanged in the urine, indicating extensive metabolism and predominantly faecal excretion [8].

The pharmacokinetics of RPV have also been assessed in HIV-positive patients [9]. In a randomized double-blind placebo-controlled Phase IIa trial, 47 HIV-infected treatment-naive men received one of four RPV doses (25, 50, 100 or 150 mg) once-daily for 7 days. Rapid absorption (approximately 4 h) and a long half-life (approximately 48 h) were again observed, and for most individuals plasma concentrations were detected up to 7 days following the last dose of study medication. Additionally, using a 50% effective concentration (EC50) of 0.5 nM, the investigators determined that concentrations achieved for each dose of RPV remained above this target level at all time points during the 7-day study period [9].

The absorption of RPV requires an acidic environment and appears to be heavily influenced by the presence of food. An investigation evaluating the concentration of RPV in 20 healthy volunteers following a 75 mg dose given under fasting conditions found the maximum concentration (Cmax) and area under the curve (AUC) concentrations to be 43% and 46% lower, respectively, compared to patients receiving RPV with a standard breakfast (533 calories and 21 g of fat) [10]. No additional benefit in absorption was observed when a high-fat meal was utilized (928 calories and 56 g of fat) and administration with a nutritional drink (300 calories and 8 g of fat) produced concentrations similar to those achieved under fasting conditions [10]. As a result, RPV is recommended to be administered with a meal that should ideally consist of ≥500 calories [2].

Currently, the manufacturer does not recommend dosage adjustments for patients with mild renal insufficiency [2]. This recommendation is the result of a population pharmacokinetic analysis that found similar RPV exposures in HIV-infected patients with normal renal function and those with mild insufficiency. Data are not available for patients with moderate to severe renal insufficiency or in patients receiving haemodialysis, although high plasma protein binding (99.7%) is thought to result in minimal removal during dialysis treatments [11].

RPV has also been evaluated in patients with hepatic dysfunction. A study evaluating RPV exposures was conducted in eight subjects with mild hepatic impairment (Child–Pugh score A) and eight subjects with moderate hepatic impairment (Child–Pugh score B) each of which were compared to eight matched controls. This study found the exposure of RPV after multiple doses was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment. Despite these changes, no dosage adjustments are currently recommended for patients with mild to moderate hepatic insufficiency [2]. Furthermore, in a separate evaluation, hepatitis B or C coinfections were not found to have a clinically relevant impact on RPV serum concentrations [12]. Data is currently not available for use in patients with severe hepatic dysfunction (Child–Pugh score C).

Drug interactions

RPV is extensively metabolized by cytochrome P450 3A4 (CYP3A4) and is therefore subject to drug interactions with medications that induce or inhibit this enzyme (Table 1) [2,8,13–24]. However, unlike EFV, NVP and ETR, RPV is not expected to have a clinically relevant impact on the metabolism of other agents that are metabolized by the cytochrome P450 enzyme system [25].

Protease inhibitors commonly inhibit the metabolism of agents that use CYP3A4 and interactions have been demonstrated with RPV. Specifically, when combined with lopinavir/ritonavir (400 mg/100 mg twice daily) or darunavir/ritonavir (800 mg/100 mg once daily) in healthy volunteers, RPV AUC concentrations were increased by 1.52- and 2.3-fold, respectively, following 150 mg RPV daily dosing [13,14]. Despite this increased exposure to RPV, no dosage adjustments have been recommended.

Aside from the protease inhibitors, an interaction between RPV and the nucleoside reverse transcriptase inhibitor (NRTI) tenofovir has been demonstrated [15]. Specifically, when combined with RPV (150 mg once daily) in a 16-day open label crossover trial (n=16
Rilpivirine: a systematic review

Table 1. Drug-drug interactions of rilpivirine with antiretrovirals and other medications

<table>
<thead>
<tr>
<th>Concomitant drug</th>
<th>RPV dose</th>
<th>Effect on RPV or concomitant drug</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiretroviral agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Didanosine 400 mg daily</td>
<td>150 mg</td>
<td>No clinically significant changes in serum concentrations for either agent</td>
<td>No dosage changes; administer didanosine on an empty stomach ≥2 h before or ≥4 h after RPV, which must be administered with a meal</td>
</tr>
<tr>
<td>Tenofovir 300 mg daily</td>
<td>150 mg</td>
<td>Tenofovir AUC concentrations increased by 23%</td>
<td>No dosage changes necessary</td>
</tr>
<tr>
<td>Darunavir/ritonavir 800 mg/100 mg daily</td>
<td>150 mg</td>
<td>RPV AUC concentrations increased by 2.3-fold</td>
<td>No dosage changes necessary</td>
</tr>
<tr>
<td>Lopinavir/ritonavir 400 mg/100 mg twice daily</td>
<td>150 mg</td>
<td>RPV AUC concentrations increased by 1.52-fold</td>
<td>No dosage changes necessary</td>
</tr>
<tr>
<td><strong>Non-antiretroviral agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atorvastatin 40 mg daily</td>
<td>150 mg</td>
<td>No clinically significant changes in serum concentrations for either agent</td>
<td>No dosage changes necessary</td>
</tr>
<tr>
<td>Ethinyl estradiol 35 µg daily</td>
<td>25 mg</td>
<td>Ethinyl estradiol AUC increased 14%; no significant changes to norethindrone</td>
<td>No dosage changes necessary</td>
</tr>
<tr>
<td>plus norethindrone 1 mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famotidine 40 mg daily</td>
<td>150 mg</td>
<td>RPV AUC concentrations decreased by 76% when administered within 2 h prior to famotidine</td>
<td>Give H2-receptor antagonists ≥12 h before or ≥4 h after RPV</td>
</tr>
<tr>
<td>Ketoconazole 400 mg daily</td>
<td>150 mg</td>
<td>RPV AUC increased 50%; ketoconazole AUC decreased 25%</td>
<td>No dosing changes necessary; monitor for breakthrough fungal infections</td>
</tr>
<tr>
<td>Methadone 60–100 mg daily</td>
<td>25 mg</td>
<td>Methadone AUC decreased 16%</td>
<td>No empiric dosing changes required; clinical monitoring and adjustment of methadone dosing during maintenance therapy may be needed in some patients</td>
</tr>
<tr>
<td>Omeprazole 20 mg daily</td>
<td>150 mg</td>
<td>RPV AUC decreased 40%</td>
<td>RPV should not be used in combination with omeprazole or other PPIs</td>
</tr>
<tr>
<td>Rifabutin 300 mg daily</td>
<td>150 mg</td>
<td>RPV AUC decreased 45%</td>
<td>RPV should not be used in combination with rifabutin</td>
</tr>
<tr>
<td>Rifampin 600 mg daily</td>
<td>150 mg</td>
<td>RPV AUC decreased 80%</td>
<td>RPV should not be used in combination with rifampin</td>
</tr>
</tbody>
</table>

AUC, area under the curve; PPI, proton pump inhibitor; RPV, rilpivirine.

Clinical trials

Treatment-naive patients

Three investigations have evaluated the clinical efficacy of RPV for the management of HIV-1 infection in treatment-naive patients [25–27]. The first was a Phase IIb dose ranging international study in which 386 participants were randomized to receive one of three blinded RPV doses (25, 75 or 150 mg once daily) or open label EFV (600 mg once daily) in combination with two NRTIs (either zidovudine/lamivudine or tenofovir/emtricitabine) [25]. All patients were naïve to therapy with a viral load of ≥5,000 copies/ml and genotypic sensitivity to NNRTIs and the selected NRTI agents. Median baseline CD4+ T-cell counts and HIV viral loads were 203 cells/mm³ and 4.85 log₁₀ copies/ml, respectively and most patients (63.6%) had baseline viral loads <100,000 copies/ml. However, a disproportionate number of patients receiving RPV (24.4%) had viral loads >300,000 copies/ml compared with those receiving EFV (11.2%) at baseline.

Overall, the proportion of patients that achieved viral suppression (viral load <50 copies/ml) after 48 weeks was comparable for all RPV doses (76.9–80%)
and was similar to EFV (80.9%). The rate of virological response was maintained through 96 weeks, as 71.4-76.3% of patients receiving RPV and 70.8% of those receiving EFV had undetectable HIV levels. Overall, virological failures were uncommon for all treatment arms at 96 weeks (8.2% for RPV and 7.9% for EFV) and were not statistically different between groups. It is noteworthy, however that among the treatment groups the rate of virological failure was numerically highest after 48 weeks in patients receiving RPV 25 mg (9.7), as opposed to 75 mg (5.3%), 150 mg (6.6%) and those receiving EFV (5.6%). This trend did not persist, however when patients were evaluated after 96 weeks.

Immunological efficacy was also similar between RPV treatment arms and patients receiving EFV. The median changes in CD4+ T-cell count after 96 weeks were 140 and 170.5 cells/mm3, respectively [25].

Overall, no RPV doses were definitively correlated with immunological or virological response during this investigation, although a trend for more adverse events leading to discontinuation was identified in patients receiving 150 mg dosing (14.3%) as opposed to 75 mg (11.6%) or 25 mg doses (8.6%). As a result, the 75 mg dose was initially chosen to be pursued in the Phase III investigations. Prior to the start of these investigations, however, additional data became available that documented QTc interval prolongation (>10 ms) in patients receiving 75 mg or 150 mg of RPV [28]. A subsequent investigation found that 25 mg of RPV did not cause QTc prolongation beyond the 10 ms threshold [29]. Given the concerns for changes in the QTc interval with the 75 mg dose in addition to the comparable efficacy of the 25 mg dose demonstrated in the Phase IIb trial described above, RPV 25 mg once daily was selected for use in all Phase III investigations.

ECHO and THRIVE are two randomized double-blind active control 96-week Phase III trials that were conducted to evaluate the efficacy, safety and tolerability of RPV 25 mg once daily versus EFV 600 mg once daily in antiretroviral-naive subjects [26,27].

The two trials differed in the nucleoside backbone used in combination with either RPV or EFV. In ECHO, subjects had a fixed NRTI background regimen of emtricitabine/tenofovir while in the THRIVE trial, subjects could receive one of three different investigator selected regimens; emtricitabine/tenofovir, lamivudine/abacavir or zidovudine/lamivudine. All subjects were aged 18 years or older and had a plasma viral load of 5,000 copies/ml or greater, and susceptibility to all drugs used in the regimen. In both trials, the baseline characteristics were well balanced.

In a pooled analysis of ECHO (n=686) and THRIVE (n=682) after 48 weeks, 84% of RPV recipients and 82% of EFV recipients had HIV RNA levels of <50 copies/ml by intention-to-treat analysis [30]. These results met predefined criteria for non-inferiority. Additionally, immunological efficacy was similar between treatment arms as CD4+ T-cell count increases were 192 cells/µl in the RPV group and 176 cells/µl in those receiving EFV. In subjects with baseline HIV RNA levels of >100,000 copies/ml, RPV recipients were numerically less likely to achieve virological suppression (77% versus 81% for the EFV group; 95% CI -9.8, 2.5). These results are in contrast to those patients with baseline HIV RNA levels of ≤100,000 copies/ml in which a higher proportion of patients receiving RPV achieved HIV RNA levels <50 copies/ml compared to EFV (90% versus 84%, respectively; 95% CI 1.6, 11.5).

When evaluating the reasons for treatment failure after 48 weeks, investigators found that more subjects receiving EFV discontinued their regimens because of adverse events (2% of the RPV group versus 6.7% of the EFV group) whereas more subjects receiving RPV experienced virological failure (9% versus 4.8% in the EFV group) [30]. The difference in virological failure between agents was particularly evident when evaluating baseline viral load data. In patients with baseline HIV RNA levels of ≤100,000 copies/ml, the rate of virological failure was the same for RPV (19/368; 5%) and EFV (16/330; 5%). By contrast, virological failure was much more common in patients with baseline HIV RNA levels >100,000 copies/ml and receiving RPV (53/318; 17%) as compared to EFV (23/352; 7%).

In a follow-up pooled analysis of the Phase III trials after 96 weeks, RPV showed sustained overall efficacy compared to EFV with 78% of subjects in each group achieving HIV RNA levels <50 copies/ml [31]. This result again confirmed non-inferiority. However, subgroup analyses again revealed potential differences in response depending upon baseline viral load. More specifically, while RPV was similar to EFV in subjects with baseline viral loads <100,000 copies/ml (83% and 80%) and viral loads between 100,000 and 500,000 copies/ml (74% and 73% <50 copies/ml), a lower response to RPV was found in patients starting treatment with >500,000 copies/ml (60% and 75% <50 copies/ml, difference -14.6%, 95% CI -31.0, 1.8). Also, similar to the 48-week data, more patients receiving RPV who had baseline viral loads >100,000 copies/ml discontinued therapy due to virological failure (11.8% with RPV and 3.8% with EFV) [30]. Overall, these data indicate the potential for a decreased virological response with RPV at higher baseline viral loads. They have also contributed to recommendations against initiating RPV therapy in treatment-naive patients with viral loads >100,000 copies/ml at baseline [32].

Treatment-experienced patients

Limited data is available describing the use of RPV in antiretroviral treatment-experienced patients. One
Table 2. Selected treatment-emergent adverse drug reactions (grades 2–4) in ≥2% of treatment-naive adults in Phase III clinical trials

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>Rilpivirine</th>
<th>Efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressive disorders</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Skin and subcutaneous disorders</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>11</td>
</tr>
</tbody>
</table>

Pooled data at week 48 (%) are shown.

Phase II open-label trial randomized 36 patients on failing protease inhibitor- (n=12) or NNRTI-based (n=24) regimens to receive one of three once-daily RPV doses (25 mg, 50 mg or 150 mg) while continuing their current NRTIs for a total of 7 days [3]. Patients had ≥1 NNRTI resistance-associated mutation and a plasma viral load of ≥1,000 copies/ml for study inclusion.

At the completion of 7 days, changes from baseline plasma viral load (minimum, maximum) were -0.87 log_{10} copies/ml (-2.3, 0.0; P<0.001), -0.95 log_{10} copies/ml (-1.8, 0.4; P<0.01) and -0.66 log_{10} copies/ml (-1.3, -0.2; P<0.01) for the 25 mg, 50 mg and 150 mg RPV dosing groups, respectively. Overall, the changes in viral load from baseline were not significantly different between dosing groups [3]. This suggests the potential for RPV 25 mg to be successful in treatment-experienced patients. However, given the limited data available, definitive recommendations cannot yet be made for RPV use in this patient population.

Switching to rilpivirine from efavirenz

RPV has also been evaluated in patients switching from an EFV-containing antiretroviral regimen [33,34]. Given the likelihood of a drug–drug interaction between EFV and RPV involving the induction of RPV metabolism, the feasibility of this approach was first evaluated in a Phase I open-label trial [33]. In this study, 17 healthy volunteers were given the following fixed sequence of treatment: RPV 25 mg once-daily for 14 days; a washout period for the following 14–21 days; then EFV 600 mg once-daily for 14 days immediately followed by RPV 25 mg once-daily for 28 days. During the first 21 days of the final 28-day period of RPV dosing, C_{max}, minimum concentration (C_{min}) and AUC values of RPV were lower than reference values. More specifically, on days 1, 14 and 21 of this dosing period, AUC values were 46%, 18% and 16% lower than reference values. By day 28, AUC values were within normal limits. By contrast, C_{min} values did not become similar to reference values by the end of the study period (day 28). C_{min} values obtained on days 14, 21 and 28 were 28%, 28% and 25% lower than reference values, respectively. Despite these decreased concentrations, the ex vivo antiviral activity of RPV was still found to be ≥50% of the reference range in >80% of subjects. As a result, the authors concluded that a treatment switch from EFV to RPV could be further evaluated in individuals infected with HIV.

Following the Phase I study, a trial of 49 HIV-positive subjects switched their EFV to RPV after achieving virological suppression for ≥3 months while receiving EFV in combination with tenofovir and emtricitabine [34]. Patients had to have a baseline genotype prior to EFV showing no reverse transcriptase mutations.

At 12 weeks after switching therapy, all 49 patients achieved the primary end point of maintaining virological suppression (viral load <50 copies/ml). RPV mean trough concentrations were 55 ng/ml and 68–85 ng/ml at 2 weeks and 4–8 weeks following the change from EFV, respectively. These values were similar to trough concentrations observed in the Phase III trials, ECHO and THRIVE (50–80 ng/ml). Overall, the authors concluded that the inductive effects of EFV on RPV metabolism are not likely to be clinically relevant in patients switching therapy who are already virologically suppressed.

Safety

The safety assessment for RPV was based on the pooled 48-week data from ECHO and THRIVE [30]. Select treatment emergent adverse drug reactions of at least moderate intensity (grade 2) reported in ≥2% of adult subjects are shown in Table 2. The pooled safety analysis found that the proportion of subjects who discontinued treatment with either RPV or EFV regardless of severity was 2% and 4%, respectively. The most common adverse drug reactions leading to discontinuation were psychiatric disorders, occurring in 1% and 2% of subjects treated with RPV or EFV, respectively. The discontinuation rate due to rash was 0.1% with RPV and 1.5% with EFV [29].

The safety of RPV in pregnancy has not been established because pregnant women have been excluded from clinical trials evaluating the drug. The embryo and fetal toxicity of RPV, however, has been evaluated in animal models. At exposures 30–80× higher than adults receiving RPV 25 mg daily, there was no
evidence of teratogenicity observed in both rat and rabbit models [35]. Overall, RPV is classified as a category B drug for use in pregnancy; therefore, RPV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Resistance

An in vitro investigation compared the activity of RPV and comparator agents against HIV-1 wild-type strains and those harbouring various NNRTI resistance mutations [36]. Among wild-type HIV-1 group M viruses, RPV had a median EC50 value (0.73 nM) that was lower than that observed for EFV, ETR and NVP by a factor of 2.4, 3.7 and 46.7, respectively.

RPV was also found to have activity in the presence of NNRTI-resistant viruses [36]. The activity of RPV was generally maintained in the presence of single NNRTI mutations at the following positions: 100, 103, 106, 138, 179, 188, 190, 221, 230 and 236. HIV viruses with the Y181C mutation were also sensitive to RPV, although the Y181I/V demonstrated resistance. Overall, RPV maintained activity in 62% of viruses that had resistance to both EFV and NVP while cross-resistant between RPV and ETR was frequently observed.

This investigation also tested varying concentrations of RPV and comparator agents to determine the minimum level at which resistance mutations would begin to develop [36]. For RPV, the selection of resistant viruses appeared at a concentration of 10 nM while resistance appeared at 200 nM for ETR and 1,000 nM for both NVP and EFV. Together these data demonstrate the relative potency of RPV and its potential to select for resistance in vitro when compared to other NNRTI agents.

Mutations emerging under the selective pressure of RPV in this study included combinations of V90I, L100I, K101E, V106A/I, V108I, E138G/K/QR, V179F/I, Y181C/I, G190E, H221Y, F227C and M230I/L. The emergence of resistance to RPV has also been evaluated in vivo using data from clinical trials [37]. Among patients with virological failure to RPV (n=72/686) and EFV (n=39/682) after 48 weeks in ECHO and THRIVE only a portion had resistance testing available (n=62/72 for RPV and n=28/39 for EFV). Overall, the number of virological failures with treatment-emergent NNRTI mutations was higher for RPV (39 versus 15) while the relative proportions between groups were similar (n=39/62, 63% for RPV and n=15/28, 54% for EFV). The most frequent NNRTI mutation to emerge upon failure with RPV was E138K (n=28/62, 45%) which was in contrast to the K103N mutation (n=11/28, 39%) that emerged with failure to EFV. Interestingly, the E138K never emerged in isolation. Rather, it always occurred with other NNRTI or NRTI mutations. This finding supports previous data suggesting that the E138K alone may not confer complete phenotypic resistance to NNRTIs, instead requiring a combination of mutations to occur for full resistance to develop [36].

Among RPV virological failures in this analysis, most patients developed a combination of NNRTI and NRTI mutations (n=37/62, 60%) as compared to EFV (n=8/28, 29%). The most frequent NRTI mutation that developed during treatment with RPV was the M184I mutation (n=29/62, 47%). This was again in contrast to the EFV-based regimen where the M184V occurred more commonly (n=6/28, 21%). Of note, however, is that the M184I occurred in nearly half of RPV treatment failures largely in combination with the E138K. Together, these mutations led to phenotypic RPV resistance as well as cross-resistance to EFV, ETR and NVP. In fact, those with phenotypic resistance to RPV in this analysis, >65% demonstrated cross-resistance to NVP and >90% had cross resistance to both EFV and ETR [37]. Also noteworthy is the loss of lamivudine and emtricitabine activity as a result of the M184I mutation. The K65R/N mutation also emerged in more patients treated with RPV in this analysis (5 versus 2). Overall, it appears that virological failure with an RPV-based regimen can have multiple consequences including NRTI resistance in addition to cross-resistance among the NNRTI class.

The frequent emergence of the E138K mutation occurring in combination with M184I is unique to antiretroviral treatment failure. In an attempt to understand the co-occurrence of these mutations among patients failing RPV, an in vitro analysis has been performed [38]. This study sought to assess the impact of each mutation on HIV replication fitness as well as the individual antiretroviral activities of RPV, emtricitabine and tenofovir.

In the presence of the E138K alone, RPV susceptibility was reduced 2.4-fold. The combination of E138K and M184I, however, reduced RPV susceptibility by 4.1-fold. This change in susceptibility was not present when the E138K was combined with M184V, suggesting that the E138K and M184I combination is advantageous for the virus. However, the presence of these mutations reduced viral fitness resulting in a decreased replication capacity. Overall, the results of this study suggest that the emergence of the E138K in combination with M184I enhances resistance to RPV at the cost of decreased viral fitness [38].

Conclusions

RPV is a second-generation NNRTI with activity against HIV strains that are resistant to first-generation agents. It is dosed once daily and has been recently coformulated with tenofovir and emtricitabine into a single-tablet regimen. Administration requires a 500 calorie meal for adequate absorption and concurrent...
acid suppressing medications should be avoided. RPV is currently approved for use in treatment-naive patients, but may offer an additional option in experienced patients with resistance to other NNRTIs pending further investigations. Documenting a baseline viral load of <100,000 copies is essential prior to starting treatment with RPV as this is predictive of virological success. Virological failure in a patient receiving RPV often leads to NNRTI and NRTI resistance with the emergence of the E138K and M184I mutations. These mutations have significant consequences for other NRTIs and NNRTIs and will therefore impact the selection of future antiretroviral treatment regimens.

Disclosure statement

WRS has received research funding and served as a consultant for Tibotec Therapeutics. JJS declares no competing interests.

References


Accepted 17 May 2012; published online 10 August 2012