Once-Daily, Single-Tablet Regimens For the Treatment of HIV-1 Infection
William R. Truong, PharmD; Jason J. Schafer, PharmD, MPH, BCPS, AAHIVP; and William R. Short, MD, MPH, AAHIVS

INTRODUCTION

Once-daily, single-tablet regimens for the management of human immunodeficiency virus type 1 (HIV-1) infection have become an integral part of initial antiretroviral therapy (ART). They provide crucial advantages for the treatment of HIV-1. The most obvious advantage is the potential for improved adherence due to a lower pill burden. Lower pill burdens have been associated with better virological suppression, and once-daily, single-tablet regimens can improve patient satisfaction.1,2

In one retrospective study, investigators compared the effects of once-daily, single-tablet therapy to regimens containing two or more pills per day to determine the effects on adherence, hospitalizations, and health care costs. The investigators discovered that patients on once-daily, single-tablet regimens, in comparison with patients whose therapy required two or more pills per day, were more likely to achieve 95% adherence and were subject to 23% fewer hospitalizations. Moreover, once-daily, single-tablet regimens resulted in a 17% reduction in health care costs.3

Another retrospective analysis of 15,600 veterans taking antiretrovirals demonstrated that once-daily, single-tablet regimens doubled the odds of at least 95% adherence compared with multitablet regimens. Adherence rates of less than 95% are associated with virological failure and development of antiretroviral drug resistance.1,5 In addition, this study demonstrated a statistically significant reduction in hospital admission rate by 26.8% in the once-daily, single-tablet group, compared with 31.3% in the multitablet group.6

Studies such as these suggest that once-daily, single-tablet regimens are highly beneficial as initial therapy in HIV-1 treatment-naïve patients because improved adherence may lead to improved therapeutic outcomes and health care cost efficiencies. The first once-daily, single-tablet agent to be approved by the Food and Drug Administration (FDA) was coformulated efavirenz (EFV), emtricitabine (FTC), and tenofovir disoproxil fumarate (TDF), under the brand name Atripla (Bristol-Myers Squibb/Gilead Sciences).7 Three other coformulated agents are currently available: rilpivirine (RPV), FTC, and TDF (Complera, Gilead Sciences); elvitegravir (EVG), cobicistat (COBI), FTC, and TDF (Stribild, Gilead Sciences); and dolutegravir (DTG), abacavir (ABC), and lamivudine (3TC) (Triumeq, Viiv Healthcare). The brand names of these once-daily, single-tablet regimens, along with their individual components, are listed in Table 1.

According to current treatment guidelines, EFV/FTC/TDF, ETV/COBI/FTC/TDF, and DTG/ABC/3TC are considered recommended regimens for the initiation of ART in treatment-naïve patients.8 RPV/FTC/TDF is also recommended for treatment-naïve patients initiating ART, but only if the patient’s HIV viral load is less than 100,000 copies/mL and the CD4 count is above 200 cells/mm3. As a reflection of their unique advantages as well as patient preference, the ongoing development of new once-daily, single-tablet agents will provide expanded options for clinicians in the near future. This article reviews the currently available and forthcoming once-daily, single-tablet regimens focusing on their pharmacokinetics (Table 2), drug–drug interactions (Table 3), safety profile, and resistance properties.

PHARMACOKINETICS

EFV/FTC/TDF (Atripla)

Each EFV/FTC/TDF tablet consists of a fixed-dose combination of 200 mg FTC, 300 mg TDF, and 600 mg EFV. TDF is a nucleotide analogue reverse transcriptase inhibitor, while FTC is a nucleoside analogue reverse transcriptase inhibitor. EFV is a non-nucleoside reverse transcriptase inhibitor (NNRTI). All three of these drugs inhibit HIV replication by preventing viral RNA transcription. A single dose of 300 mg TDF administered in the fasted state has a maximum plasma concentration (Cmax) of 0.30 ± 0.09 mcg/mL (mean ± standard deviation [SD]) and an area under the curve (AUC) of 2.29 ± 0.69 mcg·hr/mL. FTC has a steady-state Cmax of 1.8 ± 0.7 mcg/mL and an AUC

Table 1 Components of Once-Daily, Single-Tablet Regimens

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Components</th>
<th>Year of FDA Approval</th>
<th>Monthly AWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla</td>
<td>Efavirenz, Emtricitabine, Tenofovir disoproxil fumarate</td>
<td>2006</td>
<td>$2,462</td>
</tr>
<tr>
<td>Complera</td>
<td>Rilpivirine, Emtricitabine, Tenofovir disoproxil fumarate</td>
<td>2011</td>
<td>$2,463</td>
</tr>
<tr>
<td>Stribild</td>
<td>Elvitegravir, Cobicistat, Emtricitabine, Tenofovir disoproxil fumarate</td>
<td>2012</td>
<td>$2,949</td>
</tr>
<tr>
<td>Triumeq</td>
<td>Dolutegravir, Abacavir, Lamivudine</td>
<td>2014</td>
<td>$2,649</td>
</tr>
</tbody>
</table>

AWP = average wholesale price, rounded to the nearest dollar

Disclosures: The authors report no commercial or financial relationships in regard to this article.
### Table 2: Pharmacological Category and Metabolic Characteristics of Once-Daily, Single-Tablet Regimen Components

<table>
<thead>
<tr>
<th>Component</th>
<th>Pharmacological Category</th>
<th>Substrate</th>
<th>Inhibits</th>
<th>Induces</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
<td>CYP3A4, CYP2B6</td>
<td>CYP3A4</td>
<td>CYP2B6</td>
</tr>
<tr>
<td>Rilpivirine</td>
<td>Non-nucleoside reverse transcriptase inhibitor</td>
<td>CYP3A4</td>
<td>OCT2</td>
<td></td>
</tr>
<tr>
<td>Elvitegravir</td>
<td>Integrase strand transfer inhibitor</td>
<td>CYP3A4</td>
<td>CYP2C9</td>
<td></td>
</tr>
<tr>
<td>Cobicistat</td>
<td>Pharmacokinetic enhancer (no activity against HIV)</td>
<td>CYP3A4, CYP2D6</td>
<td>CYP3A4</td>
<td>CYP2D6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P-gp BCRP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MATE1</td>
</tr>
<tr>
<td>Dolutegravir</td>
<td>Integrase strand transfer inhibitor</td>
<td>UGT1A1, CYP3A4, P-gp</td>
<td>OCT2</td>
<td></td>
</tr>
</tbody>
</table>

BCRP = breast cancer resistance protein; CYP = cytochrome P450; MATE1 = multidrug and toxin extrusion protein 1; OCT2 = organic cation transporter 2; P-gp = p-glycoprotein; UGT = uridine glucuronosyltransferase

### Table 3: Pertinent Drug Interactions Among Once-Daily, Single-Tablet Agents

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>Efavirenz</th>
<th>Rilpivirine</th>
<th>Elvitegravir, Cobicistat</th>
<th>Dolutegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In Atripla</td>
<td>In Complera</td>
<td>In Stribild</td>
<td>In Triumeq</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>† Simeprevir Avoid combination</td>
<td>No clinically significant interaction</td>
<td>† Simeprevir Avoid combination</td>
<td>No clinically significant interaction expected</td>
</tr>
<tr>
<td>Sofosbuvir</td>
<td>No clinically significant interaction No dosage adjustments necessary</td>
<td>No clinically significant interaction No dosage adjustments necessary</td>
<td>No clinically significant interaction expected</td>
<td>No clinically significant interaction expected</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>† Voriconazole † EFV Combination not recommended</td>
<td>No dosage adjustments necessary; monitor for breakthrough fungal infection</td>
<td>† Voriconazole † EVG, COBI Assess benefit/risk ratio to justify administration</td>
<td>↔ DTG No dosage adjustments necessary</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>† Ketoconazole (predicted) Avoid combination unless benefit of antifungal therapy outweighs risks</td>
<td>† RPV † Ketoconazole No dosage adjustments necessary; monitor for breakthrough fungal infection</td>
<td>† Ketoconazole † EVG, COBI Limit ketoconazole dose to a maximum of 200 mg per day</td>
<td>↔ DTG No dosage adjustments necessary</td>
</tr>
<tr>
<td>Fluconazole, itraconazole, posaconazole</td>
<td>† Itraconazole † Posaconazole ↔ Fluconazole Avoid itraconazole and posaconazole unless benefit of antifungal therapy outweighs risks; no dosage adjustments necessary with fluconazole</td>
<td>No dosage adjustments necessary; monitor for breakthrough fungal infection</td>
<td>† Itraconazole † EVG, COBI Limit itraconazole dose to a maximum of 200 mg per day</td>
<td>↔ DTG No dosage adjustments necessary</td>
</tr>
</tbody>
</table>

COBI = cobicistat; DTG = dolutegravir; EFV = efavirenz; RPV = rilpivirine. A double-ended arrow (↔) means there is no significant change in drug concentrations.

*table continues*
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#### Table 3 Pertinent Drug Interactions Among Once-Daily, Single-Tablet Agents

<table>
<thead>
<tr>
<th>Concomitant Drug</th>
<th>Efavirenz</th>
<th>Rilpivirine</th>
<th>Elvitegravir, Cobicistat</th>
<th>Dolutegravir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>↓ EFV</td>
<td>↓ RPV</td>
<td>↓ EVG, COBI</td>
<td>↓ DTG</td>
</tr>
<tr>
<td></td>
<td>Additional 200 mg/day of EFV is recommended for patients ≥ 50 kg</td>
<td>Combination contraindicated; use alternative antimycobacterial</td>
<td>Combination contraindicated</td>
<td>Increase DTG dosage to 50 mg twice daily</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>↑ Rifabutin</td>
<td>↑ RPV</td>
<td>↓ EVG, COBI</td>
<td>↔ DTG</td>
</tr>
<tr>
<td></td>
<td>Increase rifabutin daily dose by 50%; if rifabutin is given 2 or 3 times a week, consider doubling rifabutin dose</td>
<td>Increase RPV dose to 50 mg once daily</td>
<td>Combination not recommended</td>
<td>Combination appropriate as an alternative to rifampin</td>
</tr>
<tr>
<td>Erythromycin, clarithromycin</td>
<td>↑ Clarithromycin</td>
<td>↑ RPV</td>
<td>↑ Clarithromycin</td>
<td>No clinically significant interaction expected</td>
</tr>
<tr>
<td></td>
<td>Erythromycin not studied in combination with EFV</td>
<td>↑ Clarithromycin ↔ Erythromycin</td>
<td>↑ Carbamazepine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider azithromycin</td>
<td>Consider azithromycin</td>
<td>Consider alternative anticonvulsant</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine, oxcarbazepine, phenobarbital, phenytoin</td>
<td>↑ Carbamazepine</td>
<td>↑ RPV</td>
<td>↑ EVG, COBI</td>
<td>↓ DTG</td>
</tr>
<tr>
<td></td>
<td>↓ Phenytoin</td>
<td>↓ RPV</td>
<td>↓ EVG, COBI</td>
<td>Avoid combination due to insufficient data to make dosing recommendation</td>
</tr>
<tr>
<td></td>
<td>↓ EFV</td>
<td>↓ RPV</td>
<td>↓ EVG, COBI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alternative anticonvulsant recommended; if coadministered, monitor anticonvulsant plasma levels</td>
<td>Combination contraindicated</td>
<td>Combination contraindicated with simvastatin and lovastatin</td>
<td></td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>↑ Simvastatin, atorvastatin, pravastatin</td>
<td>No dosage adjustments necessary</td>
<td>↑ Simvastatin and lovastatin</td>
<td>No clinically significant interaction expected</td>
</tr>
<tr>
<td></td>
<td>Possible statin dosage increase necessary</td>
<td></td>
<td>Contraindicated with simvastatin and lovastatin</td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitors</td>
<td>No significant change in EFV levels expected</td>
<td>↑ RPV</td>
<td>No clinically significant interaction</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td></td>
<td>No dosage adjustments necessary</td>
<td>Combination contraindicated</td>
<td>No dosage adjustments necessary</td>
<td>No dosage adjustments necessary</td>
</tr>
<tr>
<td>Histamine H₂ receptor antagonists</td>
<td>No significant change in EFV levels when coadministered with famotidine</td>
<td>↑ RPV</td>
<td>No clinically significant interaction</td>
<td>No clinically significant interaction (except cimetidine)</td>
</tr>
<tr>
<td></td>
<td>No dosage adjustments necessary</td>
<td>No dosage adjustments necessary</td>
<td>No dosage adjustments necessary</td>
<td>No dosage adjustments necessary</td>
</tr>
<tr>
<td>Antacids</td>
<td>No significant change in EFV levels</td>
<td>↑ EVG</td>
<td>No clinically significant interaction</td>
<td>No clinically significant interaction</td>
</tr>
<tr>
<td></td>
<td>No dosage adjustments necessary</td>
<td>Separate antacid administration by 2 hours</td>
<td>No dosage adjustments necessary</td>
<td>No dosage adjustments necessary</td>
</tr>
<tr>
<td>Oral hormonal contraceptives</td>
<td>↔ Ethinyl estradiol</td>
<td>No clinically significant interaction with ethinyl estradiol and norethindrone</td>
<td>No clinically significant interaction with ethinyl estradiol and norethindrone</td>
<td>No clinically significant interaction with ethinyl estradiol and norethindrone</td>
</tr>
<tr>
<td></td>
<td>♦ Progestin (active metabolites of norgestimate)</td>
<td>No dosage adjustments necessary</td>
<td>Consider alternative nonhormonal contraception methods</td>
<td>No dosage adjustments necessary</td>
</tr>
<tr>
<td></td>
<td>Must use reliable barrier contraception in addition to hormonal contraceptives</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cobi = cobicistat; DTG = dolutegravir; EFV = efavirenz; RPV = rilpivirine. A double-ended arrow (↔) means there is no significant change in drug concentrations.
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over a 24-hour dosing interval of 10.0 ± 3.1 mcg•hr/mL. The plasma trough concentration of FTC 24 hours post-dose is 0.09 mcg/mL. Once-daily 600 mg EFV has a mean steady-state Cmax of 12.9 ± 3.7 μM, minimum plasma concentration (Cmin) of 5.6 ± 3.2 μM, and an AUC of 184 ± 173 μM•hr observed during fasting conditions. An important clinical implication of EFV’s pharmacokinetic profile relates to its administration with food. When a 600-mg EFV tablet is given with a high-fat meal (approximately 1,000 calories, with 500–600 calories from fat), its Cmax and mean AUC have been shown to increase by 79% and 28%, respectively, relative to its administration in a fasting state. The increase in EFV plasma concentration when administered with food does not provide greater clinical efficacy but can lead to additional side effects (refer to the safety section for EFV’s adverse effects). Therefore, it is recommended that EFV be taken on an empty stomach or with a low-fat snack.

Less than 0.7% of TDF and 4% of FTC are bound to human plasma proteins. EFV is highly protein-bound, with 99.5% to 99.75% of the drug bound predominantly to albumin. TDF is not metabolized by cytochrome P450 (CYP) enzymes and at normal concentrations does not inhibit CYP enzymes. Similarly, FTC does not inhibit human CYP enzymes. EFV is primarily metabolized by CYP2B6 and CYP3A4 isoenzymes and is capable of inducing CYP enzymes, particularly CYP3A4. The half-lives of TDF and FTC are approximately 17 and 10 hours, respectively. The terminal half-life of EFV is 52 to 76 hours subsequent to single doses, and 40 to 55 hours subsequent to multiple doses due to its auto-inducing ability. A primary concern that must be considered with FTC and TDF is its use in renal impaired patients. Since FTC and TDF are primarily eliminated via the kidneys, the dosage interval must be adjusted in patients with a creatinine clearance (CrCl) of 30 to 49 mL/min, and its use should be avoided in patients with a CrCl of less than 30 mL/min. EFV does not require renal dosing, since it is not primarily eliminated via the kidneys; however, because EFV/FTC/TDF is a combination tablet with fixed doses of FTC and TDF in addition to EFV, a patient’s renal function still must be considered. Therefore, patients with a CrCl of less than 50 mL/min should not receive EFV/FTC/TDF as a single tablet, since the TDF and FTC components will require dosing adjustments in these patients. The pharmacokinetics of TDF are not substantially altered in moderate-to-severe hepatic impairment. Since FTC does not undergo significant liver-enzyme metabolism, the impact on its pharmacokinetics due to hepatic impairment is limited. EFV is not recommended in patients with moderate-to-severe hepatic impairment because of a lack of sufficient data. Caution should also be used when giving EFV to patients with mild hepatic impairment, although no dosage adjustments are recommended.

RPV/FTC/TDF (Complera)
Each RPV/FTC/TDF tablet consists of fixed doses of 25 mg RPV, a NNRTI, in addition to 200 mg FTC and 300 mg TDF. Under fasted conditions in healthy volunteers, RPV was shown to have a Cmax of 210 ± 119 ng/mL, Cmin of 67 ± 30 ng/mL, and AUC of 7,804 ± 3,101 ng•h/mL. One study of 12 healthy subjects demonstrated that RPV’s bioavailability was significantly higher when taken with food. Specifically, the Cmax increased by 71% and the AUC increased by 45%. Maximal bioavailability results when RPV is taken with a normal meal of 533 calories. Absorption does not improve when RPV is taken with a high-fat, high-calorie meal of 928 calories but can decrease by 50% when it is taken with minimal fat or a highly protein-rich meal or protein drink. As a result, in contrast to EFV, patients should be instructed to take RPV/FTC/TDF with a 400-to-500-calorie meal containing fat and protein to optimize systemic absorption.

RPV is highly protein-bound, with greater than 99% of the drug bound primarily to albumin. RPV has a half-life of 50 hours and is primarily metabolized by CYP3A isoenzymes. RPV/FTC/TDF is not recommended in patients with a CrCl of less than 50 mL/min due to the fixed FTC and TDF components, but the combination may be used in patients with mild or moderate hepatic impairment (Child-Pugh class A or B) with no dosage adjustment. It has not been studied in subjects with severe hepatic impairment (Child-Pugh class C).

EVG/COBI/FTC/TDF (Stribild)
Each EVG/COBI/FTC/TDF tablet consists of fixed doses of 150 mg EVG, 150 mg COBI, 200 mg FTC, and 300 mg TDF. EVG is an integrase inhibitor, which prevents viral replication by inhibiting the incorporation of viral DNA into host-cell DNA. COBI is a selective CYP3A inhibitor that is utilized in EVG/COBI/FTC/TDF as a pharmacokinetic booster for EVG and does not have any intrinsic activity against HIV. COBI has a Cmax of 1.7 ± 0.4 mcg/mL, Ctrough of 0.45 ± 0.26 mcg/mL, and AUC of 23.0 ± 7.5 mcg•h/mL. COBI has a Cmax of 1.1 ± 0.4 mcg/mL, Ctrough of 0.05 ± 0.13 mcg/mL, and AUC of 8.3 ± 3.8 mcg•h/mL. Similar to RPV/FTC/TDF and in contrast to EFV/FTC/TDF, it is recommended that EVG/COBI/FTC/TDF be taken with food. Its administration with a light meal (approximately 373 calories and 20% fat) increased EVG drug exposure by 34% when compared with the fasting state.

Both EVG and COBI are highly protein-bound: 98% to 99% and 97% to 98%, respectively. EVG and COBI are primarily metabolized by CYP3A isoenzymes, with COBI also being metabolized by CYP2D6 to a minor degree. When EVG and COBI are given together in each EVG/COBI/FTC/TDF tablet, the median terminal half-life is 12.9 hours for EVG and 3.5 hours for COBI. Due to COBI’s ability to inhibit multidrug and toxin extrusion protein 1 (MATE1) transporter in the kidneys, patients should only be initiated on EVG/COBI/FTC/TDF if their CrCl is 70 mL/min or greater. Despite this precaution, COBI has been shown to have no significant effect on actual glomerular filtration rate. Use of EVG/COBI/FTC/TDF without dose adjustment is acceptable in mild or moderate hepatic impairment, but should be avoided in severe hepatic impairment due to a lack of data in this patient population.

DTG/ABC/3TC (Triumeq)
Each DTG/ABC/3TC tablet consists of fixed doses of 50 mg DTG, 600 mg ABC, and 300 mg 3TC. DTG is a second-generation integrase inhibitor, while ABC and 3TC are nucleoside reverse transcriptase inhibitors. A single dose of 600 mg ABC was shown to have a Cmax of 4.26 ± 1.19 mcg/mL and an AUC of 11.95 ± 2.51 mcg•hr/mL; 3TC was shown to have a steady-state Cmax of 2.04 ± 0.54 mcg/mL and an AUC over a 24-hour dosing interval of 8.87 ± 1.83 mcg•hr/mL. Once-daily 50 mg DTG was shown to have a mean steady-state
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C\text{max} of 3.67 mcg/mL, C\text{min} of 1.11 mcg/mL, and AUC\text{0–24h} of 53.6 mcg•hr/mL. According to the package insert, DTG may be taken with or without food.\textsuperscript{27,28}

Approximately 50% of ABC and at least 98.9% of DTG are bound to human plasma proteins.\textsuperscript{26,27} ABC is primarily metabolized by alcohol dehydrogenase and glucuronyl transferase, while 3TC is eliminated in the urine unchanged. CYP enzymes do not significantly metabolize ABC and 3TC. Furthermore, ABC and 3TC do not affect this enzyme system.\textsuperscript{26} UDP-glucuronosyltransferase (UGT) 1A1 is the primary route of DTG metabolism, with some contribution from CYP3A4.\textsuperscript{27,29} The elimination half-life of ABC is 1.45 ± 0.32 hours, while that of 3TC is approximately five to seven hours.\textsuperscript{26} DTG’s terminal half-life is approximately 14 hours.\textsuperscript{27,29} Coformulated DTG/ABC/3TC should not be used in patients with a CrCl of less than 50 mL/min because the 3TC component requires a dosage reduction, which is not possible in a fixed-dose combination tablet. Further, coformulated DTG/ABC/3TC should not be used in patients with hepatic impairment (Child-Pugh score 5 and above), since the ABC component requires a dosage reduction.\textsuperscript{26}

### DRUG–DRUG INTERACTIONS

**EFV/FTC/TDF (Atripla)**

Since TDF, FTC, 3TC, and ABC have very few clinically significant drug–drug interactions, the focus for potential drug interactions should be on EFV, RPV, EVG/COBI, and DTG due to their metabolic characteristics. Important, clinically relevant drug–drug interactions with these agents are presented in Table 3.

Clinicians must be cognizant of a number of drug interactions when prescribing EFV/FTC/TDF. The EFV component is known to induce CYP3A4 and CYP2B6, leading to a decrease in plasma concentration of drugs metabolized by these isoenzymes.\textsuperscript{30,31} In addition, EFV is also a substrate of CYP2B6 and CYP3A4 and is subject to interactions with drugs that either inhibit or induce these isoenzymes.\textsuperscript{11–13} Drugs that are substrates of CYP3A4 and/or CYP2B6 may require dose adjustment to compensate for the decrease in plasma concentration when given concomitantly with EFV. Although a myriad of pharmaceuticals are metabolized by CYP3A4 and CYP2B6, certain drugs have been shown to have (or have a strong predictability for) decreased plasma concentration. These include hepatitis C protease inhibitors, anticonvulsants, antidepressants, azole antifungals, clarithromycin, rifabutin, calcium-channel blockers, HMG-CoA reductase inhibitors, and oral contraceptive agents.\textsuperscript{11}

Almost a third of HIV-infected patients in the United States are also infected with the hepatitis C virus (HCV).\textsuperscript{32} Therefore, in patients with HIV/HCV coinfection, it is imperative to consider drug interactions during treatment selection for either infection. When coadministered with EFV, the simprevir AUC decreased 71% due to EFV-induced CYP metabolism. This suggests that these drugs should not be coadministered.\textsuperscript{33,34} In contrast, EFV has been shown to have no clinically significant effects on sofosbuvir’s AUC, suggesting that sofosbuvir is safe to use with EFV.\textsuperscript{35,36} The FDA has approved or is reviewing several novel HCV treatments, including coformulated regimens of ledipasvir/sofosbuvir, ombitasvir/dasabuvir/ABT-450/ritonavir, and daclatasvir-based regimens.\textsuperscript{37} Although drug–drug interaction studies are limited for these novel agents, studies investigating the coadministration of ledipasvir/sofosbuvir with EFV/FTC/TDF and RPV/FTC/TDF have been conducted. One study determined that EFV/FTC/TDF reduced ledipasvir concentration levels but that the reduction was not considered to be clinically relevant. Ledipasvir/sofosbuvir did not affect the concentration levels of EFV; therefore, no dosage adjustments are required when ledipasvir/sofosbuvir is given with EFV/FTC/TDF.\textsuperscript{38} Another study investigated the coadministration of daclatasvir with EFV, and determined that EFV caused daclatasvir AUC and C\text{max} to decrease by 32% and 67%. Therefore, this interaction requires the daclatasvir dosage to be increased from 60 mg to 90 mg when given with EFV. Daclatasvir did not have any clinically significant effects on EFV levels.\textsuperscript{39} Currently, there is no drug interaction data on the coadministration of EFV with ombitasvir/dasabuvir/ABT-450/ritonavir, and dosage recommendations are not yet available.

The use of EFV/FTC/TDF and voriconazole at standard doses is contraindicated because EFV-induced metabolism of voriconazole may decrease antifungal activity.\textsuperscript{41} Voriconazole inhibition may also lead to supratherapeutic levels of EFV, causing increased adverse effects. If these two drugs must be used together, the voriconazole dose must be increased to 400 mg given every 12 hours and the EFV dose decreased to 300 mg given at bedtime. This can only occur if EFV, FTC, and TDF are given as individual components, which precludes the advantages of once-daily, single-tablet administration.\textsuperscript{40,41}

Coadministration of EFV/FTC/TDF with rifampin may lead to induction of EFV metabolism, resulting in potentially subtherapeutic EFV levels. Therefore, an additional 200 mg/day of EFV is recommended for patients weighing 50 kg or more who are coadministered EFV/FTC/TDF with rifampin.\textsuperscript{11,42} When coadministered with rifabutin, EFV has been shown to decrease rifabutin’s AUC.\textsuperscript{43} Increasing the daily dose of rifabutin by 50% is recommended when rifabutin is given together with EFV. If rifabutin is given two or three times a week, consideration should be given to doubling the rifabutin dose.\textsuperscript{11}

EFV interacts with clarithromycin by reducing that drug’s plasma concentration. The combination of EFV and erythromycin has not been studied. Therefore, it is recommended that azithromycin be used instead, as there is no significant change in its plasma concentration when given with EFV.\textsuperscript{13} Plasma levels of carbamazepine are reduced when coadministered with EFV. Since carbamazepine is a potent inducer of CYP3A4, EFV plasma levels may be decreased as well. Therefore, this combination is not recommended and use of an alternative anticonvulsant may be warranted.\textsuperscript{44}

EFV decreases the AUC of bupropion and sertraline by 55% and 39%, respectively.\textsuperscript{45} The dosage of these antidepressants should be titrated based on the patient’s clinical response. In contrast, EFV has no significant effects on paroxetine levels and can be coadministered without dosage adjustment. Caution should be taken when oral midazolam or triazolam are given with EFV; significant elevations in the concentrations of these benzodiazepines may occur. Parenteral midazolam may be administered with EFV if the patient is closely monitored in a setting where appropriate clinical management of respiratory depression is available. Lorazepam may be given without dosage adjustment, since EFV does not significantly affect its AUC. The coadministration of EFV with dexamethasone may lead to
decreased EFV concentrations, and alternative corticosteroids should be considered for long-term use. If dexamethasone must be used, monitoring the patient’s virological response to EFV is warranted. Although the pharmacokinetic consequences of combining EFV with St. John’s wort have not been studied, strong induction of CYP3A4 by St. John’s wort prohibits the combination of these two drugs.11

EFV generally lowers the plasma concentration of HMG-CoA reductase inhibitors by inducing their CYP3A4-mediated metabolism. It has been shown that when EFV is coadministered with simvastatin, there is a nearly 58% reduction in simvastatin AUC. EFV’s effect on atorvastatin is similar, with a median decrease in AUC of 34%. Although it is generally acknowledged that pravastatin is less likely to be affected by drug interactions due to minimal CYP3A4 metabolism, it has been shown that EFV still reduces its AUC by a median of 40%. The reduction in AUC of these commonly prescribed HMG-CoA reductase inhibitors suggests that the dose of simvastatin, atorvastatin, and pravastatin may need to be increased when taken together with EFV to reach desired cholesterol goals. In contrast, HMG-CoA reductase inhibitors have not been shown to alter the concentration of EFV.46 The novel HMG-CoA reductase inhibitor pitavastatin is an exception to EFV’s ability to reduce statin exposure, since it is not metabolized by CYP isoenzymes.47 Preliminary data suggest that EFV does not alter the plasma concentration of pitavastatin.48 There are currently no data regarding interactions between EFV and rosuvastatin. When they are given together, it is recommended that the rosuvastatin dose should be adjusted according to lipid responses without exceeding the maximum recommended dose.9

EFV may decrease the plasma concentrations of calcium-channel blockers, requiring the careful titration of calcium-channel blocker dosage based on clinical response.8 EFV is safe to use with acid-suppressing drugs, including proton pump inhibitors (PPIs), histamine H2 receptor antagonists, and antacids. Famotidine and antacids have been shown not to significantly affect EFV plasma concentrations when given together. This suggests that EFV absorption is not affected by gastric pH.11

When EFV is coadministered with ethinyl estradiol and norgestimate, the progestin component’s plasma concentration decreases significantly. The AUCs of norelgestromin and levonorgestrel have been shown to decrease by 64% and 83%, respectively. Therefore, additional barrier contraception must be used in addition to oral hormonal contraceptives when coadministration occurs with EFV.49

**RPV/FTC/TDF (Complera)**

In contrast to EFV, RPV does not induce CYP3A4. Similar to EFV, however, RPV is primarily metabolized by CYP3A4, so strong inducers or inhibitors of this isoenzyme may lead to clinically significant drug interactions.30

Unlike EFV, RPV may be coadministered with simeprevir without dosage adjustment. There was no clinically significant change in either simeprevir or RPV plasma concentration levels when they were given together.32 Similar to EFV, RPV is safe to coadminister with sofosbuvir, since there was no clinically significant change in plasma concentration for either agent.30 As with EFV/FTC/TDF, RPV/FTC/TDF may be coadministered with ledipasvir without any dosage adjustments, as RPV and ledipasvir levels were not significantly impacted when given together.38 Currently, there is no drug interaction data on the coadministration of RPV with daclatasvir or ombitasvir/dasabuvir/ABT-450/ritonavir, and dosage recommendations are not yet available.

Compared with EFV, no dose adjustments are necessary when RPV is given together with voriconazole. One randomized, open-label, crossover study showed that ketoconazole caused an increase in RPV AUC and Cmax, but the increase was deemed not to be clinically significant.34 The other widely used azole antifungals, including fluconazole, itraconazole, and posaconazole, have lower CYP3A4 inhibition properties than ketoconazole and are safe to use with RPV/FTC/TDF without any dose adjustment.52 Rifampin should not be given with RPV because it is a very strong inducer of RPV metabolism and may lead to subtherapeutic RPV levels. When they were given together, rifampin caused an 80% decrease in RPV’s AUC and a 69% decrease in Cmax.50 Rifabutin’s induction ability may also cause a decrease in RPV plasma concentrations. When given together, rifabutin caused a 46% decrease in RPV’s AUC and a 35% decrease in Cmax.50 However, rifabutin may be coadministered with RPV if the RPV dose is increased from 25 mg once daily to 50 mg once daily. The RPV dose should be decreased to 25 mg once daily once rifabutin coadministration ends.15

When RPV is given with macrolide antibiotics such as erythromycin and clarithromycin, inhibition of CYP3A4 may occur and increase the plasma concentration of RPV. Therefore, due to its poor inhibition of CYP3A4, azithromycin is recommended in patients who require treatment with a macrolide antibiotic and are on RPV-containing regimens.15

Other strong CYP3A4 inducers, such as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, St. John’s wort, and greater-than-single-dose dexamethasone should be avoided in patients being treated with RPV-containing regimens.15

In contrast to EFV, studies have shown that RPV does not have clinically significant effects on the pharmacokinetic parameters of HMG-CoA reductase inhibitors, so it is safe to use with simvastatin, atorvastatin, lovastatin, rosuvastatin, pravastatin, pitavastatin, and fluvastatin without any dose adjustments.34,55

Unlike EFV, RPV requires a low-pH environment for optimal absorption and bioavailability. Drugs that modify gastric acid can have serious drug interactions with RPV when given together within a short time. PPIs such as omeprazole, esomeprazole, rabeprazole, lanosoprazole, and pantoprazole are contraindicated with RPV and should not be given with RPV/FTC/TDF.15,56 Unlike PPIs, H2 receptor antagonists’ acid-reducing effects are shorter in duration and they may be given with RPV, but only when the administration of the two drugs is separated by adequate time to avoid interaction. It is critical that the H2 receptor antagonists, such as famotidine, cimetidine, and ranitidine, be given at least 12 hours before or four hours after RPV/FTC/TDF administration.15,57 Likewise, antacids that contain aluminum, magnesium hydroxide, or calcium carbonate should be given at least two hours before or four hours after RPV/FTC/TDF administration.15,55

RPV may also be coadministered with oral contraceptives containing ethinyl estradiol and norethindrone without interaction.58
**EVG/COBI/FTC/TDF (Stribild)**

Both the EVG and COBI components in EVG/COBI/FTC/TDF are involved in numerous drug–drug interactions. EVG, a modest inducer of CYP2C9, may decrease the plasma concentrations of drugs metabolized by this enzyme. Common drugs that are substrates of CYP2C9 include, but are not limited to, warfarin, phenytoin, angiotensin II receptor antagonists, sulfonylureas, and nonsteroidal anti-inflammatory agents. Cobimetapar, an inhibitor of CYP3A4 and CYP2D6, may increase the plasma concentration of drugs metabolized by this enzyme. It also inhibits p-glycoprotein transporter (P-gp), breast cancer resistance protein (BCRP) transporter, and MATE1.

In the treatment of HIV/HCV coinfection, the coadministration of EVG/COBI/FTC/TDF and simeprevir should be avoided because it can lead to significantly increased simeprevir exposure due to strong COBI inhibition of CYP3A4. Although there are currently no trials investigating the pharmacokinetic consequences of sofosbuvir and EVG/COBI/FTC/TDF coadministration, these two agents are not expected to interact with each other. An ongoing clinical trial is assessing the pharmacokinetic interactions between EVG/COBI/FTC/TDF and lepildapipav.

CYP inhibition by azole antifungals such as ketoconazole, itraconazole, voriconazole, and posaconazole may increase EVG and COBI levels, while COBI inhibition may lead to an increased concentration of these agents. To account for this, the maximum daily dose of ketoconazole and itraconazole should not exceed 200 mg per day when given with EVG/COBI/FTC/TDF.

Since both EVG and COBI are metabolized by CYP3A4 enzymes, strong inducers of these enzymes, such as rifampin, rifabutin, and St. John’s wort, should be avoided with EVG/COBI/FTC/TDF.

Clarithromycin and COBI are subject to a two-way interaction in which concentrations of both drugs can be altered. Clarithromycin will increase COBI plasma levels, while COBI will increase clarithromycin levels. Therefore, when the use of clarithromycin is required in patients with a CrCl of 50–60 mL/min, the clarithromycin dose should be reduced by 50%. The coadministration of clarithromycin and EVG/COBI/FTC/TDF should be discontinued in patients with a CrCl of less than 50 mL/min.

The anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, and phenytin have the potential to significantly induce EVG and COBI metabolism and result in subtherapeutic plasma concentrations. The use of alternative anticonvulsants should be considered in this situation. The plasma concentration of antidepressants, including selective serotonin reuptake inhibitors, tricyclic antidepressants, and trazodone, may be increased with EVG/COBI/FTC/TDF. When antidepressants and EVG/COBI/FTC/TDF must be given together, careful dose titration of the antidepressant coupled with clinical-response and adverse-event monitoring is recommended.

Drug interactions may occur between EVG/COBI/FTC/TDF and benzodiazepines. Benzodiazepine exposures may increase when coadministered with EVG/COBI/FTC/TDF. Specifically, triazolam and orally administered midazolam are metabolized by CYP3A4 and are contraindicated with EVG/COBI/FTC/TDF. Lorazepam, oxazepam, and temazepam may not have substantial drug interactions with EVG/COBI/FTC/TDF, since these agents are not metabolized via CYP3A4 pathways. However, these agents have not been evaluated in combination with EVG/COBI/FTC/TDF and formal recommendations have not been established. If parenteral midazolam is administered with EVG/COBI/FTC/TDF, the patient should be subject to close monitoring in a setting where appropriate clinical management of respiratory depression is available. As with RPV/FTC/TDF, clinicians must be aware that systemic dexamethasone can significantly decrease the plasma concentrations of EVG and COBI through CYP3A induction.

The use of EVG/COBI/FTC/TDF is contraindicated in patients who are taking alfaxoquin, ergot derivatives (dihydroergotamine, ergotamine, methylergonovine), and the HMG-CoA reductase inhibitors lovastatin and simvastatin. EVG/COBI/FTC/TDF has the potential to increase the plasma concentration of these drugs and lead to life-threatening adverse effects. When coadministered with EVG/COBI/FTC/TDF, rosuvastatin must be used with caution, as its AUC and Cmax have been shown to increase by 38% and 89%, respectively. Therefore, rosuvastatin should be titrated from the lowest possible dose to reach desired lipid-lowering effects. Likewise, atorvastatin should also be titrated from the lowest possible dose to reach desired lipid-lowering effects while monitoring for safety. There are no clinical data on the effects of EFV coadministration with pravastatin or pitavastatin.

Antiarrhythmics (amiodarone, bepridil, disopyramide, dronedarone, flecainide, systemic lidocaine, mexiletine, propafenone, quinidine) and digoxin exposures are increased when coadministered with EVG/COBI/FTC/TDF due to COBI inhibition of CYP3A4 and P-gp transporter. Close monitoring of therapeutic concentrations and adverse effects is warranted when using these drugs with EVG/COBI/FTC/TDF.

The plasma concentrations of beta blockers and calcium-channel blockers may be increased with EVG/COBI/FTC/TDF. Dosage reduction of these antihypertensives and clinical monitoring of their efficacy and adverse effects may be necessary when they are being coadministered with EVG/COBI/FTC/TDF.

The use of inhaled salmeterol with EVG/COBI/FTC/TDF is not recommended because increased salmeterol exposure may occur. This may lead to an increased risk for QT prolongation, palpitations, and sinus tachycardia. The use of inhaled or nasal fluticasone with EVG/COBI/FTC/TDF may increase fluticasone plasma concentration and result in reduced serum cortisol levels. Therefore, alternative corticosteroids should be used, particularly when long-term therapy is required.

EVG exposure is reduced when EVG/COBI/FTC/TDF is given with antacids due to chelation. It is recommended that the administration of antacids and EVG/COBI/FTC/TDF be separated by two hours to avoid this interaction. In contrast to RPV/FTC/TDF, PPIs and H2 receptor antagonists are safe to administer with EVG/COBI/FTC/TDF; there are no clinically significant interactions between these drugs and the EVG component.

When EVG/COBI/FTC/TDF is coadministered with ethinyl estradiol and norgestimate, the progestin component’s AUC and Cmin increased by 126% and 167%, respectively. However, the AUC and Cmin of ethinyl estradiol decreased.
by 25% and 44%, respectively. Therefore, it is suggested that alternative forms of contraception or oral agents containing at least 30 mcg of ethinyl estradiol be used.\(^8\)\(^,\)\(^7\)

**DTG/ABC/3TC (Triumeq)**

The DTG component in DTG/ABC/3TC does not inhibit CYP metabolic pathways and is not expected to cause interactions with drugs that are CYP substrates. In addition, DTG does not affect P-gp, BCRP, and organic anion transporter proteins. Since DTG undergoes UGT 1A1 and CYP3A4 metabolism, inducers and inhibitors can alter the serum concentration of DTG.\(^8\)

DTG requires a dosage increase to 50 mg twice daily when coadministered with rifampin in patients without a suspected or documented INSTI mutation. The combination should be avoided in patients with INSTI-associated resistance. The administration of rifabutin 300 mg once daily does not change DTG concentrations. Therefore, the use of rifabutin as an alternative to rifampin can be considered, since it will not require DTG dosage adjustment.\(^8\)

Strong inducers of CYP3A4, including carbamazepine, oxcarbazepine, phenytoin, phenobarbital, and St. John’s wort, should not be coadministered with DTG because of a potential decrease in DTG exposure.\(^7\)

Similar to EFV and EVG, but in contrast to RPV, DTG may be used together with PPIs and H\(_2\) antagonists, as these drugs have no significant impact on DTG concentration. However, use of antacids must be separated from use of DTG by administering DTG either two hours before or six hours after taking antacids. Multivitamins have been shown to have no clinically significant interaction with DTG.\(^7\)\(^,\)\(^9\) In addition, DTG has no clinically significant impact on the pharmacokinetics of methadone and oral contraceptives containing norgestimate and ethinyl estradiol.\(^7\)\(^,\)\(^1\)\(^2\)

DTG inhibits OCT2, which may increase the concentration of drugs that rely on this pathway for elimination.\(^8\) Strong caution must be used when administering the OCT2 substrate dofetilide with DTG due to dofetilide’s very narrow therapeutic index. Other interacting OCT2 substrates that may have increased exposure include metformin, procainamide, cimetidine, and triamterene. Close monitoring is warranted when these medications are used with DTG/ABC/3TC, and dose adjustment may be necessary.\(^8\)\(^,\)\(^7\)\(^3\)

**SAFETY**

**EFV/FTC/TDF (Atripla)**

Each coformulated agent has a unique adverse-effect profile that clinicians must know. This is vital for monitoring patient safety and ensuring adherence. The most common and significant adverse drug reactions (ADRs) associated with EFV are neuropsychiatric effects. In one cross-sectional study, 54% of patients who had been using EFV for at least a year reported having at least one neuropsychiatric effect at the time of trial interview, compared with 27% of patients who were on a stable protease inhibitor regimen.\(^7\)\(^4\) Neuropsychiatric effects experienced by patients taking EFV include, but are not limited to, dizziness, anxiety, impaired concentration, abnormal dreams, insomnia, and mood changes. Many of these neuropsychiatric effects decrease over time and often disappear after one to two months of therapy. Furthermore, instructing the patient to take this medication on an empty stomach will help reduce the incidence of EFV adverse effects because drug absorption will be reduced with no sacrifice in efficacy.\(^1\)\(^1\)\(^,\)\(^7\)\(^4\)\(^–\)\(^7\)\(^9\) One meta-analysis showed that patients taking EFV-containing antiretroviral therapy regimens were more likely to experience central nervous system events than those taking nevirapine-based regimens. Despite the higher neuropsychiatric ADRs, EFV infrequently led to treatment modification.\(^7\)\(^5\) Although it is uncommon, neuropsychiatric symptoms may persist up to a year or longer, which may require therapy modification. Consideration for therapy modification should depend on the severity of symptoms, patient input, underlying resistance, and availability of alternative regimens. Prescribers should screen patients for any history of psychiatric illness to avoid further complications with EFV therapy. A psychiatric consultation is recommended if EFV therapy is to be considered in patients who are predisposed to or have a history of psychiatric disorders.\(^7\)\(^6\)

Skin rashes are also a common ADR of EFV, occurring in up to 25% of patients.\(^1\)\(^1\) These rashes often manifest as mild-to-moderate maculopapular skin eruptions that develop within two weeks of EFV initiation. Antihistamines or corticosteroids may help accelerate the resolution of symptoms, which often occurs within one month.\(^1\)\(^1\) Rarely, the rash can be severe or prolonged and require discontinuation of EFV therapy.

**RPV/FTC/TDF (Complera)**

Safety data for RPV are based on phase 3 trials completed through 96 weeks in which RPV was compared with EFV. Similar to EFV, depressive disorders have been reported with RPV. Depressive disorders include depressed mood, depression, dysphoria, major depression, altered mood, negative thoughts, suicide attempts, and suicidal ideation. During phase 3 trials, the incidence of depressive disorder, regardless of severity and causality, was similar between RPV and EFV (9% versus 8%). Discontinuation of therapy due to depressive disorders was identical (1%) in the RPV and EFV groups.\(^1\)\(^5\)\(^,\)\(^8\) However, discontinuations due to any ADRs were lower with RPV (2%) than with EFV (5%).\(^1\)\(^5\)\(^,\)\(^8\)\(^,\)\(^9\)\(^,\)\(^2\)

RPV was also associated with lower increases in total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) than EFV. The mean changes from baseline to week 96 of pooled data from phase 3 trials for TC, HDL-C, LDL-C, and TG were 2, 4, −1, and −14 mg/dL in RPV-treated patients, respectively. The mean changes for TC, HDL-C, LDL-C, and TG in EFV-treated patients were 26, 11, 14, and 6 mg/dL, respectively.\(^1\)\(^5\)\(^,\)\(^8\)

There was no difference in the change in bone mineral density between RPV and EFV.\(^8\)\(^3\) Other common ADRs that were seen in at least 2% of subjects receiving RPV in phase 3 trials included headache (3%), insomnia (3%), rash (3%), abdominal pain (2%), fatigue (2%), and abnormal dreams (2%).\(^1\)\(^5\)\(^,\)\(^8\)

**EVG/COBI/FTC/TDF (Stribild)**

Safety data for EVG/COBI/FTC/TDF are based on phase 3 trials completed through 96 weeks in which the clinical efficacy and safety of EVG/COBI/FTC/TDF were compared with EFV/FTC/TDF and atazanavir/ritonavir/FTC/TDF. ADRs reported in 3% or more of subjects on EVG/COBI/FTC/TDF included diarrhea, nausea, headache, and abnormal dreams.
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More than 2% of the EVG/COBI/FTC/TDF group experienced liver enzyme levels greater than five times the upper limit of normal (ULN), amylase levels greater than two times the ULN, creatinine kinase at least 10 times the ULN, and urine red blood cell (RBC) levels of more than 75 RBC/HPF. Changes in bone mineral density in the EVG/COBI/FTC/TDF group were similar to the comparator groups.\textsuperscript{18,84,85} Despite a corresponding decrease in estimated glomerular filtration rate (eGFR), the elevated serum creatinine does not reflect a decline in actual renal function.\textsuperscript{23} In phase 3 trials, an increase in serum creatinine and decrease in estimated CrCl occurred early in EVG/COBI/FTC/TDF treatment, but stabilized thereafter. Patients treated with EVG/COBI/FTC/TDF showed a mean decrease in eGFR of 13.2 mL/min compared with EFV/FTC/TDF (–0.9 mL/min) and atazanavir/ritonavir/FTC/TDF (–8.6 mL/min).\textsuperscript{18,88,89} While only modest declines in eGFR have been observed and are expected with EVG/COBI/FTC/TDF treatment, certain precautions are recommended by the manufacturer.\textsuperscript{18} Specifically, close monitoring of renal function is recommended in patients whose serum creatinine increases by 0.4 mg/dL or more from baseline. Furthermore, EVG/COBI/FTC/TDF should not be initiated in patients with an estimated CrCl of less than 70 mL/min and should be discontinued in patients with an estimated CrCl of less than 50 mL/min.\textsuperscript{18}

DTG/ABC/3TC (Triumeq)

ADRs seen in at least 2% of subjects receiving DTG in the clinical trials evaluating its efficacy and safety included insomnia and headache. Increases in serum creatinine due to OCT2 inhibition were seen in patients treated with DTG. This increase occurred within the first four weeks of treatment and eventually stabilized throughout therapy. Despite an increase in serum creatinine, there was no effect on glomerular function.\textsuperscript{27,50,91} ABC may cause serious life-threatening hypersensitivity reactions in patients who carry the HLA-B*5701 allele. These reactions consist of fever, rash, gastrointestinal upset, malaise, fatigue, achiness, dysnea, cough, and/or pharyngitis. If hypersensitivity is suspected, the ABC-containing drug must be permanently discontinued immediately and never reintroduced. It is important for prescribers to screen patients for the HLA-B*5701 allele when considering initiation of an ABC-containing regimen because carriers are at a higher risk of hypersensitivity. In patients who do not carry the HLA-B*5701 allele, the development of hypersensitivity reactions is uncommon but should still warrant permanent discontinuation of ABC-containing regimens.\textsuperscript{92–94}

RESISTANCE

The nucleoside reverse transcriptase inhibitors (NRTIs) FTC and TDF can select for the M184V/I and K65R mutations, respectively, when treatment failure occurs. M184V/I commonly appears following treatment failure and results in a greater than 100-fold decrease in susceptibility to FTC and 3TC, but may modestly increase susceptibility to TDF.\textsuperscript{95} Comparatively, the K65R mutation is uncommon following treatment failure but will demonstrate intermediate or high resistance to TDF when present. The most prevalent and clinically significant mutation observed in patients who have failed EFV therapy is K103N. The K103N mutation causes rearrangement of the NNRTI-binding pocket of reverse transcriptase and decreases its affinity for EFV and nevirapine.\textsuperscript{96,97} V106M, Y188L, and G190S are other point mutations that may result in greater than 100-fold decreases in EFV susceptibility and can be seen in HIV treatment-experienced patients.\textsuperscript{38}

In contrast to EFV, RPV is active in the presence of K103N.\textsuperscript{99} However, clinical experience with RPV in treating patients with the K103N mutation is limited. During phase 3 trials, the most common mutation that developed following RPV failure was E138K. This mutation frequently occurred in combination with M184I, which conferred greater resistance to RPV than the E138K mutation alone. The combination of E138K and M184I also conferred cross-resistance to EFV, etravirine, and nevirapine.\textsuperscript{100}

Resistance to EVG consists of single-point mutations within the gene that encodes for the integrase enzyme and includes T66I/A/K, E92Q/G, T97A, S147G, Q148R/H/K, and N155H. These mutations have been identified in patients failing EVG-containing regimens in clinical trials.\textsuperscript{101} Resistance to EVG typically confers cross-resistance to raltegravir.\textsuperscript{102–104} Compared to EVG, DTG has a higher barrier to resistance, mainly due to its improved ability to resist dissociation with a mutated integrase enzyme.\textsuperscript{105} This suggests that DTG has the ability to avoid cross-resistance to EVG and raltegravir.\textsuperscript{106} However, patients with the Q148 point mutation plus two or more additional integrase mutations have demonstrated poor virological response to DTG. Therefore, patients who have been treated previously with EVG or raltegravir should be screened for integrase inhibitor resistance before initiating DTG.\textsuperscript{27}

FUTURE DIRECTIONS

A once-daily single tablet containing coformulated darunavir, cobicistat, emtricitabine, and tenofovir alafenamide fumarate is in development. Upon approval, this will be the first once-daily, single-tablet regimen containing a protease inhibitor.\textsuperscript{107} Also unique to this coformulated tablet is the inclusion of a new tenofovir formulation: tenofovir alafenamide fumarate (TAF). Compared to TDF (300 mg), TAF is more potent (10 mg) and concentrates in lymphocytes at higher levels. The result of these unique characteristics is the potential for an improved safety profile. Due to increased tenofovir levels in lymphocytes, renal and bone exposure is decreased and potential renal and bone toxicity is minimized. A coformulation of TAF with EVG, COBI, and FTC is also in development and will add to the growing options of once-daily, single-tablet treatment regimens.\textsuperscript{108,109}

CONCLUSION

Single-tablet, once-daily antiretroviral treatment regimens provide many advantages for the management of HIV infections. These include improved adherence, lower health care costs, and greater patient satisfaction. Given the preference for their use, inclusion of these agents in health-system formularies may prevent potential medication errors during hospital admission and discharge. An understanding of their pharmacokinetics, drug–drug interactions, safety profiles, and resistance patterns is important for their safe and effective use. Additional single-tablet, once-daily agents are under development and are expected to provide clinicians with expanded options in the near future.
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