The Quad Pill, a Once-Daily Combination Therapy for HIV Infection

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The quad pill is the newest single-pill, once-daily option for the treatment of human immunodeficiency virus (HIV) type 1 infection. In addition to tenofovir difumarate (TDF) and emtricitabine (FTC), the quad pill includes cobicistat (COBI; an inactivator of cytochrome P450 isoenzyme CYP3A without anti-HIV activity) and a new integrase inhibitor, elvitegravir (EVG). The quad does not have drug interactions with H2-receptor antagonists or proton pump inhibitors, does not cause central nervous system (CNS) side effects, and is pregnancy category B. It does have substantial drug interactions with medications that are metabolized using CYP3A and causes reversible declines in estimated glomerular filtration rate (eGFR) owing to inhibition of renal tubule transport of creatinine. In clinical trials, the virologic and immunologic efficacy of the quad pill is equivalent to that of other comparator regimens with low rates of discontinuation. The major side effect is nausea which is self-limited, and the primary mutations associated with treatment failure frequently lead to cross-resistance with raltegravir (RAL).

Keywords. tenofovir; emtricitabine; cobicistat; elvitegravir; HIV.

The remarkable advances in therapy for human immunodeficiency virus (HIV) infection during the last 15 years have resulted in dramatic reductions in HIV-related morbidity and mortality. In addition to improved efficacy in viral load reduction, there have been great reductions in toxicity and pill burden. The first single-pill, once-daily option for therapy (TDF/FTC/efavirenz [EFV]) was approved for use in 2006 and is currently the most commonly prescribed antiretroviral combination in the United States [1]. The major drawbacks to the use of this agent are the occurrence of CNS side effects and its pregnancy category D status. As a result, it is typically used with caution in patients with underlying psychiatric conditions or who have childbearing potential.

The second once-daily, single-pill regimen (TDF/FTC/rlpilvirine [RPV]), approved in 2011, offered lower CNS side effects and is pregnancy category B. However, owing to drug interactions, RPV must be administered 12 hours after receiving H2-receptor antagonists and cannot be used in patients taking proton pump inhibitors [2]. In addition, in a study comparing the efficacy of TDF/FTC/EFV and TDF/FTC/RPV in drug-naive HIV-infected patients, higher levels of virologic failure were noted in patients with baseline viral loads of >100 000 copies/mL [3]. Thus, whereas these agents have significantly advanced treatment options for drug-naive individuals, many patients are not suitable candidates for these therapies.

Integrate strand transfer inhibitors (INSTIs) act by inhibiting one of the major functions of HIV integrase, the strand transfer step of proviral HIV DNA integration into the host cell chromosome [4]. The first member of this drug class, RAL, was approved for use in 2007 and has been used extensively in both drug-naive and experienced individuals [5, 6]. This drug is well tolerated, highly efficacious, and has few drug-drug interactions. However, the drug is dosed twice daily, and attempts to use it in a once-daily regimen

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have been associated with higher virologic failure rates [7]. Elvitegravir (EVG) is a potent INSTI that can be dosed once daily in combination with ritonavir (RTV) [8]. Although RTV has been useful to increase drug concentrations with HIV protease inhibitors, it is associated with side effects, including gastrointestinal intolerance, increased serum lipid levels, and lipoatrophy. Cobicistat is a novel inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4) without in vitro HIV activity, which, like RTV, is effective as a pharmacokinetic booster of other antiretroviral agents, such as EVG [9]. These drugs have been coformulated along with TDF/FTC to form the quad pill, the first single-dose daily therapy including an INSTI. We will review the pharmacologic characteristics, in vitro activity, clinical data, and adverse events associated with this regimen.

PHARMACOKINETICS

Cobicistat is a new drug that is designed as an inhibitor of CYP3A4 and to be coadministered with currently available antiretroviral agents, such as EVG, darunavir, and atazanavir (ATZ) [9]. The degree of CYP3A inhibition is similar to that of RTV, and COBI is also metabolized by this enzyme. Unlike RTV, COBI is a weak inhibitor of other cytochrome P450 isoenzymes, which limits its drug-drug interactions [9]. In addition, compared with RTV, COBI has a reduced effect on adipocyte functions, such as lipid accumulation and insulin response. The clinical significance of this difference is unknown at this time. The approved dose for COBI is 150 mg once daily, coformulated with TDF, FTC, and EVG. Currently, COBI is not available for use as a single agent.

The pharmacokinetic profile of COBI was studied in healthy individuals at a range of 50–400 mg/d [9]. Drug exposure levels rose more than linearly with higher doses, because COBI inhibits its own clearance. The half-life after a single dose is 1.4–5.2 hours, and doses of 100–200 mg result in 93%–95% inhibition of CYP3A. The 150-mg dose of COBI was chosen for clinical trials based on a level of EVG boosting similar to that of 100 mg of RTV in healthy individuals [10]. Elvitegravir is a potent inhibitor of HIV-1 and HIV-2 integrase that results in a 50% effective response (EC_{50}) at concentrations of 0.6–1.2 ng/mL [11]. The drug is predominantly metabolized by CYP3A, and levels are increased substantially by coadministration with RTV and COBI [11]. Based on dose-ranging studies of antiviral efficacy, the 150-mg dose of EVG was chosen for phase 3 studies [11]. There is an increase in COBI-boosted EVG levels when EVG is taken with food, especially with a high-fat diet [12]. The maximum concentration of EVG increases 22% with a light meal and 56% with a high-calorie, high-fat meal [12]. The clinical significance of these differences is unknown.

DRUG INTERACTIONS

As a potent inhibitor of CYP3A, COBI results in a substantial number of drug interactions. In addition, COBI inhibits and is metabolized to a lesser degree by CYP2D6 and inhibits several renal transporters. Elvitegravir is affected by drugs that affect CYP3A activity and is a modest inducer of CYP2C9. Thus, whereas COBI has a greater potential for drug interactions directly, a substantial number of drugs can indirectly affect EVG metabolism because of the role of COBI boosting. Table 1 reviews established or potentially significant drug interactions associated with the quad pill. There is no dose adjustment needed when the quad pill is used in combination with H2-receptor antagonists or proton pump inhibitors. Although pH changes do not affect EVG absorption, local complexation with cations contained in antacids lowers EVG absorption, and antacid administration should be separated from quad pill administration by ≥2 hours [11]. Because the quad pill represents a complete regimen for the treatment of HIV infection, it is not recommended to be used with other anti-HIV therapies.

IN VITRO ACTIVITY AND RESISTANCE

The in vitro activity of EVG was studied using a strand transfer assay [14]. This method showed that EVG blocked integration by inhibiting integrase-mediated strand transfer. The mean EC_{50} was 0.7 ± 0.3 nmol/L against HIV-1 strains that included isolates with resistance to other classes, including reverse-transcriptase inhibitors, nonnucleoside reverse-transcriptase inhibitors, and protease inhibitors [14]. In addition, it has activity against HIV-2 strains, with mean EC_{50} values of 1.4–8.8 nmol/L [14].

Multiple-pass experiments were performed to induce EVG resistance [14]. A number of integrase mutations were noted, including Q146P, N232D, T66I, S146G, Q95Q/K, E138E/K, E92E/Q, H51H/Y, S147S/G, and E157E/Q. These mutations were correlated with an increase in EVG EC_{50}. Further phenotypic analysis demonstrated that the primary mutations leading to EVG resistance are the T66I, E92Q, Q146P, and S147G [14]. Combinations of these mutations result in a change in EVG EC_{50} by several hundredfold.

There is substantial cross-resistance between EVG and RAL, and the genetic barrier to resistance for INSTIs seems to be lower than that for protease inhibitors and most nucleoside reverse-transcriptase inhibitors [15]. The INSTIs do seem to have a higher barrier than lamivudine, FTC, nevirapine, or EFV. The 6 primary pathways to EVG resistance in vivo, which have been observed in treatment-naive and treatment-experienced patients with EVG failure, are T66I, E92Q, T97A, S147G, Q148R, and N155H [16]. The Y143 pathway, however, seems to have little effect on EVG EC_{50} [17]. The EVG
resistance mutations T66I and S147G do not affect RAL susceptibility. Fortunately, baseline minor integrase mutations seen in viral isolates from INSTI-naive patients do not seem to confer resistance to EVG or RAL [18]. HIV isolates from patients developing genotypic resistance to EVG are likely to have significant cross-resistance to RAL, and vice versa. In contrast, some HIV isolates from patients experiencing virologic failure with EVG and evidence of genotypic resistance to EVG may remain susceptible to dolutegravir, a recently approved INSTI [15].

Several studies have evaluated the INSTI mutations in patients treated with EVG in clinical trials [19–22]. Among a group of 5 patients treated with EVG during phase 2 studies and experiencing virologic failure, 3 had E92Q mutations and 2 were wild type. In a phase 3 study comparing EVG and RAL in treatment-experienced patients receiving a RTV-boosted protease inhibitor, the predominant mutations that developed in the EVG group were T66I/A, S147G, and E92Q, whereas N155H predominated among RAL recipients [20]. A phase 3 study was performed comparing the quad pill with a combination of TDF/FTC/RTV/ATZ in drug-naive individuals [21]. Among 353 patients receiving the quad pill, 4 (1.1%) developed primary INSTI mutations including Q148R in 2, N155H in 1, and 3 mutations (T66I, E92Q, and N155H) in 1. Finally, among 348 patients receiving the quad pill in another phase 3 study, 7 of 8 patients with resistance had the E92Q mutation [22]. Thus, similar patterns of mutations were seen among resistant isolates that emerged in the different trials of EVG therapy.

**Table 1. Established or Potentially Significant Drug Interactions**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect of Quad Pill on Drug Concentration</th>
<th>Effect of Drug on Quad Pill Concentration</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>Decreased elvitegravir</td>
<td>Separate by ≥2 h</td>
<td></td>
</tr>
<tr>
<td>Anti-arrhythmics b</td>
<td>May increase levels</td>
<td>Monitor levels if possible</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Increased</td>
<td>Increased cobicistat</td>
<td>CrCL &lt; 60 mL/min: reduce clarithromycin 50%</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Monitor INR</td>
</tr>
<tr>
<td>Anticonvulsants c</td>
<td>Increased carbamazepine</td>
<td>Decreased cobicistat and elvitegravir</td>
<td>Use alternative agents</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Increased clonazepam</td>
<td>Monitor clinically</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Increased levels</td>
<td>Monitor clinically</td>
<td></td>
</tr>
<tr>
<td>Azole antifungals</td>
<td>Increased levels</td>
<td>Increased cobicistat and elvitegravir</td>
<td>Limit ketoconazole-traconazole to 200 mg/d; voriconazole use only if benefits outweigh risks</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Increased levels</td>
<td>Decreased cobicistat and elvitegravir</td>
<td>Reduce colchicine dose; avoid in renal hepatic impairment</td>
</tr>
<tr>
<td>Rifamycins</td>
<td>Decreased cobicistat and elvitegravir</td>
<td>Avoid use</td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>Increased levels</td>
<td>Monitor clinically</td>
<td></td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Increased levels</td>
<td>Monitor clinically</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Decreased cobicistat and elvitegravir</td>
<td>No recommendation</td>
<td></td>
</tr>
<tr>
<td>Inhaled fluticasone</td>
<td>Increased levels</td>
<td>Use alternative agents</td>
<td></td>
</tr>
<tr>
<td>Bosentan</td>
<td>Increased levels</td>
<td>Reduce bosentan dose</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Increased levels</td>
<td>Use lowest doses of atorvastatin initially</td>
<td></td>
</tr>
<tr>
<td>Norgestimete–ethinyl Estradiol</td>
<td>Increased norgestimete, decreased ethinyl estradiol</td>
<td>Consider alternate contraception method</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressants d</td>
<td>Increased levels</td>
<td>Monitor levels</td>
<td></td>
</tr>
<tr>
<td>Neuroleptics b</td>
<td>Increased levels</td>
<td>Consider decreasing dose of neuroleptic</td>
<td></td>
</tr>
<tr>
<td>PDE5 inhibitor a</td>
<td>Increased levels</td>
<td>Reduce dose of PDE5 inhibitor</td>
<td></td>
</tr>
<tr>
<td>Sedatives f</td>
<td>Increased levels</td>
<td>Avoid oral midazolam; consider dose reductions for others</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CrCL, creatinine clearance; INR, international normalized ratio; PDE5, phosphodiesterase 5.

* Data from package insert for Stribild [13].

b Amiodarone, bepridil, digoxin, disopyramide, flecainide, systemic lidocaine, mexiletine, propafenone, and quinidine.

c Carbamazepine, oxacarbazepine, phenobarbital, phenytoin, clonazepam, and ethosuximide.

d Cyclosporine, tacrolimus, and sirolimus.

e Sildenafil, tadalafil, and vardenafil.

f Midazolam, clorazapate, diazepam, estazolam, flurazepam, buspirone, and zolpidem.
CLINICAL STUDIES

A phase 2, dose-ranging study of EVG used in combination with RTV was performed in treatment-experienced patients with $\geq 1$ protease mutation [23]. In this randomized, 48-week study, both groups received nucleoside or nucleotide reverse-transcriptase inhibitors, with or without enfuvirtide, and either a RTV-boosted protease inhibitor or EVG. Patients in the EVG arm received 20, 50, or 125 mg once daily. After week 8, the EVG 20-mg group was unblinded owing to lack of virologic efficacy, and darunavir or tipranavir was allowed to be added to the EVG arm. The patients receiving EVG, at doses of 50 and 125 mg, had significantly superior reductions in viral load at 16, 24, and 48 weeks compared with the group receiving protease inhibitors. The addition of either darunavir or tipranavir improved the virologic efficacy in the EVG group further.

Table 2 summarizes the results of 3 randomized studies comparing the quad pill with alternate regimens in drug-naive patients. All 3 studies were performed predominantly among white male patients. The quad pill was noninferior to the comparator regimens in all of the studies, and there were no differences in the primary outcome (viral load, $<50$ copies/mL at week 48) when adjusted for baseline sex, race (white vs other), viral load, or CD4 cell count. In 1 study, patients $\geq 40$ years had superior virologic efficacy at week 48 [22]. In addition, in all 3 studies, the quad pill had superior virologic efficacy at 8–12 weeks. The long-term clinical significance of this earlier virologic efficacy is unknown, because the groups were similar at weeks 24 and 48. One study showed a significantly higher increase in CD4 cell counts at week 48 in the quad pill [22].

There has also been 1 large phase 3 study comparing EVG with RAL in treatment-experienced patients [20]. Patients were eligible if they had a viral load of $>1000$ copies/mL with a treatment regimen of $>30$ days that included $\geq 2$ drug classes. Patients received an open-label background regimen that included an active, boosted protease inhibitor and a second agent and were randomized to receive either EVG (150 mg once daily) or RAL (400 mg twice daily). The groups had similar rates of virologic efficacy ($<50$ copies/mL at week 48) in modified intention-to-treat (EVG vs RAL, 59% vs 58%) and per-protocol (EVG vs RAL, 75% vs 73%) analyses. Increases in CD4 cell counts from baseline were also similar.

DRUG TOXICITY

The predominant side effect of the quad pill seems to be nausea and diarrhea, which have been noted in 17%–21% of patients [21, 22, 24]. This effect leads to rates of discontinuation that were $<1$% in these studies [21, 22]. As expected, in studies comparing the quad pill with TDF/FTC/EFV, patients receiving the quad pill had lower rates of CNS symptoms, including insomnia, abnormal dreams, and dizziness [22, 24]. The quad pill also had lower rates of icterus and abnormal bilirubin levels than TDF/FTC/RTV/ATZ [21]. From a lipid standpoint, the quad pill had less of an increase in triglyceride levels than TDF/FTC/RTV/ATZ [21] as well as lower increases in total, low-density, and high-density cholesterol levels than TDF/FTC/EFV [22]. There were also fewer increases in liver enzyme (alanine aminotransferase) levels compared with both the EFV- and RTV/ATZ-based regimens [21, 22]. There is no evidence of teratogenicity in animal studies of COBI and EVG, and the quad pill is pregnancy category B [13].

It is estimated that 10%–20% of creatinine clearance is due to secretion from renal tubules [25]. The use of estimated eGFR by age, sex, and body size may overestimate the true glomerular filtration rate (GFR). Inhibition of creatinine secretion by renal tubule cells may result in increases in creatinine that do not indicate true changes in renal function. Certain medications, such as trimethoprim, and cimetidine, reversibly inhibit renal transporters, resulting in transient increases in serum creatinine that resolve on discontinuation of therapy [26, 27]. Both COBI and RTV, in addition to other recently approved agents (RPV) and agents in advanced clinical development (dolutegravir) have effects on serum creatinine based on inhibition of renal

Table 2. Major Comparative Studies of the Quad Pill in Antiretroviral-Naive Patients

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>Comparator</th>
<th>No. of Patients</th>
<th>Virologic Efficacy, %a</th>
<th>Change in CD4 Cell Count, cells/mm³b</th>
<th>No. of Discontinuationsc</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>TDF/FTC/EFV</td>
<td>23</td>
<td>83 vs 83</td>
<td>139 vs 205</td>
<td>3 vs 3</td>
<td>Zolopa et al [23]</td>
</tr>
<tr>
<td>3</td>
<td>TDF/FTC/RTV/ATZ</td>
<td>353</td>
<td>86.8 vs 89.5</td>
<td>211 vs 207</td>
<td>18 vs 13</td>
<td>Molina et al [20]</td>
</tr>
<tr>
<td>3</td>
<td>TDF/FTC/EFV</td>
<td>352</td>
<td>84.1 vs 87.6</td>
<td>206 vs 239d</td>
<td>18 vs 13</td>
<td>DeJesus et al [21]</td>
</tr>
</tbody>
</table>

Abbreviations: ATZ, atazanavir; EFV, efavirenz; FTC, emtricitabine; RTV, ritonavir; TDF, tenofovir difumarate.

a Intent-to-treat analysis of patients with human immunodeficiency virus type 1 RNA level $<50$ copies/mL at week 48 (comparator vs quad).

b Change in CD4 cell count from baseline to week 48 (comparator vs quad).

c Number in comparator group vs quad group.

d Statistically significant difference.
transporters, resulting in early increases in serum creatinine (within the first month of therapy) that are likely to resolve rapidly with discontinuation of the agent [28, 29]. Increases in serum creatinine levels of >0.4 mg/dL after initiation of quad therapy are unlikely to be due to COBI, and alternative explanations should be sought for such increases [13]. The effect of this inhibition has been described in patients receiving RTV-based regimens, in which declines in estimated creatinine clearance were greater than in those receiving nonnucleoside reverse-transcriptase–based regimens [30]. The effect of COBI on eGFR was evaluated in patients with normal renal function and mild renal impairment (creatinine clearance, 50–79 mL/min) [30]. Patients were given COBI (150 mg/d) for 7 days, and eGFR and actual GFR (based on urine creatinine measurements) were determined on day 7 and 14. At day 7, the mean eGFR was approximately 10–12 mL/min lower than baseline values in both groups. By day 14, the eGFR returned to baseline, and the actual GFR was the same on both days 7 and 14. Because COBI inhibits transporters not involved in TDF transport, it would not be expected to increase the risk of renal toxicity with TDF use [31].

In the 2 studies comparing the quad pill with TDF/FTC/EFV, there was a decrease in eGFR in the quad group relative to the comparator group at 48 weeks [22, 24]. In the small phase 2 study, the mean decrease in eGFR was 22 versus 4 mL/min [24]. The median decreases in the phase 3 study were 14.3 in the quad and 3.0 in the TDF/FTC/EFV arm [22]. Five patients (<1%) discontinued the study because to renal events, all were in the quad arm. However, in the study comparing the quad pill with TDF/FTC/RTV/ATZ, the decreases in eGFR were similar in the 2 groups (13.3 vs 9.3 mL/min, respectively) and only 1 patient in each group discontinued therapy owing to renal impairment. Thus, although a decrease in eGFR is associated with quad pill use, it is rarely associated with serious renal events, and eGFR generally increases after discontinuation of COBI. It is currently recommended that the quad pill be started in patients with a baseline eGFR of >70 mL/min [13].

CONCLUSIONS

The quad pill is the newest addition to the single-pill, once-daily option for a complete anti–HIV-1 regimen. The safety and efficacy of 2 of the drug components (TDF and FTC) are well established, and there are substantial data from several clinical trials confirming that the efficacy of the quad pill is equivalent to that of other frequently prescribed regimens for drug-naive patients. The primary advantages of this therapy compared with other single-pill options are the lack of teratogenicity, CNS side effects, and interaction with medications that suppress gastric acid, such as H2-receptor antagonists and proton pump inhibitors. In addition, the drug has efficacy in patients with high baseline viral loads. There are substantial drug-to-drug interactions to be aware of when using the quad pill, its use is associated with nausea and a transient reduction in eGFR that rarely lead to discontinuation of therapy, and its administration should be separated from that of antacids by ≥2 hours.

In summary, the single-tablet quad pill regimen is a convenient new choice for therapy in antiretroviral-naïve patients with HIV disease but should not be used in antiretroviral-experienced patients or in patients in whom there are insufficient data to recommend its use or in whom there may be unpredictable drug interactions with other antiretroviral agents. Patients who may particularly benefit from this therapy include women of childbearing potential, patients taking long-term medications that suppress gastric acid, and patients with underlying psychiatric conditions. The newer components of this combination pill (COBI and EVG) are currently also being studied as stand-alone agents and as part of new single-tablet or combination pills that may be useful in the management of other populations of HIV-infected individuals in the future.

Note

Potential conflicts of interest. Both authors: No reported conflicts.
Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


