Review of the safety, efficacy, and pharmacokinetics of elvitegravir with an emphasis on resource-limited settings

LEE, Janice Soo Fern, et al.

Abstract

Integrase inhibitors represent an important new class of antiretroviral drugs. Elvitegravir, the second available integrase inhibitor to be submitted for regulatory approval appears to be a promising once-daily agent when combined with other antiretroviral drugs. Elvitegravir has demonstrated good efficacy and safety, with minimal side effects and no specific requirements in terms of laboratory monitoring. In addition, elvitegravir is available as a fixed-dose combination. However, the drug requires boosting and this leads to a number of drug-drug interactions and necessary dose adjustment when dosing with certain drugs, including dose reduction in the presence of atazanavir, lopinavir, rifabutin, and ketoconazole, and dose increase for ethinyl estradiol when co-administered with boosted elvitegravir. The main advantage of elvitegravir lies in its potential to be administered as a once-daily, single pill. Limitations include dose adjustment requirements, a relatively low genetic barrier to resistance, high price, and lack of data for use in children. Clinical trials addressing specific challenges encountered in [...]
Review of the safety, efficacy, and pharmacokinetics of elvitegravir with an emphasis on resource-limited settings

Janice Soo Fern Lee 1
Alexandra Calmy 1,2
Isabelle Andrieux-Meyer 1
Nathan Ford 1,3
1 Médecins Sans Frontières, 2 HIV/AIDS Unit, Infectious Disease Service, Geneva University Hospital, Geneva, Switzerland; 3 Centre for Infectious Disease Epidemiology and Research, University of Cape Town, South Africa

Abstract: Integrase inhibitors represent an important new class of antiretroviral drugs. Elvitegravir, the second available integrase inhibitor to be submitted for regulatory approval appears to be a promising once-daily agent when combined with other antiretroviral drugs. Elvitegravir has demonstrated good efficacy and safety, with minimal side effects and no specific requirements in terms of laboratory monitoring. In addition, elvitegravir is available as a fixed-dose combination. However, the drug requires boosting and this leads to a number of drug–drug interactions and necessary dose adjustment when dosing with certain drugs, including dose reduction in the presence of atazanavir, lopinavir, rifabutin, and ketoconazole, and dose increase for ethinyl estradiol when co-administered with boosted elvitegravir. The main advantage of elvitegravir lies in its potential to be administered as a once-daily, single pill. Limitations include dose adjustment requirements, a relatively low genetic barrier to resistance, high price, and lack of data for use in children. Clinical trials addressing specific challenges encountered in resource-limited settings should be encouraged.

Keywords: elvitegravir, efficacy, safety, resistance, resource-limited settings

Introduction
The last 10 years have been hailed as a “golden decade of antiretroviral drug development.”1 Almost half of all new chemical entities approved by the US Food and Drug Administration to treat human immunodeficiency virus (HIV) infection since 1986 were approved in the years since 2000, and these approvals span a range of different drug classes that target different stages of viral replication.1

Among these new drug classes, the integrase inhibitor class has been welcomed as offering a new approach to treating treatment-experienced individuals who are resistant to older generation drugs. Raltegravir, the first licensed integrase inhibitor, had been approved for use in treatment-naïve and treatment-experienced HIV-1 infected adults.2 Elvitegravir, the second integrase inhibitor that will be submitted for regulatory approval appears to be a promising once-daily agent when combined with other antiretroviral drugs. Elvitegravir is administered as a once-daily integrase inhibitor that needs boosting by either ritonavir or cobicistat as booster; elvitegravir is being tested as first-line drug in a fixed-dose combination (“Quad”) including tenofovir, emtricitabine, cobicistat and elvitegravir. Quad was submitted to the US Food and Drug Administration for regulatory approval for use in naïve patients in late 2011.

In resource-limited settings tremendous progress has been made over the last decade with now over 6 million individuals estimated to be receiving antiretroviral therapy (ART).
However, this represents less than half of the clinical need. The first priority, therefore, remains to ensure that more patients are able to access first-line ART. Nevertheless, ART availability has been gradually increasing over the last decade, and consistent with experience from developed countries, a growing number of patients are moving to second-line therapy, and a proportion of these patients are reported to be failing second-line therapy. Thus, it is important to consider to what extent new drugs and new drug classes meet the requirements of patients and programs in resource-limited settings. Drug specifications for use in resource-limited settings may be more stringent than for developed countries as issues such as treatment durability, feasibility of manufacturing fixed-dose combination, and the possibility of being used without biological or virological monitoring are even more important.

In this review, we summarize the available information on the pharmacokinetics, safety, and efficacy of elvitegravir with an emphasis on issues of particular relevance to resource-limited settings.

Search strategy
We searched the following databases from inception to March 2011 for articles containing elvitegravir or GS-9137/JTK-303: MEDLINE via PubMed (www.ncbi.nlm.nih.gov/pubmed), EMBASE (www.embase.com), and the Cochrane Central Register of Controlled Trials (www.thecochranelibrary.com). We also searched the websites of major HIV conferences, ie, all international acquired immune deficiency syndrome (AIDS) society conferences (up to Rome, July 2011), all conferences on retroviruses and opportunistic infections (up to Boston, March 2011), all abstracts from international workshops on clinical pharmacology of HIV therapy, and all abstracts from the international congresses on drug therapy in HIV infection (up to Glasgow, November 2010). No language restrictions were applied. We included all articles reporting original data on pharmacokinetics, tolerability, safety, and efficacy. This information was crosschecked against data presented in secondary reports (nonsystematic reviews, opinion articles, and news items). We also searched in the clinicaltrial.gov website (www.clinicaltrials.gov) to obtain information about ongoing studies. Finally, we complemented the search by reviewing bibliographies of relevant papers. The initial search yielded 481 titles, from which 14 full text articles and eleven conference abstracts were retained for full review.

Pharmacology of drug action
Elvitegravir (also known as GS-9137 or JTK-303) has the chemical name 6-(3-chloro-2-fluorobenzyl)-1-[(2S)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid], a molecular weight of 447.88 g/mol, and the molecular formula C23H23CIFNO5. It is part of the integrase inhibitor class of drugs that work by inhibiting HIV-1 strand transfer and integration. Integrase is one of the three enzymes required of HIV replication. Its primary role is to integrate the viral DNA into the cellular DNA of the host. Elvitegravir inhibits the integrase enzyme at this vital step, blocking viral DNA strand transfer and integration, allowing it to be metabolized by cellular enzymes. The lack of a functionally equivalent enzyme to integrase in human cells reduces the potential for drug-induced cytotoxicity.

Pharmacokinetics
The absorption of elvitegravir increases three-fold in the presence of food. It reaches a Cmax at 3–4 hours. Its half-life (t1/2) when dosed alone is approximately 3 hours while boosting with ritonavir 100 mg prolongs t1/2 to 9 hours. Pharmacokinetic data from dose finding studies in HIV-1 infected patients suggest that maintenance of effective trough concentrations are essential for antiviral activity. Elvitegravir undergoes metabolism primarily by the cytochrome (CYP) 3A4/5 and partly by glucuronidation of uridine glucuronosyltransferase (UGT) 1A1 and 1A3. The main metabolites, M1 and M4, are less potent than parent compounds and are not considered to contribute to the antiviral activity of elvitegravir. A study assessing excretion of a [14C] fluorescence tagged elvitegravir/ritonavir 50/100 mg dose found that 94.8% was recovered in feces while 6.7% was recovered in urine. In this study, once-daily elvitegravir with boosted ritonavir achieved a higher trough concentration compared to elvitegravir dosed twice-daily without boosting, achieving ≥3-fold inhibitory quotient (using protein-binding adjusted IC50). Ritonavir boosting above 100 mg does not result in additional increases in elvitegravir exposure. There is no difference between boosting with 100 mg ritonavir and 150 mg cobicistat.

Pharmacokinetics of elvitegravir drug–drug interactions
The main results of drug–drug interaction studies are described below and summarized in Table 1.

Interactions with key drugs in the management of HIV/AIDS
Tuberculosis drugs
A pharmacokinetic study among 19 healthy volunteers assessed the potential interaction between elvitegravir/
ritonavir (r) (300 mg/100 mg QD) and the tuberculosis drug rifabutin (RFB) (150 mg every other day). Exposures of RFB measured by RFB levels were not altered while its metabolite 25-O-deRFB was increased 5–20 fold.14 Total antimicrobial measured by RFB levels were not altered while its metabolite and 139% respectively.17 No significant change in exposures were reported.16 Significant interaction was noted in a study of lopinavir/ritonavir (400/100 mg BID) and elvitegravir (125 mg QD), no significant alterations in exposures of elvitegravir, amprenavir and ritonavir were reported.16 Significant interaction was noted in a study of lopinavir/ritonavir (400/100 mg BID) and elvitegravir (125 mg QD) administered to healthy volunteers, in which C_{max}, AUC_{τ}, and C_{τ} of elvitegravir increased by 52%, 75% and 139% respectively.17 No significant change in exposures were seen in lopinavir concentrations. All adverse events were grade 1 in severity with headache (elvitegravir/r) and diarrhea (both LPV/r and elvitegravir plus LPV/r) being the most common. Following a PK simulation study an elvitegravir dose reduction to 85 mg was recommended when co-administered with LPV/r.17

As atazanavir, elvitegravir, and ritonavir share similar elimination pathways, two PK studies were carried out to identify the interaction and to confirm a dose adjustment of elvitegravir when dosed with boosted atazanavir in 33 healthy subjects. In the first study co-administration of elvitegravir (200 mg) and atazanavir/r (300/100 mg) resulted in a one- to two-fold increase in elvitegravir C_{max}, AUC_{τ}, and C_{τ} while atazanavir exposures decreased by 16%, 21% and 35% respectively, indicating a significant interaction.18 In the second study, elvitegravir administered at 150 mg was compared to dose adjusted elvitegravir 85 mg and atazanavir/r (300/100 mg) in 20 healthy subjects. Elvitegravir exposures at 85 mg when co-administered with atazanavir/r 300/100 mg were similar to elvitegravir 150 mg. Atazanavir exposures were not significantly altered by elvitegravir at 85 mg. Therefore, dose adjustment of elvitegravir 85 mg is recommended when administered with atazanavir/r 300/100 mg. Since atazanavir is an inhibitor of CYP 3A and UGT 1A, another study was designed to examine the interaction between elvitegravir with unboosted atazanavir.19 A crossover design study carried out on 15 healthy subjects who were given elvitegravir/ritonavir 300/100 mg for 10 days and then atazanavir 400 mg and elvitegravir 300 mg for 10 days confirmed that atazanavir boosting of elvitegravir was mainly via CYP 3A. There was a modest decrease in elvitegravir C_{τ} by 10% which is still >10-fold in vitro IC_{50}. Atazanavir C_{τ} and AUC_{τ} when given with elvitegravir were lower than historical values.

In a drug interaction study between elvitegravir/ritonavir (150/100 mg QD) and maraviroc (150 mg BID) in 28 healthy subjects, the pharmacokinetics of elvitegravir and ritonavir were not altered while maraviroc exposures increased, with a two- to four-fold increase in C_{max}, AUC_{τ}, and C_{τ}.20 This interaction was expected as maraviroc is a known substrate for CYP 3A4 and P-glycoprotein (Pgp) transporter and ritonavir is a known CYP 3A/Pgp inhibitor. As the exposures of maraviroc are within the range of those observed when maraviroc is co-administered with other potent CYP 3A4 inhibitors, the study recommended a reduction in maraviroc dose to 150 mg BID when co-administered with elvitegravir/ritonavir.

A study of elvitegravir/ritonavir (150/100 mg QD) and etravirine (200 mg BID) found no significant changes in the exposures of elvitegravir, ritonavir or etravirine.21 The overlapping metabolic pathways of both drugs proved in

**Antiretrovirals**

Drug interaction pharmacokinetic (PK) studies were extensively conducted with at least five protease inhibitors (PIs): darunavir/ritonavir (DRV/r), tipranavir/ritonavir (TPV/r), fosamprenavir/ritonavir (FPV/r), atazanavir/ritonavir (ATV/r), lopinavir/ritonavir (LPV/r).

Forty-six healthy subjects participated in a William crossover design PK study evaluating the interaction between darunavir/ritonavir (600/100 mg BID) and tipranavir/ritonavir (500/200 mg BID) with elvitegravir (200 mg or 125 mg QD).15 The C_{max}, AUC_{τ}, and C_{τ} of elvitegravir increased by 13%, 10% and 18% but decreased for darunavir by 11%, 11% and 17% respectively when both drugs were given together with ritonavir boosting. This falls within protocol-defined lack of interaction bounds of 70%-143%. Similarly, the C_{max} of elvitegravir increased 4% and AUC_{τ} and C_{τ} decreased 8% and 10% respectively when given concurrently with boosted tipranavir, while the C_{max}, AUC_{τ}, and C_{τ} of tipranavir decreased by 8%, 11%, and 11%. The pharmacokinetics of elvitegravir did not differ if ritonavir was given once or twice daily. No dosage adjustments are therefore needed when boosted tipranavir or boosted darunavir are given with elvitegravir.

In another study of fosamprenavir/ritonavir (700/100 mg BID) and elvitegravir (125 mg QD), no significant alterations in exposures of elvitegravir, amprenavir and ritonavir were reported.16 Significant interaction was noted in a study of lopinavir/ritonavir (400/100 mg BID) and elvitegravir (125 mg QD) administered to healthy volunteers, in which C_{max}, AUC_{τ}, and C_{τ} of elvitegravir increased by 52%, 75% and 139% respectively.17 No significant change in exposures were seen in lopinavir concentrations. All adverse events were grade 1 in severity with headache (elvitegravir/r) and diarrhea (both LPV/r and elvitegravir plus LPV/r) being the most common. Following a PK simulation study an elvitegravir dose reduction to 85 mg was recommended when co-administered with LPV/r.17

As atazanavir, elvitegravir, and ritonavir share similar elimination pathways, two PK studies were carried out to identify the interaction and to confirm a dose adjustment of elvitegravir when dosed with boosted atazanavir in 33 healthy subjects. In the first study co-administration of elvitegravir (200 mg) and atazanavir/r (300/100 mg) resulted in a one- to two-fold increase in elvitegravir C_{max}, AUC_{τ}, and C_{τ} while atazanavir exposures decreased by 16%, 21% and 35% respectively, indicating a significant interaction.18 In the second study, elvitegravir administered at 150 mg was compared to dose adjusted elvitegravir 85 mg and atazanavir/r (300/100 mg) in 20 healthy subjects. Elvitegravir exposures at 85 mg when co-administered with atazanavir/r 300/100 mg were similar to elvitegravir 150 mg. Atazanavir exposures were not significantly altered by elvitegravir at 85 mg. Therefore, dose adjustment of elvitegravir 85 mg is recommended when administered with atazanavir/r 300/100 mg. Since atazanavir is an inhibitor of CYP 3A and UGT 1A, another study was designed to examine the interaction between elvitegravir with unboosted atazanavir.19 A crossover design study carried out on 15 healthy subjects who were given elvitegravir/ritonavir 300/100 mg for 10 days and then atazanavir 400 mg and elvitegravir 300 mg for 10 days confirmed that atazanavir boosting of elvitegravir was mainly via CYP 3A. There was a modest decrease in elvitegravir C_{τ} by 10% which is still >10-fold in vitro IC_{50}. Atazanavir C_{τ} and AUC_{τ} when given with elvitegravir were lower than historical values.

In a drug interaction study between elvitegravir/ritonavir (150/100 mg QD) and maraviroc (150 mg BID) in 28 healthy subjects, the pharmacokinetics of elvitegravir and ritonavir were not altered while maraviroc exposures increased, with a two- to four-fold increase in C_{max}, AUC_{τ}, and C_{τ}.20 This interaction was expected as maraviroc is a known substrate for CYP 3A4 and P-glycoprotein (Pgp) transporter and ritonavir is a known CYP 3A/Pgp inhibitor. As the exposures of maraviroc are within the range of those observed when maraviroc is co-administered with other potent CYP 3A4 inhibitors, the study recommended a reduction in maraviroc dose to 150 mg BID when co-administered with elvitegravir/ritonavir.

A study of elvitegravir/ritonavir (150/100 mg QD) and etravirine (200 mg BID) found no significant changes in the exposures of elvitegravir, ritonavir or etravirine.21 The overlapping metabolic pathways of both drugs proved in
Table 1 Interactions between elvitegravir ± ritonavir and other drugs

<table>
<thead>
<tr>
<th>Co-administered drug</th>
<th>Participants (completed study)</th>
<th>Duration</th>
<th>Dose Elvitegravir ± ritonavir</th>
<th>Co-administered drug</th>
<th>PK elvitegravir in % change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Elvitegravir ± ritonavir</td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
</tr>
<tr>
<td>Zidovudine&lt;sup&gt;23&lt;/sup&gt;</td>
<td>28 healthy subjects</td>
<td>27 days</td>
<td>200 mg + 100 mg QD</td>
<td>300 mg BID day 1-7, 8-17</td>
<td>↑5%</td>
</tr>
<tr>
<td>Didanosine&lt;sup&gt;22,30&lt;/sup&gt;</td>
<td>32 healthy subjects</td>
<td>17 days</td>
<td>200 mg + 100 mg QD</td>
<td>400 mg (EC capsule) QD day 1, 15</td>
<td>↓5%</td>
</tr>
<tr>
<td>Stavudine&lt;sup&gt;23,30&lt;/sup&gt;</td>
<td>32 healthy subjects</td>
<td>17 days</td>
<td>200 mg + 100 mg QD</td>
<td>40 mg QD day 3, 17</td>
<td>↓4%</td>
</tr>
<tr>
<td>Abacavir&lt;sup&gt;31&lt;/sup&gt;</td>
<td>26 healthy subjects</td>
<td>15 days</td>
<td>200 mg + 100 mg QD</td>
<td>600 mg day 1, 15</td>
<td>↓5%</td>
</tr>
<tr>
<td>Rifabutin&lt;sup&gt;14&lt;/sup&gt;</td>
<td>19 healthy volunteers</td>
<td>53 days</td>
<td>300 mg + 100 mg QD</td>
<td>150 mg EOD</td>
<td>↓8%</td>
</tr>
<tr>
<td>Atazanavir (boosted)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>53 healthy subjects</td>
<td>Study 1: 14 days, Study 2: 10 days</td>
<td>Study 1: 200 mg Study 2: 85 mg</td>
<td>300 mg + ritonavir 100 mg QD</td>
<td>Study 1: ↑85 Study 2: ↓19</td>
</tr>
<tr>
<td>Atazanavir (unboosted)&lt;sup&gt;19&lt;/sup&gt;</td>
<td>15 healthy subjects</td>
<td>20 days</td>
<td>300 mg</td>
<td>400 mg</td>
<td>↑8%</td>
</tr>
<tr>
<td>Darunavir&lt;sup&gt;15&lt;/sup&gt;</td>
<td>20 healthy subjects</td>
<td>42 days</td>
<td>125 mg QD</td>
<td>600 mg + ritonavir 100 mg BID</td>
<td>↑13%</td>
</tr>
<tr>
<td>Tipranavir&lt;sup&gt;15&lt;/sup&gt;</td>
<td>26 healthy subjects</td>
<td>42 days</td>
<td>200 mg QD</td>
<td>500 mg + ritonavir 200 mg BID</td>
<td>↑4%</td>
</tr>
<tr>
<td>Fosamprenavir&lt;sup&gt;16&lt;/sup&gt;</td>
<td>31 healthy subjects</td>
<td>28 days</td>
<td>125 mg QD</td>
<td>700 mg + ritonavir 100 mg BID</td>
<td>No change</td>
</tr>
<tr>
<td>Lopinavir&lt;sup&gt;17&lt;/sup&gt;</td>
<td>27 healthy subjects</td>
<td>14 days</td>
<td>125 mg QD</td>
<td>400 mg + ritonavir 100 mg BID</td>
<td>↑52%</td>
</tr>
<tr>
<td>Maraviroc&lt;sup&gt;10&lt;/sup&gt;</td>
<td>28 healthy subjects</td>
<td>20 days</td>
<td>150 mg + 100 mg QD</td>
<td>150 mg BID</td>
<td>↑1%</td>
</tr>
<tr>
<td>Etravirine&lt;sup&gt;21&lt;/sup&gt;</td>
<td>31 healthy volunteers</td>
<td>20 days</td>
<td>150 mg + 100 mg QD</td>
<td>200 mg BID</td>
<td>↑7%</td>
</tr>
<tr>
<td>Antacid&lt;sup&gt;14,46&lt;/sup&gt;</td>
<td>62 healthy subjects</td>
<td>Study 1: 11 days Study 2: 15 days</td>
<td>50 mg + 100 mg QD</td>
<td>20 mL together, 2 hours before, 2 hours after, 4 hours before, 4 hours after elvitegravir</td>
<td>Together with antacid: ↓47% 2 hours after antacid: ↓18% 4 hours after antacid: ↓5% 2 hours before antacid: ↓2% 4 hours before antacid: ↓21%</td>
</tr>
<tr>
<td>Omeprazole&lt;sup&gt;20&lt;/sup&gt;</td>
<td>62 healthy subjects</td>
<td>15 days</td>
<td>50 mg + 100 mg QD</td>
<td>40 mg QD</td>
<td>↓7%</td>
</tr>
<tr>
<td>Ketoconazole&lt;sup&gt;23&lt;/sup&gt;</td>
<td>18 healthy subjects</td>
<td>15 days</td>
<td>150 mg + 100 mg QD</td>
<td>200 mg BID</td>
<td>↑17%</td>
</tr>
<tr>
<td>Norgestimate and ethinyl estradiol&lt;sup&gt;29&lt;/sup&gt;</td>
<td>15 healthy subjects</td>
<td>56 days</td>
<td>150 mg + cobicistat 150 mg + tenofovir 300 mg + emtricitabine 200 mg</td>
<td>Combination oral contraceptive pill containing norgestimate (NGM) 0.180 mg, 0.215 mg, 0.250 mg and ethinyl estradiol (EE) 25 µg</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; QD, once a day; BID, twice a day; EOD, every other day; EC, enteric coated; EE, ethinyl estradiol; NGM, norgestimate; NGMN, norelgestromin (metabolite of norgestimate).
<table>
<thead>
<tr>
<th>AUC&lt;sub&gt;τ&lt;/sub&gt;</th>
<th>C&lt;sub&gt;τ&lt;/sub&gt;</th>
<th>PK co-administered drug in % change</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑5%</td>
<td>↑15%</td>
<td>↓12%  ↓14%  NA</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>↓3%</td>
<td>↑6%</td>
<td>↓16%  ↓14%  NA</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>↓2%</td>
<td>↑24%</td>
<td>↓0.4% ↑7%  NA</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>↓3%</td>
<td>↑6%</td>
<td>↓12%  ↓17%  NA</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>↓4%</td>
<td>↓6%</td>
<td>Rifabutin: ↓8%  25-o-dcRFB: ↑440%</td>
<td>Dose adjustment of rifabutin 150 mg EOD recommended with monitoring of adverse events</td>
</tr>
<tr>
<td>Study 1: ↑100</td>
<td>Study 1: ↑188</td>
<td>Study 1: ↓16  Study 1: ↓21</td>
<td>Study 1: ↓35%</td>
</tr>
<tr>
<td>Study 2: ↑7</td>
<td>Study 2: ↑38</td>
<td>Study 2: ↓3  Study 2: ↓11</td>
<td>Study 2: ↓17</td>
</tr>
<tr>
<td>↑7%</td>
<td>↓10%</td>
<td>3680 ng/mL  16300 ng·h/mL  74.5 ng/mL</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>↑10%</td>
<td>↑18%</td>
<td>↓11%  ↓11%  ↓17%</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>↓8%</td>
<td>↓10%</td>
<td>↓8%  ↓11%  ↓11%</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>↓7%</td>
<td>↓4%</td>
<td>↓2%  ↓1%  ↑1%</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>↑5%</td>
<td>↑139%</td>
<td>↓1%  ↓3%  ↓8%</td>
<td>Dose reduction of elvitegravir to 85 mg is recommended</td>
</tr>
<tr>
<td>↑7%</td>
<td>↑9%</td>
<td>↑115% ↑186% ↑323%</td>
<td>Dose adjustment of maraviroc 150 mg BID recommended</td>
</tr>
<tr>
<td>↑6%</td>
<td>↑6%</td>
<td>↑2%  ↓2%  ↓10%</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>Together with antacid: ↓45%</td>
<td>Together with antacid: ↓41%</td>
<td>NA  NA  NA</td>
<td>Administration of antacid and EVG should be separated by at least 2 hours</td>
</tr>
<tr>
<td>2 hours after antacid: ↓15%</td>
<td>2 hours after antacid: ↓10%</td>
<td>4 hours after antacid: ↑4% 4 hours after antacid: ↑4%</td>
<td></td>
</tr>
<tr>
<td>4 hours after antacid: ↓4%</td>
<td>2 hours before antacid: ↑2% 2 hours before antacid: no change</td>
<td>4 hours before antacid: ↓20% 4 hours before antacid: ↓20%</td>
<td></td>
</tr>
<tr>
<td>↓1%</td>
<td>↓6%</td>
<td>NA  NA  NA</td>
<td>No dosage adjustment needed</td>
</tr>
<tr>
<td>↑48%</td>
<td>↑67%</td>
<td>NA  NA  NA</td>
<td>Maximum recommended daily dose of ketoconazole is 200 mg</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>EE: ↓6% NGMN: ↑109%</td>
<td>Recommended ethinyl estradiol dose of the oral contraceptive is 30 μg</td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>EE: ↓25% NGMN: ↑126%</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>NA</td>
<td>EE: ↓41% NGMN: ↑167%</td>
<td></td>
</tr>
</tbody>
</table>

**Notes:** "Pharmacokinetic study of both didanosine and stavudine with elvitegravir was carried out in the same subjects; "pharmacokinetic study of both darunavir and tipranavir with elvitegravir was carried out in crossover design in the same subjects; "pharmacokinetic study of both antacid and omeprazole with elvitegravir was carried out in one study design.

**Abbreviations:** PK, pharmacokinetic; GMR, geometric mean ratio; C<sub>max</sub>, maximum concentration; AUC<sub>τ</sub>, area under the curve from time 0 to τ, where τ is the length of dosing interval; C<sub>τ</sub>, τ concentration; NA, not available; QD, once a day; BID, twice a day; EOD, every other day; EC, enteric coated; EE, ethinyl estradiol; NGM, norgestimate; NGMN, norelgestromin (metabolite of norgestimate).
significant and thus no dosage adjustment is warranted when they are given concomitantly. The potential interaction between elvitegravir/ritonavir and commonly used nucleoside reverse transcriptase inhibitors (NRTIs) zidovudine, didanosine, stavudine, abacavir, tenofovir and emtricitabine have also been studied.\textsuperscript{22,23} No significant change in exposures of these NRTIs or elvitegravir were found.

Acid-reducing agents

A study investigating the effect of acid-reducing agents such as antacid and omeprazole, a proton pump inhibitor, on elvitegravir exposures\textsuperscript{24} found no significant change in exposures of elvitegravir when administered with omeprazole, indicating a lack of influence of gastric pH on elvitegravir absorption. \( C_{\text{max}}, \text{AUC}_\tau, \text{and } C_t \) of elvitegravir were affected by concomitant antacid administration, with observed decreases of 47%, 45% and 41% respectively. However, when elvitegravir was given at least 2 hours apart from antacid, exposures of elvitegravir were not significantly altered. Therefore, co-administration of elvitegravir/ritonavir and antacid should be separated by at least 2 hours.

Other drugs

Ketoconazole, a well-known CYP 3A inhibitor and UGT 1A1 and 2B7 inhibitor was studied in co-administration with ritonavir-boosted elvitegravir and midazolam is used as a probe to measure additional CYP 3A inhibition. Ketoconazole was dosed at 200 mg BID (at days 12–15), elvitegravir/r 150/100 mg OD (days 2–15) and midazolam single dose on days 1, 11 and 15 in 18 healthy subjects.\textsuperscript{25} Elvitegravir exposures as measured by \( C_{\text{max}}, \text{AUC}_\tau, \text{and } C_t \) increased by 17%, 48%, and 67% respectively. There was an additional 1%–1.5% CYP 3A inhibition with ketoconazole compared to baseline of expected CYP 3A inhibition by ritonavir-boosted elvitegravir. As a result of this study a maximum daily dose of ketoconazole 200 mg is recommended.

A PK study of the fixed-dose combination of tenofovir disoproxil fumarate 300 mg, emtricitabine 200 mg; elvitegravir 150 mg; cobicistat 150 mg; and oral contraceptive (OC) pill containing norgestrel 0.180 mg, 0.215 mg, 0.250 mg, and ethinyl estradiol 25 \( \mu \)g were carried out over a period of two pill cycles in 15 healthy subjects.\textsuperscript{26} The exposures of elvitegravir and cobicistat were within the range of those reported in previous studies. However, it was noted that the exposures of ethinyl estradiol, \( C_{\text{max}}, \text{AUC}_\tau, \text{and } C_t \) decreased by 6%, 25% and 41% respectively. Measurement of serum progesterone, follicle stimulating hormone and luteinizing hormone were found to be unchanged in both OC with or without the fixed-dose combination. A dose of 30 \( \mu \)g of ethinyl estradiol is needed for adequate contraception when co-administered with the FDC.

Interactions between antiretroviral drugs and antimalarial drugs are an important consideration for resource-limited settings. However, we were unable to find any data in this regard.

Clinical efficacy

Two randomized trials have been conducted to assess the efficacy of elvitegravir across a range of doses. The first was a randomized dose-ranging monotherapy study in which 40 HIV-infected patients received elvitegravir (200 mg, 400 mg, or 800 mg twice a day; or 50 mg once a day co-administered with 100 mg ritonavir) for 10 days; this study found a significant reductions in HIV RNA in both treatment-naive and experienced patients compared to placebo.\textsuperscript{7} No patients in this study developed resistance mutations to GS-9137 or other antiretroviral agents. The second trial was a Phase II randomized, controlled, 48-week study assessing noninferiority of elvitegravir at 20 mg, 50 mg, and 125 mg doses to ritonavir-boosted protease inhibitor in 278 treatment-experienced subjects.\textsuperscript{27} The lowest dose arm was stopped early due to inferiority; the 50 mg arm demonstrated noninferiority and the 125 mg arm demonstrated superiority. The study also established superior virological suppression for those patients who were given at least one additional active drug in addition to elvitegravir. There was no relationship between elvitegravir dosage and adverse events.

The dose chosen for Phase III trial was elvitegravir 150 mg in the absence of LPV/r or ATZ/r in the background regimen (in which case the dose of 85 mg is recommended due to pharmacokinetic interactions).

Elvitegravir has been co-formulated as a single tablet together with the pharmacologic enhancer cobicistat (GS-9350), emtricitabine, and tenofovir (formulated as a fixed-dose single tablet known as “Quad”) for use in patients with no previous ART experience (naïve patients). Cobicistat is a CYP3A4 inhibitor with no antiviral activity, but is being tested as a pharmaco-enhancer with elvitegravir and also as a PK booster of protease inhibitors as a potential alternative to ritonavir.\textsuperscript{28} Data on the safety and efficacy of Quad are available from several trials. In a published Phase II, 48-week randomized trial in 71 treatment-naïve HIV-positive patients, Quad was found to have comparable efficacy to efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF);\textsuperscript{29} at 48 weeks of treatment; 90% of the patients taking Quad and 83% of patients taking EFV/FTC/TDF achieved a viral load < 50.
copies/mL. Treatment with Quad was associated with more rapid achievement of virological suppression compared to EFV/FTC/TDF. Results from two other trials have recently been released early by Gilead Sciences but have yet to be published. In the first trial, patients were randomized to receive either EFV/FTC/TDF or Quad over 96 weeks. Interim results demonstrated noninferior virological suppression at 48 weeks. The second trial, comparing Quad versus ritonavir-boosted atazanavir and truvada over a 96-week period also found noninferiority of Quad compared to boosted atazanavir in treatment-naive patients.

Finally, a randomized trial comparing the efficacy and safety of raltegravir versus elvitegravir in treatment-experienced patients has recently reported 48-week results. In this study 351 patients receiving ritonavir-boosted once-daily elvitegravir 150 mg (or 85 mg in those receiving a background protease inhibitor of either atazanavir or lopinavir) were compared against 351 receiving ritonavir-boosted twice-daily raltegravir 400 mg. Each agent was given in combination with an optimized background regimen. After 48 weeks of treatment, using the time to loss of virologic response algorithm, 59% of elvitegravir-treated patients achieved and maintained a viral load below 50 copies/mL, compared with 58% of raltegravir-treated patients (intention-to-treat analysis \( P = 0.001 \)). Unfortunately, in the preliminary results of trial, elvitegravir did not show a greater barrier to resistance when compared with raltegravir.

**Safety and tolerability**

In the Phase II randomized trial that compared elvitegravir with ritonavir-boosted PIs,\(^27\) the occurrence of adverse events and grade 3 or 4 laboratory toxicity was similar across treatment groups. The most common treatment-emergent adverse events were diarrhea and nausea. Three serious adverse events across all treatment groups were considered to be related or possibly related to study drugs: syncope in a subject exposed to elvitegravir 50 mg, a significant hypersensitivity reaction in a subject with a history of multiple drug allergies exposed to elvitegravir 20 mg, and right eye hyphema in a subject receiving the ritonavir-boosted protease inhibitor. No dose-dependent increase in type of adverse event was observed in the elvitegravir arm. None of the three deaths were observed in the elvitegravir arm (one was due to *Pneumocystis* pneumonia, one was due to B cell lymphoma, and one was due to cardiorespiratory failure) or were considered to be related to the study drug.

The Phase II trial of Quad versus EFV/FTC/TDF concluded that Quad resulted in a lower percentage of drug-related adverse events compared with EFV/FTC/TDF (35% vs 57%, respectively). In particular, Quad induced fewer central nervous system and psychiatric events. The most common adverse events observed in both study arms were: abnormal dreams/nightmares, dizziness, fatigue, somnolence, diarrhea, and headache. Glomerular filtration remained within the normal range and no participant experienced a clinical adverse event or discontinued study drug due to changes in serum creatinine or renal function. Incidence of laboratory abnormalities was similar between the two arms of the study. There were no grade 3/4 adverse events nor adverse events leading to discontinuation of the study in the Quad group of patients, while two grade 3/4 adverse events were reported among EFV/FTC/TDF patients and one patient taking EFV/FTC/TDF left the study early due to an adverse event. These data suggest that the Quad could represent a one-pill, once-daily treatment alternative for the treatment-naïve patient.

Data on efficacy, safety, and tolerability are summarized in Table 2.

**Perspectives for resource-limited settings**

The important characteristics of drugs from the perspective of resource-limited settings are efficacy, robustness, affordability, minimal side-effects (and so minimal laboratory monitoring requirements), compatibility with drugs to treat tuberculosis and other common co-infections, safety in women of child-bearing age and children, availability as fixed-dose combinations, and suitability for long-acting formulations.\(^32\)

Elvitegravir has demonstrated good efficacy and safety, with minimal side effects and no specific requirements in terms of laboratory monitoring. In addition, elvitegravir is available in a triple fixed-dose combination allowing for coformulated single-pill administration. However, elvitegravir requires boosting by either ritonavir or cobicistat and is prone to a number of important drug–drug interactions. In addition, it has a relatively low genetic barrier to resistance (lower than for protease inhibitors), with just one to two mutations needed to result in marked reductions in virus susceptibility.\(^33\) The potential for resistance development to elvitegravir has been assessed in a number of in vitro selection experiments. Primary resistance-conferring mutations occur at positions T66, E92, and Q148;\(^34\)–\(^36\) these mutations were also selected for in vivo and resulted in virological failure of elvitegravir-based therapies.\(^37\) Primary resistance mutations are associated with secondary mutations, which have been shown to further diminish the susceptibility to elvitegravir or play a role in partially restoring viral fitness.
Table 2 Summary of published data on the efficacy, safety, and tolerability of elvitegravir (EVG)

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>EVG formulation</th>
<th>Sample size</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DeJesus et al^7</td>
<td>Randomized dose-ranging monotherapy trial</td>
<td>200 mg, 400 mg, or 800 mg twice daily, or 50 mg once daily</td>
<td>40 HIV-positive treatment-naïve and experienced patients</td>
<td>Placebo</td>
<td>Significant reductions in HIV RNA in both treatment-naïve and experienced patients</td>
<td></td>
</tr>
<tr>
<td>Zolopa et al^27</td>
<td>Phase II randomized, controlled, 48-week study, Partial blinding (to dose)</td>
<td>20 mg, 50 mg and 125 mg</td>
<td>278 treatment-experienced subjects</td>
<td>Ritonavir-boosted PI</td>
<td>Lowest dose arm stopped early due to inferiority. 50 mg arm demonstrated noninferiority. 125 mg arm demonstrated superiority</td>
<td></td>
</tr>
<tr>
<td>Cohen et al^29</td>
<td>Phase II, 48-week randomized double-blinded trial</td>
<td>QUAD (EVG, cobicistat, emtricitabine and tenofovir)</td>
<td>71 treatment-naïve, HIV-positive patients</td>
<td>EFV/FTC/TDF</td>
<td>90% of the patients taking Quad and 83% of patients taking atripla achieved virological suppression</td>
<td>Quad associated with more rapid achievement of virological suppression</td>
</tr>
<tr>
<td>Molina et al^31</td>
<td>Phase III multicenter, randomized, double-blind study</td>
<td>Ritonavir-boosted once-daily elvitegravir 150 mg (or 85 mg in patients receiving a background protease inhibitor of either atazanavir or lopinavir)</td>
<td>351 receiving ritonavir-boosted twice-daily raltegravir 400 mg</td>
<td>Ritonavir-boosted PI</td>
<td>59% of elvitegravir-treated patients achieved virological suppression vs 58% for raltegravir-treated patients (intention-to-treat population; P = 0.001)</td>
<td>Preliminary results did not show greater barrier to resistance compared with raltegravir</td>
</tr>
<tr>
<td><strong>Safety and tolerability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zolopa et al^27</td>
<td>Phase II randomized trial</td>
<td>Virological suppression</td>
<td>Virological suppression</td>
<td>Ritonavir-boosted PI</td>
<td>Occurrence of adverse events and grade 3 or 4 laboratory toxicity similar across treatment groups</td>
<td>No dose-dependent increase in type of adverse event observed</td>
</tr>
<tr>
<td>Cohen et al^29</td>
<td>Phase II randomized trial</td>
<td>Quad</td>
<td>71 treatment-naïve, HIV-positive patients</td>
<td>EPV/FTC/TDF</td>
<td>Lower percentage of drug-related adverse events compared with EPV/FTC/TDF (35% vs 57%)</td>
<td>Incidence of laboratory abnormalities. No grade 3/4 adverse events nor adverse events leading to discontinuation for patients receiving Quad</td>
</tr>
</tbody>
</table>

Abbreviations: EVG, elvitegravir; EPV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; PI, protease inhibitors.
Secondary mutations selected under elvitegravir include H114Y, L74M, R20K, A128T, E138K, and S230R.\textsuperscript{38,39} Importantly, two of the three most common raltegravir-associated mutation pathways also result in elvitegravir resistance (Q148H/K/R, N155H).\textsuperscript{33} However, elvitegravir can be used in the presence of Y143, a resistance mutation induced by raltegravir.\textsuperscript{40} The clinical relevance of integrase mutations will require longer-term follow-up. In the clinical trial comparing raltegravir to elvitegravir in experienced patients there was no difference in the number of selected mutations within the two regimens – so elvitegravir robustness may not be greater in these preliminary results when compared to the first generation integrase inhibitor raltegravir.

The main advantage of elvitegravir lies in its potential to be administered as a once-daily, single pill. Dose modification in the presence of different protease inhibitors (such as atazanavir and lopinavir) can be seen as an advantage (lower dosage required) or a disadvantage (complexity of dosage). Either way, this relative ease of administration is offset against the relatively low barrier to resistance development.

Data on the safety and efficacy of elvitegravir in children are lacking. Given that children tend to have a higher rate of virological failure compared with adults,\textsuperscript{41} the relevance of elvitegravir as a therapeutic option for treatment-experienced children needs to be explored.

Finally, the price of elvitegravir, including any potential preferential pricing for resource-limited settings, is unclear. However, as the drug has recently been licensed to the Medicines Patent Pool for generic competition and supply to 99 developing countries, generic competition can be expected to lead to lower prices in the countries covered by the agreement. The only currently available integrase inhibitor, raltegravir, is priced out of reach of most developing countries, costing over US$5870 per patient per year in some developing countries.\textsuperscript{42}

**Conclusion**

Integrase inhibitors represent an important new class of antiretroviral drugs. The favorable efficacy, safety and tolerability profile of the first integrase inhibitor licensed for use, raltegravir, rapidly advanced prescribing and raltegravir is now one of the preferred agents for the treatment of naïve subjects in US treatment guidelines.\textsuperscript{43} Similarly, elvitegravir has demonstrated potent antiviral activity and the capacity to induce a rapid virologic response and a favorable safety profile.

A number of promising second-generation integrase inhibitors are in development. S/GSK-572 (also known as dolutegravir) has demonstrated in vitro antiviral activity against virus isolates resistant to raltegravir and elvitegravir,\textsuperscript{44,45} and clinical trials are underway to assess the activity of this S/GSK-572 in patients failing raltegravir. Pharmacokinetic studies\textsuperscript{46,47} and dose-ranging trials\textsuperscript{48,49} suggest potential for once-daily dosing, low dose (50 mg) without the need for boosting, making dolutegravir a good candidate for a single-tablet regimen co-formulated pill. A second drug, S/GSK-744 likewise appears to be safe and effective if administered unboosted as a once-daily dose,\textsuperscript{50} and the potential for a long-acting formulation of S/GSK-744 is also being investigated.\textsuperscript{51}

It remains to be seen what position elvitegravir and other integrase inhibitors will take in the treatment guidelines in resource-limited settings, and thus to what extent this new drug class will benefit the global majority of people living with HIV/AIDS. As outlined in this review, a number of critically important questions for developing countries remain to be answered. Clinical trials addressing specific challenges encountered in resource-limited settings should be encouraged.

**Acknowledgment**

The authors thank Dr Lillian Lou from Gilead for making available some of the pharmacokinetic data included in this review.

**Disclosure**

Dr Calmy has been supported by travel grants from Janssens-Cilag, Gilead and BMS; these grants are unrelated to the current work. The other authors report no conflicts of interest and received no funding for this work.

**References**


