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

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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. Clinical studies in experienced patients have assessed both ritonavir and 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).

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However, this represents less than half of the clinical need.³ 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,⁴ and a proportion of these patients are reported to be failing second-line therapy.^{5,6} 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 clinicaltrials.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],⁷ a molecular weight of 447.88 g/mol, and the molecular formula $C_{23}H_{23}ClFNO_5$.⁸ 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.⁹

Pharmacokinetics

The absorption of elvitegravir increases three-fold in the presence of food.¹⁰ It reaches a C_{max} at 3–4 hours. Its half-life ($t_{1/2}$) when dosed alone is approximately 3 hours while boosting with ritonavir 100 mg prolongs $t_{1/2}$ to 9 hours.⁷ Pharmacokinetic data from dose finding studies in HIV-1 infected patients suggest that maintenance of effective trough concentrations are essential for antiviral activity.⁷

Elvitegravir undergoes metabolism primarily by the cytochrome (CYP) 3A4/5 and partly by glucuronidation of uridine glucuronosyltransferase (UGT) 1A1 and 1A3.¹¹ 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 [^{14}C] fluorescence tagged elvitegravir/ritonavir 50/100 mg dose found that 94.8% was recovered in feces while 6.7% was recovered in urine.¹¹ 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 IC_{50}).⁷ Ritonavir boosting above 100 mg does not result in additional increases in elvitegravir exposure.¹² There is no difference between boosting with 100 mg ritonavir and 150 mg cobicistat.¹³

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-dcRFB was increased 5–20 fold.¹⁴ Total antimicrobial activity was increased by 50% during co-administration. Three subjects terminated the study prematurely due to a grade 4 adverse event (neutropenia). Most adverse events were mild (mainly nausea and headache). The results of this study showed that elvitegravir/ritonavir can be given at a reduced RFB dose of 150 mg every other day with appropriate monitoring of adverse events. The interaction between elvitegravir/ritonavir and rifampicin, the more common tuberculosis drug used in resource-limited settings, has not been studied, but is expected due to the inhibition of CYP 3A4 and UGT 1A by rifampicin of which are substrates of elvitegravir.

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 health 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 1A1, 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_{95} . 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 I Interactions between elvitegravir ± ritonavir and other drugs

Co-administered drug	Participants (completed study)	Duration	Dose		PK elvitegravir in % change C _{max}
			Elvitegravir ± ritonavir	Co-administered drug	
Zidovudine ²³	28 healthy subjects	27 days	200 mg + 100 mg QD day 8–27	300 mg BID day 1–7, 8–17	↑5%
Didanosine ^{23,*}	32 healthy subjects	17 days	200 mg + 100 mg QD day 5, 14–17	400 mg (EC capsule) QD day 1, 15	↓5%
Stavudine ^{23,*}	32 healthy subjects	17 days	200 mg + 100 mg QD day 5, 14–17	40 mg QD day 3, 17	↓4%
Abacavir ²³	26 healthy subjects	15 days	200 mg + 100 mg QD day 5–15	600 mg day 1, 15	↓5%
Rifabutin ¹⁴	19 healthy volunteers	53 days	300 mg + 100 mg QD	150 mg EOD	↓8%
Atazanavir (boosted) ¹⁹	53 healthy subjects	Study 1: 14 days, Study 2: 10 days	Study 1: 200 mg Study 2: 85 mg	300 mg + ritonavir 100 mg QD	Study 1: ↑85 Study 2: ↓9
Atazanavir (unboosted) ¹⁸	15 healthy subjects	20 days	300 mg	400 mg	↑8%
Darunavir ^{§,15}	20 healthy subjects	42 days	125 mg QD	600 mg + ritonavir 100 mg BID	↑13%
Tipranavir ^{§,15}	26 healthy subjects	42 days	200 mg QD	500 mg + ritonavir 200 mg BID	↑4%
Fosamprenavir ¹⁶	31 healthy subjects	28 days	125 mg QD	700 mg + ritonavir 100 mg BID	No change
Lopinavir ¹⁷	27 healthy subjects	14 days	125 mg QD	400 mg + ritonavir 100 mg BID	↑52%
Maraviroc ²⁰	28 healthy subjects	20 days	150 mg + 100 mg QD	150 mg BID	↑1%
Etravirine ²¹	31 healthy volunteers	20 days	150 mg + 100 mg QD	200 mg BID	↑7%
Antacid ^{24,σ}	62 healthy subjects	Study 1: 11 days Study 2: 15 days	50 mg + 100 mg QD	20 mL together, 2 hours before, 2 hours after, 4 hours before, 4 hours after elvitegravir	Together with antacid: ↓47% 2 hours after antacid: ↓18% 4 hours after antacid: ↓5% 2 hours before antacid: ↓2% 4 hours before antacid: ↓21%
Omeprazole ^{24,σ}	62 healthy subjects	15 days	50 mg + 100 mg QD	40 mg QD	↓7%
Ketoconazole ²³	18 healthy subjects	15 days	150 mg + 100 mg QD	200 mg BID	↑17%
Norgestimate and ethinyl estradiol ²⁴	15 healthy subjects	56 days	150 mg + cobicistat 150 mg + tenofovir 300 mg + emtricitabine 200 mg	Combination oral contraceptive pill containing norgestimate (NGM) 0.180 mg, 0.215 mg, 0.250 mg and ethinyl estradiol (EE) 25 µg	NA

AUC _τ	C _τ	PK co-administered drug in % change			Comments
		C _{max}	AUC _τ	C _τ	
↑5%	↑15%	↓12%	↓14%	NA	No dosage adjustment needed
↓3%	↑6%	↓16%	↓14%	NA	No dosage adjustment needed
↓2%	↑24%	↓0.4%	↑7%	NA	No dosage adjustment needed
↓3%	↑6%	↓12%	↓17%	NA	No dosage adjustment needed
↓4%	↓6%	Rifabutin: ↓8% 25-o-dcRFB: ↑440%	Rifabutin: ↓6% 25-o-dcRFB: ↑851%	Rifabutin: ↑16% 25-o-dcRFB: ↑1836	Dose adjustment of rifabutin 150 mg EOD recommended with monitoring of adverse events
Study 1: ↑100 Study 2: ↑7	Study 1: ↑188 Study 2: ↑38	Study 1: ↓16 Study 2: ↓3	Study 1: ↓21 Study 2: ↓11	Study 1: ↓35% Study 2: ↓17	Dose adjustment of EVG 85 mg recommended when co-administered with ATV/r 300/100 mg
↑7%	↓10%	3680 ng/mL	16300 ng·h/mL	74.5 ng/mL	Atazanavir exposures are lower than historical values
↑10%	↑18%	↓11%	↓11%	↓17%	No dosage adjustment needed
↓8%	↓10%	↓8%	↓11%	↓11%	No dosage adjustment needed
↓7%	↓4%	↓2%	↓1%	↑1%	No dosage adjustment needed
↑75%	↑139%	↓1%	↓3%	↓8%	Dose reduction of elvitegravir to 85 mg is recommended
↑7%	↑9%	↑115%	↑186%	↑323%	Dose adjustment of maraviroc 150 mg BID recommended
↑6%	↑6%	↑2%	↓2%	↓10%	No dosage adjustment needed
Together with antacid: ↓45% 2 hours after antacid: ↓15% 4 hours after antacid: ↓4% 2 hours before antacid: ↓2% 4 hours before antacid: ↓20% ↓1%	Together with antacid: ↓41% 2 hours after antacid: ↓10% 4 hours after antacid: ↑4% 2 hours before antacid: no change 4 hours before antacid: ↓20% ↓6%	NA	NA	NA	Administration of antacid and EVG should be separated by at least 2 hours
↑48%	↑67%	NA	NA	NA	No dosage adjustment needed
NA	NA	EE: ↓6% NGMN: ↑109%	EE: ↓25% NGMN: ↑126%	EE: ↓41% NGMN: ↑167%	Maximum recommended daily dose of ketoconazole is 200 mg Recommended ethinyl estradiol dose of the oral contraceptive is 30 µg

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_{max}, maximum concentration; AUC_τ, area under the curve from time 0 to tau, where tau is the length of dosing interval; C_τ, tau 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.^{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 exposures²⁴ found no significant change in exposures of elvitegravir when administered with omeprazole, indicating a lack of influence of gastric pH on elvitegravir absorption. C_{max} , AUC_{0-24} , 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 QD (days 2–15) and midazolam single dose on days 1, 11 and 15 in 18 healthy subjects.²⁵ Elvitegravir exposures as measured by C_{max} , AUC_{0-24} , 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 norgestimate 0.180 mg, 0.215 mg, 0.250 mg, and ethinyl estradiol 25 µg were carried out over a period of two pill cycles in 15 healthy subjects.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_{max} , AUC_{0-24} , 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 µg 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-naïve and experienced patients compared to placebo.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.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.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):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.³⁰ 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-naïve 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 $P = 0.001$).³¹ Unfortunately, in the preliminary results of trial, elvitegravir did not show a greater barrier to resistance when compared with raltegravir.³¹

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-re-

lated 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.²⁹ 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 events. 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)

Study	Design	EVG formulation	Sample size	Comparator	Outcomes	Comments
Efficacy						
DeJesus et al ⁷	Randomized dose-ranging monotherapy trial	200 mg, 400 mg, or 800 mg twice daily, or 50 mg once daily	40 HIV-positive treatment-naïve and experienced patients	Placebo	Significant reductions in HIV RNA in both treatment-naïve and experienced patients	
Zolopa et al ²⁷	Phase II randomized, controlled, 48-week study. Partial blinding (to dose)	20 mg, 50 mg and 125 mg daily	278 treatment-experienced subjects	Ritonavir-boosted PI	Lowest dose arm stopped early due to inferiority. 50 mg arm demonstrated noninferiority. 125 mg arm demonstrated superiority	
Cohen et al ²⁹	Phase II, 48-week randomized double-blinded trial	QUAD (EVG, cobicistat, emtricitabine and tenofovir)	71 treatment-naïve, HIV-positive patients	EFV/FTC/TDF	90% of the patients taking Quad and 83% of patients taking atripla achieved virological suppression	Quad associated with more rapid achievement of virological suppression
Molina et al ³¹	Phase III multicenter, randomized, double-blind study	Ritonavir-boosted once-daily elvitegravir 150 mg (or 85 mg in patients receiving a background protease inhibitor of either atazanavir or lopinavir)		351 receiving ritonavir-boosted twice-daily raltegravir 400 mg	59% of elvitegravir-treated patients achieved virological suppression vs 58% for raltegravir-treated patients (intention-to-treat population; $P = 0.001$)	Preliminary results did not show greater barrier to resistance compared with raltegravir
Safety and tolerability						
Zolopa et al ²⁷	Phase II randomized trial	Virological suppression	Virological suppression	Ritonavir-boosted PIs	Occurrence of adverse events and grade 3 or 4 laboratory toxicity similar across treatment groups	No dose-dependent increase in type of adverse event observed
Cohen et al ²⁹	Phase II randomized trial	Quad	71 treatment-naïve, HIV-positive patients	EFV/FTC/TDF	Lower percentage of drug-related adverse events compared with EFV/FTC/TDF (35% vs 57%)	Incidence of laboratory abnormalities. No grade 3/4 adverse events
					Quad induced fewer adverse events involving the central nervous system (drug-related central nervous system (17% vs 26%), and psychiatric (10% vs 44%))	No grade 3/4 adverse events nor adverse events leading to discontinuation for patients receiving Quad

Abbreviations: EVG, elvitegravir; EFV/FTC/TDF, efavirenz/emtricitabine/tenofovir disoproxil fumarate; PI, protease inhibitors.

Secondary mutations selected under elvitegravir include H114Y, L74M, R20K, A128T, E138K, and S230R.^{38,39}

Importantly, two of the three most common raltegravir-associated mutation pathways also result in elvitegravir resistance (Q 148 H/K/R, N155H).³³ However, elvitegravir can be used in the presence of Y143, a resistance mutation induced by raltegravir.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,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.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.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,^{44,45} and clinical trials are underway to assess the activity of this S/GSK-572 in patients failing raltegravir. Pharmacokinetic studies^{46,47} and dose-ranging trials^{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;⁵⁰ and the potential for a long-acting formulation of S/GSK-744 is also being investigated.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.

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References

1. Clayden P, Collins S, Harrington M, et al. HIV, Hepatitis C Virus (HCV), and tuberculosis drugs, diagnostics, vaccines, and preventive technologies in development. 2011 pipeline report second edition. i-Base/Treatment Action Group, New York; 2011.
2. Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Rockville, MD: DHHS; 2011 [updated November 29]. Available from: <http://aidsinfo.nih.gov/Guidelines/HTML/1/adult-and-adolescent-treatment-guidelines/1/panel-roster/>. Accessed November 30, 2011.
3. Global HIV/AIDS response: epidemic update and health sector progress towards Universal Access. Geneva: WHO/UNAIDS; 2011. Available from: http://www.who.int/hiv/pub/progress_report2011/hiv_full_report_2011.pdf. Accessed December 28, 2011.
4. Renaud-Théry F, Duncombe C, Kerr S, Thierry S, Perriens J. Adult ART in resource-limited settings: a systematic review of first-line treatment failure and attrition rates. 17th Conference on Retroviruses and Opportunistic Infections, San Francisco, February 16–20, 2010. Paper 827.

5. El-Khatib Z, Ekstrom AM, Ledwaba J, Mohapi L, Laher F, Karstaedt A, et al. Viremia and drug resistance among HIV-1 patients on antiretroviral treatment: a cross-sectional study in Soweto, South Africa. *AIDS*. 2010;24(11):1679–1687.
6. Hosseinipour MC, Kumwenda JJ, Weigel R, et al. Second-line treatment in the Malawi antiretroviral programme: high early mortality, but good outcomes in survivors, despite extensive drug resistance at baseline. *HIV Med*. 2010;11(8):510–518.
7. DeJesus E, Berger D, Markowitz M, et al. Antiviral activity, pharmacokinetics, and dose response of the HIV-1 integrase inhibitor GS-9137 (JTK-303) in treatment-naïve and treatment-experienced patients. *J Acquir Immune Defic Syndr*. 2006;43(1):1–5.
8. JTK 303 Public Chemical Database. PubChem Compound Summary (CID 5277135). Available from: <http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=5277135>. Accessed November 30, 2011.
9. Al-Mawsawi LQ, Al-Safi RI, Neamati N. Anti-infectives: clinical progress of HIV-1 integrase inhibitors. *Expert Opin Emerg Drugs*. 2008;13(2):213–225.
10. Kawaguchi I, Ishikawa T, Ishibashi M, Irie S, Kakee A. Gilead integrase inhibitor: safety and pharmacokinetics of single oral dose of JTK 303/GS-9137, a novel HIV integrase inhibitor, in healthy volunteers. 13th Conference on Retroviruses and Opportunistic Infections, Denver, USA, February 5–9, 2006. Available from: http://www.natap.org/2006/CROI/CROI_11.htm. Accessed November 30, 2011.
11. Ramanathan S, Wright M, West S, et al. Pharmacokinetics, metabolism, and excretion of ritonavir-boosted GS-9137 (Elvitegravir). Presented at: Eighth International Workshop on Clinical Pharmacology of HIV Therapy; April 16–18, 2007; Budapest, Hungary. Abstract 30.
12. Mathias AA, West S, Hui J, Kearney BP. Dose-response of ritonavir on hepatic CYP3A activity and elvitegravir oral exposure. *Clin Pharmacol Ther*. 2009;85(1):64–70.
13. Elion R, Cohen C, Gathe J, et al. Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir df in the initial treatment of HIV infection. *AIDS*. 2011;25(15):1881–1886.
14. German P, West S, Hui J, Kearney BP. Pharmacokinetic interaction between elvitegravir/ritonavir and dose-adjusted rifabutin. 9th International Workshop on Clinical Pharmacology of HIV Therapy, New Orleans, LA, April 7–9, 2008. Abstract P19. Available from: http://www.hiv-druginteractions.org/data/NewsItem/62_9PK_NewOrleans.pdf. Accessed November 30, 2011.
15. Mathias AA, Hinkle J, Shen G, et al. Effect of ritonavir-boosted tipranavir or darunavir on the steady-state pharmacokinetics of elvitegravir. *J Acquir Immune Defic Syndr*. 2008;49(2):156–162.
16. Ramanathan S, Mathias AA, Shen G, Holmes C, Kearney BP. Lack of clinically relevant drug-drug interaction between ritonavir-boosted GS-9137 (elvitegravir) and fosamprenavir/r. Poster exhibition; 4th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, July 22–25, 2007. Abstract WEPEB014.
17. Mathias A, West S, Enejosa J, Kearney B. A pharmacokinetic interaction between lopinavir/r and elvitegravir. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, USA, September 17–20, 2007. Abstract A-1418.
18. Ramanathan S, West S, Hui J, et al. Clinical pharmacokinetics of once-daily elvitegravir boosted by atazanavir versus ritonavir. 9th International Workshop on Clinical Pharmacology of HIV Therapy, New Orleans, USA, April 7–9, 2008. Abstract O18.
19. Mathias A, Ramanathan S, Hinkle J, West S, Enejosa J, Kearney B. Effect of atazanavir/r on the steady-state pharmacokinetics of elvitegravir. 47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, USA, September 17–20, 2007. Abstract A-1417.
20. Ramanathan S, Abel S, Tweedy S, West S, Hui J, Kearney BP. Pharmacokinetic interaction of ritonavir-boosted elvitegravir and maraviroc. *J Acquir Immune Defic Syndr*. 2010;53(2):209–214.
21. Ramanathan S, Kakuda TN, Mack R, West S, Kearney BP. Pharmacokinetics of elvitegravir and etravirine following coadministration of ritonavir-boosted elvitegravir and etravirine. *Antivir Ther*. 2008;13(8):1011–1017.
22. Ramanathan S, Shen G, Cheng A, Kearney BP. Pharmacokinetics of emtricitabine, tenofovir, and GS-9137 following coadministration of emtricitabine/tenofovir disoproxil fumarate and ritonavir-boosted GS-9137. *J Acquir Immune Defic Syndr*. 2007;45(3):274–279.
23. Ramanathan S, Shen G, Hinkle J, Enejosa J, Kearney BP. Pharmacokinetics of coadministered ritonavir-boosted elvitegravir and zidovudine, didanosine, stavudine or abacavir. *J Acquir Immune Defic Syndr*. 2007;46(2):160–166.
24. Ramanathan S, Shen G, Hinkle J, Enejosa J, Kearney BP. Pharmacokinetic evaluation of drug interaction with ritonavir-boosted HIV integrase inhibitor GS-9137 and acid reducing agents. 8th International Workshop on Clinical Pharmacology of HIV Therapy, Budapest, April 16–18, 2007. Abstract 69.
25. German P, Mathias A, West S, Chuck S, Kearney BP. Evaluation of ritonavir-boosted elvitegravir PK upon co-administration with a second potent CYP3A inhibitor, ketoconazole. 11th International Workshop on Clinical Pharmacology of HIV Therapy, Sorrento, Italy, April 5–7, 2010. Abstract 48.
26. German P, Wang M, Warren D, Kearney PB. Pharmacokinetic interaction between norgestimate/ethinyl estradiol and EVG/COB/FTC/TDF single tablet regimen. 12th International Workshop on Clinical Pharmacology of HIV Therapy, Miami, USA, April 13–15, 2011. Abstract 17.
27. Zolopa AR, Berger DS, Lampiris H, Zhong L, Chuck SL, Enejosa JV, et al. Activity of elvitegravir, a once-daily integrase inhibitor, against resistant HIV Type 1: results of a phase 2, randomized, controlled, dose-ranging clinical trial. *J Infect Dis*. 2010;201(6):814–822.
28. Gilead Sciences. Safety and efficacy of GS-9350-boosted atazanavir compared to ritonavir-boosted atazanavir in combination with emtricitabine/tenofovir disoproxil fumarate in HIV-1 infected, antiretroviral treatment-naïve adults. ClinicalTrials.gov identifier: NCT00892437. Ongoing study sponsored by Gilead Sciences. Trial began April 30, 2009, last updated October 12, 2011. Available from: <http://clinicaltrials.gov/ct2/show/NCT00892437?term=GS-9350&rank=1>. Accessed November 30, 2011.
29. Cohen C, Elion R, Ruane P, et al. Randomized, phase 2 evaluation of two single-tablet regimens elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate versus efavirenz/emtricitabine/tenofovir disoproxil fumarate for the initial treatment of HIV infection. *AIDS*. 2011;25(6):F7–F12.
30. Gilead Sciences. Gilead's Investigational Antiretroviral Quad Regimen Meets 48-Week Primary Objective in Pivotal Phase 3 Clinical Study 102. Press release. August 15, 2011. Available from: http://www.gilead.com/press_archive. Accessed November 30, 2011.
31. Molina J-M, LaMarca A, Andrade Villanueva J, et al; for the Study 145 Group. Elvitegravir once-daily is non inferior to raltegravir twice-daily in treatment experienced patients: 48 week results from a phase 3 multicenter, randomized, double blind study. 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Rome, July 17–20, 2011. Abstract WELBB05.
32. Ford N, Lee J, Andrieux-Meyer I, Calmy A. Safety, efficacy and pharmacokinetics of rilpivirine: a systematic review with an emphasis on resource-limited settings. *HIV/AIDS (Auckl)*. 2011;3:35–44.
33. Blanco JL, Varghese V, Rhee SY, Gatell JM, Shafer RW. HIV-1 integrase inhibitor resistance and its clinical implications. *J Infect Dis*. 2011;203(9):1204–1214.
34. Shimura K, Kodama E, Sakagami Y, et al. Broad antiretroviral activity and resistance profile of the novel human immunodeficiency virus integrase inhibitor elvitegravir (JTK-303/GS-9137). *J Virol*. 2008;82(2):764–774.

35. Goethals O, Clayton R, Van Ginderen M, et al. Resistance mutations in human immunodeficiency virus type 1 integrase selected with elvitegravir confer reduced susceptibility to a wide range of integrase inhibitors. *J Virol*. 2008;82(21):10366–10374.
36. Garvey EP, Johns BA, Gartland MJ, et al. The naphthyridinone GSK364735 is a novel, potent human immunodeficiency virus type 1 integrase inhibitor and antiretroviral. *Antimicrob Agents Chemother*. 2008;52(3):901–908.
37. McColl DJ, Fransen S, Gupta S, et al. Resistance and cross-resistance to first generation integrase inhibitors: insights from a phase 2 study of elvitegravir (GS-9137). 16th International Drug Resistance Workshop; Barbados, Bridgetown, June 12–16, 2007. Abstract 9.
38. Métifiot M, Marchand C, Maddali K, Pommier Y. Resistance to integrase inhibitors. *Viruses*. 2010;2(7):1347–1366.
39. Goethals O, Clayton R, Van Ginderen M, et al. Resistance mutations in human immunodeficiency virus type 1 integrase selected with elvitegravir confer reduced susceptibility to a wide range of integrase inhibitors. *J Virol*. 2008;82(21):10366–10374.
40. Métifiot M, Vandegraaff N, Maddali K, et al. Elvitegravir overcomes resistance to raltegravir induced by integrase mutation Y143. *AIDS*. 2011;25(9):1175–1178.
41. Davies MA, Moultrie H, Eley B, et al. Virologic failure and second-line antiretroviral therapy in children in South Africa – the leDEA Southern Africa collaboration. *J Acquir Immune Defic Syndr*. 2011;56(3):270–278.
42. Médecins Sans Frontières. Untangling the web of antiretroviral price reductions. 14th ed. Geneva, 2011.
43. Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Working Group of the Office of AIDS Research Advisory Council (OARAC): guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. October 14, 2011. Available at: <http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL>. Accessed November 30, 2011.
44. Sato A, Kobayashi M, Yoshinaga T, et al. S/GSK1349572 is a potent next generation HIV integrase inhibitor. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, South Africa, July 19–22, 2009. Abstract WEPEA097.
45. Underwood M, Johns B, Sato A, Fujiwara T, Spreen W. S/GSK1349572: a next generation integrase inhibitor with activity against integrase inhibitor resistant clinical isolates from patients experiencing virologic failure while on raltegravir therapy. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, South Africa, July 19–22, 2009. Abstract WEPEA098.
46. Min S, Song I, Borland J, et al. Pharmacokinetics (PK) and safety in healthy subjects of S/GSK1349572, a next generation, once-daily HIV integrase inhibitor (INI). 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, South Africa, July 19–22, 2009. Abstract WEPEA099.
47. Min S, Song I, Borland J, Chen S, Lou Y, Fujiwara T, et al. Pharmacokinetics and safety of S/GSK1349572, a next-generation HIV integrase inhibitor, in healthy volunteers. *Antimicrob Agents Chemother*. 2010;54(1):254–258.
48. Lalezari J, Sloan L, DeJesus E, et al. Potent antiviral activity of S/GSK1349572, a next generation integrase inhibitor (INI), in INI-Naive HIV-1-infected patients: ING111521 protocol. 5th IAS Conference on HIV Pathogenesis, treatment and prevention, Cape Town, South Africa, July 19–22, 2009. Abstract TUAB105.
49. Song I, Chen S, Lou Y, et al. Pharmacokinetic (PK) and pharmacodynamic (PD) relationship of S/GSK1349572, a next generation integrase inhibitor (INI), in HIV-1 infected patients. 5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, South Africa, July 19–22, 2009. Abstract WePeB250.
50. Min S, DeJesus E, McCurdy L, et al. Pharmacokinetics (PK) and safety in healthy and HIV-infected subjects and short-term antiviral efficacy of S/GSK1265744, a next generation once daily HIV integrase inhibitor. The Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, September 12–15, 2009. Abstract H-1228.
51. GlaxoSmithKline. A single dose escalation study to investigate the safety, tolerability and pharmacokinetics of intramuscular and subcutaneous long acting GSK1265744 in healthy subjects. ClinicalTrials.gov identifier: NCT01215006. Sponsored by Gilead Sciences. 2010 [updated June 9, 2011]. Available from: <http://clinicaltrials.gov/ct2/show/NCT01215006>. Accessed November 30, 2011.

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