Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study

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Summary

Background **Elvitegravir is a once daily inhibitor of HIV-1 integrase boosted by ritonavir. We aimed to compare the efficacy and safety of elvitegravir with raltegravir, another HIV-1 integrase inhibitor, in patients in whom previous antiretroviral treatment failed.**

Methods **We conducted a randomised, double-blind, double-dummy, phase 3 study at 234 sites in 13 countries. Eligible patients had plasma HIV RNA of 1000 copies per mL or greater, any CD4 cell count, and resistance to or 6 months' experience with at least two classes of antiretroviral drugs. They received an open-label background regimen of a fully active, ritonavir-boosted protease inhibitor and a second agent. We randomly allocated patients (1:1) by computer with a block size of four to receive either elvitegravir 150 mg once daily (n=361; 85 mg dose if given with atazanavir, or lopinavir with ritonavir) or raltegravir 400 mg twice daily (n=363). Placebo tablets were given to mask the difference in daily dosing. The primary endpoint was achievement and maintenance of virological response (HIV RNA <50 copies per mL) through week 48. Non-inferiority was prespecified with a margin of 10%. We did a modified intention-to-treat analysis. This study is registered with ClinicalTrials.gov, number NCT00708162.**

Findings **Ten patients allocated elvitegravir and 12 assigned raltegravir were excluded from the analysis (either for protocol violations or because they did not receive treatment). 207 (59%) of 351 patients allocated elvitegravir achieved virological response compared with 203 (58%) of 351 assigned raltegravir (treatment difference 1·1%, 95% CI –6·0 to 8·2), meeting the criterion for non-inferiority (p=0·001). Three patients allocated elvitegravir had serious adverse events related to study drugs compared with seven assigned raltegravir; two and eight patients died, respectively. More individuals assigned elvitegravir reported diarrhoea up to week 48 (p=0·023), and more patients assigned raltegravir had grade 3 or 4 rises in alanine aminotransferase (p=0·020) or aspartate aminotransferase (p=0·009).**

Interpretation **Elvitegravir used in combination with a ritonavir-boosted protease inhibitor in treatment-experienced patients has similar efficacy and safety to raltegravir. Since elvitegravir can be given once a day compared with twice a day for raltegravir, elvitegravir might improve patients' adherence.**

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Introduction

Elvitegravir is a potent inhibitor of HIV-1 integrase;[1,2] 1·2 nmol/L of this investigational drug blocks the strand-transfer step of HIV integration by 90% in vitro. When given in combination with ritonavir 100 mg, elvitegravir has pharmacokinetics and trough concentrations ideal for once-daily dosing, and higher or twice-daily doses of ritonavir do not increase the systemic exposure of elvitegravir further.[3]

Raltegravir is currently the only integrase inhibitor indicated for treatment of HIV infection and is approved for twice-daily administration.[4–6] Similar to raltegravir, elvitegravir has full activity against HIV resistant to nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitors (NNRTIs), and protease inhibitors,[1] all of which are used in first-line regimens. In treatment-experienced patients on second-line regimens, use of ritonavir-boosted protease inhibitors is common.

In a phase 2 study in treatment-experienced patients in whom current antiretroviral treatment was failing,[7] elvitegravir 125 mg had potent activity against HIV-1 that was durable in the presence of at least one other fully active antiretroviral drug. Subsequently, the formulation of elvitegravir was changed to a 150 mg dose (bioequivalent to the 125 mg formulation), which is better suited to commercial scale.[8,9] We did a phase 3 study in previously treated, HIV-1-infected patients to compare safety and efficacy of elvitegravir 150 mg with raltegravir.

Methods

Patients

Study GS-US-183-0145, which is registered with ClinicalTrials.gov (number, NCT00708162), is an ongoing, 96-week, phase 3, randomised, double-blind, double-dummy, non-inferiority study. Two identical studies (GS-US-183-0144 and GS-US-183-0145) that were originally set up in different territories were merged to complete enrolment faster. We did this multicentre study at 234 sites in 13 countries in Australia, North America, and Europe. The institutional review board or ethics committee for every site reviewed and approved the protocol and informed consent form. Every patient gave written informed consent.

Adults (aged ≥18 years) infected with HIV-1 were eligible for inclusion if they had plasma viral RNA of 1000 copies per mL or greater while on a stable antiretroviral regimen for at least 30 days before screening. We required patients to have documented resistance (ascertained by current International AIDS Society-USA guidelines on the screening genotype) or 6 months' experience with at least two classes of antiretroviral agents. Thus, patients could have either resistance to two antiretroviral drug classes (from NRTIs, NNRTIs, or protease inhibitors), resistance to one drug class and 6 months' experience with at least one other drug class, or 6 months' experience with two or more classes of antiretroviral drugs. Inclusion criteria were estimated glomerular filtration rate by the Cockcroft-Gault method of at least 60 mL/min, hepatic aminotransferase concentrations five or fewer times the upper limit of normal, total bilirubin of 25·65 μmol/L or less, absolute neutrophil count 1000 cells per μL or higher, platelet count 50 000 platelets per μL or higher, haemoglobin concentrations of at least 85 g/L, and a serum amylase concentration less than 1·5 times the upper limit of normal. We required no minimum CD4 cell count. We excluded patients if they had a new AIDS-defining condition within 30 days of screening (other than on the basis of CD4 cell count), previous treatment with an integrase inhibitor, ascites, encephalopathy, malignant disease, serious infection, substance abuse, were pregnant or breastfeeding, or needed a contraindicated drug.

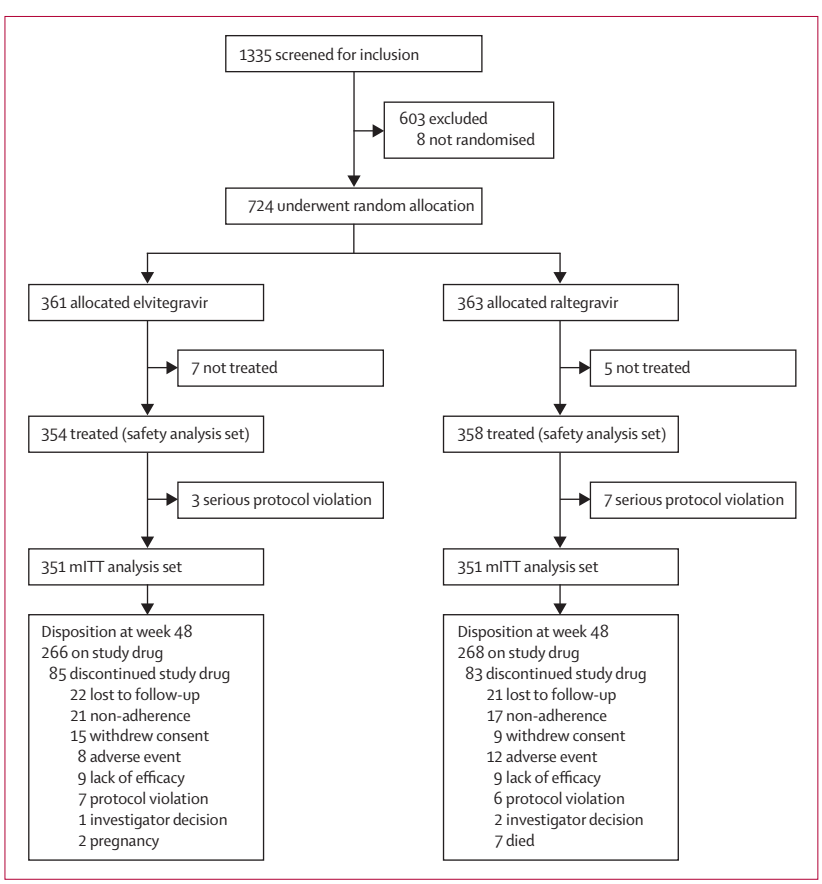

Figure 1: **Trial profile**
mITT=modified intention to treat.

Procedures

We did clinical examinations and laboratory analyses at the initial screening visit, at the baseline visit (when administration of study drugs was started), at weeks 2, 4, 8, 12, 16, 20, and 24, and then every 8 weeks up to 96 weeks. We assessed adherence on the basis of pill counts at every visit. Other assessments included CD4 cell counts, measurement of plasma HIV RNA (we used the Amplicor HIV-1 Monitor Test [version 1.5]; Roche Diagnostics, Rotkreuz, Switzerland), haematology and plasma chemistry profiles, and urinalysis. Covance Laboratories (based in Geneva, Switzerland; Indianapolis, IN, USA; and Singapore) undertook laboratory tests.

Beginning with the baseline visit, we gave all individuals an investigator-selected, open-label, background regimen consisting of a ritonavir-boosted, fully active protease inhibitor (by the screening phenotypic assessment) and a second drug that may or may not have been fully active (except in Spain, where participants had to receive a fully active second agent, as requested by the Spanish regulatory agency). Protease inhibitors that could be prescribed included atazanavir, darunavir (could be given once or twice daily, as prescribed by investigator), fosamprenavir, lopinavir with ritonavir, or tipranavir. Patients took the dose of ritonavir indicated in the prescribing information for their protease inhibitor; no additional ritonavir was needed for individuals who would receive elvitegravir. The second background drug could have been an NRTI, etravirine, maraviroc, or enfuvirtide. A dual-combination NRTI containing lamivudine or emtricitabine was permitted only if the patient had HIV with the reverse transcriptase protein mutation Met184Val or Met184Ile documented on the screening genotype, so that individuals had a maximum of two fully active background agents.

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Randomisation and masking

In addition to the background regimen, we randomly allocated patients (1:1) in a double-blind manner to receive either elvitegravir 150 mg once daily (plus placebo to match raltegravir twice daily) or raltegravir 400 mg twice daily (plus placebo to match elvitegravir once daily). The random sequence was computer-generated via an interactive system accessed via a website or telephone, and we used a block size of four. All patients and study investigators were unaware of the random allocation. To achieve treatment concealment, every patient received the same number of study drug tablets that looked like elvitegravir (active or placebo) and raltegravir (active or placebo). Because of pharmacokinetic interactions, patients receiving atazanavir, or lopinavir with ritonavir, were given 85 mg tablets of elvitegravir or placebo.[8] We stratified the randomisation by amount of HIV RNA (>100 000 or ≤100 000 copies per mL), class of second background agent (NRTI or other), and geographical region (USA or Puerto Rico, or Europe, Canada, Australia, or Mexico).

Study endpoints

Our primary study objective was to assess whether efficacy of elvitegravir is non-inferior to raltegravir, when each drug is given with a background antiretroviral regimen containing a ritonavir-boosted protease inhibitor. We did a modified intention-to-treat (mITT) analysis of efficacy, which included data for all patients who were assigned to a treatment group, who received at least one dose of study drug, and who were not at one study site that was closed early in the study for serious breaches in the protocol. Per-protocol analyses included two sets of individuals: those who received study drug up to 48 weeks and had no major protocol violation; and those who discontinued study drug before 48 weeks due to low efficacy, as judged by the investigator. Per-protocol analyses did not include patients who discontinued for other reasons.

Our primary endpoint was the proportion of patients in the mITT population who achieved and maintained an amount of HIV RNA less than 50 copies per mL at week 48, using the US Food and Drug Administration (FDA)-defined time to loss of virological response (TLOVR) algorithm.[10] Treatment was said to have failed in individuals who switched background regimen before they achieved confirmed suppression. We also assessed virological response in the mITT population with the FDA-defined snapshot analysis,[10] which scores efficacy on the basis of a snapshot of HIV RNA amounts at week 48, and a missing-as-failure analysis (missing data for HIV RNA treated as >50 copies per mL). Both these analyses were prespecified.

We analysed safety data up to week 48 for all patients who received at least one dose of study drug. Thus, safety data for individuals who enrolled early and remained in the study would have been gathered for more than 2 years and are included in this report. Safety analyses included data obtained up to 30 days after discontinuation of study drugs. Analyses of safety and discontinuations were done on a post-hoc basis.

Statistical analysis

On the basis of data available from other studies,[5,11–13] we calculated that a sample size of 700 patients would be needed to provide 85% power to assess non-inferiority with respect to the primary endpoint. We worked out percentage differences (elvitegravir–raltegravir) and associated two-sided 95% CIs with Mantel-Haenszel

	Elvitegravir (n=351)	Raltegravir (n=351)
Age (years)	44 (38–50)	45 (40–51)
Women	59 (17%)	67 (19%)
Ethnic origin		
White	211 (60%)	226 (64%)
Black	125 (36%)	113 (32%)
Asian	9 (3%)	5 (1%)
Other	6 (1%)	7 (2%)
Chronic hepatitis B virus infection	17 (5%)	12 (3%)
Chronic hepatitis C virus infection	44 (13%)	54 (16%)
HIV RNA (log_{10} copies per mL)	4·35 (3·66–5·03)	4·42 (3·60–5·02)
Individuals with >100 000 copies per mL	90 (26%)	90 (26%)
CD4 cell count (cells per μL)	227 (100–371)	215 (111–381)
Individuals with ≤200 cells per μL	151 (44%)	153 (45%)
AIDS diagnosis	126 (36%)	125 (36%)
Baseline resistance mutations		
NRTI	242 (69%)	251 (72%)
NNRTI	219 (63%)	209 (60%)
Primary protease inhibitor	107 (31%)	119 (34%)
No resistance mutations	63 (18%)	57 (16%)
One class	65 (19%)	81 (23%)
Two or more classes	222 (63%)	213 (61%)
Protease inhibitors		
Atazanavir	61 (17%)	51 (15%)
Darunavir	202 (58%)	207 (59%)
Fosamprenavir	14 (4%)	19 (5%)
Lopinavir with ritonavir	68 (19%)	68 (19%)
Tipranavir	6 (2%)	7 (2%)
Second agent (NRTIs)		
Tenofovir disoproxil fumarate	163 (46%)	171 (48%)
Tenofovir disoproxil fumarate with emtricitabine	91 (26%)	67 (19%)
Lamivudine	11 (3%)	13 (4%)
Abacavir	5 (1%)	12 (3%)
Abacavir with lamivudine	4 (1%)	8 (2%)
Second agent (other agents)		
Enfuvirtide	2 (1%)	1 (<1%)
Etravirine	45 (13%)	54 (15%)
Maraviroc	24 (7%)	18 (5%)

Data are median (IQR) or number of patients (%). Only the five most frequently used NRTIs are shown, so second agent totals do not equal 100%. NRTI=nucleoside or nucleotide reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor.

Table 1: **Baseline characteristics**

	Elvitegravir	Raltegravir	Treatment difference (95% CI)
mITT analysis			
Number of patients	351	351	..
HIV RNA <50 copies per mL	207 (59%)	203 (58%)	1·1% (–6·0 to 8·2)
Virological failure	70 (20%)	77 (22%)	..
Rebound	40 (11%)	56 (16%)	..
Never suppressed through week 48	27 (8%)	18 (5%)	..
Switched background regimen*	3 (1%)	3 (1%)	..
Death	2† (1%)	7 (2%)	..
Discontinued study drug	72 (21%)	64 (18%)	..
Adverse event	6 (2%)	12 (3%)	..
Other reasons	66 (19%)	52 (15%)	..
Per-protocol analysis			
Number of patients	271	269	..
HIV RNA <50 copies per mL	202 (75%)	197 (73%)	1·4% (–5·9 to 8·6)
Virological failure	58 (21%)	66 (25%)	..
Rebound	29 (11%)	48 (18%)	..
Never suppressed through week 48	26 (10%)	17 (6%)	..
Switched background regimen*	3 (1%)	1 (<1%)	..
Discontinued study drug	11 (4%)	6 (2%)	..
Adverse event	0	1 (<1%)	..
Other reasons	11 (4%)	5 (2%)	..

Data are number of patients (%). mITT=modified intention to treat. TLOVR=time to loss of virological response. *Patients who switched background regimen for any reason before achieving virological suppression are counted as virological failures. †Both patients discontinued study drugs, one at 21 days and one at 57 days before death and are shown in figure 1 as having discontinued study drugs due to an adverse event. For the TLOVR calculation, however, these two patients are categorised as deaths.

Table 2: **Efficacy results at week 48**

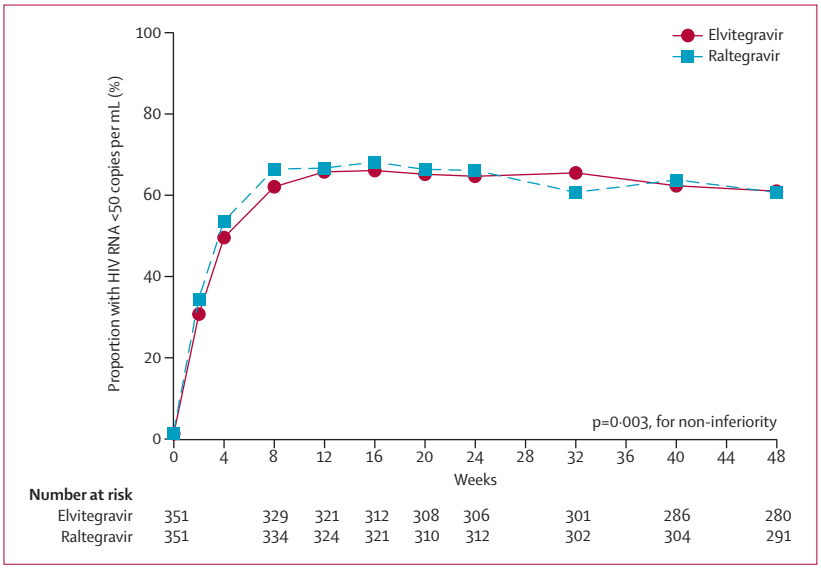

Figure 2: **Proportion of patients with an amount of HIV RNA less than 50 copies per mL at every follow-up visit**

proportions, adjusted for baseline HIV RNA amount (≤100 000 *vs* >100 000 copies per mL) and class of second agent (NRTI *vs* other). We judged elvitegravir non-inferior to raltegravir if the lower bound of the 95% CI for treatment difference was –10% or greater. We used Fisher's exact test to compare the proportion of patients with diarrhoea and raised concentrations of alanine aminotransferase and aspartate aminotransferase.

We did HIV-1 genotyping and phenotyping on blood samples obtained at screening for all patients and on samples from individuals with either suboptimum virological response (HIV RNA ≥50 copies per mL and reduction of <1 $\log_{10}$ copies per mL from baseline at week 8, confirmed at week 12), virological rebound (either confirmed increase in HIV RNA of >1 $\log_{10}$ copies per mL from nadir or confirmed rebound to ≥400 copies per mL after achieving <50 copies per mL), HIV RNA of 400 copies per mL or more at week 48, but no suboptimum virological response, or HIV RNA of 400 copies per mL or more on the last visit before discontinuing study drug. We assigned genotypic and phenotypic sensitivity scores according to findings of the Phenosense GT resistance test (Monogram Biosciences, San Francisco, CA, USA).

Role of the funding source

The sponsor of the study, Gilead Sciences, designed the study and analysed data. All authors had access to data and analyses, contributed to writing and editing, and approved the final report. J-MM and SLC had the final decision to submit the report for publication.

Results

Screening began on June 19, 2008, and all week 48 visits were completed by Dec 15, 2010. Early in the study, one of the 234 sites was closed because of several serious protocol violations; ten patients at this site were removed from the study and are not included in the mITT or per-protocol analyses (figure 1).

Patients' disposition (figure 1) and baseline characteristics and background agents (table 1) were balanced between treatment arms. Darunavir was the most widely used protease inhibitor, and the second background agent was usually an NRTI. Two-thirds of patients had mutations to two or more classes of agents (table 1).

207 (59%) of 351 individuals in the elvitegravir arm had HIV RNA of less than 50 copies per mL compared with 203 (58%) of 351 in the raltegravir arm (treatment difference 1·1%, 95% CI –6·0 to 8·2; table 2), indicating non-inferiority (p=0·001). Efficacy was similar when calculated by the FDA-defined snapshot algorithm: 210 (60%) of those assigned elvitegravir versus 202 (58%) of those allocated raltegravir (2·2%, –5·0 to 9·3; p=0·0004 for non-inferiority). The per-protocol analysis produced higher response rates than did the mITT; these were similar in both groups (table 2; p=0·001 for non-inferiority). Similar proportions of patients receiving elvitegravir or raltegravir had an amount of HIV RNA less than 50 copies per mL at every follow-up visit during the first 48 weeks (61% *vs* 61%; figure 2), indicating that the rate of virological suppression was similar between treatment arms (week 48 treatment difference 0·2%, 95% CI –6·9 to 7·3; p=0·003).

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Efficacies of elvitegravir and raltegravir at week 48 were also non-inferior across several subsets of patients (table 3). In individuals with high baseline viral load (HIV RNA >100 000 copies per mL) who achieved a level of HIV RNA less than 50 copies per mL, rates of virological failure were similar between arms (27 of 90 assigned elvitegravir *vs* 28 of 90 allocated raltegravir). In patients who received darunavir, fosamprenavir, or tipranavir and who were randomly allocated elvitegravir (thereby receiving a 150 mg dose of elvitegravir), efficacy was non-inferior to that of individuals treated with the same protease inhibitors and who were assigned raltegravir. Similarly, virological efficacy in patients allocated elvitegravir who received atazanavir, or lopinavir with ritonavir, as their protease inhibitor (thereby receiving 85 mg of elvitegravir) was non-inferior to that of individuals treated with these protease inhibitors and allocated raltegravir. Median increases from baseline in CD4 cell counts were similar in the two treatment arms (119 cells per µL in the elvitegravir arm *vs* 127 cells per µL in the raltegravir arm).

Development of resistance mutations was assessed in patients who met prespecified criteria (table 4). New mutations in reverse transcriptase, protease, and integrase genes were recorded in a few individuals, and the number and classes of resistance mutations were balanced between treatment arms. Resistance mutations selected in the HIV-1 integrase gene by elvitegravir or raltegravir were largely overlapping between arms, although alterations at Thr66 and Ser147 were noted only in patients assigned elvitegravir, and Asn155His was more common in those allocated raltegravir. Mixtures of viruses with two or more mutations in integrase were frequently identified. Phenotypic analyses showed resistance to both drugs in seven (50%) of 14 and 13 (87%) of 15 patients with phenotypic data and integrase-resistance mutations randomised to elvitegravir and raltegravir, respectively.

Adherence to study drug in the safety analysis set was analysed by pill counts. In the elvitegravir arm, patients had a median adherence of 95·3% (IQR 89·0–98·7) to all study drugs dispensed up to week 48 compared with 95·0% (86·6–98·5) in the raltegravir arm.

Table 5 shows adverse events (grade 2–4) that arose in at least 3% of individuals in either arm. The proportion of adverse events attributed to study drugs was similar between treatment arms (80 [23%] of 354 in those assigned elvitegravir *vs* 72 [20%] of 358 in those allocated raltegravir), as were rates of serious adverse events deemed related to study drugs (3 [1%] *vs* 7 [2%]). Nine patients (3%) allocated elvitegravir discontinued because of adverse events (two each because of lung cancer, nausea, and acute hepatitis, and one each end-stage liver disease, abdominal pain, and rectal haemorrhage) compared with 15 (4%) assigned raltegravir (five acute hepatitis, two each rash and substance abuse, and one each hypercholesterolaemia, hypertriglyceridaemia, lipohypertrophy, renal-cell carcinoma, abdominal pain, and lung cancer). Although significantly more patients allocated elvitegravir reported diarrhoea up to week 48 than did those assigned raltegravir (p=0·023; table 5), the proportion of patients affected was similar after the first

	Elvitegravir	Raltegravir	Treatment difference (95% CI)
Baseline HIV RNA ≤100 000 copies per mL	171/261 (66%)	168/261 (64%)	1·1% (–7·1 to 9·3)
Baseline HIV RNA >100 000 copies per mL	39/90 (43%)	34/90 (38%)	5·4% (–9·1 to 19·9)
Baseline CD4 cell count ≤200 cells per µL	72/151 (48%)	71/153 (46%)	1·8% (–9·3 to 12·9)
Baseline CD4 cell count >200 cells per µL	132/189 (70%)	128/188 (68%)	1·8% (–7·6 to 11·2)
Darunavir, fosamprenavir, or tipranavir	137/222 (62%)	137/232 (59%)	2·5% (–6·3 to 11·3)
Atazanavir, or lopinavir with ritonavir	73/129 (57%)	65/119 (55%)	2·8% (–9·5 to 15·2)
NRTI in background regimen	163/280 (58%)	156/278 (56%)	2·4% (–5·7 to 10·5)
Combination NRTI (with lamivudine or emtricitabine)	65/102 (64%)	47/82 (57%)	5·9% (–8·3 to 20·0)
Second agent other than NRTI in background regimen	47/71 (66%)	46/73 (63%)	1·5% (–13·7 to 16·7)
Background regimen GSS=1	39/50 (78%)	36/53 (68%)	11·4% (–6·2 to 29·1)
Background regimen GSS=2*	167/284 (59%)	161/291 (55%)	3·1% (–4·9 to 11·0)

Data are number of patients (%). mITT=modified intention to treat. FDA=US Food and Drug Administration. NRTI=nucleoside or nucleotide reverse transcriptase inhibitor. GSS=genotypic sensitivity score. *Includes all 34 patients enrolled at sites in Spain who were required to have two active background drugs.

***Table 3:* Patients with HIV RNA less than 50 copies per mL at week 48, using the FDA-defined snapshot algorithm (mITT population)**

	Elvitegravir	Raltegravir
Patients analysed for genotyping*	61	75
Patients with data†		
Integrase	60	72
Protease and reverse transcriptase	59	75
No new resistance mutations in protease, reverse transcriptase, or integrase‡	35 (59%)	49 (68%)
NRTI resistance mutations§	7 (12%)	10 (13%)
Lys65Arg	1 (2%)	2 (3%)
NNRTI resistance mutations¶	8 (14%)	5 (7%)
Protease inhibitor resistance mutations||	4 (7%)	3 (4%)
Integrase resistance mutations**	16 (27%)	15 (21%)
Thr66Ile/Ala	7 (12%)	0
Glu92Gln	5 (8%)	1 (1%)
Thr97Ala	3 (5%)	3 (4%)
Ser147Gly	3 (5%)	0
Gln148His/Arg	3 (5%)	4 (6%)
Asn155His	3 (5%)	9 (13%)
Tyr143Arg/Cys/His	0	1 (1%)

NRTI=nucleoside or nucleotide reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. *See Statistical analysis section for prespecified criteria. †Number of patients with data for corresponding protein, in each arm. ‡Percentages calculated from lowest number of patients with data, in each arm. §Met41Leu, Glu44Asp, Ala62Val, Lys65Arg, Asp67Asn, Thr69Asp, Thr69 insertions, Lys70Arg/Glu, Leu74Val/Ile, Val75Ile, Phe77Leu, Tyr115Phe, Phe116Tyr, Val118Ile, Gln151Met, Met184Val/Ile, Leu210Trp, Thr215Tyr/Phe, and Lys219Gln/Glu/Asn/Arg. ¶Val90Ile, Ala98Gly, Leu100Ile, Lys101Glu/His/Pro, Lys103Asn, Val106Ala/Met/Ile, Val108Ile, Glu138Ala, Val179Asp/Phe/Thr, Tyr181Cys/Ile/Val, Tyr188Leu/Cys/His, Gly190Ser/Ala, Pro225His, and Met230Leu. ||Asp30Asn, Val32Ile, Leu33Phe, Met46Ile/Leu, Ile47Val/Ala, Gly48Val, Ile50Leu/Val, Ile54Met/Leu, Gln58Glu, Leu74Pro, Leu76Val, Val82Ala/Phe/Thr/Ser/Leu, Ile84Val, Asn88Ser, and Leu90Met. **Thr66Ile/Ala/Lys, Glu92Gln/Gly, Thr97Ala, Tyr143Arg/His/Cys, Ser147Gly, Gln148His/Arg/Lys, Asn155His/Ser.

***Table 4:* Development of resistance mutations in HIV-1 genes**

	Elvitegravir (n=354)	Raltegravir (n=358)
Diarrhoea	44 (12%)	26 (7%)
Upper-respiratory-tract infection	20 (6%)	17 (5%)
Bronchitis	17 (5%)	17 (5%)
Back pain	17 (5%)	13 (4%)
Depression	16 (5%)	15 (4%)
Sinusitis	14 (4%)	13 (4%)
Arthralgia	13 (4%)	8 (2%)
Nausea	13 (4%)	8 (2%)
Urinary-tract infection	10 (3%)	15 (4%)

Adverse events=grades 2–4, reported by at least 3% of patients treated with at least one dose of study drug up to week 48 (safety analysis set)

Table 5: **Adverse events**

month of study drug (15 [4%] of 354 allocated elvitegravir *vs* 12 [3%] of 358 assigned raltegravir). No individual discontinued study drugs because of diarrhoea.

Two patients allocated elvitegravir died, one at 57 days and one at 21 days after discontinuation of study drugs (end-stage liver disease due to hepatitis C virus infection, intestinal perforation). Eight individuals assigned raltegravir died, seven of whom died before the week 48 follow-up visit (haemolytic anaemia, cardiac arrest, possible coronary event, choking, heroin overdose, cardiomegaly with mitral-valve prolapse, automobile accident, non-Hodgkin's lymphoma).

Laboratory test abnormalities noted up to week 48 were generally similar between treatment arms. Changes from baseline in fasting lipids and lipoproteins did not differ between arms. Significantly more patients allocated raltegravir had grade 3 or 4 increases in concentration of alanine aminotransferase (18 [5%] of 352) than did those assigned elvitegravir (six [2%] of 349; p=0·020); eight individuals had grade 4 rises in the raltegravir arm compared with none in the elvitegravir arm (p=0·008). Similarly, significantly more patients allocated raltegravir had grade 3 or 4 increases in concentration of aspartate aminotransferase (18 [5%] of 352) than did those assigned elvitegravir (five [1%] of 349; p=0·009); seven patients had grade 4 rises in the raltegravir arm versus none in the elvitegravir arm (p=0·015).

Discussion

Data from week 48 of our 96 week study show that the efficacy of elvitegravir is non-inferior to raltegravir in treatment-experienced patients receiving a ritonavir-boosted protease inhibitor and another agent. Efficacy was non-inferior irrespective of baseline viral load or baseline CD4 cell count or across several subsets of patients defined according to the background regimen.

Adverse events and laboratory abnormalities were generally similar between treatment arms. Although diarrhoea was reported most often by individuals assigned elvitegravir, equivalent numbers of patients in both treatment groups had diarrhoea in the first month after starting study drug. Grade 3 or 4 rises in hepatic enzymes were significantly more frequent in individuals allocated raltegravir than in those assigned elvitegravir.

Of isolates with integrase-resistance mutations selected by elvitegravir or raltegravir, phenotypic cross-resistance to both drugs was typical, preventing sequencing from one drug to the other.

We designed criteria for the background regimen in our study to ensure that every patient would be treated with a total of two or three fully active agents, including the randomly allocated integrase inhibitor. With this design, no individual would receive functional monotherapy and be destined for virological failure.[14,15] Our approach also ensured that the contribution of each randomised integrase inhibitor would be measureable. In other studies,[11–13,16–18] addition of an investigational drug to a background regimen of three fully active drugs did not lead to better efficacy in treatment-experienced patients.

The proportion of patients with virological suppression in this study is similar to those reported in previous studies overall and in individuals with only one active background drug. In the BENCHMRK studies,[5,13] 62% of patients given raltegravir achieved levels of HIV RNA of less than 50 copies per mL at week 48, and in the DUET studies,[11,12] 61% of individuals given etravirine achieved virological suppression.[19] However, in the BENCHMRK and DUET studies, more background drugs were allowed, and 20%[5] and 26%[11,12] of patients used the potent drug enfuvirtide for the first time. In the MOTIVATE studies,[20] 46% of participants receiving maraviroc had complete suppression. In the TITAN study,[21] in which a similar proportion of patients to our study were enrolled with two-class resistance, 60% of individuals treated with combined lopinavir and ritonavir achieved virological suppression compared with 71% given darunavir. In our study, efficacy of elvitegravir for virological suppression in patients with one active background drug at week 48 (78%) was similar to or greater than that reported in individuals with one active background drug treated with raltegravir (67%),[13] etravirine (63%),[19] maraviroc (45%),[18] or either combined lopinavir and ritonavir (57%) or darunavir (80%).[21]

In our study, the proportions of patients with two active background drugs who achieved virological suppression (59%) were lower than in individuals with one active background drug. These proportions are comparable to individuals with two active background drugs treated with combined lopinavir and ritonavir (61%)[21] and maraviroc (58%)[18] but are lower than those for patients treated with raltegravir (77%),[13] etravirine (78%),[19] or darunavir (68%).[21] In the single-arm ANRS TRIO trial,[22] 86% of patients had HIV RNA less than 50 copies per mL at week 48, although these individuals received three new active agents plus a background regimen.

High proportions of voluntary discontinuations—ie, attributable to withdrawal of consent, non-adherence,

Panel: Research in context

Systematic review

We searched PubMed for articles published in English up to July 31, 2011, with the terms "elvitegravir" and "randomized" in the title. Elvitegravir has been assessed in one phase 2 study in treatment-experienced patients.[7] Those findings showed that elvitegravir produced rapid virological suppression that was durable in the presence of active background treatment, and elvitegravir was well tolerated.

Interpretation

We investigated the non-inferiority of elvitegravir versus raltegravir—in combination with a fully active, ritonavir-boosted protease inhibitor and another agent—for treatment of patients in whom previous antiretroviral regimens had failed. Our findings showed non-inferiority overall and across many subsets of patients. Elvitegravir was well tolerated, with very few discontinuations attributable to adverse events. Elvitegravir had a safety profile comparable with raltegravir. Increases in concentrations of liver enzymes were less common with elvitegravir than with raltegravir, but the frequency of diarrhoea was higher. Virological failure rates were similar with both integrase inhibitors, and emergence of resistance for both drugs was lower than in previous trials of raltegravir. Elvitegravir is a new option for treatment-experienced patients failing therapy who are receiving a ritonavir-boosted protease inhibitor, with the advantage of a lower pill burden and once daily dosing.

or loss to follow-up—affected response rates in our study, particularly in the subset of patients with two active background drugs. In the DUET studies,[19] 51 (4%) of 1203 individuals discontinued by week 48; by contrast, in our study, 105 (15%) of 702 patients discontinued before 48 weeks and were counted as failures. The high proportion of discontinuations in our study was accompanied by low adherence, measured by pill counts. Significantly more voluntary discontinuations arose in patients with two active background drugs (92 [16%] of 575) compared with those with one active background drug (seven [7%] of 103; p=0·015). When patients in our study remained on their randomly allocated treatment up to week 48, three-quarters of those assigned elvitegravir achieved virological suppression (per-protocol analysis), which underlines the effect of voluntary discontinuations on modified intention-to-treat response rates.

Our study indicates a shift in the type of treatment-experienced patients in HIV clinical trials. In early studies, individuals with few therapeutic options and, thus, with motivation to adhere to treatment were enrolled. In our study, we noted that significantly more voluntary discontinuations arose in patients with two active background drugs than in those with one active background drug. Furthermore, only a quarter of patients who were tested in our study had integrase-resistance mutations compared with two-thirds of such subjects in the BENCHMRK studies.[13] Moreover, in our study, 23 (19%) of 119 tested patients with two active background drugs compared with seven of 13 (54%) with one active background drug had integrase-resistance mutations (p=0·01). Since elvitegravir or raltegravir must be present in plasma to select integrase resistance, this significant difference indicates that patients with more treatment options who had virological failure were less adherent to study drugs than were those with fewer treatment options. In future trials, stratification by the number of active background drugs should be considered. Clinical studies of drugs for diseases other than HIV infection could be affected by a similar change in behaviour of patients as treatment options increase.

Every individual in our study took active raltegravir twice daily or elvitegravir and a placebo, so the benefit conferred by once daily dosing with elvitegravir was not assessed. However, because it showed non-inferiority to raltegravir in treatment-experienced patients, elvitegravir could be added to a ritonavir-boosted protease inhibitor and a single or combination NRTI to create a once daily regimen (panel). Studies of elvitegravir as one component of a single-tablet regimen in treatment-naive subjects are ongoing.

Contributors

J-MM had full access to the original data, reviewed analyses of data and requested new analyses, edited the report extensively, and approved the final paper. ALM, JA-V, BC, and NC reviewed analyses of data, edited the report, and approved the final manuscript. SLC, AKC, and LZ designed the study protocol. J-MM, ALM, JA-V, BC, and NC enrolled patients. Y-PL and LZ oversaw statistical analyses and generation of tables, figures, and listings. NM analysed resistance data. Y-PL, LZ, NM, AKC, and SLC reviewed analyses of data and requested new analyses, edited the report, and approved the final manuscript. SLC wrote the first draft of the report and provided study supervision.

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Conflicts of interest

J-MM has acted as a consultant, participated in advisory boards, has received speaker fees, and has been an investigator for clinical trials for Tibotec, ViiV Healthcare, Gilead, Bristol-Myers Squibb, Abbott, Boehringer Ingelheim, and Merck, Sharp and Dohme. ALM has been an investigator for Alexion, Astellas, Boehringer Ingelheim, Chembio Diagnostics, GlaxoSmithKline, Gilead, Kowa, Merck, Sharp and Dohme, Napo Pharmaceuticals, Numico, Orasure, Pfizer, Samaritan Pharmaceuticals, Sanofi-Aventis, and Schering Plough. JA-V has received research grants, honoraria, or both for participation in advisory boards, conferences, or both from Boehringer Ingelheim, Bristol-Myers Squibb, Tibotec, Abbott, Merck, Sharp and Dohme, Gilead and ViiV Healthcare. BC has served as a consultant on advisory boards or participated in speakers' bureaus or conducted clinical trials with Boehringer Ingelheim, Abbott, GlaxoSmithKline, Pfizer, Gilead, Janssen, Merck, Sharp and Dohme, Shionogi, and ViiV Healthcare. NC has received speaker fees and has been an investigator for clinical trials for Abbott, Boehringer Ingelheim, Merck, Sharp and Dohme, Roche, GlaxoSmithKline, and Tibotec. Y-PL, LZ, NM, AKC, and SLC are employees of Gilead Sciences.

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