

Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study



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Summary

Background Dolutegravir (S/GSK1349572) is a once-daily HIV integrase inhibitor with potent antiviral activity and a favourable safety profile. We compared dolutegravir with HIV integrase inhibitor raltegravir, as initial treatment for adults with HIV-1.

Methods SPRING-2 is a 96 week, phase 3, randomised, double-blind, active-controlled, non-inferiority study that began on Oct 19, 2010, at 100 sites in Canada, USA, Australia, and Europe. Treatment-naive adults (aged ≥ 18 years) with HIV-1 infection and HIV-1 RNA concentrations of 1000 copies per mL or greater were randomly assigned (1:1) via a computer-generated randomisation sequence to receive either dolutegravir (50 mg once daily) or raltegravir (400 mg twice daily). Study drugs were given with coformulated tenofovir/emtricitabine or abacavir/lamivudine. Randomisation was stratified by screening HIV-1 RNA ($\leq 100\,000$ copies per mL or $>100\,000$ copies per mL) and nucleoside reverse transcriptase inhibitor backbone. Investigators were not masked to HIV-1 RNA results before randomisation. The primary endpoint was the proportion of participants with HIV-1 RNA less than 50 copies per mL at 48 weeks, with a 10% non-inferiority margin. Main secondary endpoints were changes from baseline in CD4 cell counts, incidence and severity of adverse events, changes in laboratory parameters, and genotypic or phenotypic evidence of resistance. Our primary analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01227824.

Findings 411 patients were randomly allocated to receive dolutegravir and 411 to receive raltegravir and received at least one dose of study drug. At 48 weeks, 361 (88%) patients in the dolutegravir group achieved an HIV-1 RNA value of less than 50 copies per mL compared with 351 (85%) in the raltegravir group (adjusted difference 2.5%; 95% CI -2.2 to 7.1). Adverse events were similar between treatment groups. The most common events were nausea (59 [14%] patients in the dolutegravir group vs 53 [13%] in the raltegravir group), headache (51 [12%] vs 48 [12%]), nasopharyngitis (46 [11%] vs 48 [12%]), and diarrhoea (47 [11%] in each group). Few patients had drug-related serious adverse events (three [$<1\%$] vs five [1%]), and few had adverse events leading to discontinuation (ten [2%] vs seven [2%] in each group). CD4 cell counts increased from baseline to week 48 in both treatment groups by a median of 230 cells per μL . Rates of graded laboratory toxic effects were similar. We noted no evidence of treatment-emergent resistance in patients with virological failure on dolutegravir, whereas of the patients with virologic failure who received raltegravir, one (6%) had integrase treatment-emergent resistance and four (21%) had nucleoside reverse transcriptase inhibitors treatment-emergent resistance.

Interpretation The non-inferior efficacy and similar safety profile of dolutegravir compared with raltegravir means that if approved, combination treatment with once-daily dolutegravir and fixed-dose nucleoside reverse transcriptase inhibitors would be an effective new option for treatment of HIV-1 in treatment-naive patients.

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Introduction

For almost two decades, HIV treatment guidelines have recommended use of two nucleoside reverse transcriptase inhibitors (NRTIs) plus a third antiretroviral drug for treatment-naive patients with HIV/AIDS.¹⁻⁴ Recommended drugs for use with NRTIs include non-nucleoside reverse transcriptase inhibitors (eg, efavirenz and rilpivirine), boosted protease inhibitors (eg, darunavir plus ritonavir and atazanavir plus ritonavir), and the latest addition to the HIV

armamentarium, the integrase inhibitors (eg, raltegravir). Integrase inhibitors are a promising new class of antiretroviral drug. The first approved HIV integrase inhibitor raltegravir is effective and well tolerated, but requires twice-daily dosing.^{5,6} Elvitegravir, another HIV integrase inhibitor approved in the USA in August, 2012,⁷ and under review in the European Union, must be taken with food and needs pharmacological boosting, which can lead to clinically important drug-drug interactions.^{8,9}

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Dolutegravir (S/GSK1349572) is a new integrase inhibitor with a 14 h plasma half-life that enables once-daily dosing without pharmacokinetic boosters.^{10,11} No relevant cytochrome P450 enzyme inhibition or induction or food effect has been noted, reducing the potential for interactions.^{10,12} A phase 2 study led to selection of a 50 mg once-daily dose of dolutegravir for phase 3 studies in antiretroviral-naïve patients, on the basis of rates of virological response at 96 weeks being as high as 88% in patients in that dosage group.^{13,14} We therefore undertook this phase 3 study to assess the efficacy and safety of dolutegravir versus raltegravir, in combination with two widely recommended NRTI backbones, as first-line treatment for antiretroviral-naïve adults with HIV-1.

Methods

Study design and patients

On Oct 19, 2010, we started this 96 week phase 3, randomised, double-blind, active-controlled, double-placebo, multicentre, parallel-group, non-inferiority study at 100 sites in the USA, Canada, Europe, and Australia. Eligible participants (aged ≥ 18 years) had a plasma HIV-1 RNA concentration of 1000 copies per mL or greater and no primary resistance in reverse transcriptase or protease enzymes. We included no CD4 entry criteria, but excluded patients with active US Centers for Disease Control and Prevention category C disease, except for Kaposi's sarcoma. We also excluded patients with defined laboratory values or medical characteristics, including pregnancy; moderate or severe hepatic impairment; an anticipated need for hepatitis C treatment during the study; estimated creatinine clearance of less than 50 mL/min; recent or ongoing malignancy; or treatment with an HIV-1 vaccine within 90 days of screening or with any immunomodulator within 28 days. Patients could receive abacavir only after exclusion of the *HLA-B*5701* allele.

Ethics committee approval was obtained at all participating centres in accordance with the principles of the 2008 Declaration of Helsinki. Each patient gave written informed consent before undergoing study procedures.

Randomisation and masking

Patients were randomly assigned (1:1) via a central procedure using phone and web interface to receive either dolutegravir 50 mg once daily or raltegravir 400 mg twice daily. The study statistician generated the randomisation list with GlaxoSmithKline-validated randomisation software (RandAll). At the investigators' discretion, patients received an NRTI backbone of coformulated tenofovir/emtricitabine or abacavir/lamivudine. Patients received placebo tablets matching the alternative study drug. Randomisation was stratified by screening HIV-1 RNA ($\leq 100\,000$ copies per mL or $>100\,000$ copied per mL) and NRTI backbone. Investigators were unmasked to screening HIV-1 RNA results before randomisation. Sponsor

staff were masked to treatment assignment until the week 48 analysis; investigators, site staff, and patients were masked until week 96.

Procedures

The prespecified primary endpoint was the proportion of patients with HIV-1 RNA of less than 50 copies per mL at week 48. Main secondary endpoints were changes from baseline in CD4 cell counts, incidence and severity of adverse events, changes in laboratory parameters, and genotypic or phenotypic evidence of resistance. Other secondary endpoints were dolutegravir pharmacokinetics, pharmacokinetic and pharmacodynamic relations, and health outcomes. We used EQ-5D (EuroQol, Rotterdam, Netherlands), a generic, non-disease-specific, preference-based utility measure that includes a descriptive system and a visual analogue scale, to measure health outcome at baseline and weeks 24, 48, and 96.

Study visits were at baseline, and weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, and every 12 weeks thereafter. Staff assessed treatment compliance by doing pill counts of returned drug containers at each visit. Plasma HIV-1 RNA was measured with the Abbott RealTime HIV-1 PCR assay (Abbott Molecular, Des Plaines, IL, USA). Between weeks 24 and 48, protocol-defined virological failure was defined as two consecutive plasma HIV-1 RNA values of 50 copies per mL or greater. Patients meeting this criterion before week 48 were withdrawn from the study. CD4 cell count and percentage were measured at each study visit (except for week 2) to assess immunological response. Viral genotype (reverse transcriptase and protease) was analysed by Quest Diagnostics (Valencia, CA, USA) at screening. Genotypic and phenotypic analyses (reverse transcriptase and integrase) of plasma samples from day 1, and time of confirmed virological failure for all patients with protocol-defined virological failure, were done with GenoSure, Standard Phenosense, GeneSeq Integrase, and PhenoSense Integrase assays (Monogram Biosciences, San Francisco, CA, USA).

Safety was assessed at all visits and included monitoring and recording of all adverse and serious adverse events; vital signs; laboratory parameters, such as haematology; fasting lipid profile; chemistries; dipstick urinalysis; and urine albumin to creatinine ratio. Adverse events were assessed and graded according to the Division of AIDS toxicity scales. We implemented stopping criteria based on liver chemistry thresholds to assure patient safety and to identify cause of liver inflammation. Staff took pharmacokinetic samples before and after doses during prespecified windows (1–3 h or 4–12 h) at weeks 4, 24, and 48. Dolutegravir concentration was calculated with a validated analytical method based on protein precipitation, followed by high-pressure liquid chromatography and tandem mass spectroscopy (Quest Pharmaceutical Services, Newark, DE, USA).¹⁵ The lower limit of quantification for dolutegravir was 20 ng/mL and the upper limit was 20 000 ng/mL.

Statistical analyses

We concluded non-inferiority of dolutegravir to raltegravir if the lower bound of a two-sided 95% CI for the difference in proportions (dolutegravir minus raltegravir) of patients with plasma HIV-1 RNA less than 50 copies per mL at week 48 was greater than -10%. With an assumed 75% response rate in the raltegravir group, we needed to enrol 394 evaluable patients per group to have 90% power with a 10% non-inferiority margin, and a one-sided 2.5% significance level. The study was not fully powered for secondary or subgroup analyses. We based our efficacy and safety analyses on the intent-to-treat exposed or safety populations, which consisted of all patients randomly assigned to treatment groups who received at least one dose of study drug.

We did the primary analysis by US Food and Drug Administration (FDA) snapshot analysis.^{16,17} In this analysis, we counted patients whose last HIV-1 RNA result was less than 50 copies per mL in the analysis window (ie, 48 weeks, plus or minus 6 weeks) as responders. We counted patients whose HIV-1 RNA was not suppressed or who withdrew or did not have data at the analysis timepoint as non-responders. The protocol allowed one switch in backbone NRTI for management of toxic effects; patients who switched NRTI after week 4 were regarded as non-responders according to the snapshot algorithm. The adjusted difference in proportions was based on a stratified analysis with Cochran-Mantel-Haenszel weights for baseline HIV-1 RNA, and investigator-selected backbone dual NRTIs. We compared antiviral activity over time with summaries of the proportions of responders and summaries of plasma HIV-1 RNA values, presented by treatment group and by visit.

Prespecified secondary efficacy analyses done to support primary endpoint analysis included a per-protocol analysis and Kaplan-Meier estimates of the proportion of patients without virological failure by week 48. The per-protocol population consisted of the intent-to-treat exposed population, except for patients with a protocol deviation that met prespecified criteria, such as non-compliance with the study drug. We used a secondary dataset for time-to-event analyses of failure. We used the Kaplan-Meier method to assess the effect of missing data. As such, patients were censored at the time of study discontinuation. For the treatment-related discontinuation equals failure (TRDF) analysis, we calculated the time to protocol-defined virological failure or discontinuation for treatment-related reasons, such as drug-related adverse events, protocol-defined safety stopping criteria, or lack of efficacy. Patients who had not met criteria for protocol-defined virological failure and were ongoing in the study, or who had discontinued for reasons other than those related to treatment, were censored from the TRDF analysis. We did a similar efficacy-related discontinuation equals failure analysis, based on the time to protocol-defined virological failure or discontinuation because of lack of efficacy.

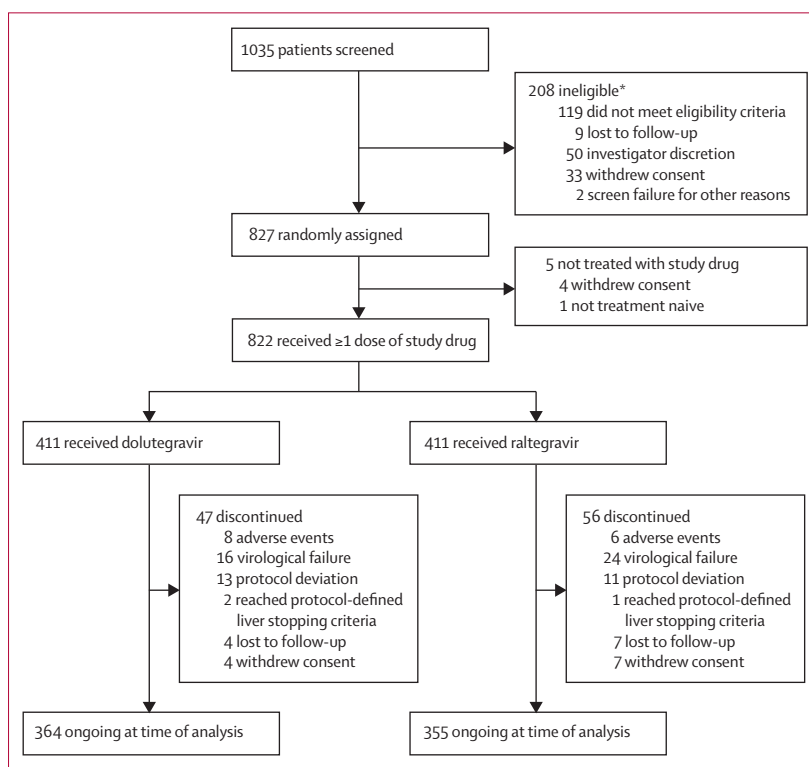


Figure 1: Trial profile

Reason for discontinuation was at the discretion of the investigator. *Number totals more than 208 because several reasons can be selected.

	Dolutegravir (n=411)	Raltegravir (n=411)
Median age (range; years)	37 (18–68)	35 (18–75)
Men	348 (85%)	355 (86%)
Race		
White	346 (84%)	352 (86%)
Black	49 (12%)	39 (9%)
Other	16 (4%)	20 (5%)
Baseline HIV-1 RNA		
Median concentration (log ₁₀ copies per mL)	4.52 (4.08–5.06)	4.58 (4.12–5.07)
>100 000 copies per mL	114 (28%)	116 (28%)
Baseline CD4 cell count		
Median (cells per μL)	359 (276–470)	362 (267–469)
<200 cells per μL	55 (13%)	50 (12%)
Hepatitis co-infection		
Hepatitis B	7 (2%)	8 (2%)
Hepatitis C	41 (10%)	35 (9%)
Hepatitis B and C	1 (<1%)	0
Dual NRTI on day 1		
Tenofovir/emtricitabine	242 (59%)	247 (60%)
Abacavir/lamivudine	169 (41%)	164 (40%)

Data are n (%), or median (IQR), unless otherwise indicated. NRTI=nucleoside reverse transcriptase inhibitor.

Table 1: Baseline demographics and disease characteristics

We compared immunological response over time with summaries of CD4 cell counts and changes from baseline at each visit. We assessed tolerability and long-term safety by analyses of the incidence of adverse and serious adverse events, and graded laboratory toxic effects. To assess the development of viral resistance in patients who had virological failure, we compared the proportions of those with both protocol-defined virological failure and

treatment-emergent genotypic or phenotypic evidence of integrase inhibitor resistance with Cochran-Mantel-Haenszel analysis. We analysed mean change in estimated creatinine clearance with the Cockcroft-Gault formula. For pharmacokinetic analyses, we calculated linear regression with Watson Laboratory Information Management System (version 6.4.0.04). Statistical analyses of pharmacokinetic data were done by Clinical Pharmacology Statistics and Programming (GlaxoSmithKline, NC, USA). Other statistical analyses were done with SAS (version 9.1). This trial is registered with ClinicalTrials.gov, number NCT01227824.

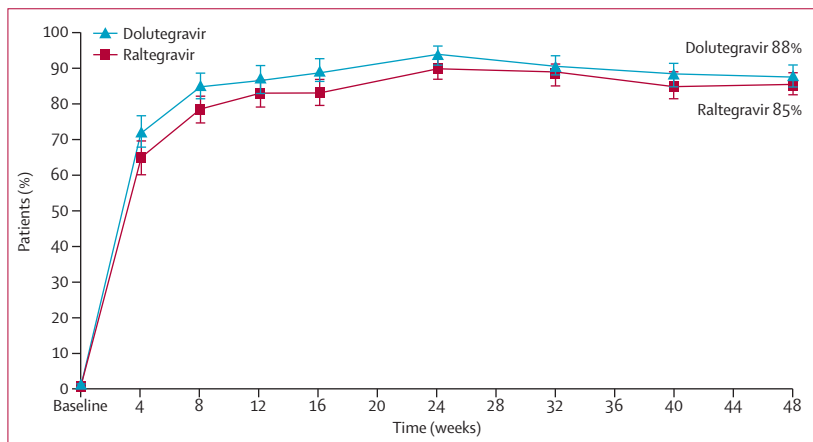


Figure 2: Proportion of patients with HIV-1 RNA less than 50 copies per mL. Error bars show 95% CIs.

Role of funding source

The sponsor participated in the study design, data collection, data analysis, and data interpretation. All authors had full access to all the data in the study and are responsible for the veracity and completeness of the data reported. The corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 822 patients received at least one dose of study drug. Baseline demographics and disease characteristics were similar between treatment groups (table 1). Most patients had HIV subtype B (data not shown). At week 8, 350 (85%) of patients on dolutegravir and 323 (79%) on raltegravir had achieved plasma HIV-1 RNA of less than 50 copies per mL (figure 2). At week 48, 361 (88%) on dolutegravir and 351 (85%) on raltegravir had reached this threshold (figure 2, table 2). The adjusted treatment difference between groups was 2.5% (95% CI -2.2% to 7.1%), which met the non-inferiority criterion. Secondary efficacy analyses (table 3) and virological outcome (table 4) by baseline stratification supported the primary results by showing non-inferiority of dolutegravir. The number of patients who achieved the primary endpoint was similar between subgroups in analyses that combined high and low HIV-1 RNA strata and backbone NRTI (figure 3).

CD4 cell counts increased from baseline to week 48 in both treatment groups by a median of 230 cells per μ L (IQR 128–338 in the dolutegravir group, 139–354 in the raltegravir group). We noted similar rates of virological response across subgroups stratified by baseline CD4 cell counts; however, a more favourable numerical response was shown in patients in the dolutegravir group with baseline CD4 cell counts of less than 350 cells per μ L (171 [86%] of 199 patients given dolutegravir vs 152 [80%] of 189 given raltegravir), or baseline counts of less than 200 cells per μ L (43 [78%] of 55 vs 34 [68%] of 50).

Fewer patients had protocol-defined virological failure in the dolutegravir group than in the raltegravir group and no patient with protocol-defined virological failure who received dolutegravir had treatment-emergent integrase or NRTI resistance (table 5). Notably, one patient in the raltegravir group with baseline plasma

	Dolutegravir (n=411)	Raltegravir (n=411)
Virological success	361 (88%)	351 (85%)
Virologic non-response*	20 (5%)	31 (8%)
Data in window not <50 copies per mL	8 (2%)	5 (1%)
Discontinued for lack of efficacy	5 (1%)	13 (3%)
Discontinued for other reasons while HIV-1 RNA not <50 copies per mL	2 (<1%)	11 (3%)
Change in ART	5 (1%)	2 (<1%)
No virological data at week 48	30 (7%)	29 (7%)
Discontinued because of adverse event or death	9 (2%)	6 (1%)
Discontinued for other reasons†	21 (5%)	23 (6%)

Data are n (%), by US Food and Drug Administration snapshot analysis. ART=antiretroviral therapy. *Virological failure. †Protocol deviation, lost to follow-up, or withdrawal of consent.

Table 2: Patients with plasma HIV-1 RNA less than 50 copies per mL at week 48

	Dolutegravir	Raltegravir	Difference (%)
Per-protocol population	348/387 (90%; 87–93)	342/387 (88%; 85–92)	1.6% (-2.7 to 5.9)
Kaplan-Meier proportion without failure			
Treatment-related discontinuation equals failure* (%)	93.1% (89.8–95.3)	91.8% (88.6–94.1)	1.2% (-2.6 to 5.1)
Efficacy-related discontinuation equals failure† (%)	94.2% (91.1–96.3)	92.7% (89.6–94.9)	1.5% (-2.1 to 5.1)

Data are n/N (%; 95% CI) or % (95% CI). *Protocol-defined virological failure or withdrawal because of drug-related adverse event, safety stopping criteria, or lack of efficacy. †Protocol-defined virological failure or withdrawal because of lack of efficacy.

Table 3: Plasma HIV-1 RNA less than 50 copies per mL at week 48 in per-protocol analysis, and Kaplan-Meier estimates

HIV-1 RNA of more than 3 million copies per mL developed both integrase-resistant and NRTI-resistant mutations; phenotype resistance at virological failure showed a raltegravir fold-change of 34 and a dolutegravir fold-change of 2.02. Two additional patients with no emergent genotypic resistance had increased phenotypic resistance to raltegravir at protocol-defined virological failure (one patient in the dolutegravir group [raltegravir fold-change 2.01, dolutegravir fold-change 0.96]; one in the raltegravir group [1.62, 1.40]).

Over 48 weeks, both study drugs had similar safety profiles, with similar rates of adverse events of all grades in both groups (appendix) and low rates of adverse events leading to discontinuation (10 [2%] patients in the dolutegravir group vs 7 [2%] in the raltegravir group). The most frequently reported clinical adverse events were nausea (59 [14%] vs 53 [13%]), headache (51 [12%] vs 48 [12%]), nasopharyngitis (46 [11%] vs 48 [12%]), and diarrhoea (47 [11%] in each group; appendix), with most events recorded as grade 1 or grade 2. Rates of serious adverse events were similar between treatment groups (appendix). Two patients died (one homicide in the dolutegravir group and one suicide in the raltegravir group); both deaths were unrelated to the study drug. For serious adverse events, irrespective of causality, only pneumonia and convulsion were reported by more than one patient (appendix). Few patients had drug-related serious adverse events (three [$<1\%$] dolutegravir, five [1%] raltegravir; appendix).

Rates of graded laboratory toxic effects were similar between treatment groups. We noted no clinically significant changes over time in the fasting lipid profile in either group (data not shown). Increases in serum creatinine were evident in both groups by week 2, but remained stable to week 48 (figure 4). Ten patients in the dolutegravir group and seven in the raltegravir group had treatment-emergent grade 1 toxic effects of creatinine, and one in the dolutegravir group had a grade 2 effect. Mean change in estimated creatinine clearance at week 48 was -16.5 mL/min (SD 14.17) in the dolutegravir group and -5.4 mL/min (13.88) in the raltegravir group. We noted no difference between groups in median change from baseline in urine albumin-to-creatinine ratio (0.00 mg/mmol [IQR -0.30 to 0.20] in the dolutegravir group vs 0.00 mg/mmol [-0.20 to 0.20] in the raltegravir group). No patients had grade 3 or 4 increases in creatinine and none in either group discontinued because of renal events in the 48 weeks.

Similar numbers of patients in each treatment group had maximum treatment-emergent increases in alanine aminotransferase of at least three times greater than the upper limit of normal (appendix). Two patients in each group had increases at least five times, but less than ten times, greater than the upper limit of normal and met liver stopping criteria, with one patient having possible dolutegravir-associated drug-induced liver injury (DILI) with hypersensitivity reaction, and another with possible

	Dolutegravir (n=411)	Raltegravir (n=411)	Difference (%; 95% CI)
Baseline plasma HIV-1 RNA			
$\leq 100\,000$ copies per mL	267/297 (90%; 86–93)	264/295 (89%; 86–93)	0.4% (–4.5 to 5.3)
$>100\,000$ copies per mL	94/114 (82%; 75–89)	87/116 (75%; 67–83)	7.5% (–3.1 to 18.0)
p value*	0.236*
Backbone dual NRTI†			
Abacavir/lamivudine	145/169 (86%; 81–91)	142/164 (87%; 81–92)	–0.8% (–8.2 to 6.6)
Tenofovir/emtricitabine	216/242 (89%; 85–93)	209/247 (85%; 80–89)	4.6% (–1.3 to 10.6)
p value*	0.264*

Treatment differences by baseline stratification. Data are n/N (%; 95% CI), unless otherwise indicated. NRTI=nucleoside reverse transcriptase inhibitor. *Unadjusted difference in proportion, p value for homogeneity. †NRTI group based on first treatment assignment.

Table 4: Plasma HIV-1 RNA less than 50 copies per mL at week 48

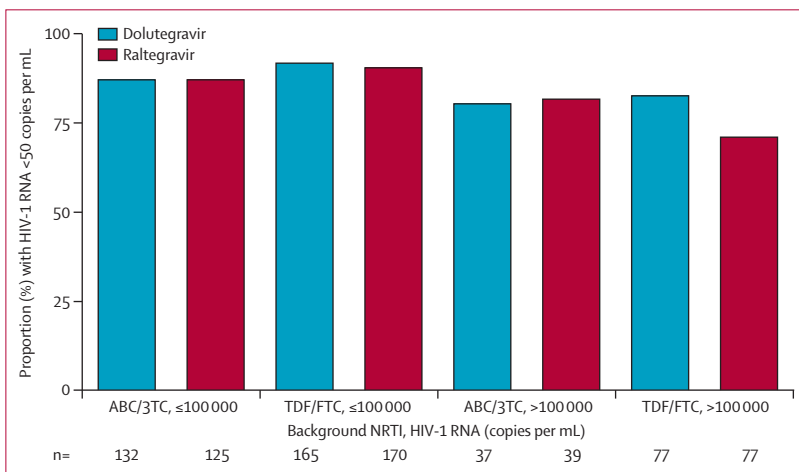


Figure 3: Treatment response by background NRTI and HIV-1 RNA
ABC/3TC=abacavir/lamivudine. TDF/FTC=tenofovir/emtricitabine. NRTI=nucleoside reverse transcriptase inhibitor.

	Dolutegravir (n=411)	Raltegravir (n=411)
PDVF	20 (5%)	28 (7%)
Integrase genotypic results at baseline and time of PDVF	8 (40%)	18 (64%)
Resistance mutations to integrase inhibitor	0	1 (6%)*
Reverse transcriptase genotypic results at baseline and time of PDVF	12 (60%)	19 (68%)
Resistance mutations to NRTI resistance	0	4 (21%)*†

Data are n (%). PDVF=protocol-defined virological failure. NRTI=nucleoside reverse transcriptase inhibitor. *Patient had integrase mutations T97T/A, E138E/D, V151V/I, and N155H and NRTI mutations A62A/V, K65K/R, K70K/E, and M184V. †One had mutation M184M/I; one had mutation A62A/V; and one had mutation M184M/V.

Table 5: Genotypic analysis at PDVF

raltegravir-associated DILI and rash.¹⁸ Seven additional patients (five in the dolutegravir group and two in the raltegravir group) met liver stopping criteria with alanine aminotransferase values of ten or more times greater than the upper limit of normal. In the dolutegravir group, these events were two acute hepatitis C virus infections, one hepatitis B virus immune reconstitution inflammatory syndrome, one possible DILI, and one antibiotic

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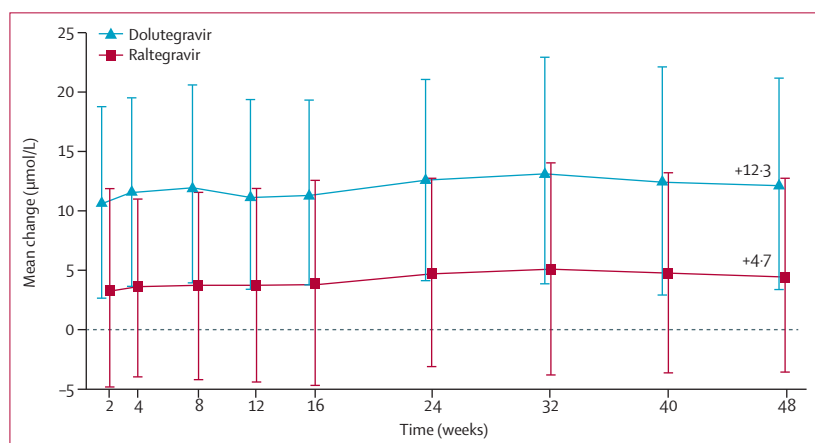


Figure 4: Mean change from baseline in serum creatinine. Error bars show SD.

toxic effect in a patient with chronic hepatitis C. In the raltegravir group, the events were one possible DILI and one acute hepatitis C infection.

Observed dolutegravir predose concentrations were similar at every visit (appendix), with the average predose concentration roughly 18 times the in-vitro protein-adjusted 90% inhibitory concentration (0.064 µg/mL). We noted no association between dolutegravir exposure and virological response, common adverse events, changes in alanine aminotransferase, or change from baseline at week 48 for total bilirubin. However, a significant ($p < 0.001$) correlation was shown between average predose concentrations of dolutegravir and maximum change in total bilirubin. Additionally, correlations were significant between average predose concentrations of dolutegravir and both change from baseline at week 48 and maximum change for creatinine ($p = 0.003$ and $p = 0.012$, respectively) and creatinine clearance ($p < 0.001$ and $p = 0.004$, respectively). Similar improvements from baseline in health outcome scores occurred in both groups (data not shown).

Discussion

SPRING-2 is the first head-to-head, double-blind comparison of efficacy and safety of two integrase inhibitor-based regimens for first-line antiretroviral therapy. At 48 weeks, once-daily dolutegravir 50 mg was non-inferior to twice-daily raltegravir 400 mg, both in combination with coformulated tenofovir/emtricitabine or abacavir/lamivudine, with 88% of patients in the dolutegravir group and 85% of those in the raltegravir group achieving plasma HIV-1 RNA concentrations of less than 50 copies per mL. This finding was supported by secondary efficacy and safety analyses, which showed similar numbers and types of safety events in both groups (panel). This study was well powered and undertaken, as shown by the low proportion of patients with protocol deviations and who were lost to follow-up. In addition to a high response rate, our results are well within the margin

of non-inferiority.¹⁹ The week 48 response rates for patients in our study who received either study drug in combination with backbone NRTI treatment are consistent with those shown for twice-daily raltegravir 400 mg in a previous study²⁰ of treatment-naïve adults with HIV-1.

Although we examined all patients with protocol-defined virological failure irrespective of HIV-1 RNA value at failure, we did not detect antiviral resistance to integrase inhibitors or the NRTI backbone in those on dolutegravir; by contrast, we detected both in some patients on raltegravir. These data are consistent with findings from a study of in-vitro passage,²¹ which showed that resistance was difficult to select for, and that single mutations in the integrase gene were associated with low-level resistance to dolutegravir. Long-term data from the phase 2b SPRING-1 study are also supportive because no patients who received dolutegravir had protocol-defined virological failure or resistance to integrase inhibitors after 96 weeks.^{13,14} Patients in the dolutegravir group of our study who had protocol-defined virological failure tended to have lower HIV-1 RNA concentrations at failure than did those receiving raltegravir, which could affect both the ability of resistance testing to detect clinically relevant genotypic or phenotypic changes, and the emergence of antiviral resistance.

The tolerability and long-term safety of both study drugs were similar in type and incidence. Importantly, changes in key laboratory measures, such as liver chemistries, occurred at similar rates in both groups. Patients who received abacavir had no cardiac complications. This finding supports the conclusions of a meta-analysis²² of abacavir use, which showed no increased risk of cardiovascular complications. However, findings from the D:A:D cohort study²³ suggest a link between abacavir exposure and increased risk of myocardial infarction. An increase in alanine aminotransferase of at least three times greater than the upper limit of normal is associated with a risk of DILI;¹⁸ such increases were noted in 13 patients on dolutegravir and 17 on raltegravir in our study. In most of these patients in our study we identified alternative causes for increases in alanine aminotransferase. Two patients in each treatment group had significant increases in alanine aminotransferase, which were potentially related to study drug. Based on this study, the overall risk of DILI was similar for both study drugs.

Changes in serum creatinine for dolutegravir were consistent with previous findings and not regarded as clinically significant.^{13,14} Dolutegravir inhibits the organic cation transporter OCT2, similar to other drugs such as trimethoprim or cimetidine,^{24,25} which decrease tubular secretion of creatinine and therefore increase concentrations of serum creatinine without affecting glomerular filtration.^{26,27} In a study²⁶ of healthy volunteers, dolutegravir 50 mg once daily and twice daily did not affect glomerular filtration, as shown by the absence of effect on iothexol clearance. In this study, small increases in serum creatinine and small reductions in creatinine

Panel: Research in context**Systematic review**

We searched Pubmed with the keywords “integrase strand transfer inhibitors”, “integrase inhibitors”, and “clinical trials” for papers published in English between Jan 1, 2006, and Aug 31, 2012. Recommendations from the International Antiviral Society–USA emphasise that initial antiretroviral regimens should be individualised according to results of resistance testing and predicted virological efficacy, toxic effects and tolerability, and convenience. Initial treatment is based on fixed-dose combinations of two nucleoside reverse transcriptase inhibitors, tenofovir/emtricitabine or abacavir/lamivudine, and a potent third drug, either a non-nucleoside reverse transcriptase inhibitor, a ritonavir-boosted protease inhibitor, or an integrase strand transfer inhibitor. Although both approved integrase strand transfer inhibitors, raltegravir and elvitegravir, have shown non-inferiority in terms of efficacy and better CNS and psychiatric tolerability compared with the preferred first-line non-nucleoside reverse transcriptase inhibitor efavirenz,^{17,20} no comparison has been done between different integrase strand transfer inhibitors in treatment-naïve patients. Furthermore, raltegravir has restricted convenience for twice-daily dosing, and elvitegravir requires pharmacological boosting and administration with food. Findings from the SPRING-1 study¹⁴ of once-daily

dolutegravir in combination with either tenofovir/emtricitabine or abacavir/lamivudine led to selection of the dolutegravir 50 mg once-daily dose for phase 3 trials.

Interpretation

We report the first phase 3 study comparing dolutegravir and raltegravir, in combination with tenofovir/emtricitabine or abacavir/lamivudine, for first-line antiretroviral treatment. The proportion of patients with virological success at week 48 in our study was high and did not differ significantly between raltegravir and dolutegravir and was similar across subgroups and different secondary analyses. Both regimens were well tolerated with a very low rate of discontinuations due to adverse events. Importantly, no treatment-emergent primary integrase or reverse-transcriptase resistance mutations were noted in patients receiving dolutegravir who had protocol-defined virological failure, but this finding was a secondary endpoint. Taken together, the results of this study suggest that dolutegravir 50 mg once daily, in combination with either tenofovir/emtricitabine or abacavir/lamivudine, is well tolerated and highly effective as initial treatment for treatment of adults with HIV infection, and is an alternative to a twice-daily raltegravir regimen.

clearance were noted early in treatment with dolutegravir (weeks 2–4) and then remained stable to week 48. No patients had grade 3 or 4 creatinine elevations, and no patients in either group discontinued the study because of a renal adverse event.

Pharmacokinetic analysis showed no association between exposure to dolutegravir and key pharmacodynamic endpoints. The probable cause for the statistically significant but small association of dolutegravir exposure to total bilirubin in our study is competitive use of the same metabolic enzyme (UGT1A1) by dolutegravir and unconjugated bilirubin.^{28,29} Similar increases in total bilirubin were noted in patients on raltegravir, which has a similar metabolic route (UGT1A1) as dolutegravir and unconjugated bilirubin.³⁰ The weak relation between dolutegravir exposure and bilirubin is probably not associated with increased risk for liver injury with dolutegravir, nor was it associated with reported jaundice. The weak correlation between dolutegravir exposure and change from baseline in serum creatinine and creatinine clearance could be a consequence of the dose–response relation between dolutegravir exposures and pharmacological inhibition of the OCT2 receptor in the renal tubules.

A limitation of this study is the low number of non-white and female patients enrolled, which is not fully representative of the HIV global epidemic. As in all phase 3 studies, the results reported apply to the population that was studied. Future studies should assess the efficacy and

safety in patients excluded from this study, and then more generally in a diverse (ie, resource-limited) health-care setting. With this aim, additional phase 3 studies with dolutegravir in treatment-experienced (ClinicalTrials.gov, number NCT01231516) and treatment-naïve patients are ongoing and have enrolled higher proportions of non-white and female participants.³¹ Trends in treatment (based on cohort studies and guidelines) to start antiretroviral therapy for all adults with HIV infection at high CD4 cell counts and thus early in the course of disease are shown in this study population. Although few patients had advanced immunosuppression in our study, an exploratory analysis showed a higher response rate for dolutegravir than for raltegravir in patients with low CD4 cell counts. Another limitation was that we could not assess the possible advantage of dolutegravir as a once-daily drug because of the double-blind, double-dummy design of the trial. Because the primary, prespecified week 48 results showed non-inferiority and no safety differences, there is little incentive for patient or investigator behaviour change between weeks 48 and 96.

On the basis of our findings, dolutegravir is expected to be an appealing treatment option for treatment-naïve patients with HIV.

Contributors

SA, DM, and SM designed the study in consultation with scientists from GlaxoSmithKline, ViiV Healthcare, and Shionogi. The SPRING-2 investigators enrolled patients in the study and were involved in the acquisition of the data, and FR, AR, H-JS, WDH, CT, CO, MB, DP, VP,

and FP collected and analysed data. DM, CB, and SM contributed to protocol concept and design, data analysis, and clinical oversight of the study. SA provided statistical expertise, input into protocol concept and design, and data analysis. All authors participated in data interpretation. The report was drafted by FR, SA, DM, CB, and SM. All authors have provided input to the report and approved the final version.

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Conflicts of interest

AR has received honoraria for participation as a consultant, member of advisory boards, and provision of continuing education, and has been an investigator in clinical trials for Bristol-Myers Squibb, Merck, Gilead Science, ViiV Healthcare, Pfizer, Abbott Labs, and Janssen. CB, DM, SA, and SM are employees of GlaxoSmithKline and hold stock in the company. CO has received honoraria and travel grants and research funding from Abbott Labs, Merck, Boehringer Ingelheim, ViiV Healthcare, Pfizer, GlaxoSmithKline (GSK), Bristol-Myers Squibb, Janssen, Tibotec, Astellas, and Gilead Sciences. CT has received financial support for participation in a scientific meeting; honoraria for speaking at scientific meetings and workshops from several pharmaceutical companies that produce antiretroviral drugs, including ViiV Healthcare, Bristol-Myers Squibb, Gilead Sciences, and Abbott Labs; and funding for undertaking researches from Gilead Sciences and Bristol-Myers Squibb. However, these potential conflicts did not affect the given contributions to this article. DP has received research grants or honoraria for advisories or conferences from Boehringer Ingelheim, GSK, Vii, Pfizer, Bristol-Myers Squibb, Abbott Labs, Gilead Sciences, Janssen, and Merck. FP has received consulting and lecture fees from Abbott Labs, Bristol-Myers Squibb, Gilead Sciences, GSK, Janssen, and ViiV Healthcare. FR has received research support from Gilead Sciences, Merck Laboratories, and Tibotec and consulting fees from Abbott Labs, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen-Cilag, Merck, Roche, Schering-Plough, ViiV Healthcare, Theratechnologies, and Avexa. HJS is a member of advisory boards for ViiV Healthcare, Abbott Labs, Gilead Sciences, Janssen-Cilag, Boehringer Ingelheim, and Bristol-Myers Squibb, and has received honoraria for scientific presentation by the above-mentioned companies and payment for expert testimony by Bristol-Myers Squibb; travel grants were provided at some point in the last 3 years by each of those companies, mostly for participation in company-sponsored symposia. MB has participated on advisory boards for ViiV Healthcare, Gilead Sciences, Merck, Abbott, Boehringer-Ingelheim, Eli Lilly, and Bristol-Myers Squibb, and has received research funding from ViiV Healthcare, Gilead Sciences, Merck, Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Novartis, Baxter Healthcare, and Janssen, and support for travel to attend scientific meetings from ViiV Healthcare, Merck, Gilead Sciences, Janssen, and Bristol-Myers Squibb. VP declares that he has no conflicts of interest. WDH has been a clinical trial investigator (via contracts between his employer, Cedars-Sinai and sponsors) and has received honoraria for participation as a consultant and advisory board member from Bionor Pharma, Gilead, ViiV/GSK, ViiV/Pfizer, and Vertex; he owns less than US\$5000 of Merck stock.

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