Coformulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380–1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial

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Summary

Background Integrase strand transfer inhibitors (INSTIs) coadministered with two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) are recommended as first-line treatment for HIV, and coformulated fixed-dose combinations are preferred to facilitate adherence. We report 48-week results from a study comparing initial HIV-1 treatment with bictegravir—a novel INSTI with a high in-vitro barrier to resistance and low potential as a perpetrator or victim of clinically relevant drug interactions—coformulated with the NRTI combination emtricitabine and tenofovir alafenamide as a fixed-dose combination to dolutegravir administered with coformulated emtricitabine and tenofovir alafenamide.

Methods In this randomised, double-blind, multicentre, placebo-controlled, non-inferiority trial, HIV-infected adults were screened and enrolled at 126 outpatient centres in 10 countries in Australia, Europe, Latin America, and North America. Participants were previously untreated adults (HIV-1 RNA ≥500 copies per mL) with estimated glomerular filtration rate of at least 30 mL/min. Chronic hepatitis B virus or hepatitis C co-infection was allowed. We randomly assigned participants (1:1) to receive oral fixed-dose combination bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg or dolutegravir 50 mg with coformulated emtricitabine 200 mg and tenofovir alafenamide 25 mg, with matching placebo, once a day for 144 weeks. Investigators, participants, study staff, and those assessing outcomes were masked to treatment group. All participants who received at least one dose of study drug were included in primary efficacy and safety analyses. The primary endpoint was the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 (US Food and Drug Administration snapshot algorithm), with a prespecified non-inferiority margin of –12%. This study is registered with ClinicalTrials.gov, number NCT02607956.

Findings Between Nov 11, 2015, and July 15, 2016, 742 participants were screened for eligibility, of whom 657 were randomly assigned to treatment (327 with bictegravir, emtricitabine, and tenofovir alafenamide fixed-dose combination [bictegravir group] and 330 with dolutegravir plus emtricitabine and tenofovir alafenamide [dolutegravir group]). 320 participants who received the bictegravir regimen and 325 participants who received the dolutegravir regimen were included in the primary efficacy analyses. At week 48, HIV-1 RNA <50 copies per mL was achieved in 286 (89%) of 320 participants in the bictegravir group and 302 (93%) of 325 in the dolutegravir group (difference –3·5%, 95·002% CI –7·9 to 1·0, p=0·12), showing non-inferiority of the bictegravir regimen to the dolutegravir regimen. No treatment-emergent resistance to any study drug was observed. Incidence and severity of adverse events were similar between groups, and few participants discontinued treatment due to adverse events (5 [2%] of 320 in the bictegravir group and 1 [<1%] 325 in the dolutegravir group). Study drug-related adverse events were less common in the bictegravir group than in the dolutegravir group (57 [18%] of 320 *vs* 83 [26%] of 325, p=0·022).

Interpretation At 48 weeks, virological suppression with the bictegravir regimen was achieved and was non-inferior to the dolutegravir regimen in previously untreated adults. There was no emergent resistance to either regimen. The fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide was safe and well tolerated compared with the dolutegravir regimen.

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Introduction

Treatment guidelines for initial therapy of HIV-1 infection recommend two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) plus a third active agent from a different drug class—a non-nucleoside reverse transcriptase inhibitor (NNRTI), a protease inhibitor, or an integrase strand transfer inhibitor (INSTI).[1–3] Since 2014, INSTIs have emerged as the preferred choice in treatment

Research in context

Evidence before this study

Since the approval of the first integrase strand transfer inhibitor (INSTI) in 2007, this drug class is now widely recommended as first-line treatment for HIV when coadministered with two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs). This regimen is increasingly becoming the standard of care for HIV treatment and these combinations are now recommended in all major treatment guidelines. Currently approved INSTIs include dolutegravir, elvitegravir, and raltegravir. Bictegravir is a novel, potent INSTI with high in-vitro activity against most INSTI-resistant viruses and low potential to perpetrate drug interactions, although it can be a victim of potent CYP3A4 inducers. Bictegravir has shown high rates of virological suppression similar to dolutegravir plus emtricitabine and tenofovir alafenamide in a phase 2 study in adults with HIV infection.

We searched PubMed for randomised trials of INSTIs in HIV-infected individuals. We used title search terms of "bictegravir", "GS-9883", "dolutegravir", "elvitegravir", or "raltegravir" with "randomised" or "randomized". Searches were limited to articles published in English between Jan 1, 1997, and July 10, 2017. Our search yielded one article for bictegravir or GS-9883, summarising results from the aforementioned phase 2 study comparing bictegravir with dolutegravir, each given with the recommended NRTI combination of emtricitabine and tenofovir alafenamide in previously untreated adults with HIV infection. We selected 11 articles for dolutegravir for further review. One article summarised results from a phase 2b study of various doses of dolutegravir versus efavirenz, confirming the dolutegravir dose used for phase 3 trials. These remaining studies compared regimens containing dolutegravir with those containing raltegravir and regimens containing dolutegravir to those containing darunavir plus ritonavir, atazanavir plus ritonavir, or efavirenz, as well as antiviral activity of dolutegravir in INSTI-resistant populations. We reviewed 16 articles for elvitegravir. One article summarised results from a phase 2b study of various doses of elvitegravir, confirming the dose used for phase 3 trials. Of the remaining 15 trials, 12 showed non-inferiority at weeks 48, 96, or 144 of the fixed-dose combination of elvitegravir, cobicistat, emtricitabine, and tenofovir disproxil fumarate compared with regimens containing ritonavir-boosted atazanavir or protease inhibitors, regimens containing non-nucleoside reverse transcriptase inhibitors, and coformulated efavirenz, emtricitabine, and tenofovir. The last four articles provided results from comparison of the tenofovir disoproxil fumarate versus tenofovir alafenamide, each coformulated with elvitegravir, cobicistat, and emtricitabine, which was non-inferior to the tenofovir disoproxil fumarate regimen and showed improved renal and bone safety. Treatment with elvitegravir was well tolerated.

In the 16 raltegravir articles reviewed, non-inferiority of raltegravir to enfuvirtide-based, efavirenz-based, or nucleoside-based regimens was confirmed. However, non-inferiority of raltegravir to lopinavir-ritonavir was not established.

Added value of this study

In this study, bictegravir was coformulated with emtricitabine and tenofovir alafenamide as a fixed-dose combination. This NRTI combination is recognised for its potency and safety advantages, particularly with respect to bone and renal measures as compared with emtricitabine and tenofovir disoproxil fumarate. It does not require *HLA-B*5701* testing before treatment, does not trigger hypersensitivity reactions, does not have any suspected association with cardiovascular events, can be used in patients with moderate to severe renal impairment, and is recommended for treatment in patients who are co-infected with HIV and hepatitis B virus. This is one of the first phase 3 clinical trials comparing the fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide with dolutegravir plus emtricitabine and tenofovir alafenamide, providing a direct comparison of bictegravir and dolutegravir by which to assess its potential for use as a coformulated one pill, once a day, integrase-containing option for HIV treatment.

Implications of all the available evidence

Results from this study showed non-inferiority of bictegravir, emtricitabine, and tenofovir alafenamide fixed-dose combination versus dolutegravir plus emtricitabine and tenofovir alafenamide. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide is a once a day, potent, unboosted INSTI-based regimen that is expected to have virological activity similar to dolutegravir administered with two NRTIs and has a low likelihood of inducing resistance.

guidelines based on their favorable efficacy and safety profile compared with the other drug classes.[4–7] Each of the currently approved INSTIs—dolutegravir, elvitegravir, and raltegravir—is listed as a recommended component of initial regimens in most treatment guidelines. Additionally, emtricitabine–tenofovir alafenamide was added to treatment guidelines in 2016 as a recommended NRTI combination for INSTI-based and protease inhibitor-based regimens given equivalent virological efficacy and favourable effects on bone and renal health compared with tenofovir disoproxil fumarate-containing treatments.[1–3]

Bictegravir is a novel INSTI with potent antiviral activity,[8] dosing once a day without the requirement for pharmacokinetic boosting, a high genetic barrier to resistance and low potential for drug–drug interactions.[9] In a phase 2, double-blind, randomised controlled trial, previously untreated patients with HIV-1 infection were randomly assigned to receive bictegravir or dolutegravir, along with the NRTI combination of emtricitabine and tenofovir alafenamide. At 48 weeks, 97% of the bictegravir-treated patients and 91% of the dolutegravir-treated patients had HIV RNA of less than 50 copies

per mL, and no individual developed treatment-emergent resistance to any study drug.[10]

Subsequently, bictegravir has been coformulated into a fixed-dose combination with emtricitabine and tenofovir alafenamide for dosing once a day. On the basis of the promising results of the phase 2 study, we completed this randomised, blinded, non-inferiority trial comparing the fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide with dolutegravir plus emtricitabine and tenofovir alafenamide as initial treatment for HIV infection.

Methods

Study design and participants

GS-US-380–1490 is a randomised, double-blind, multicentre, active-controlled, non-inferiority phase 3 trial, which was done at 126 outpatient centres in 10 countries (Australia, Belgium, France, Germany, Italy, Spain, the UK, Dominican Republic, the USA, and Canada). Study investigators enrolled adults (aged ≥18 years) with HIV-1 infection who were previously untreated, with plasma HIV-1 RNA levels of at least 500 copies per mL, with estimated glomerular filtration rate (eGFR) of at least 30 mL per min (calculated by the Cockcroft–Gault equation), and with virological resistance testing showing sensitivity to emtricitabine and tenofovir. We did not do resistance testing of the viral integrase gene at screening. Participants with chronic hepatitis B virus or hepatitis C virus infection and previous antiretroviral use for pre-exposure or post-exposure HIV prophylaxis were permitted to enter the study. This trial was done in accordance with the Declaration of Helsinki and approved by central or site-specific review boards or ethics committees. All participants gave written informed consent.

Randomisation and masking

We randomly assigned participants (1:1) to receive either fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide or dolutegravir in combination with coformulated emtricitabine and tenofovir alafenamide. Both regimens were given without regard to food. Participants also received placebo tablets matching the shape, colour, and debossing of the alternative treatment; thus, investigators, participants, and study staff giving treatment, assessing outcomes, and obtaining data were masked to treatment group. A computer-generated allocation sequence (block size 4) was created by Bracket (San Francisco, CA, USA), and randomisation was stratified by HIV-1 RNA (≤100 000 copies per mL, >100 000 to ≤400 000 copies per mL, or >400 000 copies per mL), CD4 count (<50 cells per μL, 50 to 199 cells per μL, or ≥200 cells per μL), and region (USA or outside the USA) at screening. Study investigators identified eligibility of the participant, obtained a participant number, and received automated treatment assignment based on a randomisation sequence.

Procedures

Patients received oral fixed-dose combination of either bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg; bictegravir regimen) or dolutegravir (50 mg) in combination with coformulated emtricitabine (200 mg) and tenofovir alafenamide (25 mg; dolutegravir regimen) once a day. We obtained data from study visits at weeks 4, 8, 12, 24, 36, and 48 after baseline, after which time participants continued masked, double-blinded treatment with visits every 12 weeks until week 144. Laboratory tests included haematological analysis, serum chemistry tests, fasting lipid parameters, CD4 counts, renal laboratory parameters (serum creatinine, eGFR; Covance Laboratories, Indianapolis, IN, USA), and measurement of HIV-1 RNA concentration (Roche TaqMan 2.0; Roche Diagnostics, Rotkreuz, Switzerland). Protocol-defined resistance testing consisted of genotyping and phenotyping of integrase, protease, and reverse transcriptase (Monogram Biosciences, South San Francisco, CA, USA) for any participant who had an HIV-1 RNA of at least 50 copies per mL with a confirmed HIV-1 RNA of at least 200 copies per mL or who had an HIV-1 RNA of at least 200 copies per mL at week 48 or at the last visit on study drug. Those with HIV-1 RNA of at least 50 copies per mL were allowed to continue unless they developed resistance to a component of their study medication.

Safety was assessed by physical examinations, laboratory tests, 12-lead electrocardiogram, concomitant drugs, and recording of adverse events, which were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.1). The pharmacokinetics of bictegravir, emtricitabine, and tenofovir alafenamide were assessed through an intensive pharmacokinetic substudy done on a non-randomised subset of participants. Plasma drug concentrations were determined using fully validated high performance liquid chromatography tandem mass spectroscopy bioanalytical methods. Assessment of whether adverse events were related to the masked study drugs was indicated by the investigator in a binary manner (yes or no).

Outcomes

The primary outcome was the proportion of participants who had plasma HIV-1 RNA of less than 50 copies per mL at week 48 as defined by the US Food and Drug Administration (FDA) snapshot algorithm.[11] Additional prespecified efficacy endpoints included virological efficacy by age (<50 *vs* ≥50 years), sex (male *vs* female), race (black *vs* non-black), baseline HIV-1 RNA (≤100 000 copies per mL *vs* >100 000 copies per mL), baseline CD4 count (<200 *vs* ≥200 cells per mL), geographical region (USA *vs* outside the USA), and study medication adherence (<95% *vs* ≥95%); the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 when imputing missing data as failure (M = F) and missing as excluded (M = E) and changes in $\log_{10}$ HIV-1 RNA and CD4 count from baseline at week 48.

Safety outcomes were assessed by changes from baseline in fasting glucose, lipid panels, serum creatinine, and eGFR at week 48.

Statistical analysis

We analysed the primary endpoint on all participants who were randomly assigned to treatment and had received at least one dose of the study drug, regardless of whether they returned for post-baseline assessments after enrolled participants had completed their week 48 study visit or had prematurely discontinued the study drug. We analysed the primary assessment of non-inferiority with 95% CI for the difference in virological response rates (bictegravir group–dolutegravir group) with a prespecified non-inferiority margin of –12%, for which the choice of non-inferiority margin was based on published US FDA regulatory guidance.[12] Assuming a response rate of 91% at week 48 in both treatment groups, a sample size of 600 participants would achieve at least 95% power to detect non-inferiority at a one-sided α of 0·025. We did two planned independent data monitoring committee interim analyses after about the first 50% of enrolled participants had completed their week 12 study visit or had prematurely discontinued study drugs, and when all participants completed their week 24 study visit or had prematurely discontinued study drugs. Both independent data monitoring committee interim analyses concluded that efficacy and safety findings warranted continuation of the trial. An α penalty of 0·00001 was applied for each planned interim analysis. Therefore, the significance level for the two-sided non-inferiority test at week 48 was 0·04998, corresponding to an actual 95·002% CI. We constructed the baseline stratum-weighted difference in the response rate and its 95% CI based on Mantel Haenszel proportion adjusted by baseline HIV-1 RNA stratum (≤100 000 or >100 000 copies per mL) and region stratum (USA or outside the USA). In the FDA snapshot analysis, participants were classified in one of three outcomes: HIV-1 RNA of less than 50 copies per mL[11] at week 48 (between days 295 and 378, inclusive); HIV-1 RNA of at least 50 copies per mL, including participants who had HIV-1 RNA ≥50 copies per mL at week 48, participants who discontinued study drug before week 48 because of lack of efficacy, or participants who discontinued study drug for reasons other than lack of efficacy, adverse event, or death before week 48 with a final HIV-1 RNA of at least 50 copies per mL; or no virological data in the week 48 window, including participants who discontinued study drug before week 48 because of adverse events or death, participants who discontinued study drug for reasons other than lack of efficacy, adverse events, or death before week 48 with last available HIV-1 RNA of less than 50 copies per mL, and participants still taking study drug with missing HIV-1 RNA data at week 48. We calculated the p value and the difference in response rates of the snapshot analysis on the basis of the dichotomised response (HIV-1 RNA <50 copies per mL at week 48 *vs* HIV-1 RNA ≥50 copies per mL and no virologic data at week 48 window). Additionally, we analysed subgroups of the primary endpoint on the basis of age, sex, race, baseline HIV-1 RNA, baseline CD4 count, geographical region, and study medication adherence. We categorised study drug adherence as the number of pills taken divided by the number of pills prescribed, in which the number of pills taken was the number of pills dispensed minus the number of pills returned. We also analysed the primary efficacy endpoint using a prespecified per-protocol analysis set. The per-protocol analysis excluded participants in the full analysis set who were off study drug at week 48 or had low adherence (ie, adherence at or below the 2·5th percentile of those in the study). Consistent with the International Council for Harmonisation Guidance,[13] the primary efficacy endpoint was also analysed using a post-hoc, modified snapshot analysis that excluded participants in the full

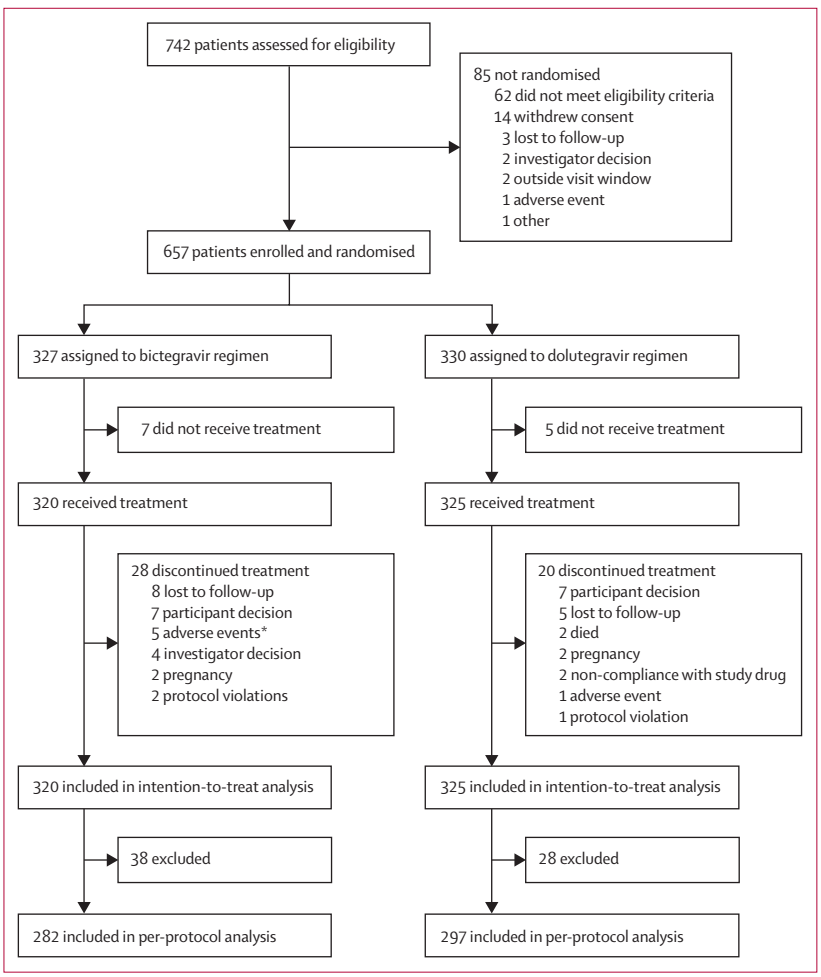

Figure 1: **Trial profile**
No participants discontinued treatment due to reasons related to efficacy. *One participant who discontinued because of an adverse event had a cardiac arrest (following appendicitis and septic shock) and died.

analysis set who did not have post-baseline HIV-1 RNA results. Additionally, we assessed the proportion of participants with HIV-1 RNA of less than 50 copies per mL with two different missing data imputation methods at week 48: the M=F analysis handled all missing data as HIV-1 RNA of at least 50 copies per mL with the denominator being the number of participants in the full analysis set; and the M=E analysis excluded missing data in the computation of the percentages (ie, missing datapoints were excluded from both the numerator and denominator in the computation), with the denominator being the number of participants in the full analysis set who had an HIV-1 RNA value at that visit.

We summarised the change from baseline in $\log_{10}$ HIV-1 RNA and CD4 count at week 48 by treatment group with descriptive statistics on the full analysis set. The differences in changes from baseline in $\log_{10}$ HIV-1 RNA and CD4 count between treatment groups and 95% CI were constructed from an analysis of variance model, including treatment group, baseline HIV-1 RNA stratum (≤100 000 copies per mL *vs* >100 000 copies per mL), and region stratum as fixed covariates in the model.

We summarised baseline characteristics with descriptive statistics for the safety analysis set, which included all participants randomly assigned to treatment who received at least one dose of study drug. All safety data are described in summary form using all data obtained after the date study drug was first given and up to 30 days after the last dose of study drug if the participant discontinued treatment. For categorical data, we calculated p values using the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data, row mean scores differ statistic was used for ordinal data) for treatment comparison. For continuous data, we used the two-sided Wilcoxon rank sum test.

We used SAS Software Version 9.4 (SAS Institute Inc, Cary, NC, USA) for all analyses. We calculated pharmacokinetic parameters with a non-linear model using standard non-compartmental analysis (WinNonlin software, version 6.4; Pharsight, Mountain View, CA, USA). This study is registered with ClinicalTrials.gov, number NCT02607956.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing the report. The corresponding author (DS) had full access to all the data in the study. PES, DS, EQ, and AC had final responsibility for the decision to submit the manuscript for publication.

Results

Between Nov 11, 2015, and July 15, 2016, 742 participants were screened for participation in this study, and 657 were randomly assigned to treatment: 327 to the bictegravir group and 330 to the dolutegravir group (figure 1). Of these, 320 participants in the bictegravir group and 325 in the dolutegravir group received at least one dose of study drug. Demographics and baseline characteristics were balanced between the two treatment groups (table 1).

	Bictegravir regimen (n=320)	Dolutegravir regimen (n=325)
Median age, years	33 (27–46)	34 (27–46)
Sex		
Women	40 (13%)	37 (11%)
Men	280 (88%)	288 (89%)
Race		
White	183 (57%)	195 (60%)
Black	97 (30%)	100 (31%)
Asian	7 (2%)	10 (3%)
Ethnic origin		
Hispanic or Latino	83 (26%)	81 (25%)
Region		
USA	193 (60%)	193 (59%)
Outside the USA	127 (40%)	132 (41%)
HIV disease status		
Asymptomatic	286 (89%)	288 (89%)
Symptomatic	10 (3%)	11 (3%)
AIDS	24 (8%)	26 (8%)
HIV risk factor*		
Heterosexual sex	81 (25%)	77 (24%)
Homosexual sex	237 (74%)	250 (77%)
Intravenous drug use	3 (1%)	6 (2%)
Median HIV-1 RNA $\log_{10}$ copies per mL	4·43 (3·95–4·90)	4·45 (4·03–4·84)
HIV-1 RNA concentration		
>100 000 to ≤400 000 copies per mL	54 (17%)	41 (13%)
>400 000 copies per mL	12 (4%)	13 (4%)
Median CD4 count (cells per µL)	440 (289–591)	441 (297–597)
CD4 count (cells per µL)		
<50	15 (5%)	13 (4%)
≥50 to <200	29 (9%)	21 (6%)
≥200 to <350	67 (21%)	77 (24%)
≥350 to <500	91 (28%)	94 (29%)
≥500	118 (37%)	120 (37%)
Median creatinine clearance (mL/min)	120·4 (100·8–141·8)	120·6 (102·8–145·1)
Patients with HIV/HBV co-infection	8 (3%)	6 (2%)
Patients with HIV/HCV co-infection	5 (2%)	5 (2%)
Median body-mass index (kg/m²)	25·0 (22·2–28·3)	24·6 (22·2–28·0)

Data are median (IQR) or n (%), except for age, which is median (range).
*A participant may fit more than one HIV risk factor category; therefore, percentages may add to more than 100%. HBV=hepatitis B virus. HCV=hepatitis C virus.

Table 1: **Baseline demographic and clinical characteristics**

See Online for appendix

The bictegravir regimen was non-inferior to the dolutegravir regimen for the primary outcome (286 [89·4%] of 320 participants *vs* 302 [92·9%] of 325, difference –3·5%, 95% CI –7·9 to 1·0, p=0·12; table 2, figure 2). The percentage of participants with HIV-1 RNA of less than 50 copies per mL for the per-protocol analysis was 279 (99%) of 282 participants in the bictegravir group and 296 (99·7%) of 297 in the dolutegravir group (difference –0·7%, 95% CI –2·6 to 1·2, p=0·33; figure 2). 11 (3%) of 320 participants in the bictegravir group and three (1%) of 325 in the dolutegravir group discontinued study drug because of other reasons (ie, lost to follow-up or withdrawn consent) and had a final available HIV-1 RNA of at least 50 copies per mL (appendix p 1). It was noted that seven participants did not provide post-baseline HIV-1 RNA results for administrative reasons (n=6; appendix p 1) or death (n=1 on day 28). As such, their last available HIV-1 RNA of at least 50 copies per mL was obtained before the first dose of study medication at their baseline study visit.

	Bictegravir regimen (n=320)	Dolutegravir regimen (n=325)	p value*	Treatment difference (95% CI)†
HIV-1 RNA <50 copies per mL	286 (89%)	302 (93%)	0·12	–3·5% (–7·9 to 1·0)
HIV-1 RNA ≥50 copies per mL	14 (4%)	4 (1%)		
HIV-1 RNA ≥50 copies per mL	3 (1%)	1 (<1%)		
Discontinued due to lack of efficacy	0	0		
Discontinued due to other reasons‡ and last available HIV-1 RNA ≥50 copies per mL	11 (3%)	3 (1%)		
No virological data	20 (6%)	19 (6%)		
Discontinued due to adverse events or death	3 (1%)	3 (1%)		
Discontinued due to other reasons‡ and last available HIV-1 RNA <50 copies per mL	11 (3%)	14 (4%)		
Missing data but on study drug	6 (2%)	2 (1%)		

Data are n (%). *p value for the superiority test comparing the percentages of subjects with HIV-1 RNA <50 copies per mL between treatment groups was from the Cochran-Mantel-Haenszel test stratified by baseline HIV-1 RNA stratum (≤100 000 *vs* >100 000 copies per mL) and region stratum (USA *vs* outside the USA). †The difference in percentages of patients with HIV-1 RNA of less than 50 copies per mL between treatment groups and its 95% CI were calculated based on the Mantel-Haenszel proportions adjusted by baseline HIV-1 RNA stratum and region stratum. ‡Other reasons include patients who discontinued study drug because of investigator's decision, participant decision, loss to follow-up, non-compliance with study drug, protocol violation, pregnancy, and study terminated by sponsor.

Table 2: **Virological outcomes at week 48**

A post-hoc modified FDA snapshot analysis excluding participants without post-baseline HIV-1 RNA results also showed non-inferiority between the two treatment groups: 286 (91·4%) of 313 participants in the bictegravir group had HIV-1 RNA of less than 50 copies per mL compared with 302 (92·9%) of 325 in the dolutegravir group (difference –1·5%, 95% CI –5·8 to 2·8, p=0·48; appendix p 2). The proportion of participants with HIV-1 RNA of less than 20 copies per mL at week 48 by FDA snapshot algorithm was lower in the bictgravir group than the dolutegravir group (263 [82·2%] 320 *vs* 283 [87·1%] of 325; difference in percentages –3·9%, 95% CI –9·4 to 1·5, p=0·16).

The prespecified M=E and M=F analyses were consistent with results from the primary analysis and sensitivity analysis (appendix p 2, figure 3). HIV-1 RNA levels decreased in each treatment group, with the fastest decreases from baseline observed in the first 4 weeks following initiation of study drugs (appendix p 8). The percentage of participants with HIV-1 RNA of less than 50 copies per mL was 288 (99·0%) of 291 in the bictegravir group and 304 (99·3%) 306 in the dolutegravir group for the M=E analysis (difference –0·4%, 95% CI –2·3 to 1·6, p=0·63) and 288 (90·0%) of 320 and 304 (93·5%) of 325 for the M=F analysis (difference –3·4%, 95% CI –7·7 to 0·9, p=0·12). Baseline demographic and clinical characteristics did not significantly influence treatment outcomes, since we observed no significant differences between the two treatment groups in efficacy in subgroups of age sex, race, baseline HIV-1 RNA concentration or CD4 count, region, and study drug adherence (appendix p 3).

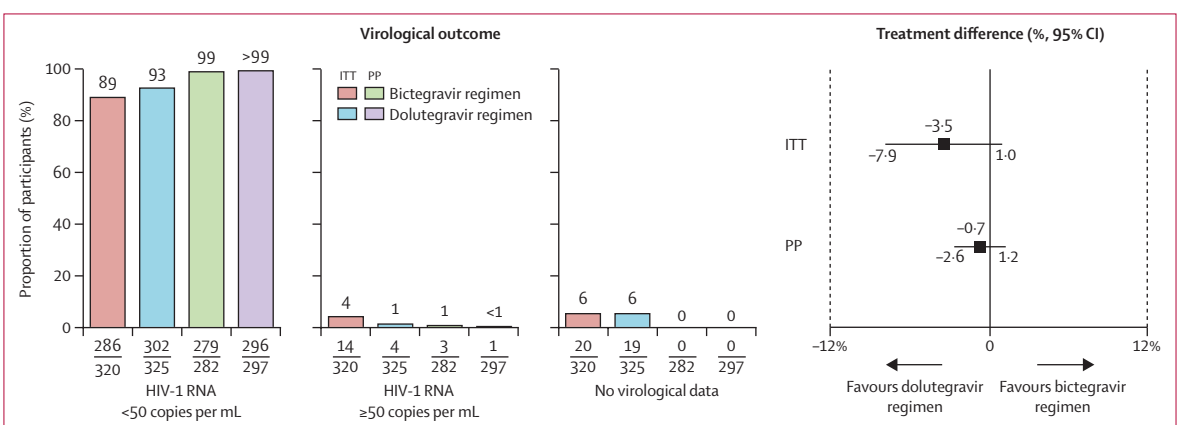

Figure 2: **Virological outcome at week 48**

The left three panels show results of the snapshot analysis, in which participants in both the ITT and PP populations were classified as having HIV-1 RNA <50 copies per mL, HIV-1 RNA ≥50 copies per mL, or no virological data. The far right panel shows the treatment difference with 95% CI for both the ITT and PP populations. ITT=intention-to-treat population. PP=per-protocol population.

Most participants in each group achieved virological suppression within the first month of treatment; 234 (75·2%) of 311 participants in the bictegravir group and 258 (79·6%) of 324 in the dolutegravir group had HIV-1 RNA of less than 50 copies per mL at week 4 (p=0·43; figure 3). At week 8 the proportions of participants with HIV-1 RNA at less than 50 copies per mL had increased to 278 (89·7%) of 310 in the bictegravir group and 285 (89·9%) of 317 in the bictegravir dolutegravir group (p=0·73). 12 participants met criteria for viral resistance testing, seven in the bictegravir group and five in the dolutegravir group. No treatment emergent resistance to the components of either treatment regimen was identified, including three of the four participants with HIV-1 RNA of more than 50 copies per mL at week 48. Two participants had been suppressed (HIV RNA of less than 50 copies per mL) until week 36 and had virological rebound at week 48, and one had HIV-1 RNA of 3·83 million copies per mL at baseline and 315 copies per mL at week 48, all in the bictegravir group. A fourth participant in the dolutegravir group had HIV-1 RNA of 56 copies per mL at week 48, and did not meet the criteria for resistance testing.

CD4 counts increased in each treatment group, with mean changes from baseline at week 48 of 180 cells per µL (SD 166·6) for the bictegravir group and 201 cells per µL (166·4) for the dolutegravir group (p=0·10).

Adverse events leading to study drug discontinuation were uncommon, occurring in five (2%) of 320 participants in the bictegravir group and one (<1%) of 325 in the dolutegravir group. No individual adverse event leading to study drug discontinuation occurred in more than one participant. Adverse events led to five participants in the bictegravir group discontinuing study medication (cardiac arrest [n=1], paranoia [n=1], chest pain [n=1], abdominal distension [n=1], and sleep disorder, dyspepsia, tension headache, depressed mood, and insomnia [n=1]); all except for the events of cardiac arrest and paranoia were considered by the investigators to be related to study drugs. Adverse events leading to study drug discontinuation in the dolutegravir group included erythema and pruritis (n=1 had both events); neither event was considered related to study drugs. Table 3 shows adverse events reported by 5% or more of participants in either treatment group. Most adverse events reported in both groups were grade 1 or 2 in severity. Participants in the bictegravir group had a lower incidence of drug-related adverse events than did those in the dolutegravir group (57 [18%] of 320 *vs* 83 [26%] of 325, p=0·022; appendix p 5). No drug-related adverse events of grade 2 or higher were reported in >2% of participants in either group. Three participants died during the study, one in the bictegravir group (cardiac arrest after appendicitis and septic shock) and two in the dolutegravir group (one from unknown causes; one from suspected pulmonary embolism). Six women, three in each group, had confirmed pregnancies. Study drugs were interrupted or discontinued by the investigator with confirmation of each pregnancy. In the bictegravir group, the pregnancies resulted in an elective abortion (n=1), uncomplicated term delivery (n=1), and outcome pending (n=1). In the dolutegravir group, the pregnancies resulted in spontaneous abortion (n=1) and uncomplicated term deliveries (n=2).

Grade 3 or 4 laboratory abnormalities were reported for 52 (17%) of 314 participants in the bictegravir group and 43 (13%) of 325 in the dolutegravir group (appendix p 5).

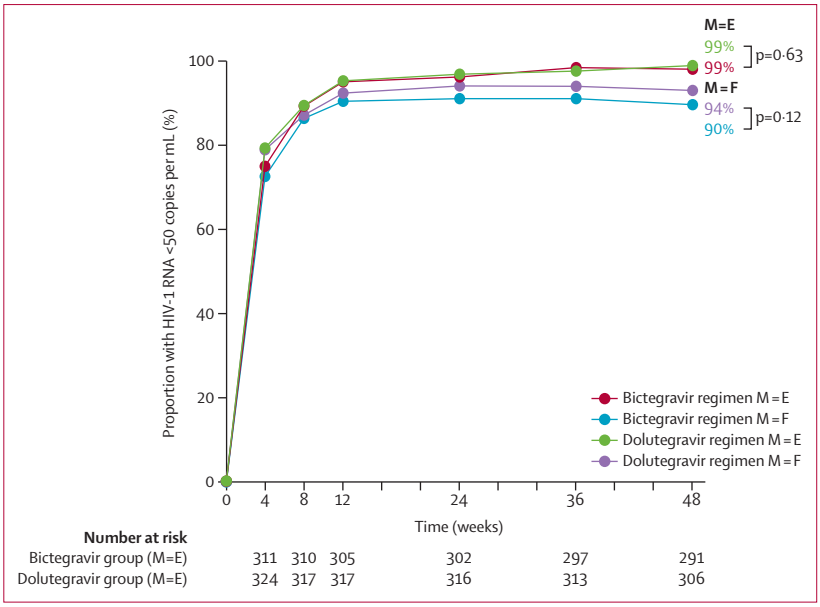

Figure 3: **Percentage of participants with HIV-1 RNA less then 50 copies per mL by visit**
Virological response rates when missing data were either failures (M = F) or excluded data (M = E). For both the M = E and M = F analyses, treatment differences were not significant. M = E, Missing=Excluded analysis, M = F, Missing=Failure analysis.

	Bictegravir regimen (n=320)	Dolutegravir regimen (n=325)
Adverse event ≥5%		
Headache	40 (13%)	40 (12%)
Diarrhoea	37 (12%)	39 (12%)
Nausea	25 (8%)	29 (9%)
Nasopharyngitis	22 (7%)	31 (10%)
Fatigue	19 (6%)	26 (8%)
Upper respiratory tract infection	15 (5%)	23 (7%)
Lymphadenopathy	17 (5%)	18 (6%)
Pyrexia	14 (4%)	21 (6%)
Back pain	11 (3%)	20 (6%)
Insomnia	16 (5%)	14 (4%)
Influenza	17 (5%)	10 (3%)
Arthralgia	16 (5%)	9 (3%)

Data are n (%).

Table 3: **Adverse events**

No trend in common grade 3 or 4 laboratory abnormalities was observed in either group. Participants in the bictegravir group with grade 3 and 4 alanine transaminase (ALT) and aspartate aminotransferase (AST) abnormalities generally had varied causes (eg, incidental hepatitis B or hepatitis C virus infection, high ALT or AST concentrations at baseline, alcohol abuse, hepatitis virus A infection). Median increases in serum creatinine and decreases in eGFR were seen at week 48 for both groups (appendix p 7). Smaller decreases in eGFR were noted in the bictegravir group than in the dolutegravir group from week 4 until week 48 (p=0·0181 at week 48). There were no discontinuations because of renal adverse effects and no cases of renal tubulopathy in either study group. Changes from baseline in fasting lipid parameters were similar between groups at week 48 (appendix p 7). There were no differences between groups in initiation of lipid-modifying agents during the study (five [2%] of 320 in the bictegravir group *vs* six [2%] of 325 in the doltegravir group; p=1·00).

An intensive pharmacokinetic analysis was done in a subset of the study participants in the bictegravir group. The plasma concentrations of bictegravir, emtricitabine, and tenofovir alafenamide were assessed and the pharmacokinetic parameters were identified. In this subset of 17 participants , the mean trough concentrations (C_{tau}) of bictegravir were 2576 (% coefficient of variance [CV] 52) ng/mL (appendix p 4), which is about 16 times higher than the protein adjusted effective concentration (162 ng/mL) against wild type HIV-1 virus. Exposures of emtricitabine (mean area under the plasma concentration–time curve during the dosing interval [AUC_{tau}] 11200 (%CV 28) hr·ng/mL) and tenofovir alafenamide (mean AUC_{tau} 259 [%CV 60] hr·ng/mL) were similar to those observed in the phase 2 study after administration of bictegravir 75 mg plus coformulated emtricitabine and tenofovir alafenamide and consistent with historical data of these approved agents in HIV-infected participants.[14,15]

Discussion

In this randomised, double-blind, multicentre, phase 3, non-inferiority trial, the fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide showed non-inferior efficacy compared with the regimen of dolutegravir plus coformulated emtricitabine and tenofovir alafenamide. As in the phase 2 clinical trial, virological failure was infrequent in both treatment groups. No study participant randomised to either regimen discontinued treatment because of lack of efficacy, and no emergent drug resistance was found in the small number of study participants who met criteria for virological failure and were tested for genotypic and phenotypic resistance. Baseline demographic and clinical characteristics did not significantly influence treatment outcomes, though some of the subgroups were small in number.

The proportion of participants with HIV-1 RNA of less than 50 copies per mL was 89·4% in the bictegravir group and 92·9% in the dolutegravir group, a treatment response difference that was not significant. Rates of virological failure were similar and low (<1%) in both groups. The numerically lower response rate for the bictegravir group was primarily driven by a higher percentage of participants with early discontinuations than in the dolutegravir group (11 *vs* three) due to other reasons (eg, lost to follow-up or withdrawn consent) with their final HIV-1 RNA greater than 50 copies per mL, including six participants who received the bictegravir regimen but never returned for virological testing after their baseline visit. In a post-hoc analysis excluding these study participants as well as an additional participant who did not provide a post-baseline HIV-1 RNA due to death at day 28, the difference between the two groups was reduced (91·4% vs 92·9%). Similarly, prespecified sensitivity analyses confirmed that the bictegravir regimen was non-inferior to the dolutegravir regimen with regard to HIV suppression at week 48. Rapid virological suppression was observed in both treatment groups, with over 80% of participants achieving HIV-1 RNA of less than 50 copies per mL by week 8 of treatment. The combined results indicate that the virological outcome of initial HIV treatment with the bictegravir regimen is expected to be similar to the outcome observed with the dolutegravir regimen.

The bictegravir regimen was well tolerated. Discontinuations due to adverse effects ascribed to study medications occurred rarely in both groups and none occurred in more than one participant, indicating a lack of a pattern to these events. Fewer drug-related adverse events were reported with the bictegravir regimen than with the dolutegravir regimen. No drug-related adverse events of grade 2 or higher were reported in >2% of participants in either group. Changes in fasting lipids were similar between regimens. Generally, the decrease in eGFR was significantly less for the bictegravir regimen than the dolutegravir regimen from weeks 4 to 48. The likely explanation for this difference is a greater inhibition of tubular secretion of creatinine via organic cation transporter-2 by dolutegravir than by bictegravir,[16] rather than any nephrotoxic effect of either treatment strategy. No discontinuations due to renal adverse events or cases of tubulopathy were reported.

The results of this study suggest that bictegravir, emtricitabine, and tenofovir alafenamide fixed-dose combination could be a simple, effective, and well tolerated initial treatment for HIV. Multiple HIV treatment guidelines currently recommend initial therapy with an INSTI plus the NRTI combination of tenofovir (alafenamide or disoproxil fumarate) and emtricitabine or abacavir and lamivudine.[1–3] Selection of dolutegravir as the comparator for this phase 3 clinical trial was based on its favourable results in comparative clinical trials,[4–7] and its high resistance barrier compared with raltegravir

and elvitegravir. Emergent dolutegravir resistance in previously untreated patients has not been reported in randomised trials; only two case studies have been reported with combination therapy in clinical practice.[17,18] The lack of emergent drug resistance in our study is consistent with the potency of bictegravir against wild type and integrase-resistant HIV variants and its high in-vitro barrier to resistance[16,19–21] and suggests that treatment with the bictegravir regimen will also be associated with a low risk of drug resistance in the long term.

Although this is a contemporary study of two NRTIs in combination with an integrase inhibitor within a population representative of patients currently untreated for HIV in a broad geographical range of developed nations, the trial has some limitations. A small number of participants had advanced HIV-related immunosuppression (12%) or high HIV-1 RNA at baseline (19%), which is likely to reflect recent recommendations to treat all people with HIV, regardless of CD4 count or viral load.[1–3] Additionally, a small number of women enrolled; to address the ensuing knowledge gap, a study assessing 471 women with HIV treated with coformulated bictegravir, emtricitabine, and tenofovir alafenamide is ongoing in the USA, Russia, Uganda, and Thailand, which will provide data for this new combination in women and also in settings outside of developed countries in North America and Europe (NCT02652624). Our study also was unable to assess potential benefits of a regimen that is one pill versus two pills a day, because the masked study design required that all study participants take three pills a day.

In summary, in this randomised, double-blind clinical trial, the bictegravir, emtricitabine, and tenofovir alafenamide fixed-dose combination showed non-inferior efficacy to dolutegravir plus emtricitabine and tenofovir alafenamide. Both treatment regimens provided rapid and high levels of virological efficacy, no emergence of drug resistance, and good tolerability with infrequent discontinuations for adverse events. Similarly, a separate randomised, double-blind study compared the bictegravir fixed-dose combination with the co-formulated dolutegravir, abacavir, and lamivudine regimen, and also showed non-inferior efficacy.[22] Together, these studies suggest that the bictegravir, emtricitabine, and tenofovir alafenamide fixed-dose combination might offer a new treatment option for individuals with HIV initiating antiretroviral therapy.

Contributors

All authors were involved in the development of the primary manuscript, interpretation of data, and have read and approved the final version. PES, AP, MLM, EK, EDJ, H-JS, AA, KWo, JS, and JR enrolled participants, analysed data and independently interpreted the results, and edited and approved the report. AC and DS designed the study. WG analysed the data, which were reviewed and interpreted by JC, KWh, DS, EQ, and AC. The first draft was written by PES and AC. All authors contributed to edits of the final report.

Declaration of interests

PES reports receiving grants or research support from Bristol-Myers Squibb, GlaxoSmithKline/ViiV, and Gilead Sciences and honoraria or consultation fees from AbbVie, Bristol-Myers Squibb, GlaxoSmithKline/ViiV, Gilead Sciences, Janssen, and Merck. AP reports personal fees from Gilead Sciences, Viiv, Merck, and Janssen. MLM has received personal fees from Gilead Sciences, ViiV, Janssen, AbbVie, Bristol-Myers Squibb, and Merck. EDJ has received research grant support from Abbott Laboratories, Achillion Pharmaceuticals, Avexa, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Idenix, Janssen, Merck, Sangamo, Taimed, and Tobira; and consulting fees as a member of advisory boards for Gilead Sciences and Janssen. H-JS has received personal fees for presentations and/or scientific advice from Gilead Sciences, Janssen, AbbVie, Bristol-Myers Squibb, Merck, and Teva, and trial documentation fees from ViiV/GlaxoSmithKline, and Janssen. AA reports receiving grants or research support from Bristol-Myers Squibb, Gilead Sciences, Janssen, and ViiV, and honoraria or consultation fees from Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV. JS reports personal fees from Gilead Sciences and Viiv. JR reports grants and consulting fees from Gilead Sciences, Janssen, Merck, and ViiV. WG, JC, KWh, DS, AC, and EQ are employees of Gilead and hold stock interest in the company. All other authors declare no competing interests.

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