Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial

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Summary

Background The single-tablet regimen consisting of bictegravir, emtricitabine, and tenofovir alafenamide is recommended for treatment of HIV-1 infection on the basis of data from 48 weeks of treatment. Here, we examine the longer-term efficacy, safety, and tolerability of bictegravir, emtricitabine, and tenofovir alafenamide compared with dolutegravir plus co-formulated emtricitabine and tenofovir alafenamide at week 96.

Methods This ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial was done at 126 outpatient centres in ten countries. We enrolled treatment-naive adults (aged ≥18 years) with HIV-1 infection who had an estimated glomerular filtration rate of at least 30 mL/min and sensitivity to emtricitabine and tenofovir. People with chronic hepatitis B or C infection, or both, and those who had used antivirals previously for prophylaxis were allowed. We randomly assigned participants (1:1) to receive treatment with either co-formulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg (the bictegravir group) or dolutegravir 50 mg with co-formulated emtricitabine 200 mg and tenofovir alafenamide 25 mg (the dolutegravir group), each with matching placebo, once daily for 144 weeks. Treatment allocation was masked to all participants and investigators. All participants who received at least one dose of study drug were included in primary efficacy and safety analyses. We previously reported the primary endpoint. Here, we report the week 96 secondary outcome of proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 96 by US Food and Drug Administration snapshot algorithm, with a prespecified non-inferiority margin of –12%. This study was registered with ClinicalTrials.gov, number NCT02607956.

Findings Between Nov 13, 2015, and July 14, 2016, we screened 742 individuals, of whom 657 were enrolled. 327 participants were assigned to the bictegravir group and 330 to the dolutegravir group. Of these, 320 in the bictegravir group and 325 in the dolutegravir group received at least one dose of study drug. At week 96, HIV-1 RNA less than 50 copies per mL was achieved by 269 (84%) of 320 participants in the bictegravir group and 281 (86%) of 325 in the dolutegravir group (difference –2·3%, 95% CI –7·9 to 3·2), demonstrating non-inferiority of the bictegravir regimen compared with the dolutegravir regimen. Both treatments continued to be well tolerated through 96 weeks; 283 (88%) of 320 participants in the bictegravir group and 288 (89%) of 325 in the dolutegravir group had any adverse event and 55 (17%), and 33 (10%) had any serious adverse event. The most common adverse events were diarrhoea (57 [18%] of 320 in the bictegravir group *vs* 51 [16%] of 325 in the dolutegravir group) and headache (51 [16%] of 320 *vs* 48 [15%] of 325). Deaths were reported for three (1%) individuals in each group (one cardiac arrest, one gastric adenocarcinoma, and one hypertensive heart disease and congestive cardiac failure in the bictegravir group and one unknown causes, one pulmonary embolism, and one lymphoma in the dolutegravir group); none were considered to be treatment related. Adverse events led to discontinuation in six (2%) participants in the bictegravir group and five (2%) in the dolutegravir group; one of these events in the bictegravir group versus four in the dolutegravir group occurred between weeks 48 and 96. Study drug-related adverse events were reported for 64 (20%) participants in the bictegravir group and 92 (28%) in the dolutegravir group.

Interpretation These week 96 data support bictegravir, emtricitabine, and tenofovir alafenamide as a safe, well tolerated, and durable treatment for people living with chronic HIV.

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Research in context

Evidence before this study

We searched PubMed for randomised clinical trials comparing dolutegravir with bictegravir in treatment-naive people with HIV-1, using the search terms "dolutegravir", "bictegravir", and their relevant abbreviations, together with "randomized" or "randomised". Searches were limited to clinical trials that compared different integrase strand transfer inhibitors (INSTIs) for initial therapy and were published in English between Jan 1, 1997, and Jan 30, 2019. We excluded studies using the same INSTI and those comparing INSTI-containing regimens to other antiretroviral drug classes. Our search yielded four clinical trials. One trial (NCT01227824) showed non-inferiority of dolutegravir compared with another INSTI, raltegravir, each in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). The other three studies reported 48-week endpoints comparing a regimen of bictegravir, emtricitabine, and tenofovir alafenamide to one of two dolutegravir-containing regimens. One phase 2 study (NCT02397694) compared bictegravir with dolutegravir, each in combination with emtricitabine and tenofovir alafenamide, and showed high efficacy for both drugs and similar safety between the drugs. Our ongoing phase 3 study (GS-US-380-1490; NCT02607956) compared co-formulated bictegravir, emtricitabine, and tenofovir alafenamide with dolutegravir plus co-formulated emtricitabine and tenofovir alafenamide. At week 48, bictegravir was non-inferior and had led to fewer drug-related adverse events than dolutegravir. The fourth study (GS-US-380-1489; NCT02607930) showed non-inferior efficacy, less nausea, fewer drug-related adverse events, and similar bone and renal safety with co-formulated bictegravir, emtricitabine, tenofovir alafenamide than with dolutegravir, abacavir, and lamivudine.

Added value of this study

INSTIs are generally well tolerated potent inhibitors of HIV-1, though some notable differences exist between members of the class. Raltegravir and elvitegravir have a lower barrier to resistance than other INSTIs, raltegravir has a greater pill burden, and elvitegravir requires a pharmacological booster, which increases the potential for drug–drug interactions. Bictegravir and dolutegravir have a higher barrier to resistance than other INSTIs, can be dosed once daily, and are generally preferred in some, but not all treatment guidelines. Until recently, clinical trials of treatment-naive participants have rarely made direct comparisons between INSTIs for initial treatment and longer-term outcomes for co-formulated bictegravir, emtricitabine, tenofovir alafenamide have not been available. This study provides longer-term follow-up of week 96 efficacy and safety results of a randomised, double-blind comparison between co-formulated bictegravir, emtricitabine, and tenofovir alafenamide and dolutegravir plus emtricitabine and tenofovir alafenamide. Both recommended INSTIs are combined with the same NRTI combination, which allows for a direct comparison of INSTIs and also enables the inclusion of participants co-infected with hepatitis B virus, those with moderate to severe renal impairment, and did not require HLA-B*5701 testing before treatment. This study is among the first to report long-term efficacy, safety, and tolerability of bictegravir, emtricitabine, and tenofovir alafenamide.

Implications of all the available evidence

Results from our study show non-inferiority of efficacy of co-formulated bictegravir, emtricitabine, and tenofovir alafenamide compared with dolutegravir plus emtricitabine and tenofovir alafenamide, with no treatment-emergent resistance and fewer drug-related adverse events in longer-term follow-up. These results complement the week 96 outcomes from the GS-US-380-1489 study and, together, these studies illustrate the durable efficacy and safety of co-formulated bictegravir, emtricitabine, and tenofovir alafenamide as initial treatment for people with HIV.

Introduction

Modern treatment regimens consisting of an integrase strand transfer inhibitor (INSTI) and two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) have become the standard of care for initial HIV-1 therapy worldwide. INSTIs have largely replaced other antiretroviral classes as the preferred third drug in major treatment guidelines because of their potency, safety, and tolerability.[1–4] Bictegravir is a potent, once-daily, unboosted INSTI with a high in-vitro barrier to resistance and in-vitro activity against most virus variants resistant to elvitegravir and raltegravir, and some variants that have reduced susceptibility to dolutegravir. Bictegravir is co-formulated with emtricitabine and tenofovir alafenamide, a guideline-recommended NRTI combination with bone and renal safety advantages over tenofovir disoproxil fumarate. This single-tablet regimen does not require HLA-B*5701 testing before initiation, nor is there any evidence of the potential cardiovascular risk that is associated with abacavir.[5–7] Emtricitabine and tenofovir alafenamide are also active against hepatitis B virus and regimens containing these two NRTIs are recommended in patients with HIV-1 and hepatitis B co-infection or with unknown hepatitis B status.

The single-tablet regimen of bictegravir, emtricitabine, and tenofovir alafenamide was safe and showed high and non-inferior virological efficacy compared with dolutegravir, abacavir, and lamivudine in a phase 3 study.[8] Treatment with bictegravir, emtricitabine, and tenofovir alafenamide was associated with more favourable tolerability, including a significant difference in incidence of nausea, when compared with dolutegravir, abacavir, and lamivudine.[8,9] Additionally, patient-reported outcome analyses showed fewer neuropsychiatric symptoms, including dizziness, difficulty sleeping, depressed mood, and anxiety with bictegravir, emtricitabine, and tenofovir

alafenamide than with dolutegravir, abacavir, and lamivudine. In this study, bictegravir, emtricitabine, and tenofovir alafenamide was compared with dolutegravir plus emtricitabine and tenofovir alafenamide and showed high and non-inferior efficacy at the week 48 endpoint.[10] Bictegravir, emtricitabine, and tenofovir alafenamide are recommended by European and US treatment guidelines as a regimen for most people with HIV-1. Here, we present the key secondary week-96 results of a phase 3 trial comparing fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide with dolutegravir plus co-formulated emtricitabine and tenofovir alafenamide as initial treatment for people with HIV-1 infection.

Methods

Study design and participants

This ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial was done at 126 outpatient centres in ten countries (Australia, Belgium, Canada, Dominican Republic, France, Germany, Italy, Spain, the UK, and the USA). Detailed methods have been previously published.[8] Study investigators enrolled adults (aged ≥18 years) with HIV-1 infection who were treatment naive with estimated glomerular filtration rate (eGFR) of at least 30 mL/min (calculated by the Cockcroft–Gault equation), and with virological resistance testing showing sensitivity to emtricitabine and tenofovir; resistance testing of the viral integrase gene was not performed at screening but was obtained retrospectively. Participants with chronic hepatitis B or hepatitis C infection and those with previous antiretroviral use for 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 the bictegravir group (bictegravir, emtricitabine, and tenofovir alafenamide) or dolutegravir group (dolutegravir with emtricitabine and tenofovir alafenamide). Participants also received placebo tablets matching the alternative treatment. Randomisation was stratified by HIV-1 RNA (≤100 000 copies per mL, 100 001–400 000 copies per mL, or >400 000 copies per mL), CD4 count (<50 cells per μL, 50–199 cells per μL, or ≥200 cells per μL), and region (in the USA or outside the USA) at screening.

Procedures

Participants in the bictegravir group received once-daily, oral fixed-dose combination bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg and those in the dolutegravir group received once-daily oral dolutegravir 50 mg with once-daily, oral fixed-dose combination of emtricitabine 200 mg and tenofovir alafenamide 25 mg. Both regimens were given regardless of food intake. We did study visits at weeks 4, 8, and 12 after baseline, and every 12 weeks thereafter, with masked treatment visits planned until week 144 as previously reported.[10] Laboratory tests included haematological analysis, serum chemistry tests, fasting lipids, CD4 counts, renal function (serum creatinine and eGFR; Covance Laboratories, Indianapolis, IN, USA), and HIV-1 RNA plasma measurements (Roche TaqMan 2.0; Roche Diagnostics, Rotkreuz, Switzerland). Protocol-defined resistance testing (Monogram Biosciences Inc, San Francisco, CA, USA) was done for any participant who had HIV-1 RNA of at least 50 copies per mL with a confirmed HIV-1 RNA of at least 200 copies per mL at the consecutive visit, or who had HIV-1 RNA of at least 200 copies per mL at week 48, week 96, or the last visit on study drug after week 8, and who did not subsequently have HIV-1 RNA less than 50 copies per mL while on study drug.

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 21.0). Relatedness of adverse events to blinded study drugs was assessed by the investigator in a binary manner (yes or no).

Outcomes

We have previously reported the primary outcome:[10] the proportion of participants who had plasma HIV-1 RNA less than 50 copies per mL at week 48, as defined by the US Food and Drug Administration (FDA) snapshot algorithm.[11] Secondary analyses of efficacy were planned for week 96 and week 144 using the same method; here we report week 96 results.

We also did assessments of virological efficacy (ie, proportion of patients who achieved HIV-1 RNA of <50 copies per mL) at week 96 by prespecified subgroups of age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, geographic region, and study medication adherence; and the proportion of participants with plasma HIV-1 RNA less than 50 copies per mL when imputing missing as failure and missing as excluded data.

Week 96 efficacy analyses were also done with proportion of participants with plasma HIV-1 RNA less than 20 copies per mL at week 96 by snapshot algorithm; change in CD4 cell count from baseline; and safety. Other outcomes were change from baseline in serum creatinine, eGFR, fasting lipids, and hepatitis B virus DNA at week 96.

Statistical analysis

Sample size justification was previously reported.[8] Statistical analyses at week 96 followed the same methods previously reported for week 48.[10] We assessed plasma HIV-1 RNA of less than 50 copies per mL at week 96 (days 631–714 inclusive) in the full analysis set (all participants who received at least one dose of their assigned study drug), either when participants had

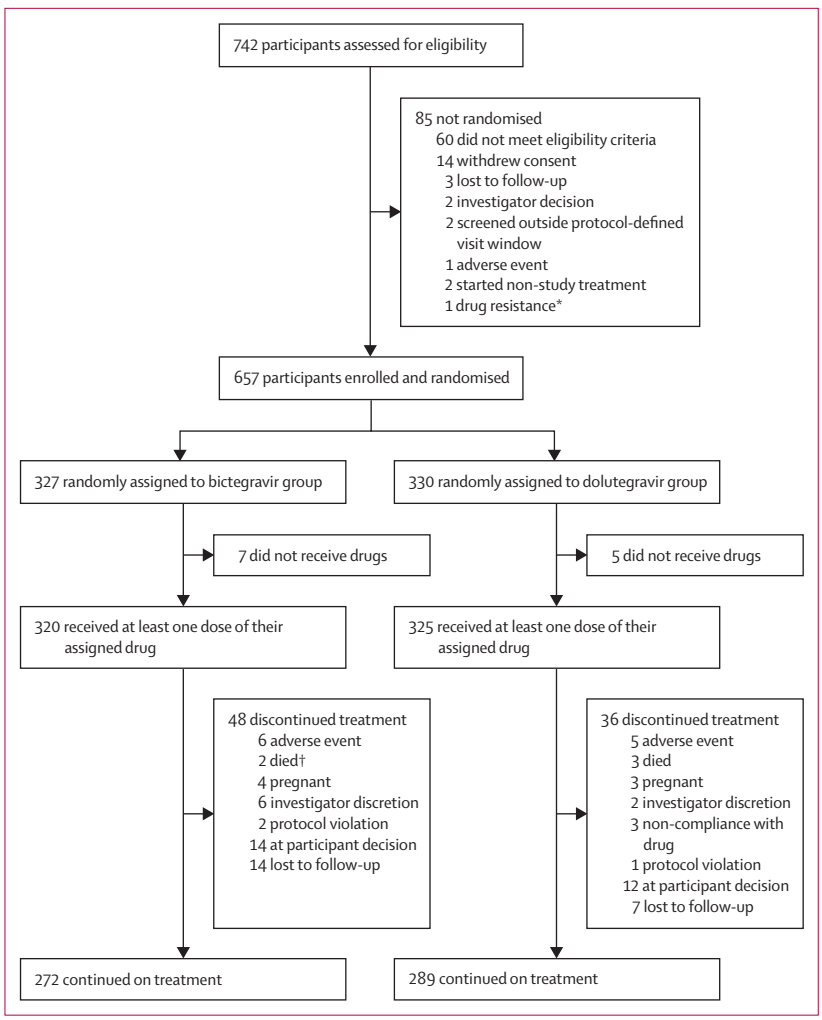

Figure 1: **Trial profile through week 96**
No participants discontinued treatment for efficacy reasons. *Excluded by investigator on the basis of local laboratory genotype result. †One participant who discontinued because of an adverse event had a cardiac arrest (after appendicitis and septic shock) and died.

completed their week 96 study visit or had prematurely discontinued the study drug. We did a per-protocol analysis excluding participants who had low adherence (ie, adherence at or below the 2·5th percentile among those in the study) or did not have available on-treatment HIV-1 RNA in the week 96 analysis window.

Change from baseline in CD4 cell count at week 96 was summarised by treatment group with descriptive statistics based on the full analysis set. Presence of hepatitis B virus co-infection was defined as positive hepatitis B surface antigen or a negative hepatitis B surface antibody with a positive hepatitis B core antibody and hepatitis B virus DNA of at least 20 international units (IU) per mL at baseline. We assess the proportion of hepatitis B virus co-infected participants with maximum hepatitis B virus DNA of 29 IU/mL at week 96 with missing as excluded imputation.

We summarised baseline characteristics with descriptive statistics for the safety analysis set, which included all randomly assigned participants who received at least one dose of study drug. For categorical data, we calculated p values with the Cochran-Mantel-Haenszel test (general association statistic was used for nominal data, the 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. For comparison of incidence of adverse events, we used Fisher's exact test. No adjustments were made for multiple comparison; all p values for secondary outcomes were exploratory.

We used SAS software, version 9.4 (SAS Institute Inc; Cary, NC, USA) for all analyses. We assessed non-inferiority with a conventional 95% CI approach for the difference in proportions of participants with a virological response (bictegravir group minus dolutegravir group) with a prespecified non-inferiority margin of –12%, based on published US FDA regulatory guidance.[12]

This study was done according to protocol without substantial deviations and is registered with ClinicalTrials.gov, number NCT02607956.

Role of the funding source

The funder of the study had the lead role in study design, data collection, data analysis, data interpretation, and (along with H-JS) writing of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Nov 13, 2015, and July 14, 2016, 742 individuals were screened, of whom 85 were excluded and 657 were enrolled. 327 participants were randomly assigned to the bictegravir regimen and 330 to the dolutegravir regimen (figure 1). Of these, 320 people in the bictegravir group and 325 in the dolutegravir group received at least one dose of their assigned drug. Two participants were excluded before randomisation because of pre-existing resistance to emtricitabine or tenofovir alafenamide reported in their study genotype, one with Met184Met/Val and one with Met184Val, Met41Leu, Leu210Trp, Thr215Tyr, and Lys219Gln. One other participant was excluded by the investigator on the basis of a local laboratory genotype. Demographic and baseline characteristics were balanced between the two treatment groups (table 1).

269 (84%) of 320 participants in the bictegravir group and 281 (86%) of 325 in the dolutegravir group had plasma HIV-1 RNA less than 50 copies per mL at week 96 (difference –2·3%; 95% CI –7·9 to 3·2; table 2, figure 2); therefore the bictegravir regimen was non-inferior to the dolutegravir regimen in the US FDA snapshot analysis. For the prespecified per-protocol analysis, 263 (100%) of 263 participants in the bictegravir group and 276 (98%) of 281 in the dolutegravir group had HIV-1 RNA less than

	Bictegravir group (n=320)	Dolutegravir group (n=325)
Age, years	33 (27–46)	34 (27–46)
Sex		
Women	40 (13%)	37 (11%)
Men	280 (88%)	288 (89%)
Race		
White	183 (57%)	195 (59%)
Black	97 (30%)	100 (31%)
Asian	7 (2%)	10 (3%)
Ethnicity		
Hispanic or Latino	83 (26%)	81 (25%)
Not Hispanic or Latino	237 (74%)	244 (75%)
Region		
USA	193 (60%)	193 (60%)
Outside 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%)
HIV-1 RNA, log_{10} copies per mL	4·43 (3·95–4·90)	4·45 (4·03–4·84)
HIV-1 RNA concentration, copies per mL		
100 001—400 000	54 (17%)	41 (13%)
>400 000	12 (4%)	13 (4%)
CD4 count, cells per µL	440 (289–591)	441 (297–597)
CD4 cell count, cells per µL		
<200	44 (14%)	34 (10%)
200–499	158 (49%)	171 (53%)
≥500	118 (37%)	120 (37%)
Creatinine clearance by Cockcroft-Gault formula, mL/min	120·4 (100·8–141·8)	120·6 (102·8–145·1)
HIV and hepatitis B virus co-infection	8 (3%)	6 (2%)
HIV and hepatitis C virus co-infection	5 (2%)	5 (2%)
Body-mass index, kg/m²	25·0 (22·2–28·3)	24·6 (22·2–28·0)

(Table 1 continues in next column)

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	Bictegravir group (n=320)	Dolutegravir group (n=325)
Primary resistance-associated mutations		
INSTI†	3 (1%)	6 (2%)
NRTI‡	10 (3%)	5 (2%)
NNRTI§	41 (13%)	41 (13%)
Protease inhibitor¶	4 (1%)	10 (3%)

Data are median (IQR) or n (%). INSTI=integrase strand transfer inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. *A participant can fit more than one HIV risk factor category. †Thr66Ala/Ile/Lys, Glu92Gly/Gln, Thr97Ala, Phe121Tyr, Tyr143Cys/His/Arg, Ser147Gly, Gln148His/Lys/Arg, Asn155His/Ser, and Arg263Lys. ‡Met41Leu, Lys65Glu/Asn/Arg, Asp67Asn, Thr69 insertions, Lys70Glu/Arg, Leu74Ile/Val, Tyr115Phe, Gln151Met, Met184Val/Ile, Leu210Trp, Thr215Tyr/Phe, and Lys219Glu/Asn/Gln/Arg. §Leu100Ile, Lys101Glu/Pro, Lys103Asn/Ser, Val106Ala/Met, Val108Ile, Glu138Ala/Gly/Lys/Gln/Arg, Val179Leu, Tyr181Cys/Ile/Val, Tyr188Cys/Leu/His, Gly190Ala/Glu/Gln/Ser, His221Tyr, Pro225His, Phe227Cys, and Met230Ile/Leu. ¶Asp30Asn, Val32Ile, Met46Ile/Leu, Ile47Ala/Val, Gly48Val, Ile50Val/Leu, Ile54Leu/Met, Gln58Glu, Thr74Pro, Leu76Val, Val82Ala/Phe/Leu/Thr/Ser, Asn83Asp, Ile84Val, Asn88Ser, and Leu90Met.

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

50 copies per mL (difference 1·8%, 95% CI –0·3 to 3·9). 14 (4%) participants in the bictegravir group and four (1%) in the dolutegravir group discontinued study drug because of reasons not related to study treatment and had last available HIV-1 RNA measurements of at least 50 copies per mL.[10] Seven of these participants from the bictegravir group did not have any HIV-1 RNA data after baseline. As such, their only available HIV-1 RNA, which was used to assess efficacy, was collected before the first dose of study medication at their baseline study visit. A week-96 modified snapshot analysis excluding participants without HIV-1 RNA results after baseline also showed non-inferiority between the two treatment groups: 269 (86%) of 313 participants in the bictegravir group versus 281 (86%) of 325 in the dolutegravir group had HIV-1 RNA less than 50 copies per mL (difference –0·5%, 95% CI –5·9 to 4·9). The prespecified missing as excluded and missing as failure analyses were consistent with results from the full and per-protocol analyses (table 2), showing high overall efficacy and no differences between the treatment groups. The proportion of participants with HIV-1 RNA less than 20 copies per mL at week 96 by FDA snapshot algorithm was 248 (78%) of 320 for the bictegravir group and 261 (80%) of 325 for the dolutegravir group (difference –2·5%, 95% CI –8·8 to 3·8). Subgroup analyses showed that age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, region, and study drug adherence did not significantly influence treatment outcomes (appendix p 5). Testing for homogeneity found no significant interactions between treatment and subgroup.

See Online for appendix

CD4 cell counts increased in both treatment groups, with mean changes from baseline at week 96 (observed data, on-treatment value) of 237 (SD 204) cells per µL for the bictegravir group and 281 (209) cells per µL for the dolutegravir group (p=0·008). CD4 cell percentages also increased from baseline in both treatment groups, with mean changes from baseline at week 96 of 10·7% (SD 6·3) and 11·0% (5·5; p=0·37). Mean CD4 cell counts at week 96 were 693 (SD 271) cells per µL for the bictegravir group and 733 (303) cells per µL for the dolutegravir group.

Through week 96, we did resistance analyses for 13 participants, seven in the bictegravir group and six in the dolutegravir group. No participants in the bictegravir group and three participants in the dolutegravir group had resistance testing between week 48 and week 96.

	Bictegravir group (n=320)	Dolutegravir group (n=325)	Percentage difference*
HIV-1 RNA <50 copies per mL	269 (84%)	281 (86%)	−2·3% (−7·9 to 3·2)
HIV-1 RNA ≥50 copies per mL	14 (4%)	9 (3%)	..
HIV1 RNA ≥50 copies per mL at week 96 window	0	5 (2%)	..
Discontinued because of no efficacy	0	0	..
Discontinued because of other reasons† and last available HIV-1 RNA ≥50 copies per mL	14 (4%)	4 (1%)	..
No virological data at week 96 window	37 (12%)	35 (11%)	..
Discontinued because of adverse event or death	8 (3%)	8 (2%)	..
Discontinued because of other reasons† and last available HIV-1 RNA <50 copies per mL	26 (8%)	23 (7%)	..
Missing data but on study drug	3 (1%)	4 (1%)	..
HIV-1 RNA <50 copies per mL by per-protocol snapshot analysis‡	263/263 (100%)	276/281 (98%)	1·8% (−0·3 to 3·9)
Modified snapshot analysis	269/313 (86%)	281/325 (86%)	−0·5% (−5·9 to 4·9)
HIV-1 RNA <50 copies per mL by missing as failure§	276/320 (86%)	286/325 (88%)	−1·6% (−6·8 to 3·6)
HIV-1 RNA <50 copies per mL by missing as excluded§	276/276 (100%)	286/291 (98%)	1·7% (−0·3 to 3·8)
HIV-1 RNA <20 copies per mL	248/320 (78%)	261/325 (80%)	−2·5% (−8·8 to 3·8)

Data are n (%) and % (95% CI). The week-96 window is between days 631 and 714 (inclusive). *The difference in percentages of participants with HIV-1 RNA <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. †Investigator's decision, participant decision, lost to follow-up, non-compliance with study drug, protocol violation, pregnancy, and study termination by funder. ‡Per-protocol analysis excluded patients in full analysis set who were off the study drug at week 96 or had low adherence (ie, adherence less than or equal to 2·5th percentile among those in study). §Difference in percentages and 95% CIs are based on a dichotomised response: HIV-1 RNA <50 copies per mL versus HIV-1 RNA ≥50 copies per mL; patients with missing HIV-1 RNA at week 96 were considered ≥50 copies per mL for missing as failure approach and were excluded for missing as excluded approach.

Table 2: **Virological outcomes at week 96**

Genotypic and phenotypic results after baseline for at least one gene were available for all seven assessed participants in the bictegravir group and five of six in the dolutegravir group. No resistance developed to any component of either treatment regimen. We did baseline HIV-1 integrase genotyping retrospectively for 642 of 645 participants, showing that primary mutations associated with resistance to integrase inhibitors were present in nine (1%) participants, all of whom had pre-existing Thr97Ala mutations that did not affect virological outcomes at week 96. Pretreatment primary resistance-associated mutations affecting NRTIs were present in 2% of participants, those affecting non-nucleoside reverse transcriptase inhibitors (NNRTIs) were present in 13%, and those affecting protease inhibitors were present in 2% of participants; they did not affect the efficacy of either regimen (table 1).

14 (2%) of 645 participants had HIV-1 and hepatitis B co-infection at baseline, eight (3%) of 320 in the bictegravir group and six (2%) of 325 in the dolutegravir group. At week 96 in the missing as excluded analysis, all four (100%) participants in the bictegravir group and four (67%) of six in the dolutegravir group had hepatitis B virus DNA less than 29 IU per mL and HIV-1 RNA less than 50 copies per mL. The two participants from the dolutegravir group with hepatitis B virus DNA more than 29 IU per mL at week 96 had baseline pretreatment hepatitis B virus DNA greater than the upper limit of quantification of the assay (>170 million IU per mL) with a decrease to 55 IU per mL in one patient and 70 IU per mL in the other at week 96. Among participants without a hepatitis B virus DNA result at week 96 in the missing as excluded analysis, three (75%) of the four achieved hepatitis B virus DNA less than 29 IU per mL at their last study visit before week 96 and the remaining one had no data after baseline.

Both treatments were well tolerated for a median exposure of 101 weeks (IQR 98–107 for bictegravir and 98–108 for dolutegravir), with most adverse events reported as mild or moderate in severity. Adverse events leading to study drug discontinuation were uncommon, occurring in six (2%) of 320 participants in the bictegravir group and five (2%) of 325 in the dolutegravir group (table 3). No individual adverse event leading to study drug discontinuation occurred in more than one participant. Adverse event-related study drug discontinuations in the bictegravir group included one each of cardiac arrest; paranoia; chest pain; abdominal distension; sleep disorder, dyspepsia, tension headache, depressed mood, and insomnia all before week 48; and depression between weeks 48 and 96. In four of six patients with events leading to discontinuation in the bictegravir group, except cardiac arrest and paranoia (which were associated with recreational drug use), the events were considered by the investigators to be related to study drugs. Adverse events leading to study drug discontinuation in the dolutegravir group included one erythema and pruritis before week 48; and two depression; one lipoatrophy; and one supraventricular tachycardia all between weeks 48 and 96. Two of these events (one depression and one lipoatrophy) were considered related to study drugs.

Fewer participants had drug-related adverse events in the bictegravir group than in the dolutegravir group (p=0·02; table 3; appendix p 6). Drug-related adverse events classified as gastrointestinal disorders (MedDRA system organ class) were reported in fewer participants in the bictegravir group (29 [9%]) than in the dolutegravir group (47 [14%]) but no single adverse event (MedDRA preferred term) met the 5% threshold for between-group statistical difference (appendix p 6). No drug-related adverse events of grade 3 or higher were reported in more than 2% of participants in either group. Six participants died during the study, three (1%) participants in the bictegravir group and three (1%) in the dolutegravir group. None of the events leading to death were considered related to study drugs. There were no abnormal electrocardiogram findings associated with either treatment regimen.

Nine women had eleven confirmed pregnancies, five women with seven confirmed pregnancies in the bictegravir group and four women with four confirmed pregnancies in the dolutegravir group. Study drugs were interrupted or discontinued by the investigator when each pregnancy was confirmed. In the bictegravir group, the pregnancies resulted in an elective abortion in one woman, spontaneous abortion in three women, and uncomplicated term delivery in three women. In the dolutegravir group, the pregnancies resulted in elective abortion in one woman and uncomplicated term deliveries in three women.

In participants with measurements available after baseline, grade 3 or 4 laboratory abnormalities were reported for 66 (21%) of 314 in the bictegravir group and 61 (19%) of 325 in the dolutegravir group (appendix p 9). Grade 3 or 4 liver-related laboratory abnormalities were uncommon and generally transient and unrelated to study treatment. Grade 3 or 4 alanine aminotransferase or aspartate aminotransferase increases were reported in ten participants in the bictegravir group and 11 participants in the dolutegravir group. The causes of these abnormalities in the bictegravir group were three hepatitis C virus infection, two hepatitis B virus infection, one alcohol abuse, one hepatitis A virus infection, two associated with creatinine kinase increase from physical exertion, and one participant had isolated grade 3 alanine aminotransferase increase without a diagnosis that resolved without interruption of study drugs. The causes of these abnormalities in the dolutegravir group were two hepatitis C virus infection, one acute hepatitis A infection, six associated with creatinine kinase increase from physical exertion, one with a history of steatohepatitis had progressive increase in both alanine aminotransferase and aspartate aminotransferase, and one participant had an isolated alanine aminotransferase increase without diagnosis that resolved without interruption of study medications. Small increases in median serum creatinine and decreases in eGFR were seen at week 96 for both groups (appendix p 10). No participants discontinued study treatment because of renal adverse events and no patients had renal tubulopathy. Changes from baseline in fasting lipid parameters were similar between groups at week 96 (appendix p 10). Initiation of lipid-modifying drugs did not differ between groups during the study: 11 (3%) of 320 in the bictegravir group and 12 (4%) of 325 in the dolutegravir group (p=1·00). At week 96, the median change in bodyweight in the bictegravir group was 3·5 kg (IQR 0·1–8·2) compared with 3·9 kg (0·8–7·4) in the dolutegravir group.

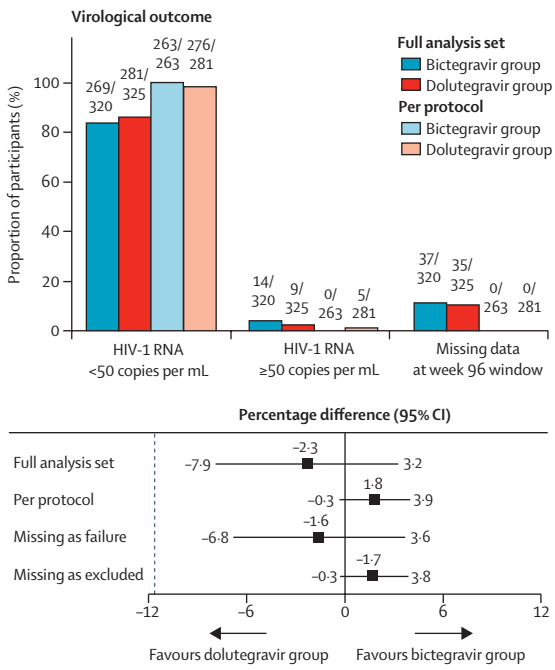

Figure 2: **Virological outcomes at week 96**

	Bictegravir group (n=320)	Dolutegravir group (n=325)
All adverse events	283 (88%)	288 (89%)
Grade 3 or 4 adverse event	43 (13%)	38 (12%)
Serious adverse event	55 (17%)	33 (10%)
Study drug-related adverse event	64 (20%)	92 (28%)
Study drug-related serious adverse event	3 (1%)	2 (1%)
Any adverse event leading to study drug discontinuation	6 (2%)	5 (2%)
Death	3 (1%)	3 (1%)
Adverse events occurring in at least 10% of participants		
Diarrhoea	57 (18%)	51 (16%)
Headache	51 (16%)	48 (15%)
Nasopharyngitis	35 (11%)	52 (16%)
Upper respiratory tract infection	31 (10%)	43 (13%)
Nausea	30 (9%)	36 (11%)
Fatigue	26 (8%)	34 (10%)

Data are n (%). Deaths in the bictegravir group included one cardiac arrest after appendicitis and septic shock before week 48; one gastric adenocarcinoma and one hypertensive heart disease and congestive cardiac failure between weeks 48 and 96. Deaths in the dolutegravir group included one unknown cause and one pulmonary embolism with ongoing chronic obstructive pulmonary disease before week 48; and one lymphoma between weeks 48 and 96.

Table 3: **Adverse events through week 96**

Discussion

In this phase 3, double-blind, randomised controlled trial, the fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide showed non-inferior efficacy at week 96 compared with the regimen of dolutegravir plus co-formulated emtricitabine and tenofovir alafenamide, confirming durability of antiviral efficacy. Viral rebound was rare throughout the study, few participants had HIV-1 RNA ≥50 copies per mL at week 96, and no participant discontinued study treatment

because of poor efficacy. None of seven tested participants in the bictegravir group and three of six tested in the dolutegravir group met criteria for resistance testing between weeks 48 and 96. No participants in either treatment group had treatment-emergent resistance, which underscores the high barrier to resistance of these regimens. Both treatments were well tolerated. There was a significantly lower incidence of drug-related adverse events in the bictegravir group than in the dolutegravir group. These differences between the groups were greatest for gastrointestinal side-effects and neuropsychiatric and sleep-related symptoms. Variations in creatinine concentrations are probably a result of inhibition of tubular secretion of creatinine via organic cation transporter 2 (also known as solute carrier family 22 member 2) by dolutegravir and to a lesser degree by bictegravir,[13] rather than any nephrotoxic effect of either treatment or a decline in actual glomerular filtration. The magnitude of change is consistent with what is observed when dolutegravir is combined with the other NRTIs abacavir and lamivudine.[14]

The eligibility criteria placed few restrictions on HIV-related factors aside from most cancers and active HIV-related infections; patients with NNRTI and protease inhibitor resistance were eligible. Participants with any CD4 cell count were enrolled, and there was no upper limit placed on pretreatment HIV-1 RNA. At week 96, no differences in efficacy were seen among participants with a baseline HIV-1 RNA greater than 100 000 copies per mL or CD4 counts less than 200 cells per µL, although these subgroups were small. Overall, 60 participants (8%) who were screened did not meet eligibility criteria, but only two (<1%) were excluded because of resistance to emtricitabine or tenofovir. Integrase genotypic and phenotypic resistance testing was not required for eligibility. Retrospective analysis showed that nine participants (1%) had a pretreatment Thr97Ala primary integrase resistance-associated mutation, which, as in studies of other INSTI-based three-drug regimens, did not affect the efficacy of either regimen.

Additionally, emtricitabine and tenofovir alafenamide were selected as the NRTIs for both treatment groups, which allowed us to enrol participants with hepatitis B co-infection and treat both HIV infection and hepatitis B virus infection. Thus, these treatment regimens might also be promising options for rapid treatment initiation before baseline laboratory results are available, which has been linked to improved retention in care and viral suppression.[15–18]

Our study has several important limitations. Participants were young, a small proportion had advanced HIV, and only a small proportion were women. To participate, women of child-bearing potential also had to meet the protocol's birth control requirements, which were further reinforced after the finding of a possible association between dolutegravir and neural tube defects in a surveillance study in Botswana.[19] Enrolment sites encompassed a large geographic range but in middle-income and high-income countries; thus, study participants do not reflect demographics of people with HIV infection globally. The study was unable to assess the effect of taking a one-pill versus two-pill regimen because the placebo-controlled design required all participants to take three pills daily. Likewise, any effect that the three-pill requirement had on adherence was not measured.

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 through 96 weeks. Drug resistance did not emerge in either treatment group, discontinuation for adverse events was infrequent, and fewer drug-related adverse events occurred with the bictegravir regimen than the dolutegravir regimen. These data support bictegravir, emtricitabine, and tenofovir alafenamide as an effective, well tolerated treatment option for antiretroviral-naive individuals with HIV.

Contributors

H-JS, JRA, JLS, HA, PES, FM, CC, and CTM enrolled participants and edited and approved the draft manuscript. HM designed the study. XW and RA did the data analyses, which were reviewed and interpreted by H-JS, JRA, JLS, HA, PES, FM, CC, CTM, RA, SEC, DB, and HM. The first draft of the manuscript was written by H-JS and SEC. All authors contributed to edits of the final report.

Declaration of interests

H-JS reports honoraria for presentations or scientific advice from Gilead Sciences, Janssen, AbbVie, BMS, Merck, and Teva and trial documentation fees for clinical trials from ViiV Healthcare, GlaxoSmithKline, and Janssen. JRA has received personal fees for speaking and participation in advisory boards from Merck, ViiV, Gilead Sciences, Janssen, and Alexa. JLS has received grants from Gilead. PES reports non-financial support from Bristol-Myers Squibb research grants paid to his institution from Gilead and ViiV-GlaxoSmithKline and consulting fees from Gilead, Janssen, Merck, and ViiV-GlaxoSmithKline. FM has served on advisory boards for Abbvie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, and Tibotec and has received research grants to ASST Papa Giovanni XXIII from Abbvie, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, and Janssen. CTM has received research grants and personal fees from Gilead and Janssen and speaker's bureau fees from fees from AbbVie, Theratechnologies, Jeanseen, ViiV Healthcare, and Gilead. XW, RA, SEC, DB, and HM are employees of Gilead and shareholders of Gilead. All other authors report no competing interests.

Data sharing

Anonymised individual participant data and study documents can be requested by email (datarequest@gilead.com) for further research.

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