Bictegravir combined with emtricitabine and tenofovir alafenamide versus dolutegravir, abacavir, and lamivudine 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 Bictegravir co-formulated with emtricitabine and tenofovir alafenamide as a fixed-dose combination is recommended for treatment of HIV-1-infection and might be better tolerated than other integrase inhibitor-based single-tablet regimens, but long-term outcomes data are not available. We assessed the efficacy, safety and tolerability of bictegravir, emtricitabine, and tenofovir alafenamide compared with co-formulated dolutegravir, abacavir, and lamivudine at week 96.

Methods This ongoing, randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial was done at 122 outpatient centres in nine countries. We enrolled adults (aged ≥18 years) living with HIV who were treatment naive and HLA-B*5701 negative, did not have hepatitis B virus infection, and had an estimated glomerular filtration rate of at least 50 mL/min. We randomly assigned participants (1:1) to receive co-formulated bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg (the bictegravir group) or co-formulated dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 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 NCT02607930.

Findings Between Nov 13, 2015, and July 14, 2016, we screened 739 participants, of whom 108 were excluded and 631 enrolled and randomly assigned to bictegravir, emtricitabine, and tenofovir alafenamide (n=316) or dolutegravir, abacavir, and lamivudine (n=315). Two participants in the bictegravir group did not receive at least one dose of their assigned drug and were excluded from analyses. At week 96, bictegravir, emtricitabine, and tenofovir alafenamide was non-inferior to dolutegravir, abacavir, and lamivudine, with 276 (88%) of 314 participants in the bictegravir group versus 283 (90%) of 315 participants in the dolutegravir group achieving HIV-1 RNA less than 50 copies per mL (difference –1·9%; 95% CI –6·9 to 3·1). The most common adverse events were nausea (36 [11%] of 314 for the bictegravir group *vs* 76 [24%] of 315 for the dolutegravir group), diarrhoea (48 [15%] *vs* 50 [16%]), and headache (41 [13%] *vs* 51 [16%]). 36 (11%) participants in the bictegravir group versus 39 (12%) participants in the dolutegravir group had a serious adverse event. Two individuals died in the bictegravir group (recreational drug overdose and suicide, neither of which was treatment related) and none died in the dolutegravir group. No participants discontinued because of adverse events in the bictegravir group compared with five (2%) of 315 in the dolutegravir group. Study drug-related adverse events were reported for 89 (28%) participants in the bictegravir group and 127 (40%) 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 HIV-1 with no emergent resistance.

Funding Gilead Sciences, Inc.

Introduction

The evolution of HIV therapeutics has been marked by a shift from multiple pill regimens given two to three times per day to once-daily, single-tablet formulations with improved potency and tolerability. Two single-tablet regimens are recommended as initial

Lancet HIV 2019

Published Online
May 5, 2019
http://dx.doi.org/10.1016/S2352-3018(19)30077-3

See Online/Comment
http://dx.doi.org/10.1016/S2352-3018(19)30135-3

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Research in context

Evidence before this study

We searched PubMed on Jan 30, 2019, for randomised clinical trials of dolutegravir and bictegravir in people living with HIV-1, with title or abstract search terms of "dolutegravir" and "bictegravir" and "randomised" or "randomized". We used internet search engines to identify governmental, non-governmental, and professional medical society practice guidelines relevant to bictegravir and dolutegravir. Searches were limited to English language publications between Jan 1, 1997, and Jan 30, 2019. Our search yielded reports of week-48 outcomes from six phase 2 and phase 3 studies of bictegravir, emtricitabine, and tenofovir alafenamide in treatment-naive and treatment-experienced participants. Included in these articles were the week-48 outcomes from this clinical trial (GS-US-380-1489), which showed non-inferior efficacy and less nausea with bictegravir, emtricitabine, and tenofovir alafenamide than with dolutegravir, abacavir, and lamivudine in treatment-naive participants at that timepoint. Three other phase 3 studies showed non-inferior efficacy of bictegravir, emtricitabine, and tenofovir alafenamide and confirmed safety at week 48; one in treatment-naive participants compared with dolutegravir, emtricitabine, and tenofovir alafenamide and two in virologically suppressed participants switching to bictegravir, emtricitabine, and tenofovir alafenamide compared with continuing either dolutegravir, abacavir, and lamivudine or a protease inhibitor-based regimen. Through 48 weeks, co-formulated bictegravir, emtricitabine, and tenofovir alafenamide had a similar renal, bone, and lipid safety profile relative to most comparators, with improved fasting lipid profile for those switched away from a boosted protease inhibitor, abacavir, and lamivudine. Based on week 48 data from the phase 3 trials, co-formulated bictegravir, emtricitabine, and tenofovir alafenamide became a guidelines-recommended regimen for initial treatment of adults with HIV, although longer-term data are needed to inform clinical care.

Added value of this study

This study is a randomised, double-blind phase 3 trial and among the first to provide evidence of the longer-term safety and efficacy of bictegravir, emtricitabine, and tenofovir alafenamide through 96 weeks. Compared with another guidelines-recommended treatment regimen (dolutegravir, abacavir, and lamivudine), co-formulated bictegravir, emtricitabine, and tenofovir alafenamide showed non-inferior efficacy. No participants on either regimen had virological failure with emergent resistance, further demonstrating the high barrier to resistance of the study regimens. Similar to week 48, nausea and other drug-related adverse effects were fewer in those treated with co-formulated bictegravir, emtricitabine, and tenofovir alafenamide than those treated with dolutegravir. This study provides longer-term data to support the durable efficacy and continued tolerability of bictegravir, emtricitabine, and tenofovir alafenamide, with no treatment-emergent resistance. Data from this trial also offers a continued look at the different safety profiles of these two single-tablet regimens.

Implications of all the available evidence

Data from this study complement those from another 96-week report of co-formulated bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir with emtricitabine and tenofovir alafenamide in treatment-naive individuals. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide can be administered once daily, does not require HLA B*5701 testing, and provides guideline-recommended therapy for people with HIV and with HIV and hepatitis B virus co-infection. The efficacy of switching to co-formulated bictegravir, emtricitabine, and tenofovir alafenamide in people with virological suppression on other antiretroviral regimens has been shown in different populations of patients. Together, these studies offer longer-term efficacy and safety data to guide treatment decisions for people living with HIV-1.

therapy of HIV-1 infection by major treatment guideline panels: co-formulated bictegravir, emtricitabine, and tenofovir alafenamide and co-formulated dolutegravir, abacavir, and lamivudine.[1–3]

These regimens containing integrase strand transfer inhibitors (INSTIs) are free from pharmacological boosters, and therefore have few drug interactions and can be taken with or without food. Both are also recommended for individuals regardless of pretreatment HIV-1 RNA level or CD4 cell count. Dolutegravir, abacavir, and lamivudine cannot be used in individuals who have the HLA-B*5701 allele associated with hypersensitivity to abacavir, are co-infected with hepatitis B virus, or have an estimated glomerular filtration rate (eGFR) less than 50 mL/min.[2,4] By contrast, bictegravir, emtricitabine, and tenofovir alafenamide can be used in such individuals and is approved for those with an eGFR greater than 30 mL/min.[2,5]

Although both regimens have been shown in clinical trials to be potent and well tolerated, they had not previously been directly compared until this randomised controlled trial, comparing these two regimens in adults living with HIV and without previous antiretroviral therapy. We previously reported the primary endpoint at 48 weeks after the start of treatment, showing that bictegravir, emtricitabine, and tenofovir alafenamide was non-inferior to dolutegravir, abacavir, and lamivudine; virological failure was rare and treatment resistance was not detected in any participants.[6] However, bictegravir, emtricitabine, and tenofovir alafenamide had better gastrointestinal tolerability in adverse event reporting and patient-reported outcome questionnaires.[6,7]

Here, we report on the 96-week outcomes of this trial to provide longer-term data on the relative efficacy and safety, including tolerability and renal, bone, and lipid

profiles, of these two once-daily, single-tablet, INSTI-containing regimens in individuals without previous HIV-1 therapy.

Methods

Study design and participants

This randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial was done at 122 outpatient centres in nine countries: Belgium, Canada, Dominican Republic, France, Germany, Italy, Spain, the UK, and the USA. Detailed methods have been previously published.[6] Briefly, study investigators enrolled adults (aged ≥18 years) with HIV-1 infection who were treatment naive, did not have HLA-B*5701 mutation or hepatitis B virus infection, and had eGFR of at least 50 mL/min (calculated by the Cockcroft–Gault equation). This study was done in accordance with the Declaration of Helsinki and was 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 either the bictegravir group (bictegravir, emtricitabine, and tenofovir alafenamide) or dolutegravir group (dolutegravir, abacavir, and lamivudine). 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 were given once-daily, oral fixed-dose combination of either bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg or dolutegravir 50 mg, abacavir 600 mg, and lamivudine 300 mg. Both regimens were given without regard to food. 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.[6] Laboratory tests included haematological analysis, serum chemistry tests, fasting lipids, CD4 counts, renal function (eGFR, urine albumin-to-creatinine ratio, retinol binding protein-to-creatinine ratio, β2-microglobulin-to-creatinine ratio; 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.

We did dual-energy x-ray absorptiometry scans for hip and lumbar spine bone mineral density before drug administration at baseline and then at weeks 24, 48, and 96. One centre masked to treatment group assignment read all scans (BioClinica, Newtown, PA, USA). Safety was assessed by physical examinations, laboratory tests, 12-lead electrocardiogram, concomitant drugs, and recording of adverse events, which were coded with 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 previously reported the primary outcome:[6] 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.[6,8] Secondary analyses of efficacy were planned for week 96 and week 144 using the same methods. Here we report the 96 week results.

We also assessed virological efficacy at week 96 in prespecified subgroups of age, sex, race, baseline HIV-1 RNA, baseline CD4 cell count, geographic region, and study medication adherence. Other secondary efficacy analyses included the proportion of participants with plasma HIV-1 RNA less than 50 copies per mL at week 96 when imputing missing as failure and missing as excluded data; the proportion of participants with plasma HIV-1 RNA <20 copies per mL at week 96 by snapshot algorithm; change from baseline in CD4 cell count; and changes from baseline in hip and lumbar spine bone mineral density.

Adverse event incidence and changes in fasting lipids at week 96 were assessed by treatment group. Renal safety assessments included the change from baseline in serum creatinine and eGFR at week 96, treatment-emergent proteinuria through week 96, and percentage changes from baseline in urine retinol binding protein to creatinine ratio, urine β2-microglobulin-to-creatinine ratio and urine albumin-to-creatinine ratio at week 96.

Statistical analysis

Sample size justification was previously reported based on the primary outcome.[6] Statistical analyses at week 96 followed the same methods previously reported for week 48. We assessed plasma HIV-1 RNA less than 50 copies per mL at week 96 (between days 631 and 714, inclusive) in the full analysis set (all participants who received at least one dose of their assigned study drug) either when participants had completed their week 96 study visit or had prematurely discontinued the study drug. We did a per-protocol analysis excluding participants who had measurements missing for HIV-1 RNA at week 96 (unless this was due to discontinuation because of no efficacy), low adherence (ie, adherence at or below the

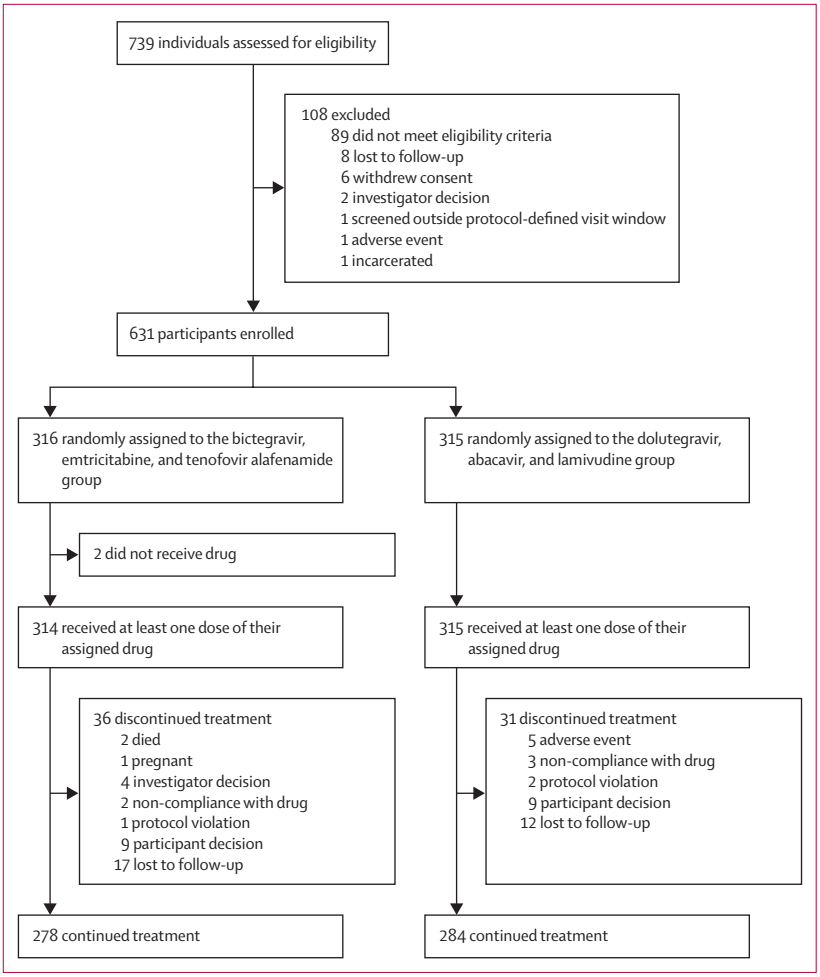

Figure 1: **Trial profile through week 96**

2·5th percentile among those in the study), or were taking medications prohibited by the protocol at study entry.

Change from baseline in CD4 cell count at week 96 was summarised by treatment group with descriptive statistics based on the full analysis set using observed on-treatment data.

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 using 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. We used Fisher's exact test for any adverse events occurring with a more than 5% difference in incidence between treatment groups. For bone mineral density data, the p values, the differences in percentage changes from baseline between treatment groups, and their 95% CIs were constructed with analysis of variance model,

	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=314)	Dolutegravir, abacavir, and lamivudine group (n=315)
Age, years	31 (25–41)	32 (26–40)
Sex		
Women	29 (9%)	33 (10%)
Men	285 (91%)	282 (90%)
Race		
White	180 (57%)	179 (57%)
Black	114 (36%)	112 (36%)
Asian	6 (2%)	10 (3%)
Ethnicity*		
Hispanic or Latino	72 (23%)	65 (21%)
Not Hispanic or Latino	240 (77%)	249 (79%)
HIV disease status		
Asymptomatic	286 (91%)	286 (91%)
Symptomatic	16 (5%)	14 (4%)
AIDS	12 (4%)	15 (5%)
HIV risk factor†		
Heterosexual sex	61 (19%)	62 (20%)
Homosexual sex	251 (80%)	250 (79%)
Intravenous drug use	5 (2%)	4 (1%)
HIV-1 RNA, $\log_{10}$ copies per mL	4·42 (4·03–4·87)	4·51 (4·04–4·87)
HIV-1 RNA concentration category, copies per mL		
≤100 000	261 (83%)	265 (84%)
>100 000	53 (17%)	50 (16%)
Median CD4 count, cells per μL	443 (299–590)	450 (324–608)
CD4 cell count category, cells per μL		
<200	36 (11%)	32 (10%)
200–499	156 (50%)	149 (47%)
≥500	122 (39%)	134 (43%)
Creatinine clearance by Cockcroft–Gault formula, mL/min	126 (108–146)	123 (107–144)
Body-mass index, kg/m²	25·1 (22·4–28·7)	24·9 (22·5–29·1)
Primary resistance-associated mutations		
INSTI‡	4 (1%)	4 (1%)
NRTI§	6 (2%)	5 (2%)
NNRTI¶	36 (11%)	51 (16%)
Protease inhibitor‖	12 (4%)	11 (3%)

Data are median (IQR) or n (%). INSTI=integrase strand transfer inhibitor. NRTI=nucleoside reverse transcriptase inhibitor. NNRTI=non-nucleoside reverse transcriptase inhibitor. *Collection of race and ethnicity data was not permitted for two participants in the bictegravir group and one in the dolutegravir group per local regulations. †A participant may fit more than one HIV risk factor category. ‡Thr66Ala/Ile/Lys, Glu92Gly/Gln, Thr97Ala, Phe121Tyr, Tyr143Cys/His/Arg, Ser147Gly, Gln148His/Lys/Arg, Asn155His/Ser, Arg263Lys. §Met41Leu, Lys65Glu/Asn/Arg, Asp67Asn, Thr69 insertions, Lys70Glu/Arg, Leu74Ile/Val, Tyr115Phe, Gln151Met, Met184Val/Ile, Leu210Trp, Thr215Tyr/Phe, 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, Met230Ile/Leu. ‖Asp30Asn, Val32Ile, Met46Ile/Leu, Ile47Ala/Val, Gly48Val, Ile50Val/Leu, Ile54Leu/Met, Gln58Glu, Thr74Pro, Leu76Val, Val82Ala/Phe/Leu/Thr/Ser, Asn83Asp, Ile84Val, Asn88Ser, Leu90Met.

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

including treatment group as a fixed-effect in the model. 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 proportion of patients with a virological response (bictegravir group minus dolutegravir group) with a prespecified non-inferiority margin of –12%, based on published US FDA regulatory guidance.[9]

This study was done according to protocol without substantial deviations and is registered with ClinicalTrials.gov, number NCT02607930.

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 DAW, 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, 739 participants were screened for this study, of whom 108 were excluded and 631 were enrolled. 316 participants were assigned to the bictegravir group and 315 to the dolutegravir group (figure 1). Of these, 314 received at least one dose of bictegravir, emtricitabine, and tenofovir alafenamide and 315 of dolutegravir, abacavir, and lamivudine. Demographics and baseline characteristics were balanced between the two treatment groups (table 1).

At 96 weeks, 276 (88%) of 314 participants in the bictegravir group had plasma HIV-1 RNA less than 50 copies per mL compared with 283 (90%) of 315 in the dolutegravir group (difference –1·9%, 95% CI –6·9 to 3·1; table 2, figure 2); therefore, the bictegravir regimen was non-inferior to the dolutegravir regimen in the US FDA snapshot analysis. Two (1%) participants in the bictegravir group and seven (2%) in the dolutegravir group had HIV-1 RNA of 50 copies per mL or more at week 96 or when last tested. Differences existed between treatment groups in the subgroups with cumulative adherence less than 95% and those who were older than 50 years (appendix p 7). In both cases, the difference was driven by participants who did not have available data in the analysis window and whose last on-treatment assessment of HIV-1 RNA was less than 50 copies per mL (appendix pp 5–6), rather than any evidence of virological failure. No significant differences were detected between the two treatments in the other subgroups and no interactions between treatment and subgroup for other prespecified subgroups, including baseline viral load and CD4 strata (appendix p 7).

The proportion of participants with HIV-1 RNA less than 20 copies per mL at week 96 by FDA snapshot algorithm was 262 (83%) of 314 participants in the bictegravir group and 267 (85%) of 315 in the dolutegravir group (percentage difference –1·2%, 95% CI –6·9 to 4·6).

	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=314)	Dolutegravir, abacavir, and lamivudine group (n=315)	Percentage difference*
HIV-1 RNA <50 copies per mL	276 (88%)	283 (90%)	–1·9% (–6·9 to 3·1)
HIV-1 RNA ≥50 copies per mL	2 (1%)	7 (2%)	..
HIV1 RNA ≥50 copies per mL at week 96 window	1 (<1%)	3 (1%)	..
Discontinued because of no efficacy	0	0	..
Discontinued because of other reasons† and last available HIV-1 RNA ≥50 copies per mL	1 (<1%)	4 (1%)	..
No virological data at week 96 window	36 (11%)	25 (8%)	..
Discontinued because of adverse event or death‡	1 (<1%)	5 (2%)	..
Discontinued because of other reasons† and last available HIV-1 RNA <50 copies per mL	32 (10%)	17 (5%)	..
Missing data but on study drug	3 (1%)	3 (1%)	..
HIV-1 RNA <50 copies per mL by missing as failure§	276/314 (88%)	286/315 (91%)	–2·9% (–7·8 to 2·1)
HIV-1 RNA <50 copies per mL by missing as excluded§	276/279 (99%)	286/288 (99%)	–0·4% (–2·5 to 1·7)
HIV-1 RNA <20 copies per mL	262/314 (83%)	267/315 (85%)	–1·2% (–6·9 to 4·6)
HIV-1 RNA <50 copies per mL by per-protocol analysis	275/276 (>99%)	278/281 (99%)	0·7% (–1·3 to 2·7)

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. †Other reasons include investigator's decision, participant decision, lost to follow-up, non-compliance with study drug, protocol violation, pregnancy, and study termination by funder. ‡One death in the bictegravir, emtricitabine, and tenofovir alafenamide occurred after the participant achieved the week 96 outcome. §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**

In the per-protocol analysis, the proportion of participants with HIV-1 RNA less than 50 copies per mL was high in both treatment groups: 275 (>99%) of 276 for bictegravir, emtricitabine, and tenofovir alafenamide and 278 (99%) of 281 for dolutegravir, abacavir, and lamivudine (difference 0·7%, 95% CI –1·3 to 2·7). Results from the missing as failure and missing as excluded analyses were consistent with the main analysis (table 2). CD4 cell count increased in both treatment groups, with mean changes from baseline at week 96 of 287 (SD 207) cells per µL in the bictegravir group and 288 (247) cells per µL in the dolutegravir group.

Five participants with protocol-defined criteria for resistance testing were included in the week 96 resistance analysis population; all were in the dolutegravir, abacavir, and lamivudine group. One discontinued study drug before week 48, two had resistance testing before week 48 and again met criteria and discontinued study drug between weeks 48 and 96, and two met criteria and discontinued between weeks 48 and 96. One participant in

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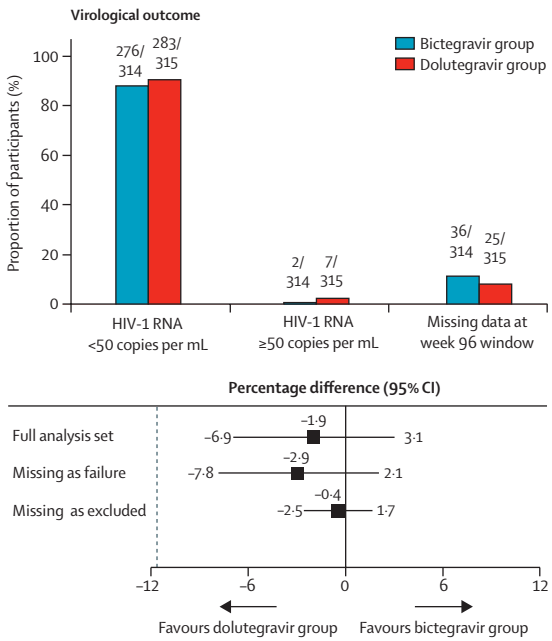

Figure 2: **Virological outcomes at week 96**
Bictegravir group=bictegravir, emtricitabine, and tenofovir alafenamide group. Dolutegravir group=dolutegravir, abacavir, and lamivudine group.

	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=314)	Dolutegravir, abacavir, and lamivudine group (n=315)
All adverse events	292 (93%)	302 (96%)
Adverse event in at least 10% of participants		
Nausea	36 (11%)	76 (24%)
Diarrhoea	48 (15%)	50 (16%)
Headache	41 (13%)	51 (16%)
Upper respiratory tract infection	33 (11%)	51 (16%)
Nasopharyngitis	36 (11%)	39 (12%)
Syphilis	27 (9%)	39 (12%)
Fatigue	27 (9%)	35 (11%)
Back pain	25 (8%)	30 (10%)
Insomnia	22 (7%)	31 (10%)
Grade 3 or 4 adverse events	42 (13%)	37 (12%)
Serious adverse events	36 (11%)	39 (12%)
Study drug-related adverse events	89 (28%)	127 (40%)
Study drug-related adverse events in at least 5% of participants		
Nausea	18 (6%)	55 (17%)
Diarrhoea	19 (6%)	13 (4%)
Headache	16 (5%)	16 (5%)
Study drug-related serious adverse events	3 (1%)*	1 (<1%)
Any adverse events leading to study drug discontinuation	0	5 (2%)
Death	2 (1%)	0

Data are n (%). *One of these was reported as related at the time of analysis and was subsequently updated to unrelated when additional information was available to the investigator.

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

the bictegravir group who met inclusion criteria for resistance analysis at week 48 achieved HIV-1 RNA of less than 50 copies per mL on study drug and, therefore, is not included in the resistance analysis population at week 96. No emergent resistance developed to any component of either treatment regimen. Baseline primary nucleoside reverse transcriptase inhibitor (NRTI) resistance-associated mutations were present in 11 (2%) participants and consisted of Tyr115Phe or thymidine analogue mutations.[10] Baseline integrase genotyping data was assessed retrospectively by deep sequencing and analysed at mutation frequencies of at least 15%. Pretreatment INSTI resistance-associated mutations were present in eight (1%) participants; one had Gln148His and Gly140Ser substitutions at greater than 99% frequency and seven had Thr97Ala. The presence of NRTI or INSTI resistance-associated mutations did not impact treatment outcomes. Notably, the participant with Gln148His and Gly140Ser (confirmed by population Sanger sequencing, with phenotypic resistance to raltegravir and elvitegravir, partial sensitivity to dolutegravir, and full sensitivity to bictegravir) was in the bictegravir group and had HIV-1 RNA less than 50 copies per mL at week 96.

Both treatments were generally well tolerated, with most adverse events reported as mild or moderate in severity. The most common adverse events were nausea, which was more common in the dolutegravir group than the bictegravir group (p=0·0001), diarrhoea, and headache (table 3). Prevalence and incidence of nausea declined over the 96-week study period (appendix p 10). No participants in the bictegravir group had adverse events that led to study drug discontinuation, whereas five (2%) participants in the dolutegravir group did. No neuropsychiatric adverse events met the more than 5% difference in incidence threshold for statistical testing. However, the frequency of dizziness and sleep disorder (MedDRA preferred terms) were two times higher in the dolutegravir group than in the bictegravir group (18 [6%] of 315 *vs* nine [3%] of 314 for dizziness and 13 [4%] *vs* three [1%] for sleep disorder). 36 (11%) participants in the bictegravir group versus 39 (12%) participants in the dolutegravir group had a serious adverse event. Five participants had adverse events that led to study drug discontinuation in the dolutegravir group: one nausea and generalised rash (day 4); one thrombocytopenia (day 50); one chronic pancreatitis and steatorrhoea (day 134); one depression (day 248); and one renal failure (day 621). All except the renal failure were considered by the investigator to be related to study drugs; all were grade 3 except one nausea and one depression, which were grade 2 (table 3). Participants in the bictegravir group had a lower incidence of drug-related adverse events than did those in the dolutegravir group (89 [28%] of 314 *vs* 127 [40%] of 315, p=0·002); these events were primarily mild or moderate in severity and most occurred before

week 48. The difference between groups was driven mainly by the significant difference in drug-related nausea which occurred in 18 (6%) of 314 in the bictegravir group versus 55 (17%) of 315 in the dolutegravir group (p<0·0001). Study drug-related serious adverse events were originally reported for three participants in the bictegravir group (one sudden death, one generalised tonic-clonic seizure, and one spontaneous abortion) versus one patient in the dolutegravir group (gastroenteritis, steatorrhoea, and acute pancreatitis). One event in the bictegravir group (sudden death) was subsequently attributed to suicide and not related to study drug. Adverse events were similar to those reported at week 48, with no new safety findings between weeks 48 and 96 for either treatment group. No abnormal electrocardiogram findings were associated with either treatment.

Between weeks 48 and 96, two deaths occurred, both in the bictegravir group. These events were recreational drug overdose (one) and suicide (one; in a participant with ongoing substance abuse); both events were considered unrelated to study treatment.

Three women had confirmed pregnancies while on study, two in the bictegravir group and one in the dolutegravir group. One of the two participants in the bictegravir group was taken off study treatments when pregnancy was confirmed and subsequently delivered a healthy full-term infant. The other woman in the bictegravir group had a spontaneous abortion at an estimated 2 weeks' gestation; the participant recovered from the event without complications. The pregnancy in the dolutegravir group was terminated with an elective abortion and study drugs were continued.

One or more grade 3 or 4 laboratory abnormalities were reported for 71 (23%) of 314 participants in the bictegravir group and 62 (20%) of 315 in the dolutegravir group; incidence and types of abnormalities were generally balanced between treatment groups (appendix p 8). Most abnormalities were transient and resolved on therapy. The overall laboratory safety profiles were similar to those observed at week 48. No proximal tubulopathy or Fanconi syndrome were reported in either group. No study participant in the bictegravir group discontinued because of a renal adverse event. One individual in the dolutegravir group with a medical history of poorly controlled diabetes and hypertension discontinued treatment because of an adverse event of renal failure on day 621. Small increases from baseline in median serum creatinine and decreases in eGFR occurred at week 96 for both groups (table 4). At 96 weeks, percentage changes in quantitative proteinuria (total urinary albumin-to-urine creatinine ratio) and tubular proteinuria (retinol binding protein and β2-microglobulin-to-urine creatinine ratios) were also similar between groups (table 4).

Changes from baseline in fasting high-density lipoprotein and triglycerides were similar between groups at week 96 (appendix p 9). Significant differences were measured in the median changes from baseline in fasting total cholesterol, low-density lipoprotein, and total cholesterol-to-high-density lipoprotein ratio at week 96 (appendix p 9). Initiation of lipid-modifying drugs during the study through week 96 was not different between the groups.

There were small changes from baseline in hip and lumbar spine bone mineral density that were similar between the two groups; mean percentage changes at week 96 in hip density were –1·13% (SD 2·77) in the bictegravir group versus –1·26% (2·85) in the dolutegravir group (p=0·59) and changes in lumbar spine density were –0·71% (3·87) versus –0·22% (3·52; p=0·14; figure 3). Weight increases after treatment initiation occurred in both groups. The median change was 3·6 kg (IQR 0·0–8·5) in the bictegravir group and 2·4 kg (–0·4 to 5·8) in the dolutegravir group.

	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=314)		Dolutegravir, abacavir, and lamivudine group (n=315)		p value
	n	Median (IQR)	n	Median (IQR)	
Serum creatinine, mg/dL					
Baseline	314	0·90 (0·80 to 1·00)	315	0·91 (0·81 to 0·99)	0·92
Change at week 96	277	0·08 (0·01 to 0·15)	286	0·09 (0·03 to 0·17)	0·067
Estimated glomerular filtration rate,* mL/min					
Baseline	314	125·9 (107·7 to 146·3)	315	123·0 (107·0 to 144·3)	0·76
Change at week 96	277	–7·8 (–16·4 to 3·6)	286	–9·6 (–19·9 to –0·4)	0·01
Urine albumin-to-creatinine ratio, mg/g					
Baseline	309	5·5 (3·7 to 9·2)	312	5·4 (3·7 to 9·1)	0·72
Percentage change at week 96	272	–0·3 (–33·5 to 59·6)	284	5·2 (–25·9 to 57·0)	0·25
Urine β2-microglobulin-to-creatinine ratio, μg/g					
Baseline	307	108·1 (71·7 to 184·4)	311	109·8 (77·6 to 191·8)	0·92
Percentage change at week 96	271	–30·8 (–58·1 to 20·9)	283	–29·4 (–57·6 to 12·1)	0·96
Urine retinol binding protein-to-creatinine ratio, μg/g					
Baseline	308	81·0 (58·3 to 122·4)	312	83·7 (59·8 to 120·4)	0·55
Percentage change at week 96	272	21·2 (–12·2 to 66·5)	284	22·1 (–12·8 to 78·7)	0·91

*As calculated by the Cockcroft–Gault formula. p values were calculated from the two-sided Wilcoxon rank-sum test to compare the two treatment groups.

Table 4: **Changes in quantitative measures of proteinuria from baseline at week 96**

Discussion

Maximal and durable suppression of plasma HIV-1 RNA as well as the enhancement of quality of life are among the major goals of treatment of HIV-1 infection.[2] Here, we report data showing non-inferiority of co-formulated bictegravir, emtricitabine, and tenofovir alafenamide over co-formulated dolutegravir, abacavir, and lamivudine at 96 weeks after initiation in treatment-naive people living with HIV-1 infection. Viral rebound was rare throughout the study. Overall, these virological outcomes data are consistent with those reported at week 48.[6]

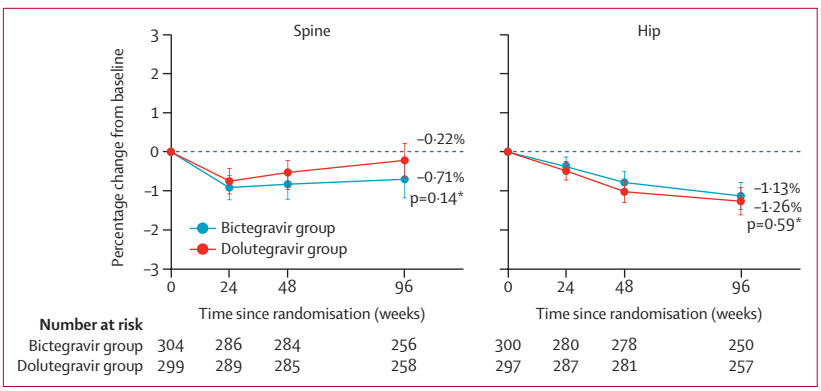

Figure 3: **Percentage change from baseline at weeks 24, 48, and 96 in lumbar spine and hip bone mineral density by dual-energy x-ray absorptiometry**
Data points are means, error bars are 95% CIs. *p values are at week 96 by analysis of variance.

As expected, given the inhibition of renal creatinine transporters by both bictegravir and dolutegravir, both groups had small median increases from baseline in serum creatinine and decreases in eGFR that occurred early and were sustained.[11] Likewise, small but similar decreases in bone mineral density occurred in both study groups. Larger changes from baseline in total cholesterol and direct low-density lipoprotein cholesterol occurred in participants in the bictegravir group. Use of lipid-lowering therapy during the trial was low in both study groups, suggesting the clinical relevance of this 10 mg/dL difference between the two groups was minimal. The greater increase in low-density lipoprotein cholesterol in the bictegravir group was unexpected given previously reported week 48 data on the lipid profiles of both study regimens. Notably, in a study of treatment-naive individuals initiating bictegravir, emtricitabine, and tenofovir alafenamide versus dolutegravir, emtricitabine, and tenofovir alafenamide, significant differences in the median change in lipid concentrations at 96 weeks, including low-density lipoprotein cholesterol, were not observed.[12]

Several observational studies have described differential increases in weight after the initiation of or switch to different classes of antiretrovirals.[13–15] Some, but not all, of these reports suggest that weight gain is greater among those treated with INSTIs.[16–18] As expected for a treatment-naive trial, median increases from baseline in weight were observed in both study groups. Longer-term trends in weight and the factors associated with changes from baseline will be examined in future planned analyses.

Overall, these results show that both regimens were efficacious and well tolerated. In distinguishing between the two, the higher frequency of investigator-reported and patient-reported nausea should be considered. Additionally, the limitations of the use of dolutegravir, abacavir, and lamivudine, including among those with hepatitis B virus co-infection or with an eGFR less than 50 mL/min, as well as the requirement for HLA-B*5701 screening, might favour the use of bictegravir, emtricitabine, and tenofovir alafenamide in some individuals.

As described previously, there are limitations to this investigation that should be considered when interpreting these data. Foremost, the proportion of women enrolled in the trial was low. However, in a study that enrolled only women (n=470) with suppressed plasma HIV-1 RNA who were randomly assigned either to continue prestudy antiretroviral therapy or to switch to bictegravir, emtricitabine, and tenofovir alafenamide, more than 95% of the participants in each treatment group maintained viral suppression at week 48 with no discontinuations of study drug due to adverse events.[19] Neuropsychiatric adverse effects of INSTI-containing regimens have been previously reported; however, each individual adverse effect is described as relatively uncommon.[20–22] Therefore, this trial probably had too few participants to detect differences between the regimens in any neuropsychiatric adverse event as reported by investigators. Furthermore, although 96-week data provide a valuable assessment of the durability of the efficacy and safety of these regimens, the need for HIV therapy remains lifelong. Longer-term data is needed to provide insights into the advantages and disadvantages of these therapeutic options. Participants in this study will continue to be followed up until week 144.

In summary, as was observed at week 48, bictegravir, emtricitabine, and tenofovir alafenamide after 96 weeks of therapy was non-inferior to dolutegravir, abacavir, and lamivudine, with no emergent drug resistance or tubulopathy detected, but with a better gastrointestinal tolerability profile. Bictegravir, emtricitabine, and tenofovir alafenamide can be used in those co-infected with hepatitis B virus and eGFRs as low as 30 mL/min and does not require HLA-B*5701 screening. Therefore, bictegravir, emtricitabine, and tenofovir alafenamide is a potent and well tolerated option for people with HIV-1 infection initiating treatment.

Contributors

DAW, YY, AB, AC, MAT, CB, DH, MNR, and AA enrolled participants. XW and HM designed the study. XW and RA did the data analyses, which were reviewed and interpreted by DAW, SEC, DB, and HM. The first draft was written by SEC and DAW. All authors reviewed and interpreted analyses of data, contributed edits of the final report, and approved the draft manuscript. DAW and SEC made the decision to submit the manuscript for publication.

Declaration of interests

DAW reports receiving honoraria for advisory board participation and consultancy from Gilead Sciences, ViiV, Merck, and Janssen; and research grant support from Gilead Sciences, ViiV, Janssen, and Merck and Co. AB has served on speakers bureaus for AbbVie, Bristol-Myers Squibb (BMS), Gilead, and Janssen; and advisory boards for AbbVie, BMS, Gilead, and Merck Sharp & Dohme (MSD). AC reports receiving conference travel bursaries and consultancy fees from Gilead Sciences and ViiV Healthcare. XW, RA, SEC, DB, and HM are employees of Gilead Sciences and own stock in the company. MAT has received research funding paid to the AIDS Research Consortium of Atlanta from BMS, CytoDyn, GlaxoSmithKline, Gilead, MSD, Roche Laboratories, Taimed, and ViiV. CB reports grants from Gilead Sciences, Braintree, Novo Nordisk, ViiV Healthcare, CoLucid, SlieaGen, Shionogi, Sanofi, Daiichi Sankyo, and Theratechnologies; and personal fees from

Gilead Sciences and Theratechnologies. MNR has served on the speakers' bureau for Gilead, Janssen, Abbvie, and Allergan; and has consulted for Gilead, Viiv, and Merck. AA has received grants from AbbVie, BMS, Gilead, Merck, ViiV, and Janssen Cilag. 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.

Acknowledgments

This study was sponsored by Gilead Sciences, Inc. We thank the individuals who participated in this trial and their families, the principal investigators (appendix pp 1–4), and their staff, the Gilead study staff, and Anna Kido (Gilead employee) for providing editorial assistance. Parts of this study have been presented at IDWeek; San Francisco, CA, USA; Oct 3–7, 2018.

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