Switching to fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir plus abacavir and lamivudine in virologically suppressed adults with HIV-1: 48 week results of a randomised, double-blind, multicentre, active-controlled, phase 3, non-inferiority trial

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Summary

Background Bictegravir, co-formulated with emtricitabine and tenofovir alafenamide, has shown good efficacy and tolerability, and similar bone, renal, and lipid profiles to dolutegravir, abacavir, and lamivudine, in treatment-naive adults with HIV-1 infection, without development of treatment-emergent resistance. Here, we report 48-week results of a phase 3 study investigating switching to bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir, abacavir, and lamivudine in virologically suppressed adults with HIV-1 infection.

Methods In this multicentre, randomised, double-blind, active-controlled, non-inferiority, phase 3 trial, HIV-1-infected adults were enrolled at 96 outpatient centres in nine countries. Eligible participants were aged 18 years or older and on a regimen of 50 mg dolutegravir, 600 mg abacavir, and 300 mg lamivudine (fixed-dose combination or multi-tablet regimen); had an estimated glomerular filtration rate of 50 mL/min or higher; and had been virologically suppressed (plasma HIV-1 RNA <50 copies per mL) for 3 months or more before screening. We randomly assigned participants (1:1), using a computer-generated randomisation sequence, to switch to co-formulated bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg; herein known as the bictegravir group), or to remain on dolutegravir, abacavir, and lamivudine (herein known as the dolutegravir group), once daily for 48 weeks. The investigators, participants, study staff, and individuals assessing outcomes were masked to treatment assignment. The primary endpoint was the proportion of participants with plasma HIV-1 RNA of 50 copies per mL or higher at week 48 (according to the US Food and Drug Administration snapshot algorithm); the prespecified non-inferiority margin was 4%. The primary efficacy and safety analyses included all participants who received at least one dose of study drug. This study is ongoing but not actively recruiting participants and is in the open-label extension phase, wherein participants are given the option to receive bictegravir, emtricitabine, and tenofovir alafenamide for an additional 96 weeks. This trial is registered with ClinicalTrials.gov, number NCT02603120.

Findings Between Nov 11, 2015, and July 6, 2016, 567 participants were randomly assigned and 563 were treated (282 received bictegravir, emtricitabine, and tenofovir alafenamide, and 281 received dolutegravir, abacavir, and lamivudine). Switching to the bictegravir regimen was non-inferior to remaining on dolutegravir, abacavir, and lamivudine for the primary outcome: three (1%) of 282 in the bictegravir group had HIV-1 RNA of 50 copies per mL or higher at week 48 versus one (<1%) of 281 participants in the dolutegravir group (difference 0·7%, 95·002% CI −1·0 to 2·8; p=0·62). Treatment-related adverse events were recorded in 23 (8%) participants in the bictegravir group and 44 (16%) in the dolutegravir group. Treatment was discontinued because of adverse events in six (2%) participants in the bictegravir group and in two (1%) participants in the dolutegravir group.

Interpretation The fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide might provide a safe and efficacious option for ongoing treatment of HIV-1 infection.

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Introduction

Bictegravir is a novel, potent, unboosted integrase strand transfer inhibitor (INSTI) with a high in-vitro barrier to resistance and low potential for drug interactions.[1,2] Three large phase 3 studies[3–5] in previously untreated or virologically suppressed adults with HIV-1 infection compared bictegravir (plus emtricitabine and tenofovir alafenamide) with dolutegravir (plus abacavir and lamivudine or emtricitabine and tenofovir alafenamide) or boosted protease inhibitor regimens. The bictegravir

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Research in context

Evidence before this study

We searched PubMed for randomised clinical trials comparing bictegravir with dolutegravir in individuals with HIV-1 using the search terms "bictegravir" and "dolutegravir" or "randomised" or "randomized". Searches were limited to articles published in English between Jan 1, 1997, and Nov 1, 2017. Our search yielded three articles, all of which summarised results from phase 2 or 3 studies of bictegravir with emtricitabine and tenofovir alafenamide compared with dolutegravir given with either emtricitabine and tenofovir alafenamide or abacavir and lamivudine in treatment-naive adults with HIV-1. Both treatments showed high efficacy and were well tolerated through 48 weeks. Bictegravir was non-inferior to dolutegravir in all trials, most notably in the two phase 3 studies, which were randomised, double blinded, and active controlled.

Added value of this study

Integrase strand transfer inhibitors (INSTIs) are recommended for first-line antiretroviral therapy in combination with two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs). Virologically suppressed individuals with HIV-1 might switch from their existing regimen because of safety or tolerability concerns, for regimen simplification, or because of other reasons. To our knowledge, this study is the first phase 3 clinical trial to investigate switching to the fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir, abacavir, and lamivudine. We found that co-formulated, fixed-dose bictegravir, emtricitabine, and tenofovir alafenamide was non-inferior to dolutegravir, abacavir, and lamivudine in maintaining virological suppression (plasma HIV-1 RNA <50 copies per mL) through 48 weeks, and had a similar safety and tolerability profile. Fewer participants in the dolutegravir group discontinued treatment because of adverse events, but fewer treatment-related adverse events were reported in the bictegravir group. To our knowledge, this study is also the first to combine an unboosted INSTI with the guideline-recommended NRTI backbone of emtricitabine and tenofovir alafenamide, which is recognised for its potency and safety advantages, particularly with respect to bone and renal measures, compared with tenofovir disoproxil fumarate. This NRTI backbone does not require testing for HLA-B*5701 before treatment and does not have any known association with cardiovascular events.

Implications of all the available evidence

Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide might be an effective alternative to dolutegravir, abacavir, and lamivudine in virologically suppressed adults with HIV-1, potentially avoiding the neuropsychiatric adverse events associated with dolutegravir and the cardiovascular adverse events linked to abacavir. Additionally, our results complement those from phase 2 and 3 studies of bictegravir, emtricitabine, and tenofovir alafenamide in treatment-naive adults, suggesting that this regimen could be a safe and efficacious option for initial or ongoing treatment of HIV-1 infection.

regimen was well tolerated and showed high rates of HIV-1 suppression, without virological failure resulting from treatment-emergent resistance. Therefore, fixed-dose, combination bictegravir, emtricitabine, and tenofovir alafenamide might be a potent, convenient, tolerable, and practical regimen for long-term treatment in many patients with HIV-1 infection.

Switching to bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir, abacavir, and lamivudine has the potential to maintain high rates of suppression while avoiding the potential side-effects of abacavir, such as cardiovascular events.[6–8] Additionally, this switch might avoid adverse effects on the CNS and treatment discontinuation, which have been reported more frequently with dolutegravir in clinical practice and cohort studies than in published results of clinical trials.[9–11] This regimen also contains two NRTIs with activity against hepatitis B virus (HBV), and the tablet is less than half the size of co-formulated abacavir, lamivudine, and dolutegravir, which might improve acceptability among patients.[12–15]

In this study, we investigated the efficacy and safety of switching to fixed-dose, combination bictegravir, emtricitabine, and tenofovir alafenamide from dolutegravir, abacavir, and lamivudine in virologically suppressed adults with HIV-1 infection.

Methods

Study design and participants

GS-US-380-1844 is a 48 week, randomised, double-blind, multicentre, active-controlled, non-inferiority, phase 3 trial done at 96 outpatient centres in nine countries (Australia, Belgium, Canada, France, Germany, Italy, Spain, the UK, and the USA). Participants who completed the week 48 visit were invited to participate in an open-label extension phase for an additional 96 weeks. Investigators enrolled adults (aged ≥18 years) with HIV-1 infection who had been virologically suppressed (plasma HIV-1 RNA <50 copies per mL) for 3 months or more before screening and were on a stable (no changes to regimen in past 3 months), once-daily antiretroviral regimen consisting of dolutegravir plus co-formulated abacavir and lamivudine or fixed-dose, co-formulated dolutegravir, abacavir, and lamivudine. Previous changes in antiretroviral treatment to improve tolerability or to simplify the regimen were allowed. Time since start of initial antiretroviral treatment was not reliably available.

Eligible participants had an estimated glomerular filtration rate of 50 mL/min or higher and no documented or suspected resistance to emtricitabine, tenofovir, dolutegravir, abacavir, or lamivudine. Individuals with chronic hepatitis C virus (HCV) infection were permitted

to enrol, whereas those with chronic HBV infection (defined as positive hepatitis B surface antigen [HBsAg] and negative hepatitis B surface antibody [HBsAb], or positive hepatitis B core antibody and negative HBsAb, regardless of HBsAg status, at screening) were excluded because no component of the dolutegravir regimen provides effective therapy for HBV infection.

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 provided written informed consent.

Randomisation and masking

We randomly assigned participants (1:1) with a computer-generated allocation sequence (block size 4) created by Bracket (San Francisco, CA, USA), to switch to the fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide, or to continue the fixed-dose combination of dolutegravir, abacavir, and lamivudine. Participants also received placebo tablets matching the alternative treatment; thus investigators, participants, and study staff who administered treatments, assessed outcomes, and collected data were masked to treatment assignment. Study investigators established participant eligibility, obtained participant numbers, and received automated treatment assignments on the basis of a randomisation sequence.

Procedures

Participants received co-formulated bictegravir (50 mg), emtricitabine (200 mg), and tenofovir alafenamide (25 mg) or fixed-dose, combination dolutegravir (50 mg), abacavir (600 mg), and lamivudine (300 mg) once a day for 48 weeks. All participants received two tablets (active treatment and placebo) once a day. Both regimens were given without regard to food.

We did post-baseline study visits in the randomised (blinded) phase at week 4, 8, 12, 24, 36, and 48, after which participants were invited to receive open-label bictegravir, emtricitabine, and tenofovir alafenamide, with visits every 12 weeks, in an extension phase up to an additional 96 weeks. Blood and urine samples were collected at baseline, at week 4, 8, and 12, and then every 12 weeks up to week 48. Plasma viral loads were measured by the central laboratory (Covance Laboratories, Indianapolis, IN, USA; Geneva, Switzerland; or Singapore) with Roche TaqMan 2.0 (Roche Diagnostics, Rotkreuz, Switzerland).

Laboratory tests were done by Covance Laboratories and included haematological analysis, serum chemistry tests, and measurement of fasting lipid parameters (total cholesterol, LDL and HDL cholesterol, total cholesterol to HDL ratio, triglycerides), CD4 cell counts (absolute and percentage), renal function parameters (serum creatinine, estimated glomerular filtration rate [calculated with the Cockcroft-Gault equation], and ratios of albumin to creatinine, retinol binding protein to creatinine, and β2-microglobulin to creatinine in urine). Resistance testing, done by Monogram Biosciences (South San Francisco, CA, USA), consisted of genotypic and phenotypic analysis of integrase, protease, and reverse transcriptase in participants with confirmed HIV-1 RNA of 50 copies per mL or higher whose confirmation sample (taken 2–3 weeks after the date of the original test indicating HIV-1 RNA ≥50 copies per mL) had HIV-1 RNA of at least 200 copies per mL or in those with HIV-1 RNA of 50 copies per mL or higher at study drug discontinuation or week 48. Retrospective HIV-1 proviral DNA genotyping of baseline samples was also done in participants who qualified for resistance testing.

We tested hip and spine lumbar bone mineral density before drug administration at baseline and then at week 24 and 48 using dual energy x-ray absorptiometry. Individuals at a centralised centre (BioClinica, Newtown, PA, USA), who were masked to treatment assignment, read all of the scans.

Safety was assessed by physical examinations, laboratory tests, 12-lead electrocardiograms, and recording of concomitant drugs and adverse events coded with the Medical Dictionary for Regulatory Activities version 19.1. Study treatment was discontinued if requested by the participant and in cases of unacceptable toxic effects, pregnancy, or development of active tuberculosis infection.

The pharmacokinetics of bictegravir, emtricitabine, and tenofovir alafenamide were assessed in a subset of participants who provided written informed consent in the bictegravir group. Post-dose blood samples were obtained from these individuals at 0·5, 1, 1.5, 2, 3, 4, 6, 8, and 24 h after an observed dose at the clinic, and trough blood samples were obtained at the week 4 or 8 visit at 20–28 h after the last dose of study drug. We then measured plasma concentrations of bictegravir, emtricitabine, and tenofovir alafenamide with fully validated high-performance liquid chromatography tandem mass spectroscopy bioanalytical methods, which were performed and validated by QPS Holdings (Newark, DE, USA).

Outcomes

The primary outcome was the proportion of participants with plasma HIV-1 RNA of 50 copies per mL or more at week 48, as defined by the US Food and Drug Administration (FDA) snapshot algorithm.[16] Other prespecified efficacy endpoints were the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL and less than 20 copies per mL at week 48, according to the FDA-defined snapshot algorithm, and change in CD4 cell count (absolute and percentage) from baseline to week 48.

Safety outcomes were incidence of adverse events and laboratory abnormalities, percentage changes from baseline to week 48 in hip and lumbar spine bone mineral densities, and changes from baseline to week 48 in renal function parameters and fasting lipid parameters. We also summarised the number of participants who initiated treatment with lipid-modifying drugs during the study.

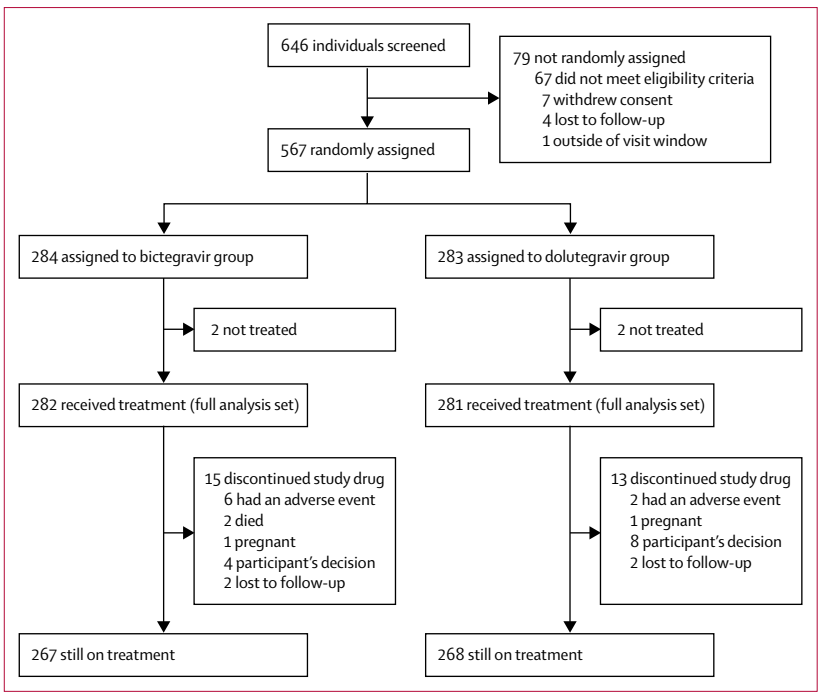

Figure: **Trial profile**
Participants in the bictegravir group received bictegravir, emtricitabine, and tenofovir alafenimide. Participants in the dolutegravir group received dolutegravir, abacavir, and lamivudine.

Statistical analysis

Assuming that 2% of participants in each treatment group would have HIV-1 RNA of 50 copies per mL or higher at week 48, a sample size of 520 participants would achieve at least 90% power to detect non-inferiority at a one-sided α of 0·025. Non-inferiority for the primary efficacy endpoint was established if the upper bound of the 95% CI for the difference between the groups (bictegravir group minus dolutegravir group) was less than 4%. Power was calculated for the primary efficacy endpoint only; the study was not powered to detect differences in secondary endpoints.

We did the primary analysis after all enrolled participants had completed their week 48 study visit or had prematurely discontinued the study drug. The primary efficacy analysis used the full analysis set, which was defined as all randomised participants who received at least one dose of study drug. We also analysed the primary efficacy endpoint using the per-protocol analysis set, which excluded participants in the full analysis set who did not have a plasma HIV-1 RNA value in the week 48 analysis window (days 295–378 inclusive) because of study drug discontinuation for reasons other than lack of efficacy, who had low adherence (defined as adherence below the 2·5th percentile), and who violated key entry criteria.

We did two planned interim analyses that were reviewed by the independent data monitoring committee. The first was done after roughly the first 50% of enrolled participants had completed their week 12 study visit or had prematurely discontinued study drugs, and the second was done when all participants had completed their week 24 study visit or had prematurely discontinued study drugs. Both 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 for the primary endpoint at week 48 was 0·04998, corresponding to a 95·002% CI.

We calculated the point estimate of treatment difference in the proportion of participants with HIV-1 RNA of 50 copies per mL or higher at week 48, and the associated two-sided 95·002% CI, using an unconditional exact method with two inverted one-sided tests. In the snapshot analysis, participants were classified according to three outcomes: those with plasma HIV-1 RNA of 50 copies per mL or higher at week 48 or at the last visit before discontinuation of study drug at or before week 48 because of lack of efficacy or other reasons; those with plasma HIV-1 RNA of less than 50 copies per mL at week 48; and those with no virological data in the week 48 window, including those who discontinued study drug for reasons other than lack of efficacy at or before week 48 whose last available plasma HIV-1 RNA was less than 50 copies per mL, and those who were still on study drug but were missing data in the week 48 window.

The proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 was analysed similarly to the primary efficacy endpoint, except that non-inferiority was defined if the lower bound of the 95·002% CI of the difference in virological response between the groups (bictegravir group minus dolutegravir group) was greater than –10%. We also assessed the proportion of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 according to the subgroups of age, sex, race, geographic region, and study drug adherence, and with missing data imputed as treatment failure or participant exclusion. We estimated study drug adherence as number of pills taken divided by number of pills prescribed, where number of pills taken was number dispensed minus number returned. The proportion of participants with HIV-1 RNA of less than 20 copies per mL at week 48 according to the FDA-defined snapshot algorithm was analysed similarly to the proportion of participants with HIV-1 RNA of less than 50 copies per mL at week 48.

Change from baseline to week 48 in CD4 cell count (absolute and percentage) in the full analysis set was summarised by treatment group with descriptive statistics. We calculated differences between the groups in changes from baseline to week 48 in CD4 cell counts (absolute and percentage), and their corresponding 95% CIs, using ANOVA, with inclusion of treatment group as a fixed effect in the model.

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. Safety data are described using all data collected between baseline and either the data cutoff date for the week 48 analysis (April 26, 2017) or, for participants who discontinued treatment early, up to 30 days after the last dose of study drug. For categorical baseline data, p values were calculated with the Cochran-Mantel-Haenszel test (the general association statistic was used for nominal data, and the row mean scores differ statistic was used for ordinal data). For continuous baseline data, p values were derived from the two-sided Wilcoxon rank-sum test.

For certain prespecified renal and lipid continuous laboratory data, we used the two-sided Wilcoxon rank-sum test. For bone mineral density data, we calculated differences in percentage changes from baseline to week 48 between treatment groups, and their corresponding p values and 95% CIs, using ANOVA, with inclusion of treatment group as a fixed effect. Fisher's exact test was used to compare differences between treatment groups in the incidence of adverse events.

We used SAS Software version 9.4 for all statistical analyses. Pharmacokinetic parameters were calculated with a non-linear model using standard non-compartmental analysis in Phoenix WinNonlin version 6.4.

This study is registered with ClinicalTrials.gov, number NCT02603120.

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 the first author, writing of the manuscript. All authors had access to the data. 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 11, 2015, and July 6, 2016, 646 participants were screened for eligibility and 567 were randomly assigned to bictegravir, emtricitabine, and tenofovir alafenamide (n=284) or to dolutegravir, abacavir, and lamivudine (n=283; figure). Four randomised participants, two in each group, did not receive study drugs because of withdrawal of consent or protocol violation. The median duration of treatment was 49·9 weeks (IQR 45·1–56·3) in the bictegravir group and 50·3 weeks (45·1–56·3) in the dolutegravir group. Demographic and baseline characteristics were generally balanced between the groups (table 1), with the exception of baseline CD4 cell counts, which were higher in the bictegravir group than in the dolutegravir group.

The proportion of participants with plasma HIV-1 RNA 50 copies per mL or more at week 48 did not differ between groups (table 2), showing non-inferiority of the bictegravir regimen relative to the dolutegravir regimen. These results were consistent in the per-protocol analysis, in which one (<1%) of 257 participants in the bictegravir group had an HIV-1 RNA of 50 copies per mL or higher at week 48 compared with none of the 256 participants in the dolutegravir group (difference 0·4%, 95·002% CI –1·1 to 2·2; p=1·00).

Other secondary outcomes supported the primary efficacy outcome. The small differences in proportions of participants with plasma HIV-1 RNA of less than 50 copies per mL at week 48 were not significant (table 2), which was also true in subgroup analyses (appendix p 4), and when missing data were imputed as treatment failures or participant exclusions (table 2). 254 (90%) of

See Online for appendix

	Bictegravir group (n=282)	Dolutegravir group (n=281)
Age (years)	47 (21–71)	45 (20–70)
Sex		
Men	247 (88%)	252 (90%)
Women	35 (12%)	29 (10%)
Race*		
White	206/282 (73%)	202/278 (73%)
Black	59/282 (21%)	62/278 (22%)
Asian	9/282 (3%)	9/278 (3%)
Native Hawaiian or Pacific Islander	3/282 (1%)	0
Native American or Alaska Native	2/282 (1%)	2/278 (1%)
Other	3/282 (1%)	3/278 (1%)
Ethnicity*		
Hispanic or Latino	46/282 (16%)	52/279 (19%)
HCV co-infection	0	1 (<1%)
eGFR (mL/min)	101 (85–119)	101 (85–122)
Body-mass index (kg/m^2)	26·3 (23·7–29·3)	25·9 (23·9–29·1)
HIV-1 RNA <50 copies per mL	278 (99%)	272 (97%)
Median CD4 count (cells per µL)	732 (554–936)	661 (478–874)
CD4 count (cells per µL)		
<50	0	0
50–199	6 (2%)	4 (1%)
200–349	16 (6%)	30 (11%)
350–499	33 (12%)	42 (15%)
≥500	227 (80%)	205 (73%)
HIV disease status		
Asymptomatic	243 (86%)	245 (87%)
Symptomatic HIV Infection	9 (3%)	9 (3%)
AIDS	30 (11%)	27 (10%)
Regimen at baseline		
ABC/DTG/3TC FDC	270 (96%)	265 (94%)
ABC/3TC FDC plus DTG	12 (4%)	15 (5%)
ABC plus 3TC plus DTG	0	1 (<1%)
Time on regimen before study drug dosing (years)	1·1 (0·8–1·6)	1·2 (0·9–1·6)

Data are median (IQR), n (%), or n/N (%), except for age, which is median (range). HCV=hepatitis C virus. eGFR=estimated glomerular filtration rate by Cockcroft-Gault. ABC=abacavir. DTG=dolutegravir. 3TC=lamivudine. FDC=fixed-dose combination. *Race and ethnicity were not provided for all participants.

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

	Bictegravir group (n=282)	Dolutegravir group (n=281)	Difference (95·002% CI); p value
HIV-1 RNA ≥50 copies per mL	3 (1%)	1 (<1%)	0·7% (−1·0 to 2·8); 0·62
HIV1 RNA ≥50 copies per mL in week 48 window	1 (<1%)	0	..
Treatment discontinued before week 48 because of lack of efficacy	0	0	..
Treatment discontinued before week 48 because of adverse events or death with last available HIV-1 RNA ≥50 copies per mL	1 (<1%)	0	..
Treatment discontinued before week 48 for reasons* other than lack of efficacy, adverse events, or death with last available HIV-1 RNA ≥50 copies per mL	1 (<1%)	1 (<1%)	..
No virological data available	15 (5%)	13 (5%)	..
Discontinued study drug because of adverse event or death with last available HIV-1 RNA <50 copies per mL	5 (2%)	2 (1%)	..
Discontinued study drug because of reasons* other than lack of efficacy, adverse events, or death with last available HIV-1 RNA <50 copies per mL	5 (2%)	9 (3%)	..
On study drug but missing data in week 48 window	5 (2%)	2 (1%)	..
HIV-1 RNA <50 copies per mL	264 (94%)	267 (95%)	−1·4% (−5·5 to 2·6); 0·59
Missing data imputed as treatment failure	268/282 (95%)	268/281 (95%)	−0·3% (−4·1 to 3·4); 1·00†
Missing data imputed as participant exclusion	268/269 (100%)	268/268 (100%)	−0·4% (−2·1 to 1·1); 1·00†

Data are n (%) or n/N (%). *Other reasons include investigator's decision, participant's decision, loss to follow-up, non-compliance with study drug, protocol violation, pregnancy, and study terminated by sponsor. †Data are difference (95% CI); p value.

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

282 participants in the bictegravir group had plasma HIV-1 RNA of less than 20 copies per mL at 48 weeks compared with 257 (91%) of 281 participants in the dolutegravir group (difference −1·4%, 95% CI −6·4 to 3·5; p=0·66).

CD4 cell counts from baseline to week 48 decreased by 31 cells per µL (SD 181) in the bictegravir group and increased by 4 cells per µL (191) in the dolutegravir group (difference in least squares mean [LSM] −35 cells per µL, 95% CI −67 to −3; p=0·031). After adjusting for baseline CD4 cell count, the difference in mean CD4 count changes from baseline to week 48 between groups was not significant (difference in LSM −21 cells per µL, 95% CI −51 to 9; p=0·18). Mean CD4 cell counts at week 48 were similar between treatment groups: 724 cells per µL (SD 282) in the bictegravir group versus 691 cells per µL (302) in the dolutegravir group (difference in LSM 33 cells per µL, 95% CI −17 to 83; p=0·19). Mean changes from baseline to week 48 in CD4 percentages were similar between groups (1·0% [SD 3·8] in the bictegravir group *vs* 0·5% [3·8] in the dolutegravir group; difference in LSM 0·5%, 95% CI −0·1 to 1·2; p=0·12).

Five participants met protocol-defined criteria for resistance testing and underwent genotypic and phenotypic resistance analysis, including three in the bictegravir group and two in the dolutegravir group. No virological resistance developed to any component of either regimen. Two of the five participants, one in each group, had several unreturned pill bottles, suggesting possible intermittent adherence; HIV-1 RNA was resuppressed to less than 50 copies per mL in both without a change in regimen. Two participants in the bictegravir group discontinued the study early with HIV-1 RNA greater than 200 copies per mL: one at week 24 with HIV-1 RNA of 499 copies per mL and several unreturned pill bottles, and one at week 12 with HIV-1 RNA of 928 copies per mL and 94% adherence by pill count. No archived primary resistance mutations to study drugs were observed in their baseline samples, and data were not available for their early discontinuation samples because of assay failure or insufficient sample volume for testing. One participant with good adherence (98% by pill count) in the dolutegravir group discontinued the study at week 8 with HIV-1 RNA of 12 600 copies per mL. A baseline sample for this individual was not available for resistance testing, and no resistance to study drugs was detected in their early discontinuation sample.

In the 15 participants included in the intensive pharmacokinetic substudy, mean trough concentration of bictegravir was 2282·9 ng/mL (coefficient of variation 61·7%; appendix p 5), which is more than 14 times higher than the protein-adjusted 95% effective concentration (162 ng/mL) against wild-type HIV-1 virus.[2] This finding was consistent with pharmacokinetic results reported in studies of treatment-naive individuals.[3,4] The pharmacokinetics of emtricitabine and tenofovir alafenamide (appendix p 5) were also consistent with historical data in HIV-1-infected people.[17,18]

Both treatments were well tolerated, and most adverse events were mild or moderate in severity (table 3). Adverse events leading to study drug discontinuation were uncommon, occurring in six (2%) of 282 participants in the bictegravir group and in two (1%) of 281 participants in the dolutegravir group. Adverse events leading to study drug discontinuation in the bictegravir group were headache (n=2), abnormal dreams (n=1), cerebrovascular accident (n=1), suicidal ideation (n=1), and vomiting (n=1); all were considered by the investigator to be related

to study drug, except suicidal ideation, which was not thought to be treatment related because of the participant's extensive psychiatric history at baseline. Adverse events leading to study drug discontinuation in the dolutegravir group were headache (n=1) and pruritus (n=1); both were thought to be treatment related. Fewer treatment-related adverse events occurred in the bictegravir group than in the dolutegravir group, and most were mild or moderate in severity. The difference between groups in incidence of treatment-related adverse events was mainly a result of drug-related gastrointestinal (ie, flatulence, nausea, diarrhoea) and neuropsychiatric (ie, abnormal dreams, insomnia) adverse events in the dolutegravir group (table 3).

Two participants in the bictegravir group died during the study; neither death was considered related to study drugs. One individual died from sudden cardiac death resulting from hypertensive atherosclerotic cardiovascular disease. The other participant died from mixed alcohol and opioid toxicity. No deaths occurred in the dolutegravir group. Two pregnancies were reported during the study; one in each group. In these individuals, study drugs were discontinued and non-study antiretroviral therapies were initiated by the investigators. Incidence of grade 3 or 4 laboratory abnormalities was similar between groups (appendix p 6). With the exception of elevated LDL (5% in both groups), no laboratory abnormalities occurred in more than 3% of participants in either group. The differences between the groups (eg, in alanine aminotransferase and amylase concentrations) were explained by non-treatment-related causes.

Small increases from baseline to week 48 were seen in hip and lumbar spine bone mineral densities, and these were similar between the groups (appendix p 9). Fractures were reported in five (2%) of 282 participants in the bictegravir group and in seven (3%) of 281 participants in the dolutegravir group. No fracture was considered by the investigator to be treatment related, and none resulted in discontinuation of study drugs.

No cases of proximal tubulopathy or Fanconi syndrome, or treatment discontinuations because of renal adverse events, were reported in either group. Median serum creatinine concentration did not change from baseline to week 48 in the bictegravir group (median change from baseline was 0·00 mg/dL, IQR –0·07 to 0·06), whereas it had increased slightly by week 4 in the dolutegravir group (0·02 mg/dL, –0·05 to 0·09; p=0·019), and this increase remained stable through week 48. The median estimated glomerular filtration rate increased slightly between baseline and week 48 in the bictegravir group, whereas it decreased slightly in the dolutegravir group (median change from baseline was 1·0 mL/min [IQR –5·2 to 9·4] in the bictegravir group *vs* –1·8 mL/min [–9·0 to 4·8] in the dolutegravir group; p=0·0002). These differences were observed by week 4 and were generally stable through week 48. At 48 weeks, percentage changes from baseline in quantitative proteinuria (total urinary albumin to urine creatinine ratio) and tubular proteinuria (ratio of retinol binding protein or β2-microglobulin to urine creatinine) were similar between groups (appendix p 7).

	Bictegravir group (n=282)	Dolutegravir group (n=281)	p value
Any adverse event	225 (80%)	225 (80%)	1·00
Most common adverse events*			
Upper respiratory tract infection	29 (10%)	27 (10%)	0·89
Nasopharyngitis	20 (7%)	22 (8%)	0·75
Headache	19 (7%)	21 (7%)	0·75
Diarrhoea	24 (9%)	14 (5%)	0·13
Arthralgia	19 (7%)	10 (4%)	0·13
Insomnia	8 (3%)	14 (5%)	0·20
Grade 3 or 4 adverse event	16 (6%)	10 (4%)	0·32
Serious adverse event	15 (5%)	22 (8%)	0·24
Treatment-related adverse event	23 (8%)	44 (16%)	0·006
Treatment-related serious adverse event	1 (<1%)†	0	1·00
Adverse event leading to study drug discontinuation‡	6 (2%)	2 (1%)	0·29
Death§	2 (1%)	0	0·50
Most common treatment-related adverse events¶			
Headache	7 (2%)	8 (3%)	0·80
Diarrhoea	2 (1%)	4 (1%)	0·45
Abnormal dreams	1 (<1%)	5 (2%)	0·12
Fatigue	1 (<1%)	3 (1%)	0·37
Flatulence	0	5 (2%)	0·030
Nausea	0	5 (2%)	0·030
Insomnia	0	3 (1%)	0·12

Data are n (%).*Occurring in ≥5% of participants in either group. †Cerebrovascular accident. ‡Included headache (n=2), abnormal dreams (n=1), cerebrovascular accident (n=1), suicidal ideation (n=1), and vomiting (n=1) in the bictegravir group, and headache (n=1) and pruritus (n=1) in the dolutegravir group. §Causes included sudden cardiac death due to hypertensive and atherosclerotic cardiovascular disease (n=1) and mixed alcohol and opioid toxicity (n=1). ¶Occurring in ≥1% of participants in either group.

Table 3: **Summary of adverse events**

Changes from baseline to week 48 in fasting total cholesterol, LDL cholesterol, and HDL cholesterol, and in the ratio of total cholesterol to HDL cholesterol, were similar between groups (appendix p 8). The median change from baseline to week 48 in fasting triglyceride concentrations was –5 mg/dL in the bictegravir group compared with 3 mg/dL in the dolutegravir group (p=0·028). Three (1%) of 282 participants in the bictegravir group initiated treatment with lipid-modifying drugs during the study versus 11 (4%) of 281 participants in the dolutegravir group (p=0·033).

Discussion

Switching to bictegravir, emtricitabine, and tenofovir alafenamide maintained high rates of efficacy and was non-inferior to remaining on dolutegravir, abacavir, and lamivudine, with only a few participants in each group having plasma HIV-1 RNA of 50 copies per mL or higher at week 48. Other efficacy outcomes confirmed the primary endpoint. Both regimens were well tolerated, with fewer participants in the dolutegravir group

discontinuing the study drug because of adverse events, but also fewer participants in the bictegravir group having drug-related adverse events. This difference was mainly driven by more treatment-related gastrointestinal and neuropsychiatric adverse events in the dolutegravir group than in the bictegravir group.

Changes in hip and lumbar spine bone mineral densities were not significantly different between treatment groups, nor were changes in renal function parameters, with no renal-related discontinuations or cases of proximal tubulopathy or Fanconi syndrome observed in either group. Small increases in the estimated glomerular filtration rate were observed with the bictegravir regimen, compared with small decreases with the dolutegravir regimen. These differences were not considered clinically relevant and probably reflect differences in affinity for renal tubular transporters between bictegravir and dolutegravir. Changes in fasting lipid parameters were generally similar between groups. The essentially indistinguishable bone, renal, and lipid profiles indicate that switching from an abacavir-containing to a tenofovir alafenamide-containing regimen was not associated with changes in bone and renal parameters indicative of tenofovir disoproxil fumarate toxicity or with adverse changes in lipid parameters.

This study has several limitations. The trial was not powered for secondary outcomes; thus, the incidence of treatment-related adverse events might be higher over longer treatment durations and in larger participant populations. Other limitations are that the participants represented a reasonably healthy population, with only a small proportion of them having advanced HIV disease or co-infection with chronic HCV, and that women were under-represented in the study. Finally, because of the double-blind, active-controlled study design, the effect of switching from the larger fixed-dose combination tablet of co-formulated abacavir, lamivudine, and dolutegravir to the smaller co-formulated tablet of bictegravir, emtricitabine, and tenofovir alafenamide could not be directly assessed with regard to tablet size, acceptability, or palatability.

The results of this study are consistent with those from two large clinical trials[3,4] that showed that bictegravir, emtricitabine, and tenofovir alafenamide had good efficacy and tolerability, and did not induce resistance, in treatment-naive adults with HIV-1 infection, as well as with those from another phase 3 study[5] in which virologically suppressed adults switched to bictegravir, emtricitabine, and tenofovir alafenamide from boosted protease inhibitor regimens. In this study, switching to bictegravir, emtricitabine, and tenofovir alafenamide was non-inferior to continuing dolutegravir, abacavir, and lamivudine for maintenance of virological suppression, with low rates of virological failure and no emergence of drug resistance. Our findings suggest that the tolerability profile for bictegravir, emtricitabine, and tenofovir alafenamide is similar to that of dolutegravir, abacavir, and lamivudine, including in measures of bone, renal, and lipid safety. This finding is particularly notable within the context of a switch study, in which the enrolled participants are presumably already tolerating their original regimen and, in many switch studies, more adverse events are reported in the switch group than in the group that receives baseline treatment. Together, our results suggest that the fixed-dose combination of bictegravir, emtricitabine, and tenofovir alafenamide is an efficacious and well tolerated regimen for the initial and ongoing treatment of individuals with HIV-1 infection.

Contributors

J-MM, DW, IB, AM, H-JS, LL-C, PR, DP, and CB enrolled participants, analysed data, and independently interpreted the results. HM, AC, and EQ designed the study. HL did the data analyses, which were reviewed and interpreted by JC, KA, HM, AC, and EQ. The first draft was written by J-MM and HM. All authors were involved in the development of the primary manuscript and interpretation of the data, contributed to editing of the manuscript, and have read and approved the final version for publication.

Declaration of interests

J-MM reports serving on advisory boards for Gilead Sciences, Merck, ViiV Healthcare, Janssen, Bristol-Myers Squibb (BMS), and Teva, and has received research grants from Gilead Sciences. DW reports grants and personal fees for research, speakers' bureau, and serving on advisory boards from Gilead Sciences and ViiV Healthcare. IB reports grants from Gilead Sciences, during the conduct of the study, and grants and personal fees from Gilead Sciences and Janssen, and grants from GlaxoSmithKline, outside the submitted work. AM reports grants and personal fees from Gilead Sciences; grants from ViiV Healthcare, Merck, and BMS; and personal fees from ViiV and Merck. 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. PR reports research support from AbbVie, BMS, Gilead Sciences, GlaxoSmithKline, Idenix, Janssen, and Merck, and consulting fees from AbbVie, Gilead Sciences, and Janssen, and serves on the speakers' bureau for Abbvie, Gilead Sciences, Janssen, and ViiV Healthcare. DP reports research grants and honoraria for participation in advisories or conferences from ViiV Healthcare, Pfizer, BMS, Gilead Sciences, Janssen, and Merck. 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. JC, HL, KA, HM, AC, and EQ are employees of Gilead Sciences and hold stock interest in the company. All other authors declare no competing interests.

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