Maintenance therapy with dolutegravir and lamivudine versus bictegravir, emtricitabine, and tenofovir alafenamide in people with HIV (PASO-DOBLE): 48-week results from a randomised, multicentre, open-label, non-inferiority trial

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Summary

Background Although single-tablet, oral bictegravir, emtricitabine, and tenofovir alafenamide or dolutegravir and lamivudine are preferred regimens in several major guidelines and are widely used in many countries, they have not been compared in a fully powered trial. This study aimed to prospectively compare the 48-week results of dolutegravir and lamivudine versus bictegravir, emtricitabine, and tenofovir alafenamide as maintenance therapies for people with HIV.

Methods PASO-DOBLE is a randomised, multicentre, open-label, non-inferiority trial done over 48 weeks at 30 sites in Spain. Adults (aged ≥18 years) with HIV-1, without previous viral failure, who had reached virological suppression on oral regimens containing at least one pill a day, cobicistat, efavirenz, or tenofovir disoproxil fumarate and no previous use of dolutegravir or bictegravir, and plasma HIV-1 RNA <50 copies per mL for at least 24 weeks were eligible. Participants were randomly assigned (1:1) to switch regimens to dolutegravir 50 mg and lamivudine 300 mg or bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg once daily, using random block permutation, stratified by tenofovir alafenamide presence at baseline and sex assigned at birth. The primary endpoint was the proportion of participants with HIV RNA ≥50 copies per mL at week 48 in the intention-to-treat exposed population (ie, all participants who received at least one dose of study medication). The primary and safety analysis was done in the intention-to-treat exposed population. The non-inferiority margin was 4%. This trial is registered with ClinicalTrials.gov NCT04884139 and is incomplete.

Findings Between July 14, 2021, and March 24, 2023, 553 participants initiated dolutegravir and lamivudine (n=277) or bictegravir, emtricitabine, and tenofovir alafenamide (n=276). The difference in the proportion of participants with HIV RNA ≥50 copies per mL between the dolutegravir and lamivudine group (six [2%] of 277) and bictegravir, emtricitabine, and tenofovir alafenamide group (two [1%] of 276) was 1·4% (95% CI –0·5 to 3·4; p=0·16), showing non-inferiority. The most common adverse events occurring in at least 10% of participants in either group were infections, musculoskeletal, gastrointestinal, metabolic, and psychiatric events. Adverse events were usually mild or moderate and considered unrelated to the study drugs. More grade 3–4 adverse events occurred in the bictegravir group (ten [3%]) than in the dolutegravir group (three [1%]; p=0·049). Very few participants discontinued dolutegravir and lamivudine (n=1) or bictegravir, emtricitabine, and tenofovir alafenamide (n=2) due to adverse events. There were no deaths in either group.

Interpretation These results provide further evidence that might be useful in shared decision-making between physicians and people living with HIV regarding switching oral antiretroviral therapy.

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For the Spanish translation of the abstract see **Online** for appendix 1

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Introduction

Most people with HIV treated with antiretroviral therapy reach virological suppression.[1] However, some still receive suboptimal regimens containing more than one pill a day, boosting agents, or drugs with cumulative toxicity, such as tenofovir disoproxil fumarate or efavirenz.[2] Switching otherwise effective regimens to alternative regimens, because of pill burden or food restrictions, risk of drug interactions, toxicity, or negative effects on age-related comorbidities, is becoming increasingly important.

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See **Online** for appendix 2

Research in context

Evidence before this study

Optimisation of antiretroviral therapy is of paramount importance as continuous treatment is needed for life. Bictegravir, emtricitabine, tenofovir alafenamide and dolutegravir and lamivudine are oral reference regimens in major guidelines but they have not been compared in fully powered trials. The regimens containing second-generation integrase inhibitors dolutegravir or bictegravir and the nucleoside reverse transcriptase inhibitor tenofovir alafenamide have been associated with more weight gain than other regimens, although the specific role of these individual drugs on promoting weight gain has been questioned. We searched PubMed, with no start date or language restrictions, using the search terms "bictegravir/emtricitabine/tenofovir alafenamide" and "dolutegravir/lamivudine" and "randomised trial" for articles published to May 19, 2025. We identified three publications: the DEBATE, RUMBA, and DYAD trials. All trials were performed in people with HIV with virological suppression. DEBATE aimed to address immunological changes, and RUMBA aimed to address viral reservoir; none of these publications reported on other efficacy outcomes or weight changes. DYAD addressed virological outcomes and reported weight changes but included exclusively people with HIV receiving bictegravir, emtricitabine, and tenofovir alafenamide who switched to dolutegravir and lamivudine or maintained bictegravir, emtricitabine, and tenofovir alafenamide.

Added value of this study

Dolutegravir and lamivudine and bictegravir, emtricitabine, and tenofovir alafenamide have previously shown non-inferior efficacy to standard triple therapies in clinical trials. We hypothesised that switching to dolutegravir and lamivudine would be non-inferior to switching to bictegravir, emtricitabine, and tenofovir alafenamide in people with HIV with virological suppression. At 48 weeks, non-inferiority (4% margin) of dolutegravir and lamivudine versus bictegravir, emtricitabine, and tenofovir alafenamide was shown. The bictegravir group showed greater weight gain and clinically significant weight gain (considered as >5% from baseline) than the dolutegravir group. These findings add value to existing evidence suggesting that, in people with HIV with virological suppression, switching to bictegravir, emtricitabine, and tenofovir alafenamide might be associated with higher weight gain than switching to dolutegravir and lamivudine, particularly when tenofovir disoproxil fumarate or abacavir are components in the discontinued regimen. Both study regimens are convenient and effective options for switching antiretroviral regimens, although weight gain with both regimens was greater than expected in the general population.

Implications of all the available evidence

In people with HIV with virological suppression, switching to dolutegravir and lamivudine is as highly effective as switching to bictegravir, emtricitabine, and tenofovir alafenamide. The risk of virological failure is low and there is no emerging genotypic resistance. Both regimens are associated with greater weight gain than that reported for the general population, but the weight gain is higher with bictegravir, emtricitabine, and tenofovir alafenamide than with dolutegravir and lamivudine. Discontinuation of tenofovir disoproxil fumarate or abacavir and the introduction of tenofovir alafenamide appeared to be necessary factors to explain the greater proportion of participants with clinically significant weight gain in the bictegravir group than the dolutegravir group, although the underlying mechanisms responsible for weight gain remain unknown.

Despite single-tablet oral regimens of bictegravir, emtricitabine, and tenofovir alafenamide and dolutegravir and lamivudine being preferred in major guidelines and being widely used in many countries, no fully powered trials have compared them. Regimens containing the second-generation integrase inhibitors dolutegravir or bictegravir and the nucleoside reverse transcriptase inhibitor tenofovir alafenamide have been associated with greater weight gain than other regimens,[3] although the causative role of these drugs on weight gain has been questioned.[4]

We hypothesised that switching regimens to dolutegravir and lamivudine would be non-inferior to switching to bictegravir, emtricitabine, and tenofovir alafenamide. If dolutegravir and bictegravir have been associated with similar weight gain in people with HIV who have reached virological suppression[5] and concomitant use of tenofovir alafenamide induces additional weight gain,[6] we also hypothesised that switching regimens to bictegravir, emtricitabine, and tenofovir alafenamide might result in greater weight gain than switching to dolutegravir and lamivudine. This study aimed to prospectively evaluate the efficacy and safety of switching regimens to dolutegravir and lamivudine versus bictegravir, emtricitabine, and tenofovir alafenamide in adults with established virological suppression at 48 weeks.

Methods

Study design

PASO-DOBLE is a phase 4, randomised, multicentre, parallel-group, open-label, non-inferiority trial conducted over 96 weeks at 30 hospitals in Spain.

The protocol was approved by institutional review boards at each site and the Spanish Agency of Medicines and Medical Devices (AEMPS). The study is registered with EudraCT, 2020–003686–18, and ClinicalTrials.gov, NCT04884139 and is incomplete.

Participants

Asymptomatic, clinically stable adults (aged ≥18 years) with HIV-1, without previous viral failure, on any oral regimen containing one or more pill a day, or cobicistat, efavirenz, or tenofovir disoproxil fumarate, and plasma HIV-1 RNA <50 copies per mL for at least 24 weeks were eligible. Sex assigned at birth was collected via hospital files, and gender data were self-reported; the options provided were female, male, or other. Women of reproductive age were required to have a negative pregnancy test and agree to use highly effective contraception.

Exclusion criteria included pregnancy or lactation, resistance mutations to study drugs, previous therapy with dolutegravir and bictegravir, chronic hepatitis B or untreated hepatitis C, abnormal liver function (defined by alanine aminotransferase ≥5 times upper limit of normal [ULN] or aspartate aminotransferase ≥3 times ULN and total bilirubin ≥1·5 times ULN [with >35% direct bilirubin]), unstable liver disease (defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, oesophageal or gastric varices, or persistent jaundice), cirrhosis, known biliary abnormalities (apart from hyperbilirubinemia due to Gilbert's syndrome or asymptomatic gallstones), estimated glomerular filtration rate (eGFR; as measured by the Chronic Kidney Disease Epidemiology Collaboration equation) <50 mL/min per 1·73 m³, or any clinical condition diagnosed within 6 months or concomitant therapy that might primarily affect weight or body composition including but not limited to endocrine disorders, osteoporosis, or medications to treat these clinical conditions, with the exception of controlled diabetes. Participants were collected via electronic case report form (in Spanish). A complete list of eligibility criteria can be found in the protocol (appendix 2 pp 42–368). All participants provided written informed consent.

Randomisation and masking

Participants were randomly assigned (1:1) to dolutegravir and lamivudine (dolutegravir group) or bictegravir, emtricitabine, and tenofovir alafenamide (bictegravir group). Randomisation was performed centrally by the sponsor, using a web-based computer-generated randomisation list with random permuted blocks (size of 4), stratified by sex assigned at birth and presence of tenofovir alafenamide at screening. We stratified by sex at birth and tenofovir alafenamide at screening because these factors were known to be associated with weight gain at the time of trial design. We did not stratify by centre because some participating centres were expected to recruit few participants, and stratifying simultaneously by sex, centre, and tenofovir alafenamide at screening would have resulted in some strata with participants in only one treatment group, and thus we would have needed to collapse small centres.

Procedures

Each participant was prescribed to switch their regimens to either dolutegravir 50 mg and lamivudine 300 mg or bictegravir 50 mg, emtricitabine 200 mg, and tenofovir alafenamide 25 mg once daily. Participants were followed up at weeks 6, 24, and 48. At baseline, demographic, clinical, and HIV characteristics were collected. At each visit, participants had a physical examination, including taking weight and height, and at least 8-h fasting blood was drawn for chemistry, CD4 cell count, CD8 cell count, and plasma HIV-1 RNA concentration. Data on adverse events and non-antiretroviral medications were collected, simplified self-administered questionnaires on diet quality,[7] physical activity,[8] and adherence[9] were completed, and a pregnancy test was performed in women of childbearing age. Adverse effects were classified according to the Medical Dictionary for Regulatory Activities.

Participants were withdrawn from the study in the case of pregnancy, consent withdrawal, non-adherence, treatment discontinuation due to adverse events, any predefined liver-related stopping criteria,[10] grade 3 or worse allergic reactions, grade 4 eGFR decrease, loss to follow-up, any other concurrent process or protocol deviation precluding study participation, or termination of the trial by the sponsor. Protocol-defined virological failure (HIV-1 RNA ≥50 copies per mL followed by a consecutive assessment ≥200 copies per mL 2–4 weeks later) was not considered a discontinuation criterion; in this case, plasma was analysed locally to detect genotypic resistance mutations.

Outcomes

The primary endpoint was the proportion of people with HIV with HIV RNA ≥50 copies per mL at week 48 in the intention-to-treat exposed population (ie, all participants who received at least one dose of study medication). The study could allow claiming for superiority. Key secondary outcomes were the change in weight and the proportion of participants with >5% weight change at 48 weeks. Other secondary endpoints reported in this paper are changes in CD4 and CD8 cell counts; genotypic resistance mutations in the case of virological failure; adverse events; changes in concentrations of fasting glucose, insulin, glycated haemoglobin (HbA1c), and plasma lipids, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) value, liver function tests, fibrosis-4 index score, and eGFR value; and the proportion of people who needed to start lipid-lowering, anti-diabetic, or anti-hypertensive medications. Additional secondary endpoints included questionnaires for patient-reported outcomes on quality of life, anxiety, depression, and sleep quality; imaging studies with dual-X-absorptiometry scans for body composition and bone mineral density; and imaging studies with abdominal CT scans for abdominal fat. These additional secondary endpoints will be reported separately. There are four planned substudies on omics, senescence, liver steatosis, and fat biopsies; the results of these planned substudies will be reported separately.

Statistical analysis

If 2% of participants in each group had HIV RNA ≥50 copies per mL at week 48, a sample size of 520 participants would be required to achieve at least 90% power to show 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 dolutegravir group and bictegravir group was less than 4%. If 5% of patients were not valid for analysis, a total sample size of 550 patients was needed. The study was also powered to detect a difference in weight change. If switching to either dolutegravir or bictegravir would be associated with a 1 kg (SD 4) increase in bodyweight (based on the NEAT022 study[11]), and if tenofovir alafenamide would result in an additional 1 kg increase in bodyweight, a sample size of 504 participants would be needed to achieve at least 80% power to detect a 1 kg weight difference between groups at a one-sided α of 0·025.

We performed a descriptive analysis of all study variables, using medians and IQRs for the quantitative variables and absolute frequencies and percentages of each category for qualitative characteristics.

Guidance from health authorities underscores that in non-inferiority trials, especially for chronic conditions like HIV, non-inferiority should be supported by evidence from the intention-to-treat and per-protocol populations. The snapshot algorithm encompasses data from randomisation to week 48. As the algorithm provides a longitudinal assessment of participants, it might be appropriate to modify the population to include participants who received the randomised intervention based on the endpoint. Therefore, a US Food and Drug Administration (FDA)-derived snapshot algorithm in the intention-to-treat exposed population was planned to assess the primary endpoint at 48 weeks (window ±6 weeks). Treatment difference was calculated using Wald CIs for the proportion difference. We performed additional sensitivity analyses to assess the proportion of people with HIV with RNA ≥50 copies per mL at 48 weeks in the intention-to-treat exposed population: a Cochran–Mantel–Haenszel test adjusted by sex assigned at birth and tenofovir alafenamide in the discontinued regimen (window ±6 weeks), and an FDA-derived snapshot algorithm (window ±8 weeks). We also performed an FDA-derived algorithm to assess the proportion of people with HIV with RNA ≥50 copies per mL at 48 weeks in the per-protocol population (ie, all participants who received at least one dose of study medication and did not meet any withdrawal or dropout criteria) and an analysis of therapeutic efficacy defined by the proportion of people with HIV with RNA <50 copies per mL (FDA snapshot algorithm, 8% non-inferiority margin) in the intention-to-treat exposed population at 48 weeks. Exploratory subgroup (including sex assigned at birth, age, race or ethnicity, previous AIDS, CD4 cell count, baseline nucleoside reverse transcriptase inhibitors [NRTIs], and core drugs) analyses of efficacy defined by the proportion of people with HIV <50 copies per mL across subgroups were also assessed in the intention-to-treat exposed population. Tenofovir disoproxil fumarate, abacavir, and tenofovir alafenamide were considered NRTI-1s, lamivudine and emtricitabine were considered NRTI-2s, and core drugs were considered non-NRTIs, protease inhibitors, or integrase inhibitors.

Safety outcomes were analysed descriptively in the intention-to-treat exposed population. Mixed models for repeated measures were used to assess treatment differences of change in weight and all other secondary quantitative outcomes over time. Diagnostic checks included visual inspection of residual plots and Q-Q plots

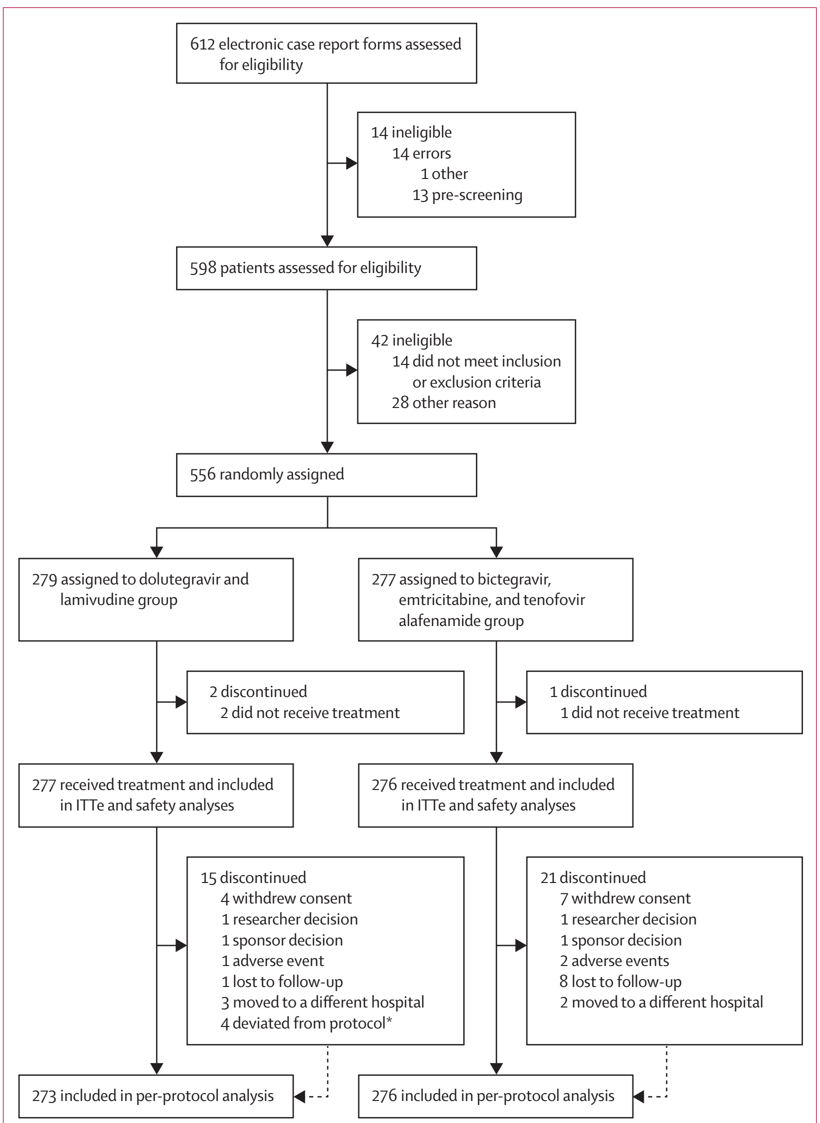

Figure 1: **Trial profile**
ITTe=intention-to-treat exposed.*Four participants who deviated from the protocol were not included in the per-protocol analysis.

for normality. Variance homogeneity tests were used to assess assumptions of linear mixed models including linearity, normality of residuals, homoscedasticity, and independence of residuals. No major violations were detected. Models included the baseline value as a covariate, with visit as the repeated factor. Logistic regression was used to assess treatment differences in patients with >5% weight gain at week 48. Models were adjusted by sex, presence of tenofovir alafenamide at screening, age, and race or ethnicity. We performed an exploratory analysis of the effect of baseline nucleoside reverse transcriptase inhibitors and core drugs on weight changes by calculating the proportion of participants with >5% weight gain by treatment group.

Values for missing data were not imputed. Only participants with complete data were included in the secondary endpoint analyses. Tests were two-tailed (except otherwise stated) and the significance level was set at 5%. All statistical analyses were done using Stata, version 18.

Role of the funding source

The funders of the study contributed to the design of the trial and approved the final protocol, contributed to the interpretation of the data, and reviewed and commented on the study report; but had no role in the collection or analysis of data or in the decision to submit the paper for publication.

Results

Between July 14, 2021, and March 24, 2023, 598 people with HIV were screened, and 556 were randomly assigned to the dolutegravir group (n=279) and bictegravir group (n=277; figure 1). 277 participants and 276 participants received each treatment, respectively. 406 (73%) of 553 participants were male and 147 (27%) were female. Participants were predominantly White (402 [73%] of 553), but a reasonable proportion self-identified as Latino (133 [24%]). Median age was 50·0 years (IQR 40·0–57·3; table 1). Median duration of antiretroviral exposure, virological suppression, and previous antiretroviral therapy were 11·4 years (IQR 7·0–19·3), 100·5 months (42·1–165·2), and 66·2 months (43·5–97·1), respectively. Median weight was 72·8 kg (IQR 63·0–82·4), and 277 (50%) of 553 participants met criteria for overweight or obesity. There were no differences in baseline diet among participants with available data at week 48 (inadequate diet: nine [3%] of 277 participants in the dolutegravir group *vs* six [2%] of 276 participants in the bictegravir group), partly adequate diet (199 [76%] *vs* 194 [77%]), adequate diet (32 [12%] *vs* 27 [11%]), and diet unknown (23 [9%] *vs* 24 [10%]; p=0·084). The raw data of the three-way cross-tabulation treatment by sex assigned at birth and tenofovir alafenamide use, and further stratified by virological outcome is shown in appendix 2 (p 5).

	Dolutegravir and lamivudine group (n=277)	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=276)
Age, years	49·6 (41·1–57·0)	50·6 (39·1–57·6)
Sex assigned at birth		
Male	203 (73%)	203 (74%)
Female	74 (27%)	73 (26%)
Race or ethnicity*		
White non-Latino	201 (73%)	201 (73%)
White Latino	66 (24%)	67 (24%)
Black African	4 (1%)	5 (2%)
Other	6 (2%)	3 (1%)
Tobacco consumption		
None or rarely	154 (56%)	152 (55%)
Regularly	117 (42%)	119 (43%)
Unknown	6 (2%)	5 (2%)
Alcohol consumption		
None or rarely	128 (46%)	118 (43%)
Regularly	129 (47%)	133 (48%)
Unknown	20 (7%)	25 (9%)
Height, cm	170·0 (163·0–176·0)	170·0 (165·0–175·0)
Weight, kg	72·8 (63·4–83·3)	72·8 (63·0–81·8)
BMI, kg/m²	25·1 (22·3–28·4)	24·8 (22·0–27·8)
Systolic blood pressure, mm Hg	124·0 (114·0–135·0)	125·0 (111·0–137·0)
Diastolic blood pressure, mm Hg	79·0 (71·0–85·0)	76·0 (69·0–85·0)
Heart rate, beats per min	74·0 (66·5–84·0)	73·0 (65·0–81·0)
Respiratory rate, breaths per min	16·0 (14·0–18·0)	16·0 (14·0–17·0)
Temperature, °C	36·1 (35·7–36·4)	36·0 (35·6–36·4)
Exposure to ART, years	11·7 (7·2–19·3)	11·1 (7·0–19·2)
HIV RNA <50 copies per mL, months	103·4 (43·0–170·2)	97·7 (41·5–163·3)
Duration of previous ART, months	66·2 (43·5–97·0)	62·8 (41·1–88·7)
Probable HIV transmission route		
Heterosexual relations	85 (31%)	86 (31%)
Homosexual relations	138 (50%)	130 (47%)
Parenteral drug use	31 (11%)	28 (10%)
Blood products	2 (1%)	3 (1%)
Other or unknown	21 (8%)	29 (11%)
NRTI-1		
Tenofovir alafenamide	77 (28%)	78 (28%)
Abacavir	59 (21%)	52 (19%)
Tenofovir disoproxil fumarate	92 (33%)	103 (37%)
No tenofovir alafenamide, abacavir, or tenofovir disoproxil	49 (18%)	43 (16%)
NRTI-2		
Lamivudine	70 (25%)	64 (23%)
Emtricitabine	182 (66%)	190 (69%)
No lamivudine or emtricitabine	25 (9%)	22 (8%)
Core drug		
Non-NRTI†	138 (50%)	141 (51%)
Integrase inhibitor	44 (16%)	49 (18%)
Protease inhibitor	93 (34%)	82 (30%)
More than one core drug	2 (1%)	4 (1%)
CD4 cells per µL	712·0 (516·3–918·4)	684·1 (473·2–859·0)

(Table 1 continues on next page)

	Dolutegravir and lamivudine group (n=277)	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=276)
(Continued from previous page)		
CD8 cells per µL	666·0 (511·5–879·2)	628·5 (478·6–817·4)
CD4 to CD8 ratio	1·0 (0·8–1·4)	1·1 (0·8–1·4)
Nadir CD4, cells per µL	293·0 (144·0–472·0)	302·0 (159·0–476·0)
Previous AIDS (CDC criteria)		
No	215 (78%)	224 (82%)
Yes	61 (22%)	50 (18%)
Glucose, mg/dL	91·0 (84·0–98·0)	90·0 (83·0–98·0)
Insulin, mU/L	10·1 (6·4–17·3)	9·6 (5·9–14·9)
Haemoglobin A1c	5·3% (5·2–5·5)	5·3% (5·1–5·6)
Total triglycerides, mg/dL	112·0 (83·0–160·0)	119·5 (84·5–165·0)
Total cholesterol, mg/dL	193·0 (169·0–214·8)	189·0 (164·5–218·0)
HDL cholesterol, mg/dL	51·0 (41·0–61·5)	52·0 (42·0–62·0)
LDL cholesterol, mg/dL	112·0 (93·0–129·0)	110·0 (93·0–135·0)
AST, UI/L	22·0 (18·0–28·0)	23·0 (19·0–29·0)
ALT, UI/L	20·0 (16·0–30·0)	23·0 (17·0–30·0)
GGT, UI/L	28·0 (20·0–44·0)	29·0 (20·0–44·0)
Alkaline phosphatase, UI/L	80·0 (61·0–99·0)	81·0 (64·5–103·5)
Estimated GFR, mL/min per 1·73 m²‡	91·0 (86·3–91·0)	91·0 (85·6–91·0)
Energy expenditure, min per week§	1120·0 (482·5–3426·6)	1072·8 (295·0–2839·4)
Short Diet Quality Screener	20·0 (18·0–23·0)	20·0 (18·0–22·0)

Data are n (%) or median (IQR). ART=antiretroviral therapy. ALT=alanine transaminase. AST=aspartate aminotransferase. CDC=Centers for Disease Control and Prevention. GFR=glomerular filtration rate. GGT=gamma-glutamyl transferase. NRTI=nucleoside reverse transcriptase inhibitor. *Race or ethnicity was self- identified. †73 participants on efavirenz in the dolutegravir and lamivudine group and in the bictegravir, emtricitabine, and tenofovir alafenamide group. ‡Estimated GFR measured according to Chronic Kidney Disease Epidemiology Collaboration equation. §Energy expenditure according to moderate to vigorous intensity physical activity measured by the metabolic equivalent task.

Table 1: **Baseline demographics and clinical characteristics in the intention-to-treat exposed population**

The difference in the proportion of participants with HIV RNA ≥50 copies per mL at 48 weeks between the dolutegravir group (six [2%] of 277) and the bictegravir group (two [1%] of 276) was 1·4% (95% CI –0·5 to 3·4; p=0·16) showing non-inferiority of dolutegravir and lamivudine to bictegravir, emtricitabine, and tenofovir alafenamide (figures 2A, B). There was no clustering by centre as the eight participants with HIV RNA ≥50 copies per mL at 48 weeks were distributed across seven centres. Viral load evolution among participants with HIV-1 RNA ≥50 copies per mL snapshot at week 48 in the intention-to-treat exposed population is shown in appendix 2 (p 22). Sensitivity intention-to-treat analyses showed consistent results (appendix 2 p 6). In the per-protocol analysis at 48 weeks (n=549), the difference in the proportions of participants with HIV RNA ≥50 copies per mL between the dolutegravir group (six [2%] of 273) and bictegravir group (two [1%] of 276) was 1·5 percentage points (95% CI –0·5 to 3·5). The difference in the proportions of participants with HIV RNA <50 copies per mL in the intention-to-treat population at 48 weeks between the dolutegravir group and the bictegravir group was 3·3 percentage points (95% CI –1·4 to 7·9; figure 2C). Virological outcomes across subgroups were generally consistent with those in the overall population (appendix 2 p 23). One participant (in the bictegravir group) met the criteria for protocol-defined virological failure, but no genotypic resistance mutations were detected. In participants with HIV RNA ≥50 copies per mL (n=8), HIV RNA levels were low (≤282 copies per mL), and adherence to study medication in the previous week had been <95% in five of them; all continued assigned therapy and HIV RNA levels returned to <50 copies per mL in the next

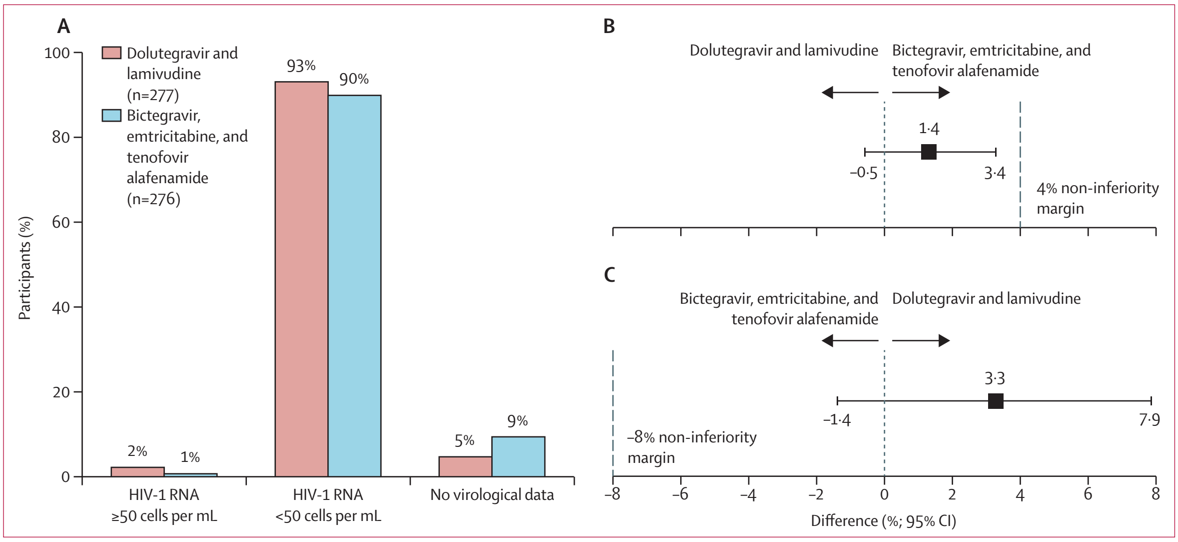

Figure 2: **Virological efficacy at 48 weeks**

(A) Proportion of participants meeting the primary endpoint in the dolutegravir group and bictegravir group. (B) Difference in the proportion of participants with HIV RNA ≥50 copies per mL at 48 weeks between groups. (C) Difference in the proportion of participants with HIV RNA <50 copies per mL in the intention-to-treat exposed population at 48 weeks between the groups.

follow-up assessment. Mean change from baseline in CD4 cells per μL, CD8 cells per μL, and CD4 to CD8 cell count ratio did not significantly differ between groups (appendix 2 pp 24–26). Regarding adherence to study medication, less than 5% of missed doses in the week before baseline and at weeks 6, 24, and 48 were reported in 247 (89%) of 277 participants, 228 (82%), 223 (81%), and 216 (78%) in the dolutegravir group and 244 (88%) of 276 participants, 255 (82%), 215 (78%), and 216 (78%) in the bictegravir group (appendix 2 pp 7–14).

The most common adverse events occurring in at least 10% of participants in one of the groups were infections, musculoskeletal, gastrointestinal, metabolic, and psychiatric events (table 2). Gastrointestinal disorders and hepatobiliary disorders were more common in the dolutegravir group than in the bictegravir group, whereas infections were less common in the dolutegravir group than in the bictegravir group. Adverse events were usually mild or moderate and considered unrelated to the study drugs. Statistically significantly more grade 3–4 adverse events occurred in the bictegravir group (ten [3%]) than in the dolutegravir group (three [1%]; p=0·049). Treatment discontinuation due to adverse events occurred in three participants (one patient with general discomfort and arthromyalgia in the dolutegravir group and one patient with insomnia and one with sleep disturbances in the bictegravir group).

Weight increased from baseline to week 48 in both groups (figure 3A). Changes in estimations of energy expenditure in moderate-to-vigorous physical activity and quality of diet did not differ between groups and were not statistically significantly associated with changes in weight in the study population (appendix 2 p 15). Weight change from baseline increased statistically significantly more in the bictegravir group (mean adjusted change 1·81 kg [95% CI 1·28–2·34]) than in the dolutegravir group (0·89 kg [0·37–1·41]). The difference in mean weight change at 48 weeks between the bictegravir group and the dolutegravir group was 0·92 kg (0·17–1·66; p=0·016; figure 3A). BMI changes were consistent with weight changes (appendix 2 p 27). The proportion of participants with >5% weight gain at 48 weeks was 75 of 251 (29·9% [95% CI 24·4–36·0]) in the bictegravir group and 52 of 263 (20·0% [15·4–25·3]) in the dolutegravir group (adjusted odds ratio [OR] for the effect of treatment 1·81 [95% CI 1·19–2·76]; p=0·006; figure 3B). In participants who discontinued regimens containing tenofovir disoproxil fumarate, >5% weight gain at 48 weeks occurred in 17 (20%) of 87 in the dolutegravir group and 37 (41%) of 91 in the bictegravir group (figure 3C). Although most participants gained weight over 48 weeks of follow-up, some participants lost weight. The proportion of participants by category of percentage weight change from baseline to weeks 6, 24, and 48 is shown in appendix 2 (p 28). There was a negative correlation between baseline weight and weight change (appendix 2 p 29).

	Dolutegravir and lamivudine group (n=277)	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=276)	p value
Any adverse event			
No	70 (25%)	60 (22%)	0·33
Yes	207 (75%)	216 (78%)	··
Grade 3–4			
No	274 (99%)	266 (96%)	0·049
Yes	3 (1%)	10 (4%)	··
Severe			
No	265 (96%)	263 (95%)	0·83
Yes	12 (4%)	13 (5%)	··
Drug-related			
No	258 (93%)	249 (90%)	0·21
Yes	19 (7%)	27 (10%)	··
Drug-related severe			
No	277 (100%)	276 (100%)	NA
Leading to withdrawal			
No	276 (<100%)	274 (99%)	0·56
Yes*	1 (<1%)	2 (1%)	··
Deaths			
No	277 (100%)	276 (100%)	NA
Clinical adverse events			
Blood and lymphatic system disorders			
No	272 (98%)	272 (99%)	0·74
Yes	5 (2%)	4 (1%)	··
Cardiac disorders			
No	263 (95%)	266 (96%)	0·41
Yes	14 (5%)	10 (4%)	··
Ear and labyrinth disorders			
No	265 (96%)	263 (95%)	0·83
Yes	12 (4%)	13 (5%)	··
Eye disorders			
No	274 (99%)	271 (98%)	0·47
Yes	3 (1%)	5 (2%)	··
Gastrointestinal disorders			
No	229 (83%)	247 (89%)	0·021
Yes	48 (17%)	29 (11%)	··
General disorders and administration site conditions			
No	258 (93%)	257 (93%)	0·99
Yes	19 (7%)	19 (7%)	··
Hepatobiliary disorders			
No	261 (94%)	273 (99%)	0·0020
Yes	16 (6%)	3 (1%)	··
Immune system disorders			
No	273 (99%)	273 (99%)	0·71
Yes	4 (1%)	3 (1%)	··
Infections and infestations			
No	175 (63%)	151 (55%)	0·043
Yes	102 (37%)	125 (45%)	··

(Table 2 continues on next column)

	Dolutegravir and lamivudine group (n=277)	Bictegravir, emtricitabine, and tenofovir alafenamide group (n=276)	p value
(Continued from previous column)			
Injury, poisoning, and procedural complications			
No	266 (96%)	260 (94%)	0·32
Yes	11 (4%)	16 (6%)	··
Metabolism and nutrition disorders			
No	239 (86%)	250 (91%)	0·11
Yes	38 (14%)	26 (9%)	··
Musculoskeletal and connective tissue disorders			
No	223 (81%)	225 (82%)	0·76
Yes	54 (19%)	51 (18%)	··
Neoplasms benign, malignant, and unspecified (including cysts and polyps)			
No	270 (97%)	265 (96%)	0·33
Yes	7 (3%)	11 (4%)	··
CNS disorders			
No	258 (93%)	256 (93%)	0·86
Yes	19 (7%)	20 (7%)	··
Psychiatric disorders			
No	250 (90%)	239 (87%)	0·18
Yes	27 (10%)	37 (13%)	··
Renal and urinary disorders			
No	262 (95%)	260 (94%)	0·85
Yes	15 (5%)	16 (6%)	··
Laboratory adverse events (grade 3 or 4)			
ALT			
No	277 (100%)	275 (<100%)	0·32
Yes	0	1 (<1%)	··
AST			
No	277 (100%)	274 (99%)	0·16
Yes	0	2 (1%)	··
Total cholesterol			
No	274 (99%)	272 (99%)	0·70
Yes	3 (1%)	4 (1%)	··
Triglycerides			
No	276 (<100%)	275 (<100%)	1·00
Yes	1 (<1%)	1 (<1%)	··
LDL cholesterol			
No	271 (98%)	270 (98%)	1·00
Yes	6 (2%)	6 (2%)	··
Alkaline phosphatase			
No	277 (100%)	276 (100%)	NA
eGFR			
No	247 (89%)	250 (91%)	0·58
Yes	30 (11%)	26 (9%)	··

ALT=alanine aminotransferase. AST=aspartate aminotransferase. eGFR=estimated glomerular filtration rate. NA=not applicable. *Adverse events leading to withdrawal were general discomfort and arthromyalgia (one patient in the dolutegravir and lamivudine group), insomnia (one patient in the bictegravir, emtricitabine, and tenofovir alafenamide group), and sleep disturbances (one in the bictegravir, emtricitabine, and tenofovir alafenamide group).

Table 2: **Summary of adverse events in the safety population**

Weight gain was associated with increases in triglyceride concentration and HOMA-IR value and decreases in HDL cholesterol concentration (appendix 2 p 16). Although the proportion of participants with >5% weight gain in the dolutegravir group was similar regardless of the baseline regimen, the proportion of individuals who gained >5% weight in the bictegravir group was similar to that in the dolutegravir group when previous regimens contained tenofovir alafenamide or no NRTI-1s but higher when regimens contained abacavir or tenofovir disoproxil fumarate (figure 3C). The proportion of individuals who gained >5% weight in the bictegravir group was lower than those in the dolutegravir group with regimens containing no NRTIs (eg, protease inhibitor monotherapy), similar with regimens containing protease inhibitors or integrase inhibitors (generally containing tenofovir alafenamide or no NRTI-1s), and higher with regimens containing lamivudine, emtricitabine, or non-NRTIs (generally containing tenofovir disoproxil fumarate or abacavir; figures 3D, E; appendix 2 pp 17–19). Changes in BMI categories over time showed more participants meeting criteria for overweight or obesity in the bictegravir group than in the dolutegravir group (appendix 2 p 30).

Total concentrations of cholesterol, triglycerides, and alkaline phosphatase, and eGFR score statistically significantly decreased from baseline in both groups; however, there were no statistically significant differences between groups. No statistically significant changes occurred within or between groups in fasting glucose concentration, HOMA-IR, HbA1c concentration, and fibrosis-4 index score. There were small statistically significant increases but no clinically significant increases in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) concentrations in the bictegravir group. No statistically significant changes occurred in AST or ALT concentrations in the dolutegravir group (appendix 2 pp 31–40). A few participants were prescribed new lipid-lowering (four in the dolutegravir group and three in the bictegravir group), anti-diabetic (two and one), or antihypertensive (two and two) drugs at 48 weeks, and numbers were similar in both groups (appendix 2 pp 20–21).

Discussion

Switching regimens to dolutegravir and lamivudine showed non-inferior virological efficacy to bictegravir, emtricitabine, and tenofovir alafenamide at 48 weeks in people with HIV who had reached virological suppression. Both regimens had previously shown non-inferior efficacy to standard triple therapies in switching trials.[12–16] Few participants had HIV RNA ≥50 copies per mL at 48 weeks, which was re-suppressed while maintaining study therapy. Only one participant had protocol-defined virological failure, with no emerging resistance mutations, thus confirming the high genetic barrier of both regimens. The regimens were well tolerated, with exceptional discontinuations due to adverse events.

Both groups had statistically significant weight gain at 48 weeks, exceeding the annual weight gain reported in European adults aged 45–64 years (0·25 kg/year).[17] Switching to dolutegravir from boosted protease inhibitors in the NEAT022 study[18] or from efavirenz in the extension of the ADVANCE study[19] resulted in weight gains at 48 weeks. As bictegravir is formulated as a fixed combination with tenofovir alafenamide, the individual effect of switching to bictegravir on weight has been more difficult to assess, although the effect appears to be similar to that in dolutegravir.[11]

Switching to dolutegravir and lamivudine was associated with less weight gain than switching to bictegravir, emtricitabine, and tenofovir alafenamide at 48 weeks. A cutoff of 5% has been suggested as an endpoint of clinically significant weight gain in non-diabetic individuals switching to integrase inhibitors,[20] as well as in adults aged mean 55 years (SD 6) in the general population.[21] The proportion of participants gaining >5% weight in the bictegravir group was statistically significantly higher than the >5% weight gain in the dolutegravir group at 48 weeks. There were also greater increases in the proportions of overweight and obese BMI categories in the bictegravir group than in the dolutegravir group.

Weight effects in antiretroviral switching studies might be associated not only with the newly introduced drug but also with the discontinued drug, or both. Although the proportion of participants with >5% weight gain in the dolutegravir group remained stable regardless of the discontinued medications, the proportions of participants with a >5% weight gain in the bictegravir group were higher than in the dolutegravir group when the baseline regimens contained tenofovir disoproxil fumarate or abacavir. Because of the weight-suppressing effect of tenofovir disoproxil fumarate,[22] it has been considered that weight gain in individuals switching from tenofovir disoproxil fumarate-containing regimens to tenofovir disoproxil fumarate-free ones could be fully explained by discontinuing tenofovir disoproxil fumarate.[4] If this was the case, a weight gain effect like that seen in participants who switched from tenofovir disoproxil fumarate-containing regimens to bictegravir, emticitabine, and tenofovir alafenamide should also have been seen in participants switching from tenofovir disoproxil

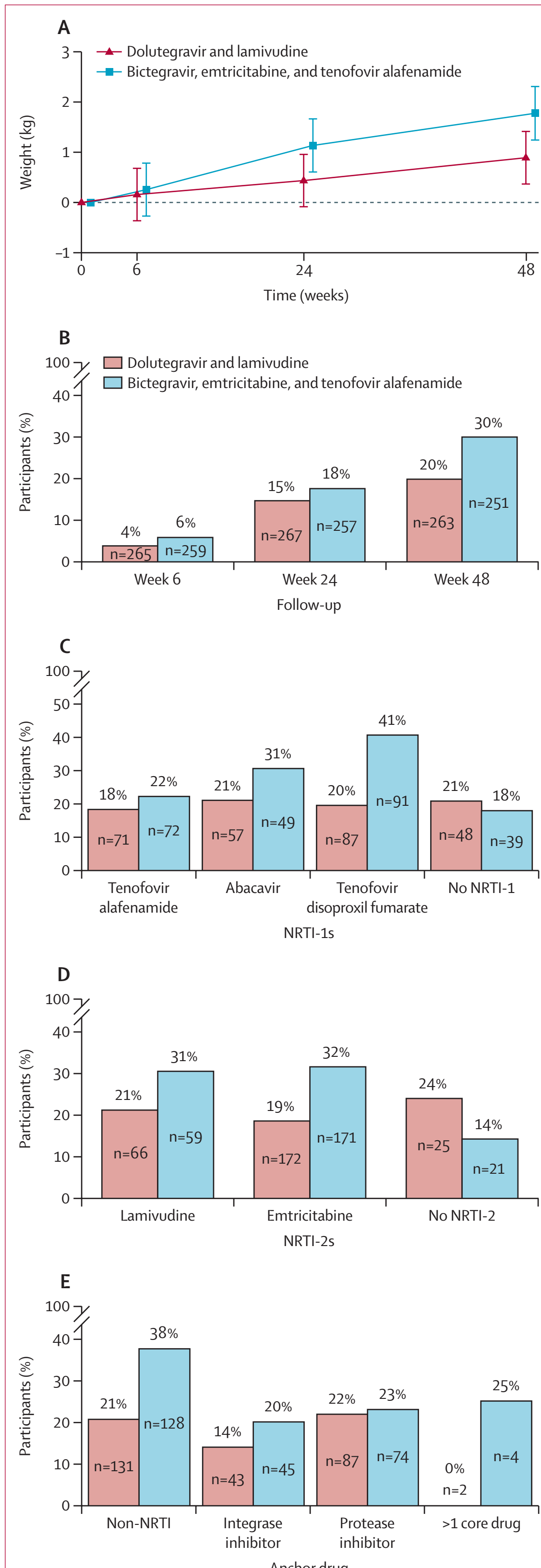

***Figure 3:* Absolute weight change and proportion of participants with >5% weight gain from baseline to week 48**

Weight change from baseline to week 48 (A), and proportion of participants with >5% weight gain from baseline to week 48 in the overall population (B), stratified by NRTI-1 (C), NRTI-2 (D), or core drug (E) at baseline. NRTI-1=nucleoside reverse transcriptase inhibitors tenofovir disoproxil fumarate, abacavir, and tenofovir alafenamide. NRTI-2=nucleoside reverse transcriptase inhibitors lamivudine and emtricitabine.

fumarate-containing regimens to dolutegravir and lamivudine. In this PASO-DOBLE study, discontinuation of abacavir was also associated with greater weight gain in the bictegravir group than in the dolutegravir group, and this effect is consistent with the weight gain observed when switching from abacavir to tenofovir alafenamide in randomised clinical trials[5] and cohort studies.[23] These data suggest that discontinuation of regimens with tenofovir disoproxil fumarate or abacavir is associated with a different effect on weight depending on whether regimens are switched to bictegravir, emtricitabine, and tenofovir alafenamide or dolutegravir and lamivudine.

When the regimens at baseline contained tenofovir alafenamide or did not contain any NRTI-1, switching to bictegravir, emtricitabine, and tenofovir alafenamide or dolutegravir and lamivudine resulted in similar proportions of participants gaining >5% weight. In this PASO-DOBLE study, the regimens that did not contain tenofovir disoproxil fumarate, abacavir, or tenofovir alafenamide were composed of protease inhibitor monotherapy or dual therapy with protease inhibitor plus lamivudine. In the TANGO study, individuals who continued tenofovir alafenamide-containing regimens gained a similar amount of weight as those who switched to dolutegravir and lamivudine,[12] suggesting that maintaining tenofovir alafenamide-based antiretroviral therapy (versus discontinuing tenofovir alafenamide) is not necessarily associated with weight gain. Altogether these data argue against a direct effect of tenofovir alafenamide introduction per se on weight gain.

Discontinuation of tenofovir disoproxil fumarate or abacavir alone or introduction of tenofovir alafenamide alone does not fully explain the different results observed in the proportions of participants with weight gain >5% between the two groups. The fact that the introduction of tenofovir alafenamide in people with HIV who had reached virological suppression was associated with greater weight gain only when tenofovir disoproxil fumarate or abacavir were discontinued suggests that both interventions might be necessary and interdependent. Of note, regimens containing tenofovir alafenamide plus a second-generation integrase inhibitor have been associated with the greatest weight gain in people with HIV and naive to antiretroviral therapy in randomised clinical trials[24] and cohort studies.[25] It is unknown what underlying factors might be common in both settings, but the adipocyte mitochondrial toxicity, which has been reported with tenofovir disoproxil fumarate and abacavir in people with HIV who reached virological suppression or those with antiretroviral-naive HIV with uncontrolled viral replication, might play a role in the greater weight gain effect when a second-generation integrase inhibitor and tenofovir alafenamide are introduced concomitantly.[26–30]

This study had limitations. In contrast to bictegravir, emtricitabine, and tenofovir alafenamide, dolutegravir and lamivudine is not recommended in pregnancy or in people with hepatitis B, and consequently these people were excluded. The open-label design is vulnerable to bias due to the absence of masking for participants and investigators. However, participants in each group received the same intervention, which consisted of changing the therapies to a new single-tablet combination. Participants were only stratified by sex assigned at birth and tenofovir alafenamide use at baseline because these factors were known to be associated with weight gain when the trial was designed; associations of tenofovir disoproxil fumarate and efavirenz with weight suppression became clearer after the study began. The study population is not representative of some races or ethnicities, such as Black or African. HIV might be a higher risk for weight gain in people from these racial or ethnic backgrounds; however, they are uncommon in Spain. This study also had some strengths. Although a possible imbalance of tenofovir disoproxil fumarate or efavirenz at baseline between the study groups could at least partly explain the differences in weight gain between participants in the dolutegravir group and the bictegravir group, both tenofovir disoproxil fumarate and efavirenz were fairly balanced as expected from a randomised clinical trial. The number of participants assigned to tenofovir disoproxil fumarate or efavirenz at baseline was 92 and 73 in the dolutegravir group and 103 and 73 in the bictegravir group, respectively, and the number of participants with tenofovir disoproxil fumarate at baseline contributing to the analyses of weight changes >5% was 87 in the dolutegravir group and 91 in the bictegravir group. Although we have focused our discussions on specific NRTI-1 medications to explain the differential effect on weight in both groups of the study, differences in specific integrase inhibitors or cytosine analogues could also play a role.

In summary, switching from antiretroviral regimens deserving optimisation to dolutegravir and lamivudine or bictegravir, emtricitabine, and tenofovir alafenamide in people with HIV with virological suppression showed similarly high levels of virological efficacy, no emergence of resistance, and few discontinuations due to adverse events at 48 weeks. Switching to bictegravir, emtricitabine, and tenofovir alafenamide was associated with greater weight gain than switching to dolutegravir and lamivudine, although weight gain with each of the study regimens was greater than expected in the general population. Although the small weight gain per year might seem modest, if sustained, it could lead to obesity over time. Both discontinuation of tenofovir disoproxil fumarate or abacavir and introduction of tenofovir alafenamide appeared to be necessary factors to explain the greater proportion of clinically significant weight gain in participants assigned to bictegravir, emtricitabine, and tenofovir alafenamide compared with those assigned to dolutegravir and lamivudine, although the underlying mechanisms responsible for weight gain are unknown. Weight differences between the two study regimens did not show a differential effect on concentration of plasma lipids or insulin resistance at 48 weeks. Longer follow-up and the results of planned substudies will provide useful information to understand whether weight changes persist, what the overall clinical effect related to weight gain is, and what pathogenetic mechanisms might be involved. These results provide further evidence that could be useful in shared decision making between physicians and people living with HIV regarding switching to oral antiretroviral therapy.

Contributors

EM designed the study. BA undertook the statistical analyses. All authors were involved in the interpretation of data. MdM, BA, and EM accessed and verified the underlying data reported in the manuscript. EM drafted the manuscript with input from the rest of authors. All authors critically reviewed and subsequently approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

The full protocol is available as supplementary de-identified participant data, and a data dictionary defined in the data set can also be made available on request. The protocol and data can be requested from the corresponding author, and a signed data access agreement will be required for access.

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